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## Fetal Growth: Evaluation and Management

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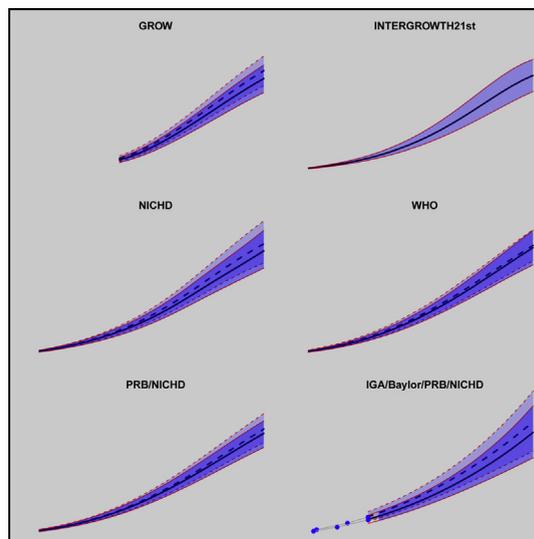
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Customized growth charts are a useful, internationally applicable standard to assess fetal growth; their implementation has helped to reduce stillbirths.

### S619 The World Health Organization fetal growth charts: concept, findings, interpretation, and application

Torvid Kiserud; Alexandra Benachi; Kurt Hecher; Rogelio González Perez; José Carvalho; Gilda Piaggio; Lawrence D. Platt

World Health Organization fetal growth charts that were established on multiple populations, which were intended for international use, document geographic variation and differential effects of maternal factors on the percentiles.

### S630 The INTERGROWTH-21<sup>st</sup> fetal growth standards: toward the global integration of pregnancy and pediatric care



Aris T. Papageorghiou; Stephen H. Kennedy; Laurent J. Salomon; Douglas G. Altman; Eric O. Ohuma; William Stones; Michael G. Gravett; Fernando C. Barros; Cesar Victora; Manorama Purwar; Yasmin Jaffer; Julia A. Noble; Enrico Bertino; Ruyan Pang; Leila Cheikh Ismail; Ann Lambert; Zulfiqar A. Bhutta; José Villar; for the International Fetal and Newborn Growth Consortium for the 21<sup>st</sup> Century (INTERGROWTH-21<sup>st</sup>) Human skeletal growth from the 1<sup>st</sup> trimester of pregnancy to childhood is similar across populations with adequate health, nutrition and low risk of adverse pregnancy outcomes.

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### S641 Fetal growth standards: the NICHD fetal growth study approach in context with INTERGROWTH-21st and the World Health Organization Multicentre Growth Reference Study

Katherine L. Grantz; Mary L. Hediger; Danping Liu;  
Germaine M. Buck Louis

Three recent longitudinal cohort studies, one in the United States and two international, have developed intrauterine fetal growth charts that vary in design and conclusions and that require understanding for application.

### S656 Individualized growth assessment: conceptual framework and practical implementation for the evaluation of fetal growth and neonatal growth outcome

Russell L. Deter; Wesley Lee; Lami Yeo; Offer Erez; Uma Ramamurthy;  
Medha Naik; Roberto Romero

Fetal growth abnormalities can pose significant consequences on perinatal morbidity and mortality of nonanomalous fetuses and can be evaluated with individual anatomical parameters or sets of parameters.

## ORIGINAL RESEARCH

### OBSTETRICS

### S679 A new customized fetal growth standard for African American women: the PRB/NICHD Detroit study

Adi L. Tarca; Roberto Romero; Dereje W. Gudicha; Offer Erez;  
Edgar Hernandez-Andrade; Lami Yeo; Gaurav Bhatti; Percy Pacora;  
Eli Maymon; Sonia S. Hassan

We report a customized fetal growth standard for African American women that considers maternal height, weight, and parity, and fetal sex. This standard takes into account novel features of fetal growth discovered herein such as timing of the effect of covariates and the differential effect on the different centiles of estimated fetal weight.

### S692 Customized vs INTERGROWTH-21<sup>st</sup> standards for the assessment of birthweight and stillbirth risk at term

Andre Francis; Oliver Hugh; Jason Gardosi

INTERGROWTH-21<sup>st</sup> rates of small- and large-for-gestational-age birthweight vary with physiological pregnancy characteristics and miss the majority of pregnancies at risk of stillbirth.

## EXPERT REVIEWS

### S700 Fetal growth velocity and body proportion in the assessment of growth

Liran Hiersch; Nir Melamed

Serial ultrasound evaluations and assessment of fetal body proportions may improve the diagnosis of fetal growth restriction.

## ORIGINAL RESEARCH

## OBSTETRICS

**S712** What birthweight percentile is associated with optimal perinatal mortality and childhood education outcomes?

Ellie C. McEwen; Steven L. Guthridge; Vincent YF. He; John W. McKenzie; Thomas J. Boulton; Roger Smith

Birthweights between 50th-93rd percentiles were consistently associated with low perinatal mortality and high reading and numeracy scores.

## EXPERT REVIEWS

**S725** Screening for fetal growth restriction using fetal biometry combined with maternal biomarkers

Francesca Gaccioli; Irving L. M. H. Aye; Ulla Sovio; D. Stephen Charnock-Jones; Gordon C. S. Smith

Combining fetal biometry and biomarkers reflective of placental insufficiency will help develop screening tests able to differentiate between healthy and growth restricted small-for-gestational-age fetuses.

## ORIGINAL RESEARCH

## OBSTETRICS

**S738** The effect of customization and use of a fetal growth standard on the association between birthweight percentile and adverse perinatal outcome

Ulla Sovio; Gordon C. S. Smith

Use of fetal weight standards and customizing percentiles may overestimate associations with adverse perinatal outcome through confounding by preterm birth and maternal obesity.

## EXPERT REVIEWS

**S745** Pathophysiology of placental-derived fetal growth restriction

Graham J. Burton; Eric Jauniaux

Deficient remodeling of the uterine arteries and resultant malperfusion compromise placental function through infarction, reduced villous surface area and vascularization, and dysregulation of transporter activity.

**S762** Is there a role for placental senescence in the genesis of obstetric complications and fetal growth restriction?

Zakia Sultana; Kaushik Maiti; Lee Dedman; Roger Smith

This review examines cellular senescence and how senescence is regulated and the role of physiological placental senescence and how aberrant placental senescence alters placental function, contributing to the pathophysiology of fetal growth restriction, preeclampsia, spontaneous preterm labor/birth, and unexplained fetal death.

(continued)

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**SYSTEMATIC REVIEWS**

**S774 Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: a systematic review and meta-analysis**  
J. Caradeux; R. J. Martinez-Portilla; T. R. Basuki; T. Kiserud; F. Figueras  
Early-onset growth-restricted fetuses with either umbilical artery or ductus venosus absent or reserved end-diastolic velocities are at a substantially increased risk for fetal death.

**EXPERT REVIEWS**

**S783 Outcome in early-onset fetal growth restriction is best combining computerized fetal heart rate analysis with ductus venosus Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe**  
 Tiziana Frusca; Tullia Todros; Christoph Lees; Caterina M. Bilardo; TRUFFLE Investigators  
Monitoring early fetal growth restriction with ductus venosus Doppler combined with computerized fetal heart rate is associated with optimal short- and long-term outcomes.

**S790 Diagnosis and surveillance of late-onset fetal growth restriction**  
Francesc Figueras; Javier Caradeux; Fatima Crispi; Elisenda Eixarch; Anna Peguero; Eduard Gratacos  
In late fetal growth restriction, a combination of biometrical parameters, with Doppler criteria of placental insufficiency, offers a classification tool which correlates to adverse perinatal outcome.

**S803 A placenta clinic approach to the diagnosis and management of fetal growth restriction**  
 John C. Kingdom; Melanie C. Audette; Sebastian R. Hobson; Rory C. Windrim; Eric Morgen  
A placenta clinic approach to manage pregnancies with suspected fetal growth restriction is described focusing on prenatal diagnosis of specific placental diseases and their significance.

**S818 Antenatal glucocorticoids, magnesium sulfate, and mode of birth in preterm fetal small for gestational age**  
Joseph Y. Ting; John C. Kingdom; Prakesh S. Shah  
Small-for-gestational-age fetuses undergo substantial physiologic adaptations and consequently their responses to standard perinatal interventions for preterm birth may differ from appropriately grown fetuses.

**S829 The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction**  
Katie M. Groom; Anna L. David  
This was a review of the current evidence for preventative and treatment options for fetal growth restriction with some insights into new therapies on the horizon.

## ORIGINAL RESEARCH

## OBSTETRICS

**S841** The satisfactory growth and development at 2 years of age of the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards cohort support its appropriateness for constructing international standards

José Villar; Leila Cheikh Ismail; Eleonora Staines Urias; Francesca Giuliani; Eric O. Ohuma; Cesar G. Victora; Aris T. Papageorghiou; Douglas G. Altman; Cutberto Garza; Fernando C. Barros; Fabien Puglia; Roseline Ochieng; Yasmin A. Jaffer; Julia A. Noble; Enrico Bertino; Manorama Purwar; Ruyan Pang; Ann Lambert; Cameron Chumlea; Alan Stein; Michelle Fernandes; Zulfiqar A. Bhutta; Stephen H. Kennedy; for the International Fetal and Newborn Growth Consortium for the 21<sup>st</sup> Century (INTERGROWTH-21<sup>st</sup>)

Follow-up study of the cohort on which the international INTERGROWTH-21<sup>st</sup> fetal growth standards are based demonstrates satisfactory growth and development at 2 years of age.

## EXPERT REVIEWS

**S855** Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy

Lesley M. McCowan; Francesc Figueras; Ngairé H. Anderson

A review of current evidence-based national guidelines for the management of suspected fetal growth restriction, with recommendations for improved consensus and future research.

**S869** Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease

Fatima Crispi; Jezid Miranda; Eduard Gratacós

Fetal growth restriction has a strong influence in cardiovascular health that open opportunities to improve public health by the identification of perinatal factors that strongly can determine the individual's health and potentially accelerate the implementation of preventive strategies starting from fetal or early postnatal life.

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# Fetal size standards to diagnose a small- or a large-for-gestational-age fetus



Roberto Romero, MD, DMedSci; Adi L. Tarca, PhD

There has been a proliferation of fetal size standards, and practicing obstetricians are faced with several choices. This special supplement of the *American Journal of Obstetrics & Gynecology* presents the work of six groups of investigators.

The [Figure](#) illustrates the different choices and here we review the assumptions made by the investigators when they developed the size standards.

## Customized Gestation-Related Optimal Weight (GROW) Chart

The image (top left) illustrates the approach proposed by Gardosi et al.<sup>1</sup> and is known as the customized Gestation-Related Optimal Weight (GROW) Chart. This method assumes that maternal weight, height, ethnicity, and parity, as well as fetal sex, have a proportional effect on estimated fetal weight. The investigators have generated customization coefficients based on birthweight data — these coefficients allow adjustment of the expected birthweight and estimated fetal weight generated with ultrasound biometry. The continuous lines in the [Figure](#) correspond to the 10th, 50th, and 90th percentiles of estimated fetal weight for a female fetus of a nulliparous mother in the U.S. The interrupted lines correspond to a male fetus of a mother in her third pregnancy. In both cases, the mothers are African American, 163 cm (5 feet, 4 inches) tall, and weighed 64 kg (141 pounds) at the first visit. A key concept is that maternal variables and fetal gender affect estimated fetal weight.

## INTERGROWTH-21st

The International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) developed fetal size charts from longitudinal fetal biometry data collected in an international cohort of healthy, well-nourished women who were at low risk of adverse maternal and perinatal outcomes.<sup>2</sup> The investigators proposed that these charts represent “optimal fetal size,” regardless of ethnic origin. The investigators included patients from 8 urban areas in Brazil,

Italy, Oman, UK, USA, China, India, and Kenya. These growth charts are accompanied by birthweight and infant standards to the age of 2 years.

## Fetal Growth Study by NICHD

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) fetal size charts<sup>3</sup> were developed by studying pregnant women of different ethnic groups living in the U.S. (Caucasian, African-American, Hispanic, and Asian). Unlike the customized approach of GROW, the authors did not assume that ethnicity has a proportional effect on estimated fetal weight during gestation; hence, the investigators derived separate charts for each ethnic group. The study included a low-risk population of women who delivered at term. The lines in the [Figure](#) (middle left) correspond to the chart (10th, 50th, and 90th percentiles) that the investigators labeled “non-Hispanic Blacks” (continuous lines) and “non-Hispanic Whites” (interrupted lines). Please note that the estimated fetal weight for non-Hispanic Blacks is lower than for non-Hispanic Whites.

## World Health Organization (WHO)

The WHO fetal size charts (middle right) were derived from an international low-risk population of women who delivered either at term or preterm, under the assumption that, of all factors considered, only fetal sex has a sizable effect on estimated fetal weight (female: continuous lines; male: interrupted lines).<sup>4</sup> In this study, the authors noted differences in fetal weight depending upon maternal country of origin (ethnic distribution was approximately 20% African, 20% Asian, and 60% Caucasian).

## Perinatology Research Branch (PRB/NICHD)

The Perinatology Research Branch of NICHD developed a fetal size chart derived from longitudinal estimated fetal weight data from African American women in Detroit.<sup>5</sup> The investigators observed that fetal sex and maternal height have a proportional effect during gestation, while maternal weight and parity have an increasing effect on estimated fetal weight with advancing gestational age. The size chart illustrated in the [Figure](#) (bottom left) defines fetal size for a pregnancy with optimal conditions (excluding the effect of clinical pathology, in a manner similar to that described by the customized approach of Gardosi et al.<sup>1</sup>, or GROW).

The continuous lines in the [Figure](#) correspond to the 10th, 50th, and 90th percentiles of estimated fetal weight for a female fetus of a nulliparous mother in the U.S. The interrupted lines correspond to a male fetus of a mother in her third pregnancy. In both cases, the mothers are African American, 163 cm (5 feet, 4 inches) tall, and weighed 64 kg (141 pounds) at the first visit.

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From the Perinatology Research Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development/National Institutes of Health/Department of Health and Human Services, Bethesda, MD, and Detroit, MI (Dr Romero and Dr Tarca); and Department of Obstetrics and Gynecology, Wayne State University School of Medicine (Dr Tarca) and Department of Computer Science, College of Engineering, Wayne State University, Detroit, MI (Dr Tarca). The authors report no conflicts of interest.

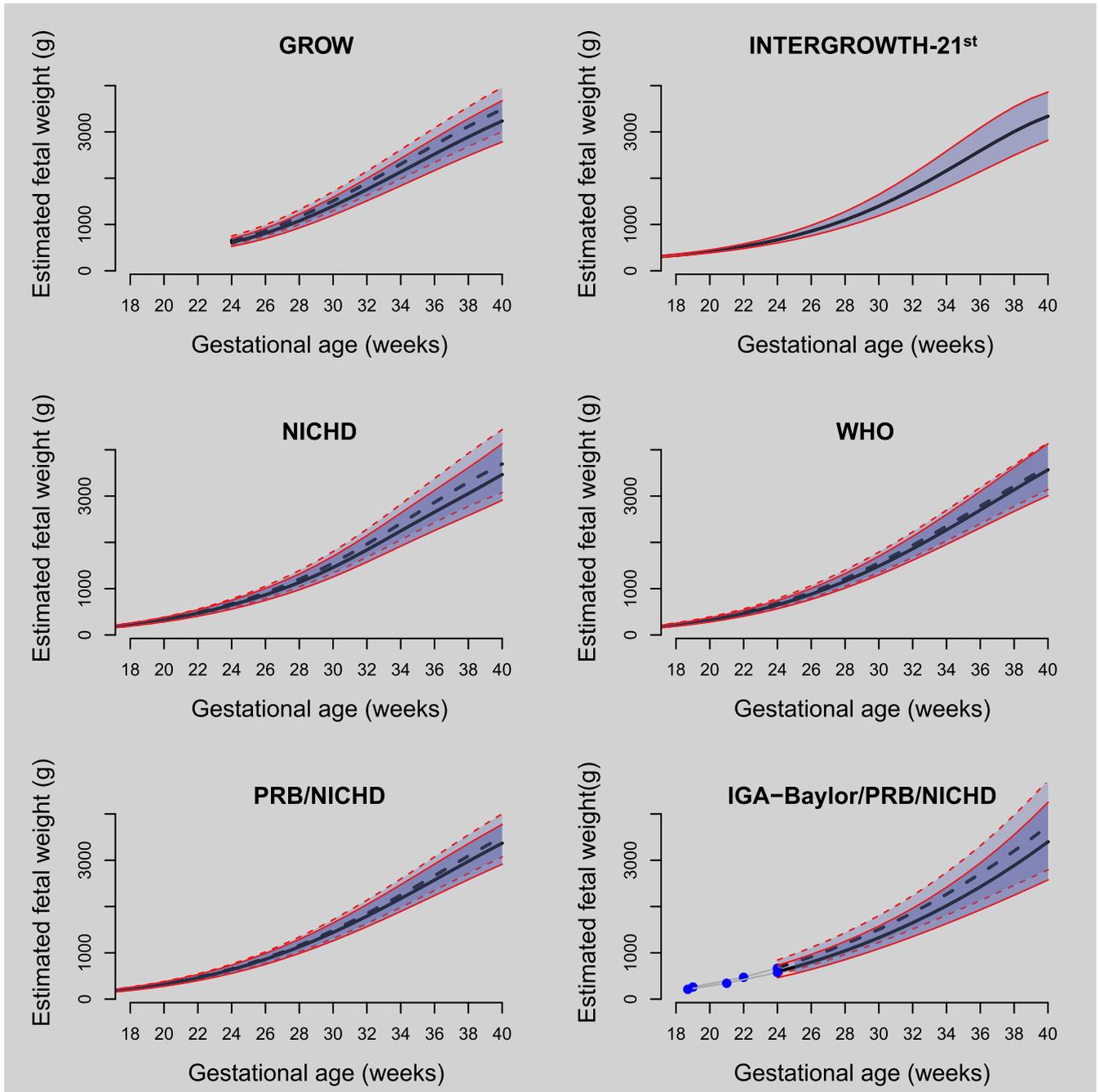
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**FIGURE**  
Standards for estimated fetal weight as a function of gestational age



Thick black lines (continuous or interrupted) correspond to the 50<sup>th</sup> centile of estimated fetal weight (EFW) while the thin red lines (continuous or interrupted) correspond to 10<sup>th</sup> and 90<sup>th</sup> centiles of EFW. For all, except the INTERGROWTH-21<sup>st</sup>, the continuous and interrupted lines correspond to two different pregnancies, as described in the text for each standard.

Romero. Fetal growth standards: it is all in the assumptions. *Am J Obstet Gynecol* 2018.

**Individualized Growth Assessment (IGA-Baylor/PRB of NICHD)**

The Individualized Growth Assessment (IGA)<sup>6</sup> (bottom right) assumes that the growth potential of a fetus can be

inferred from the rate of growth (gray lines) derived from two or three observations during the second trimester (blue dots). The fetus-specific size chart (10th, 50th, 90th centiles) shown in the [Figure](#) corresponds to two fetuses

of African-American women growing at different rates (fetus 1, continuous lines; fetus 2; interrupted lines). ■

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# Fetal Growth: Evaluation and Management



Roberto Romero, MD, DMedSci; John Kingdom, MD; Russell Deter, MD; Wesley Lee, MD; Anthony Vintzileos, MD

This special issue was conceived during a conversation with John Kingdom, Chair of Obstetrics and Gynecology at the University of Toronto, who hosted the 5<sup>th</sup> International Fetal Growth Meeting in November 2016 (Figure). Many of the authors of articles in this issue were at that meeting, which made possible lively debate among investigators, clinicians, and scientists dealing with topical subjects on fetal growth and, in particular, the topics of customization, optimal growth, and different standards for size and growth that have been recently published. The conference also covered issues related to the management of fetal growth disorders, and in particular, critical matters related to timing of delivery, placental examination, and the role of Doppler velocimetry in the assessment of fetal growth, among others.

We are grateful to the authors for their exceptional contributions, and the reviewers for providing constructive and timely feedback. Andrea Boccelli, Publisher of AJOG at Elsevier, deserves credit for seeing the value of this special issue, and for securing the support of Elsevier, Inc. for this project. The articles herein will be freely available on the website of the *American Journal of Obstetrics & Gynecology* ([ajog.org](http://ajog.org)), courtesy of Elsevier.

Our Editorial Managers, Donna Stroud and Sandra Perrine, were especially dedicated to working under short deadlines in order to accomplish timely publication of this supplement. Brian Arnold, Journal Manager of AJOG at Elsevier, also made extraordinary efforts to make publication possible.

Our hope is that this special issue will stimulate dialogue and debate, promote research in this important field, and improve patient care. ■

## FIGURE

Image from the 5<sup>th</sup> International Fetal Growth Meeting, Toronto, Ontario, Canada, 2016

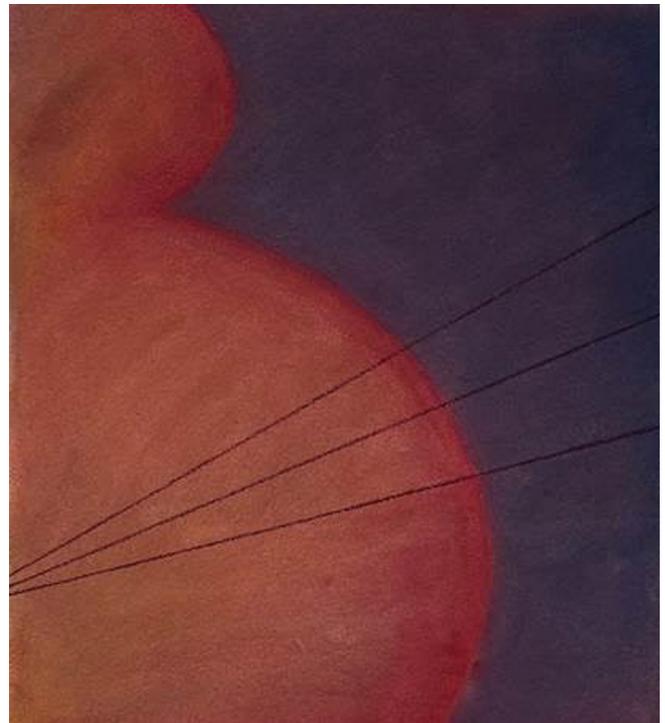


Figure courtesy of Ms. Aoife Ryan, Toronto, Ontario, Canada.

Romero. *Fetal Growth: Evaluation and Management*. *Am J Obstet Gynecol* 2018.

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From the Perinatology Research Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development/National Institutes of Health/Department of Health and Human Services (Dr Romero); Department of Obstetrics & Gynaecology, Mount Sinai Hospital, Toronto, Ontario, Canada (Dr Kingdom); Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX (Drs Deter and Lee); and Department of Obstetrics and Gynecology, New York University Winthrop Hospital, Mineola, NY (Dr Vintzileos).

The authors report no conflicts of interest.

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# Customized growth charts: rationale, validation and clinical benefits



Jason Gardosi, MD, FRCOG; Andre Francis, MSc; Sue Turner, BSc, RM; Mandy Williams, MSc, RM

Accurate standards for antenatal surveillance of fetal growth are essential for early recognition of the fetus who is at risk in an unfavorable intra-uterine environment. Standards are also important after delivery, to assess the neonate's risk of immediate and long-term morbidity and for audit, benchmarking, and epidemiologic investigations.

## One Size Does Not Fit All

A series of recent publications by the Intergrowth 21 project promote the use of a single universal standard for fetal growth and birthweight.<sup>1-3</sup> The data were derived from educated, affluent, clinically healthy women with adequate nutritional status in 8 countries. The authors call the standard "multiethnic" because it included different populations, with the implication that it is therefore suitable to be applied to multiple ethnic groups. The authors considered differences to be marginal and likely to be due to socioeconomic or other nonphysiologic factors and argued for the adoption of a single, prescriptive, universally applicable standard.

At the time of writing, there has still been no evidence presented to suggest that Intergrowth improves the identification of fetuses or neonates at an increased risk of adverse outcome. To the

Appropriate standards for the assessment of fetal growth and birthweight are central to good clinical care, and have become even more important with increasing evidence that growth-related adverse outcomes are potentially avoidable. Standards need to be evidence based and validated against pregnancy outcome and able to demonstrate utility and effectiveness. A review of proposals by the Intergrowth consortium to adopt their single international standard finds little support for the claim that the cases that it identifies as small are due to malnutrition or stunting, and substantial evidence that there is normal physiologic variation between different countries and ethnic groups. It is possible that the one-size-fits-all standard ends up fitting no one and could be harmful if implemented. An alternative is the concept of country-specific charts that can improve the association between abnormal growth and adverse outcome. However, such standards ignore individual physiologic variation that affects fetal growth, which exists in any heterogeneous population and exceeds intercountry differences. It is therefore more logical to adjust for the characteristics of each mother, taking her ethnic origin and her height, weight, and parity into account, and to set a growth and birthweight standard for each pregnancy against which actual growth can be assessed. A customized standard better reflects adverse pregnancy outcome at both ends of the fetal size spectrum and has increased clinicians' confidence in growth assessment, while providing reassurance when abnormal size merely represents physiologic variation. Rollout in the United Kingdom has proceeded as part of the comprehensive Growth Assessment Protocol (GAP), and has resulted in a steady increase in antenatal detection of babies who are at risk because of fetal growth restriction. This in turn has been accompanied by a year-on-year drop in stillbirth rates to their lowest ever levels in England. A global version of customized growth charts with over 100 ethnic origin categories is being launched in 2018, and will provide an individualized, yet universally applicable, standard for fetal growth.

**Key words:** birthweight, customized chart, fetal growth, GROW, LGA, maternal size, perinatal, SGA, stillbirth

contrary, there is evidence of significant variation between different populations and individuals and mounting evidence against a one-size-fits-all approach: First, their "multiethnic" concept is challenged by studies that have shown substantial ethnic variation, even in selected low-risk populations, that support the notion that observed differences are physiologic, not pathologic. This evidence has included analyses of databases of birthweight<sup>4-6</sup> and prospective evaluation of growth curves in different ethnic groups in the National Institute of Child Health and Human Development fetal growth studies.<sup>7</sup>

Second, there is mounting evidence against the utility and safety of the

Intergrowth standard by investigators who applied it to their own local population.<sup>8-10</sup> The concept of a universal standard has also been challenged from the perspective of developmental origins and fetal adaptive responses, because many biologic and cultural factors can influence fetal growth that should not be viewed as abnormal.<sup>11</sup>

The recently published World Health Organization (WHO) standard for fetal growth used similar methods to that of Intergrowth, selecting low-risk pregnancies from 10 countries.<sup>12</sup> They found differences in growth between countries and between individual maternal characteristics such as height, weight, and parity and concluded that

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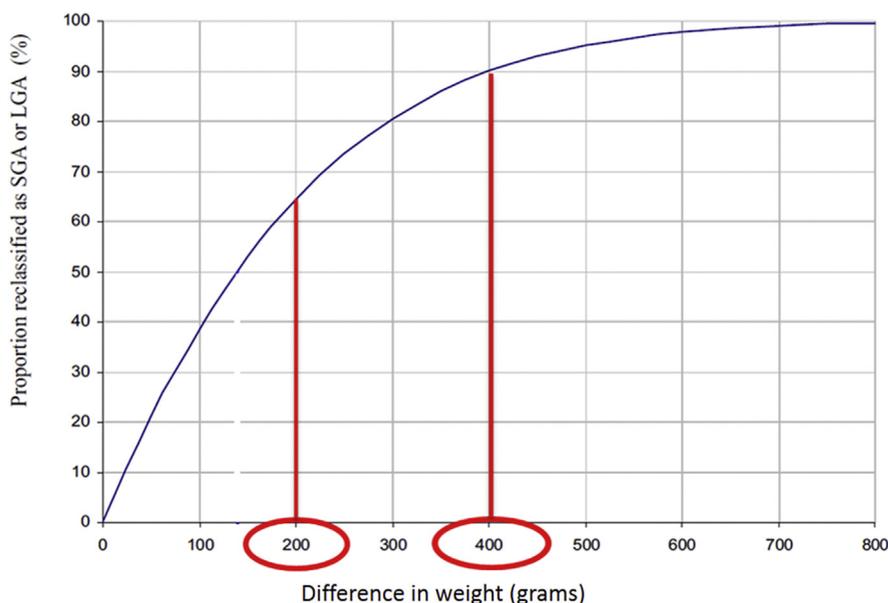
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**FIGURE 1**  
Effect of mean birthweight shift on SGA/LGA rate



Proportion of cases at SGA/AGA or AGA/LGA limit that need to be reclassified, in a population with a birthweight distribution with standard error 382.6 g, if average birthweight varies by 200 g (64% reclassified) and 400 g (90% reclassified), respectively (see examples in text). Adapted from Gardosi J, Francis A. A customized standard to assess fetal growth in a US population. *Am J Obstet Gynecol* 2009;201:25.e1-7.<sup>28</sup> With permission.

AGA, appropriate-for-gestational age; LGA, large-for-gestational-age; SGA, small-for-gestational-age.

Gardosi. Customized growth charts. *Am J Obstet Gynecol* 2018.

such variation needs to be taken into account.

Intergrowth's own tables showed intercountry differences, despite their selection of low-risk, well-nourished mothers. For example, in Table 1 in the article of Villar et al,<sup>2</sup> the term birthweight for mothers from Italy is 3.3 kg and from the United Kingdom 3.5 kg, which is a 200-g difference that is unlikely to be explained by variation in nutritional status or socioeconomic deprivation between 2 Western European countries. In any average term birthweight distribution, a shift by 200 g results in >60% of small-for-gestational-age (SGA) or large-for-gestational-age (LGA) cases being misclassified (Figure 1). For Indian mothers, the mean Intergrowth birthweight was 2.9 kg, which is 400 g less than the average for their whole population (3.3 Kg); a shift by 400 g would reclassify 90% of SGA or LGA cases (Figure 1).

A multinational study of 1.2 million term pregnancies by Francis et al,<sup>13</sup>

published in this issue of *AJOG*, confirmed significant differences in mean birthweights and hence SGA rates between ten country cohorts using the Intergrowth birthweight standard, and showed that these were not due to pathological factors as represented by stillbirth rates; instead, the different SGA rates merely reflected physiological variation, throwing further doubt on the utility of Intergrowth as an international standard.

The potential adverse effect of applying the wrong standard in international comparisons becomes all too apparent in a recent publication in which the Intergrowth standard was applied to low and middle income country data from the Child Health Epidemiology Reference Group (CHERG).<sup>14</sup> They reported that 34% of births in India were SGA (<10th Intergrowth percentile) while only 5% and 6% were SGA in their Eastern Asia and Northern Africa populations, respectively. Such high SGA rates are unlikely to be explained by malnourished,

stunted, or socioeconomically disadvantaged pregnancies in India; and the low SGA rates in Northern Africa are unlikely to be explained by anything other than that the standard is misleading. Applied at local level, such findings may result in unnecessary antenatal investigations and interventions, postnatal overfeeding to compensate for presumed growth restriction, parental anxiety, and the possibility that real SGA and its associated risk is ignored; conversely, in populations that are assigned a low SGA rate, the standard will put babies at risk because real SGA may be missed.

### Defining the Growth Potential

Customized charts adjust for constitutional or physiologic variation and exclude pathologic factors that affect growth, thereby defining an optimized standard that represents the growth potential of each individual fetus.<sup>15,16</sup> As a result, they improve the prediction of birthweight in an uncomplicated pregnancy and improve the identification of abnormal growth.

An alternative method for defining fetal growth potential is the Deter-Rossavik model of Individualized Growth Assessment to specify expected third-trimester size trajectories and birth characteristics from second-trimester measurements of several anatomic parameters.<sup>17</sup> This approach seeks to address the problems that are inherent with a population standard by using each fetus as its own control. Analyses recently have been extended to a larger database of 119 longitudinally scanned pregnancies with normal neonatal outcomes,<sup>18</sup> but the model has not been applied widely in clinical settings. One conceptual concern<sup>19</sup> is that the fetus could already be affected by intrauterine growth restriction in the second trimester, which is known to increase the risk of adverse outcomes early<sup>20</sup> or late<sup>21</sup> in pregnancy. Use of measurements from such a fetus could project an individual curve that does not reflect the true growth potential and, by normalizing the pathologic factors, be less likely to allow identification of abnormal growth.

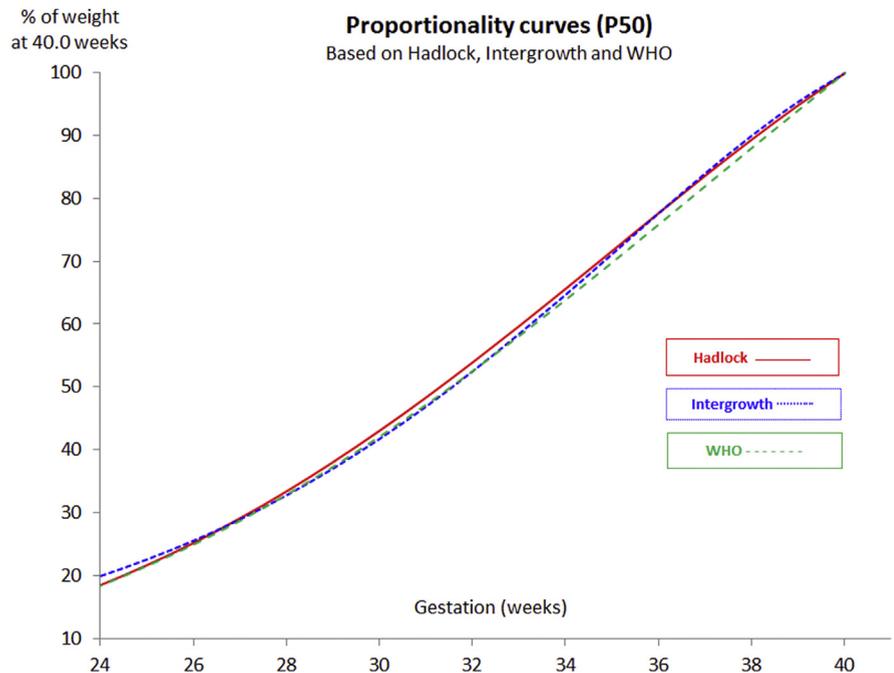
In the customized model, the variables for adjustment are derived from

birthweights of normally formed fetuses who were delivered at the end of uncomplicated pregnancies at term. The physiologic variables that significantly affect birthweight are consistent in many cohort studies and are quantified through multivariable analysis: fetal sex, maternal height, weight in early pregnancy, parity, and ethnic origin. Adjustment for maternal height and weight is made within normal body mass index (BMI) limits only.<sup>16</sup> Pathologic factors that are known at the beginning of pregnancy include hypertension, diabetes mellitus, smoking, and low and high BMI. Social deprivation may appear in the univariate analysis but does not tend to remain significant after adjustment for other factors, such as smoking and abnormal BMI.<sup>22</sup> The model adjusts for the physiologic but not pathologic variables, and results in a constant that represents an expected optimal birthweight at the end of an uncomplicated pregnancy.

Sets of coefficients have now been derived from suitable databases from more than 25 countries and published for populations in the United Kingdom,<sup>16</sup> Sweden,<sup>23</sup> Australia,<sup>24</sup> New Zealand,<sup>25</sup> France,<sup>26</sup> Spain,<sup>27</sup> United States,<sup>28</sup> and Ireland,<sup>29</sup> with others in preparation. International comparisons have demonstrated remarkable between-country similarities in the growth potential that a baby of a standard mother can expect to reach at the end of an uncomplicated pregnancy. For example, a nulliparous mother of (Anglo-) European origin with a height of 163 cm and early pregnancy weight of 64 kg would, after an uncomplicated pregnancy, be expected to give birth to a baby who weighs 3453 g in the United States, 3456 g in the United Kingdom, 3464 g in Australia, and 3464 g in New Zealand.<sup>28</sup>

In practice, maternal characteristics are entered into a software program (GROW; Gestation Network; Birmingham, UK, [www.gestation.net](http://www.gestation.net)) to calculate an individually adjusted term optimal weight for 40.0 weeks (280 days) gestation. This predicted weight endpoint is then combined with a standard proportionality function<sup>16</sup> to provide a gestation-related optimal weight (GROW) curve. We used the standard

**FIGURE 2**  
**Comparison of proportionality curves**



Derived from Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. *Radiology* 1991;181:129-33; Stirnemann J, Villar J, Salomon LJ, et al. International estimated fetal weight standards of the INTERGROWTH-21st Project. *Ultrasound Obstet Gynecol* 2017;49:478-86; and Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization Fetal Growth Charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. *PLOS Med* 2017;14:e1002220, according to method described previously.<sup>16</sup> WHO, World Health Organization.

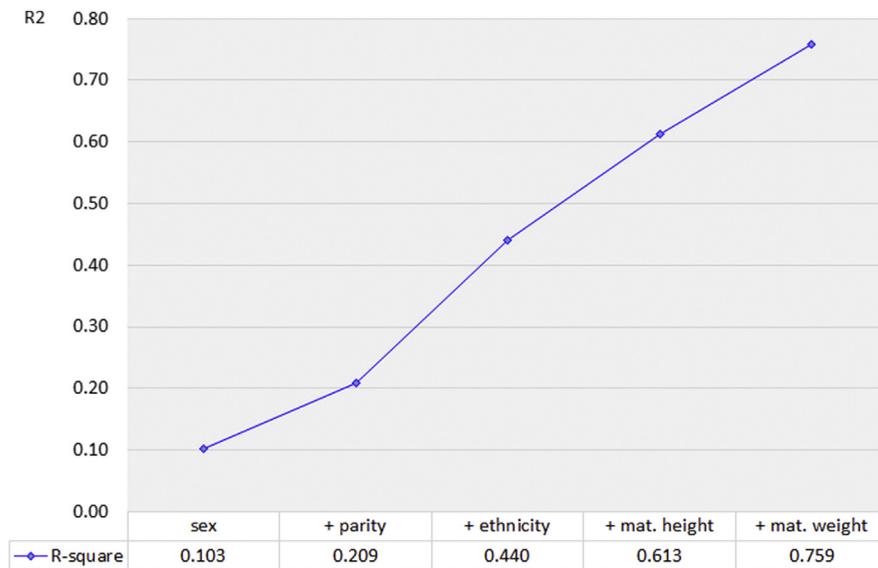
Gardosi. Customized growth charts. *Am J Obstet Gynecol* 2018.

Hadlock estimated fetal weight (EFW) curve<sup>30</sup> and converted it from a fetal weight-by-gestation curve to a percent of term weight-by-gestational age curve, with the Hadlock 40-week weight assigned 100%. This allows any term optimal weight to be substituted for 100%, thereby specifying the expected weight for gestational age trajectory (GROW curve) up to that predicted endpoint. We have since compared the proportionality curve based on Hadlock<sup>30</sup> with ones based on the 2 recently published EFW curves by Intergrowth<sup>3</sup> and WHO.<sup>12</sup> As Figure 2 shows, the results are remarkably similar, despite the fact that the underlying curves originate from different studies, and suggest that the proportionality method is a robust way to outline the growth trajectory to the term optimal weight.

The use of a fetal-, rather than a neonatal, weight-based standard helps to highlight the association between fetal growth restriction and preterm birth<sup>16,31</sup> because the standard is derived from normal term pregnancies; the prevalence of SGA in preterm babies tends to be hidden by the use of a neonatal curve that is derived from preterm birthweights that are abnormal by definition. The normal range around the GROW curve is derived from the standard error of the multiple regression model and the term optimal weight that together give a coefficient of variation (CV) of 11%; the 90<sup>th</sup> and 10<sup>th</sup> percentile limits are then reached by  $\pm 1.28 \times CV$ , or  $\pm 14\%$  of the term optimal weight.<sup>16</sup>

It is worth noting that the use of term weight with a fetal weight-derived

**FIGURE 3**  
**Birthweight prediction**



R square of model, with gestational age-controlled residuals of birthweight within mid tertile of the distribution. Stepwise addition of variables (sex, parity, ethnicity, maternal height, maternal weight). Data source: West Midlands singleton births 2009-2013; n=131,570.

mat, maternal.

Gardosi. Customized growth charts. *Am J Obstet Gynecol* 2018.

proportionality function makes the GROW curve a standard that can be applied to assess fetal as well as neonatal weight.

### Validation

One test of the customized method is to assess the correlation between predicted and actual birthweight in normal pregnancy, according to the number of physiologic variables entered. The multivariable regression provides an  $R^2$  of the model; although this has been shown to increase by 50% when adjustment is made for maternal variables (from  $R^2=0.18$  to 0.29),<sup>32</sup> the overall correlation is still poor. However, because the model is not designed to predict pathologic factors, but optimal weight free from pathology, it is more appropriate to assess the additional contribution of each physiologic variable within the mid tertile of the distribution, where most growth-related pathologic factors are likely to have been excluded.<sup>33</sup> This analysis shows that the  $R^2$  value rises stepwise with each variable entered, to an  $R^2$  of 0.76, which indicates that,

together, these factors account for 76% of normal variation within this central part of the birthweight distribution (Figure 3).

More clinically relevant is the effect of adjustment of the standard on the cut-offs for LGA and SGA. The effect of customization at the LGA end has been examined by relatively few studies to date. Larkin et al,<sup>34</sup> Cha et al,<sup>35</sup> and Gonzalez et al,<sup>36</sup> who studied a cohort with diabetes mellitus, all found that the customized model identified previously unrecognized LGA populations who were at risk of intrapartum morbidity. Sjaarda et al<sup>37</sup> found hitherto unidentified pregnancies at risk because of LGA if the model was adjusted to exclude maternal weight. Constantine et al<sup>38</sup> compared fully customized with partially customized LGA that was adjusted for ethnicity and sex only and found both methods to be associated similarly with adverse outcomes; however, primary outcome cases (a composite of neonatal outcomes that are associated with fetal overgrowth and gestational diabetes mellitus) had a

significantly higher average percentile and a 50% higher LGA rate (19.3% vs 13.2%) when the fully customized LGA standard was used.<sup>38</sup>

At the SGA end of the spectrum, a number of studies have shown that customized SGA was associated more closely with pathologic outcomes than various local or national standards.<sup>23,39-44</sup> Typically, customized assessment resulted in an additional group being identified as SGA, which was also associated significantly with increased perinatal mortality risk. A systematic review found that both customized and population-based SGA had higher rates of adverse outcomes, but the reported point estimates for customized SGA tended to be higher and, in the instance of fetal death, were more than double that for population-based SGA, albeit with overlapping 95% confidence intervals (95% CI): customized, 7.8 (95% CI, 4.2–12.3), vs population based, 3.3 (95% CI, 1.9–5.0).<sup>45</sup>

Application of the fetal weight–based proportionality curve in the optimality model, as explained earlier, results in more preterm babies being identified as SGA.<sup>31,46,47</sup> Hutcheon et al<sup>48</sup> suggested that this is the main advantage of the customized growth chart, and adjustment for individual variation had little additional effect. Using a Swedish dataset, they compared a customized model with the Hadlock curve adjusted for sex only and reported similar relative risks of SGA for stillbirth and neonatal death. However, this conclusion has been questioned on several grounds.<sup>32,33</sup> Although the authors claimed to use our original method for customizing percentiles, their model adjusted for maternal size only in wide categories rather than continuous variables, which would have blunted the effect. They also did not identify and exclude pathologic factors to allow customized percentiles to reflect the full growth potential. Even so, although relative risk values were similar, their comparative tables still suggest that 5–10% more deaths were identified by their modified customization method.

Carberry et al<sup>49</sup> looked at term birthweight in an Australian cohort and found no advantages in a customized

SGA over a locally derived population standard. The study has added interest because it assessed outcome through perinatal morbidity indices and neonatal body fat with the use of air displacement plethysmography. However, information on maternal and pregnancy characteristics for customization was based mostly on maternal recall. In a large database in Scotland, partial customization (maternal height and parity) was compared with an unspecified population standard at term,<sup>50</sup> and the investigators found that this model did not improve association of SGA with stillbirth and infant death. It is uncertain whether the results were affected by an absence of maternal weight and ethnicity variables or by the missing data on maternal height. Also, the analysis used the Net Reclassification Index, the statistical reliability of which has been questioned.<sup>51</sup>

Mikolajczyk et al<sup>52</sup> analyzed WHO Global Survey data from 24 low- and middle-income countries and compared the association between pregnancy outcomes and SGA defined by either the standard Hadlock fetal weight curve or the use of the proportionality fetal weight equation,<sup>16</sup> adjusted by country-specific average term birthweight, or stepwise increasing the adjustment up to a fully customized model including sex, maternal height and weight, and parity. The data posed challenges that included dating of pregnancies, and maternal weight was obtained mostly at the end of pregnancy or in labor. However, the investigators showed clearly that adjustment by country average weight was the main improvement over the single (Hadlock) weight standard and that additional adjustment, even for sex of the neonate, added no demonstrable advantages.

### Analysis within Maternal Subgroups

It is possible therefore that, in fetuses who have survived to term, fetal growth deficit is more subtle and not marked enough to demonstrate differences in the cohort as a whole, even if the method is sound and all variables for customization are available. Instead, their benefits become apparent with analysis of

the effect of customization on the constituent subgroups of any heterogeneous maternity population.

We undertook such analyses<sup>32</sup> in the same Swedish birth registry dataset as that referenced above,<sup>23</sup> applying customized and uncustomized standards with the same fetal weight–based proportionality curve. We first looked at parity and found customized SGA to be better aligned to perinatal mortality risk; the uncustomized standard showed an exaggerated SGA rate for nulliparous women that did not reflect a rise in mortality rate. Although first pregnancies can have more complications, such as preeclampsia and prolonged labor, increased clinical awareness and appropriate management should not have to rely on defining more babies as SGA if they are not, and can lead to unnecessary investigations and interventions.

In the same study,<sup>32</sup> we analyzed SGA rates in 4 BMI groups (<20, 20–25, 25–30,  $\geq 30$  kg/m<sup>2</sup>). Perinatal mortality rates were directly proportional to BMI; SGA defined by customized percentiles also increased with BMI and was well-aligned with the perinatal mortality trend. In contrast, uncustomized SGA rates were statistically different from the mortality risk, being very high in thin mothers and low in obese mothers. This finding contradicts previously held assertions, which were based on data from the same Swedish register of births, that obesity was protective of SGA.<sup>53</sup> In fact, population-based percentiles obscure the fact that a baby may be relatively small compared with its growth potential. Application of the customized standard identifies that obese mothers have an increased risk of having a growth-restricted baby.<sup>32,54</sup>

We also looked at maternal size groups predefined according to height and weight, within a subgroup of pregnancies with normal BMI (20–25 kg/m<sup>2</sup>; ie, symmetrically small and large mothers). Here, the perinatal mortality rate was similar for all groups, and customized SGA rates were correspondingly similar; but the population-based standard showed a high SGA rate for small mothers and a low SGA rate for large mothers and hence did not reflect the perinatal mortality trend.<sup>32</sup>

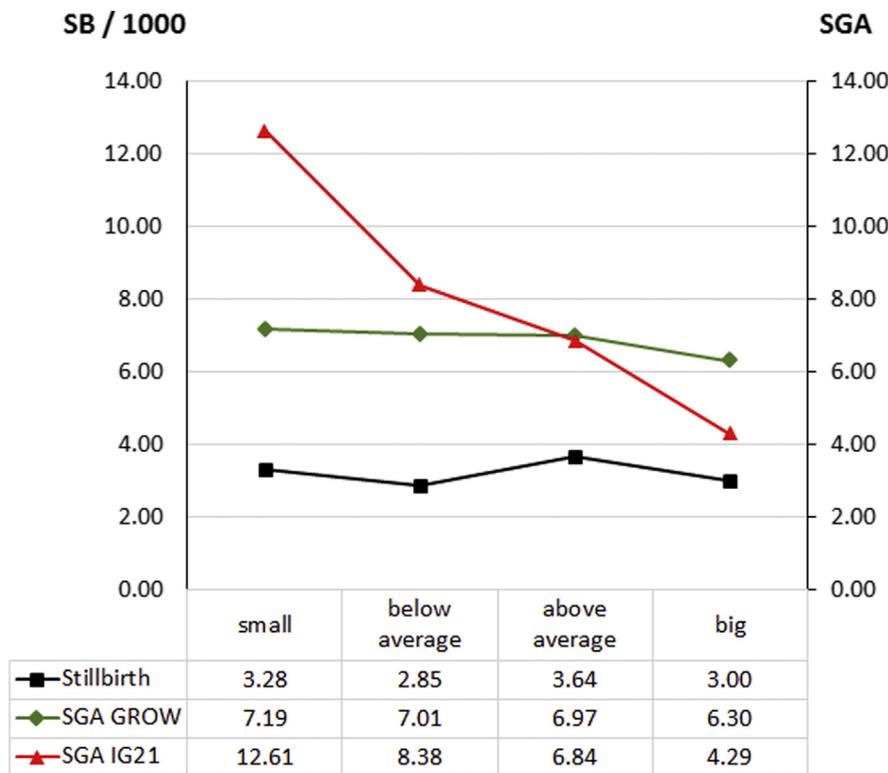
We repeated this assessment after the publication of the Intergrowth fetal weight standard,<sup>3</sup> applying it to a previously described English database<sup>22</sup> using stillbirth as the outcome. The results show again good alignment between maternal size groups and stillbirth risk when SGA was customized but not when the Intergrowth standard is applied (Figure 4). The clinical implication is that small mothers with normally small babies may be subjected to unnecessary investigations, interventions, and anxiety and that large mothers are reassured falsely when being assessed with the use of a one-size-fits-all chart that does not take individual variation into account.

Customized charts reduce false-positive diagnoses of SGA when ultrasound estimated fetal weight measurements are plotted on customized vs uncustomized fetal weight curves.<sup>55</sup> This becomes most apparent in our multi-ethnic population, a large proportion of which are of South Asian origin. It was a frequent clinical observation that scan measurements that were plotted on the prevalent Hadlock EFW chart<sup>30</sup> returned many SGA results. In our West Midlands database, 56% of these scans would not plot as SGA on the customized GROW chart. This group had the same risk for perinatal death as the non-SGA group (relative risk, 1.2; 95% CI, 0.5–3.0), which confirmed that an uncustomized standard applied in this subgroup results in the majority of cases identified as SGA are false positives.<sup>56</sup>

### Clinical Application

The use of customized percentiles is recommended by the Royal College of Obstetricians and Gynaecologists Guidelines<sup>57</sup> for the assessment of birthweight and antenatal surveillance of fetal growth. Customized percentile calculators are freely available via the Gestation Network ([www.gestation.net](http://www.gestation.net)) that is administered by the Perinatal Institute and have been or are currently in use by over 300 clinicians and researchers in 30 countries. They can be applied in case-by-case assessment of neonatal weight or in spreadsheet format to analyze whole databases for audit or research. A global version of the GROW

**FIGURE 4**  
Maternal size, small-for-gestational-age and stillbirth risk



Stillbirth rate and smallness for gestational age according to Intergrowth-21st and GROW standards equalized for <10th percentile cases by Intergrowth =7.7%. Data source: West Midlands database 2009-2013; singleton, normally formed, n=62,652. Maternal size groups defined in 4 weight and corresponding height ranges to remain within body mass index range of 20-25 kg/m<sup>2</sup>: (1) *small*: weight, <57 kg; height, 148–167 cm; (2) *below average*: weight, 57.0–60.3 kg; height, 153–171 cm; (3) *above average*: weight, 60.3–65.0 kg; height, 157–174 cm; (4) *big*: weight, ≥65.0 kg; height, 161–180 cm.

BMI, body mass index; GROW, gestation-related optimal weight; IG21, Intergrowth21; SGA, small for gestational age. Gardosi. Customized growth charts. *Am J Obstet Gynecol* 2018.

percentile calculator was recently released and includes coefficients for over 100 ethnic or country of origin groups.

For antenatal surveillance, customized GROW charts are produced at the beginning of pregnancy, once the expected date of delivery is confirmed by the ultrasound dating scan. The chart is either printed out at the beginning of pregnancy or can be displayed electronically, either as a stand-alone GROW application or integrated with the hospital's maternity information system. It displays the calendar dates for each week of gestation on the X axis and has 2 Y axes for plotting fundal height measurement

in centimeters and for EFW in grams. Individual parameters (head circumference, abdominal circumference, femur length) are not plotted because (1) there are no validated coefficients for individual adjustment or customization, (2) EFWs are more meaningful for the mother and clinician in the assessment of small as well as large babies, and (3) accuracy of EFW and antenatal identification of SGA and LGA can be audited through birthweight as a gold standard, whereas no such standards exist for individual ultrasound measurement. Although abdominal circumference is the main component in determining EFW, the latter has been shown to be

able to detect additional at-risk cases compared with abdominal circumference alone.<sup>58</sup> Serial EFW measurement has also been found to be as good as or better than serial abdominal circumference in the prediction of adverse outcome.<sup>59</sup>

GROW charts provide not only the optimal predicted birthweight endpoint for that pregnancy but also the slope of the normal growth curve that will lead to this point, together with upper and lower limits that can be set at 90th and 10th or 95th and 5th percentiles. The weight of the fetus at any point in the third trimester can be assessed within the customized limits for that pregnancy. In pregnancies with suspected SGA and normal umbilical artery Doppler, customized assessment of fetal size was a better predictor of adverse outcome than growth velocity.<sup>60</sup> Yet, serial measurements are also important and can be evaluated with reference to the predicted customized slope of the GROW curve. The measurements may be within normal limits; however, if the trajectory is slower than that predicted, action in terms of further investigations or expedited delivery has to be considered.<sup>61</sup>

Currently, the slope of the curve is assessed visually, but the application is moving towards digital quantification. The concept of a fetus' growth trajectory 'crossing percentile lines' is insufficient because it ignores the time element (ie, the period over which the growth deficit has extended). In a serially scanned cohort of Dutch primiparous women, fetal weight gain was significantly slower in pregnancies that required admission to the neonatal intensive care unit (20 g/d) than if the pregnancy was uncomplicated (24 g/d).<sup>62</sup> In time, there will be more information on antenatal growth velocity and outcome on which to base recommendations, and the next version of GROW will link growth trajectories that are adjusted for each pregnancy with action prompts and decision support.

GROW charts are provided as part of the Growth Assessment Protocol (GAP), a comprehensive program that includes hands-on and remote training supported by e-learning, competency

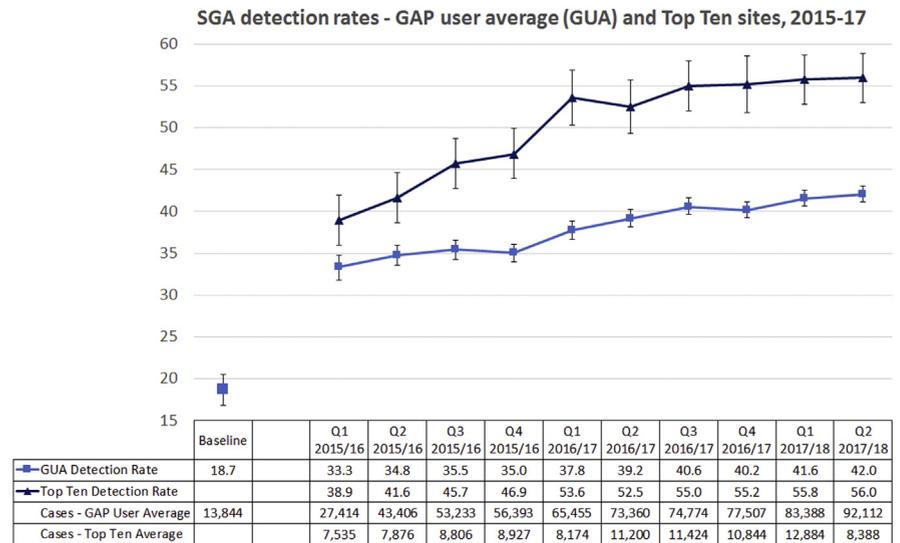
assessment, and evidence-based protocol templates for local adaptation. In the United Kingdom, GAP has been implemented in just under 80% of hospitals ([www.perinatal.org.uk/gap-uptake.aspx](http://www.perinatal.org.uk/gap-uptake.aspx)), generating customized charts for >600,000 pregnancies each year. In the Netherlands, the Royal Midwifery Association has licensed a Dutch version of GROW for their membership, and New Zealand has recently commenced a Maternal Fetal Medicine Network and health ministry recommended national roll-out. Individual clinicians and institutions in a number of countries have also commenced implementation.

### Antenatal Detection of SGA

Although there has been progress with biomarkers and uterine artery Doppler to screen for preeclampsia and early onset intrauterine growth restriction (IUGR), the majority of growth restriction is late in onset, with the growth of the fetus outstripping placental function and reserve, the prediction of which has been poor.<sup>61</sup> Therefore, the emphasis has to be on surveillance and on raising awareness of the importance of fetal risk caused by IUGR. A fetus that is SGA by customized percentiles has a 7-fold increased risk of intrauterine death.<sup>22</sup>

Surveillance protocols are based on early pregnancy risk assessment, with algorithms that identify 36% of our population as being at significantly increased risk of SGA and stillbirth.<sup>63</sup> This leads to 2 main care pathways: (1) low risk, which in health systems with well-established midwifery services is monitored with serial fundal height measurements, and (2) increased risk, which requires serial ultrasound scans throughout the third trimester. A controlled study has shown that training in standardized fundal height measurement and plotting on customized charts significantly increased antenatal detection of SGA and LGA fetuses while reducing false-positive diagnoses.<sup>64</sup> Detection of SGA in high-risk pregnancies is proportional to the number of third-trimester scans, which are usually performed only 2–3 times and only up to 34–36 weeks gestation, because of chronic shortages in ultrasound

**FIGURE 5**  
Detection of small for gestational age



Trend of antenatal detection rate of newborn infants with SGA birthweight (<10th customized percentile). Baseline rates, GAP user average, and average for top ten performing units are shown.

GAP, Growth Assessment Protocol; GUA, GAP user average; SGA, small for gestational age.

Gardosi. Customized growth charts. *Am J Obstet Gynecol* 2018.

resources in the National Health Service (NHS).<sup>65</sup> In a nonresearch environment, a routine or indicated scan at 36 weeks gestation has only a 36% chance to predict SGA birthweight,<sup>66</sup> which is likely to be due to the fact that most customized i.e. non-constitutional SGA at term is due to late onset IUGR.

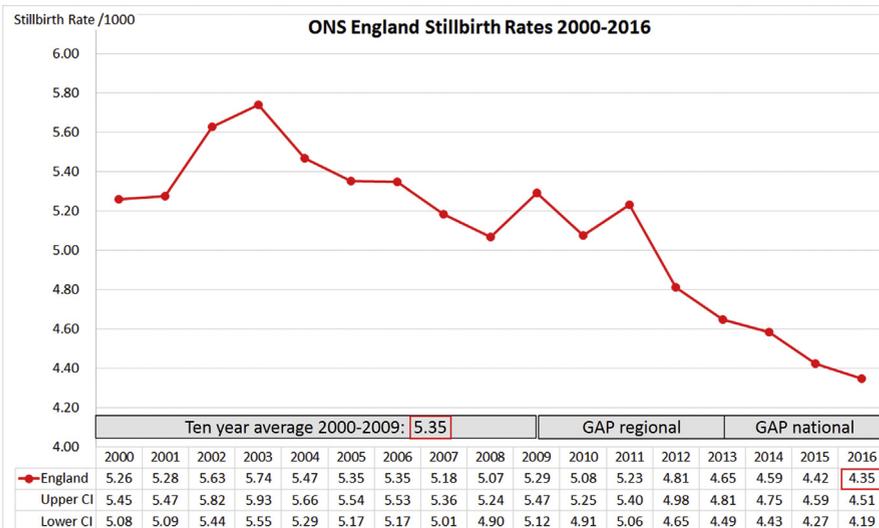
Antenatal detection of SGA has been established as an auditable key performance indicator and is facilitated by the GROW application. Trained staff enter details of the outcome of pregnancy, and the software then calculates the customized birthweight percentile and referral, detection and false positive rates. The results are available through automated local reports and provide benchmarking and trend analysis. The audit is not mandated, but its uptake has increased steadily because clinicians and managers realize the advantages of monitoring service improvements.

Maternity units are required to undertake a baseline audit before implementation of GAP and are often surprised how low their detection rates are, averaging 18.7% (95% CI,

16.8–20.5), which in fact is similar to historic published reports of 15–16% in low-risk populations.<sup>67,68</sup> Figure 5 shows, against this baseline, the quarterly trend in detection rates for the last 2 years in units that have established routine post-natal audit. There was a gradual, overall rise to 42.0% (95% CI, 41.1–43.0), which represents a 2.5-fold increase from baseline, and a more pronounced improvement to 56.0% (95% CI, 53.0–58.9) for the top 10 performing units. These centers can be characterized as most engaged with the protocol, training, and audit program, which highlights that performance is effort related.

Software is also available to undertake missed case audit, which facilitates more focused and structured investigations into reasons that newborn SGA cases are missed, such as a lack of referral, poor scan quality, or system issues such as shortages in ultrasound services or a lack of up-to-date protocols for surveillance or management. A limitation of such routine audits is that it cannot evaluate instances of growth restriction that occur without the fetus falling below the SGA cut-off limit.

**FIGURE 6**  
Trend in stillbirth rates in England



Stillbirth rates (per 1000) in England: ONS.<sup>75</sup> The rate remained similar over a 10-year period (2000, 5.26; 2009, 5.29) and averaged 5.35; the fall to 4.35 by 2016 following the implementation of the GAP program represented a 19% drop ( $P < .01$ ).

CI, confidence interval; GAP, Growth Assessment Protocol; ONS, Office of National Statistics.

Gardosi. Customized growth charts. *Am J Obstet Gynecol* 2018.

## Reducing Avoidable Stillbirths

The effect of any composite intervention is difficult to assess as perinatal death, and other 'hard' outcome measures are relatively rare. Randomized trials, usually the gold standard, are not very feasible, (1) because of the large numbers required to have sufficient power, (2) because the relative simplicity of a randomized, controlled trial design is challenged by the large learning component, competency assessment, and need to raise overall awareness; and (3) randomized assessment, individually or in clusters, requires clinical equipoise that cannot be guaranteed if a method is already recommended on the basis of observational evidence and clinical guidelines, such as those in place from the Royal College of Obstetricians and Gynaecologists.<sup>57</sup>

The relevant model therefore is "evaluation in practice," which is a rigorous before-and-after assessment of the impact of wide-ranging implementation, as was undertaken in the successful "back to sleep" campaign for sudden unexplained deaths in infancy<sup>69</sup> and which was never investigated by a

randomized, controlled trial. Stillbirth rates are a suitable measure of the effects of such a program. Nine-tenths of fetal deaths occur antenatally, and one-half of all normally formed stillbirths (counted in the United Kingdom from 24 weeks gestation) are SGA, even after adjustment for delay between fetal death and assessment of weight at delivery,<sup>70,71</sup> although an additional unknown number are IUGR without being SGA. Traditionally, two-thirds of stillbirths used to be categorized as "unexplained" and, by implication, unavoidable; however, a new classification of 'relevant conditions' rather than 'causes' and inclusion of a category of SGA defined by customized percentiles found that the majority of such unexplained deaths were in fact SGA and, by implication, IUGR.<sup>71</sup> Confidential case reviews by independent panels have furthermore shown that, at least two-thirds of SGA deaths are associated with substandard care.<sup>72</sup> Such findings helped to prioritize stillbirth as a potentially avoidable outcome; they also led to better explanations given to grieving parents who were trying to come to terms with their

loss and assisted clinicians in planning subsequent pregnancies and to improve antenatal services overall.

Customized charts are considered a central component of this program, because they give clinicians more confidence when assessing whether the situation is reassuring or calls for action. Fetal weights that plot as SGA or are on a slow trajectory on customized growth curves are less likely to be considered constitutionally small, and management recommendations in national guidelines<sup>57</sup> are further encouragement to adopt a proactive clinical approach.

According to the aforementioned observations, it is estimated that up to two-thirds of normally formed stillbirths are SGA or IUGR and that two-thirds of these are considered to have had substandard care that was likely to have caused or contributed to fetal death; this would make >40% of stillbirths potentially avoidable. Therefore, in health systems where one-half of pregnancies with SGA or IUGR are identified antenatally, a 20% reduction in stillbirth rates should be achievable with increased awareness, education, and the appropriate evidence-based protocols.

## The Growth Assessment Protocol (GAP)

GAP was commenced in the West Midlands, a health region with one of the highest perinatal mortality rates in the United Kingdom. Its implementation led to the first ever drop in stillbirth rates to below the national average, and further analysis found that this reduction was confined to pregnancies with SGA/IUGR.<sup>73</sup> Subsequently, implementation extended to 2 additional health regions, which together demonstrated a significant reduction in stillbirth rates, while they remained the same in regions that did not take up GAP.<sup>74</sup> Although this was an evaluation in practice rather than a trial, examination of Bradford Hill causality criteria confirmed that the reduction in stillbirths was attributable to the implementation of GAP.<sup>74</sup>

Since then, there has been a national roll-out of the program and, to date, includes almost 80% of all Hospital

Trusts and Health Boards across the United Kingdom. GAP has led to a year-on-year reduction in stillbirth rates (per thousand) in England to 4.35 by 2016<sup>75</sup>, their lowest ever level, which represents a 19% drop from the preceding 10-year average (2000–2009) of 5.35 (Figure 6). Scotland also implemented GAP in 12 (86%) of its 14 Health Boards as part of a nationally commissioned program, while also benefitting from an ongoing national maternity quality improvement program; its own 10-year (2000–2009) average stillbirth rate of 5.41 dropped similarly by 20% to 4.31 by 2016.<sup>76</sup>

Ongoing work includes the development and provision of electronic tools to facilitate routine audit, risk assessment, auto-plotting of measurements, and decision support, which prompt evidence-based referral protocols and management pathways. Hitherto country specific, the global version of customized antenatal GROW charts with over 100 ethnic/country of origin categories will be launched in 2018 to provide an individualized, yet universally applicable, standard for fetal growth. ■

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# The World Health Organization fetal growth charts: concept, findings, interpretation, and application



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Ultrasound biometry is an important clinical tool for the identification, monitoring, and management of fetal growth restriction and development of macrosomia. This is even truer in populations in which perinatal morbidity and mortality rates are high, which is a reason that much effort is put onto making the technique available everywhere, including low-income societies. Until recently, however, commonly used reference ranges were based on single populations largely from industrialized countries. Thus, the World Health Organization prioritized the establishment of fetal growth charts for international use. New fetal growth charts for common fetal measurements and estimated fetal weight were based on a longitudinal study of 1387 low-risk pregnant women from 10 countries (Argentina, Brazil, Democratic Republic of Congo, Denmark, Egypt, France, Germany, India, Norway, and Thailand) that provided 8203 sets of ultrasound measurements. The participants were characterized by median age 28 years, 58% nulliparous, normal body mass index, with no socioeconomic or nutritional constraints (median caloric intake, 1840 calories/day), and had the ability to attend the ultrasound sessions, thus essentially representing urban populations. Median gestational age at birth was 39 weeks, and birthweight was 3300 g, both with significant differences among countries. Quantile regression was used to establish the fetal growth charts, which also made it possible to demonstrate a number of features of fetal growth that previously were not well appreciated or unknown: (1) There was an asymmetric distribution of estimated fetal weight in the population. During early second trimester, the distribution was wider among fetuses <50th percentile compared with those above. The pattern was reversed in the third trimester, with a notably wider variation >50th percentile. (2) Although fetal sex, maternal factors (height, weight, age, and parity), and country had significant influence on fetal weight (1–4.5% each), their effect was graded across the percentiles. For example, the positive effect of maternal height on fetal weight was strongest on the lowest percentiles and smallest on the highest percentiles for estimated fetal weight. (3) When adjustment was made for maternal covariates, there was still a significant effect of country as covariate that indicated that ethnic, cultural, and geographic variation play a role. (4) Variation between populations was not restricted to fetal size because there were also differences in growth trajectories. (5) The wide physiologic ranges, as illustrated by the 5th–95th percentile for estimated fetal weight being 2205–3538 g at 37 weeks gestation, signify that human fetal growth under optimized maternal conditions is not uniform. Rather, it has a remarkable variation that largely is unexplained by commonly known factors. We suggest this variation could be part of our common biologic strategy that makes human evolution extremely successful. The World Health Organization fetal growth charts are intended to be used internationally based on low-risk pregnancies from populations in Africa, Asia, Europe, and South America. We consider it prudent to test and monitor whether the growth charts' performance meets the local needs, because refinements are possible by a change in cut-offs or customization for fetal sex, maternal factors, and populations. In the same line, the study finding of variations emphasizes the need for carefully adjusted growth charts that reflect optimal local growth when public health issues are addressed.

**Key words:** birthweight, estimated fetal weight, fetal development, fetal growth, fetus, growth standard, maternal characteristic, multicenter, population variation, reference range, ultrasound

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**B**irthweight that reflects intrauterine growth is an important determinant for perinatal morbidity and death<sup>1,2</sup> and, in recent years, has been shown to be a marker of postnatal life-course health risks.<sup>3</sup> Correspondingly, ultrasound biometry has become the cornerstone of diagnosis and management of fetal growth deviation,<sup>4,5</sup> but it is also used for the study of fetal growth dynamics underlying postnatal health development<sup>6-10</sup>; the ultimate aim is to develop lifestyle strategies for adolescent and pregnant women and to improve off-spring life-course health.<sup>11</sup>

Perinatal mortality rates are particularly high in the large populations of middle- and low-income countries where 98% of the world's neonatal deaths occur,<sup>12</sup> which is a reason that there are international efforts to make ultrasound technology available to those societies. However, it is of concern that available reference ranges for fetal ultrasound biometry are derived largely from single populations in industrialized societies with uncertain applicability in a world of ethnic variation.<sup>5</sup> Based on a review of the literature on birthweight as a health outcome, an expert panel convened by the World Health Organization (WHO) documented a need for fetal and child growth charts for international use.<sup>13</sup> Accordingly, the WHO published a child growth standard based on a multicenter study in 2006<sup>14</sup> and followed up with the study on fetal growth to be discussed here.<sup>15,16</sup>

In the mean-time a couple of large studies appeared. First, the multicenter Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project (hereafter called Intergrowth-21st) was published and presented fetal biometrical standards<sup>17</sup> followed by an article on estimated fetal weight (EFW).<sup>18</sup> Second, another relevant large study appeared from the United States, the National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies.<sup>19</sup> Together with the WHO study, they form the main basis for a renewed discussion on reference ranges.

### Extract of the Study Methods

The WHO fetal growth charts are based on a prospective longitudinal observational study that was conducted from 2009–2014 and was carried out at 10 ultrasound centers in Argentina, Brazil, Democratic Republic of Congo, Denmark, Egypt, France, Germany, India, Norway, and Thailand.<sup>16</sup> Totally, 1439 women provided written consent; each woman had a singleton pregnancy between gestational week 8+0 and 12+6 according to a regular and reliable last menstrual period that was corroborated by the crown-rump length within  $\pm 7$  days as assessed by ultrasound imaging.<sup>20</sup> Requirements were prescriptive (ie, age, 18–40 years; body mass index, 18–30 kg/m<sup>2</sup>; and no known health, environmental, nutritional, or socioeconomic constraints). In addition to anthropometric and nutritional assessment, the participants attended 7 ultrasound sessions to measure fetal head circumference, biparietal diameter, abdominal circumference and femur length, and EFW was calculated with the use of formula III from Hadlock et al.<sup>21</sup> After withdrawals, lost to follow up, miscarriages, medical abortions, and intrauterine deaths, 1387 participants had data that entered the statistical analysis that applied quantile regression to establish growth chart percentiles.

### Quantile Regression

Because quantile regression, which is a nonparametric method that was used in the present study, is less familiar to many colleagues, we here point out a few features that were decisive for our choice of method. (1) It is a well-established statistical method,<sup>22-24</sup> increasingly used, with important applications in different fields that includes fetal growth curves.<sup>25</sup> Its use has become accessible with the development of computer power that can handle intensive computations. It has the advantage of being independent of any distributional assumption or transformation to normality because it estimates distributions directly determining the quantiles (in our study: percentiles), thus being a more direct method of representing the observations and their distributional differences. (2)

The method is more robust against outliers. (3) It is easy to incorporate covariates in a model and use well-known statistics to assess their effect on a dependent variable. (4) There is relevant goodness of fit techniques available to assess the appropriateness of a model.

Because the mean and standard deviation (SD) are statistics that are informative in the case of normal distributions, they are not suited for use with quantile regression because, with this approach, quantile estimates are obtained directly without going through procedures that convert a distribution (after many steps) to a normal distribution to obtain Z-scores. With our procedure, the user can obtain a quantile instead of a Z score to assess the location of a fetus of a particular gestational age in relation to the reference population. (Example: A fetus of gestational age 30 weeks with EFW 1288 g would be between the 5th [1247 g] and 10th percentile [1313 g] according to the WHO fetal growth chart. By interpolation, a more specific percentile can be calculated:

$$\begin{aligned} &10 \text{ percentile} - [10 \text{ percentile} - 5 \text{ percentile}] \\ &\bullet [1313 \text{ g} - 1288 \text{ g}] / [1313 \text{ g} - 1247 \text{ g}] \\ &= 8.1 \text{ percentile.} \end{aligned}$$

That is, the fetus is at the 8th percentile).

### Population Characteristics: What We May Infer

The participating women had no socioeconomic constraints, had median caloric intake of 1848 calories/day (interquartile range [IQR], 1487–2222), age 28 years (IQR, 25–31), height 163 cm (IQR, 157–168), weight 61 kg (IQR, 55–68), body mass index (BMI), 23.1 kg/m<sup>2</sup> (IQR, 21.0–25.4); 58% of the women were nulliparous. Overall, the cesarean rate was 32%, but with substantial variation: Brazil, 70%; Egypt, 50%; India, 36%; Thailand, 49%; Democratic Republic of Congo, 6%; and Norway, 9%. The overall median of 67% spontaneous onset of labor and substantial country variation ranged from 29% in Brazil to 91% in Norway, reduced the number of observations near term, and constituted an increasing

risk of selection bias, particularly for the estimation of percentiles for 39 weeks gestation and beyond (Figure 1).

Although the study was not designed primarily to discern ethnic differences, data on self-reported ethnicity were collected. However, because it was greatly confounded with country, this design variable (instead of ethnicity) was used for modeling EFW changes with gestational age. We acknowledge the limitation of self-reported ethnicity and relation between ethnicity, social and cultural traditions, and the geographic influences on individual lives that contribute to differences among populations (eg, participants who lived  $\geq 1500$  meters above sea level were not included in the WHO study).

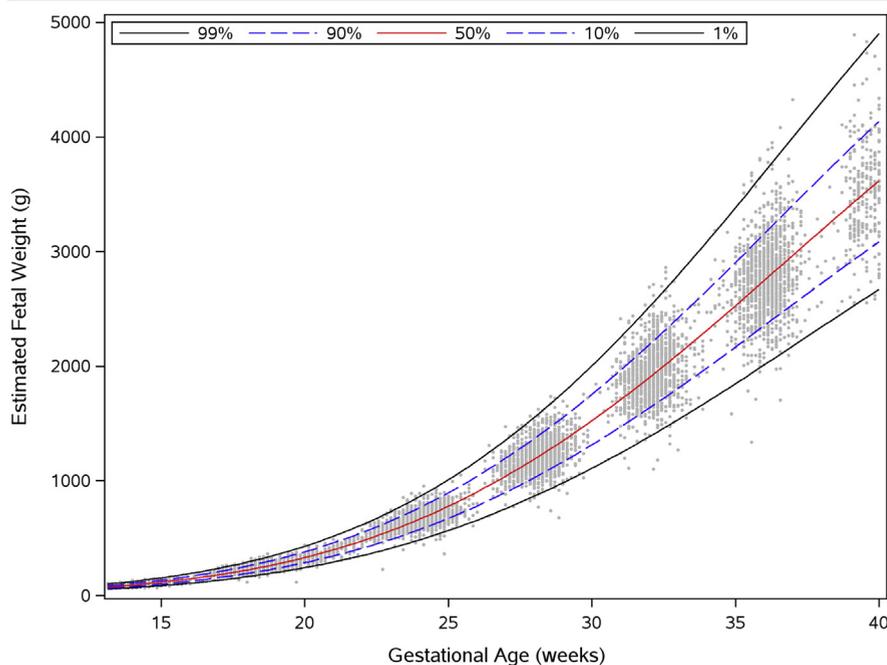
Although the number and worldwide distribution of populations that were included in the WHO study make the growth charts more generally applicable, we acknowledge that the selected populations for the study represent a very restricted fraction of the genetic, ethnic, cultural, and geographic variation around the world; Democratic Republic of Congo and Egypt represent the African continent, which contains a larger genetic diversity than the entire rest of the world<sup>26</sup>; and participants from India and Thailand, who represent the varied populations of Asia, are also small samples of their own countries' ethnic diversities.

### Pregnancy Outcomes

The median gestational age at birth was 39 weeks 3 days (IQR, 38wk+3d–40wk+2d), with significant differences between countries ( $P < .001$ ); the lowest was in India (38wk+4d), and the highest was in Norway (40wk+3d). Preterm births ( $< 37$  weeks gestation) were 7.5%; the lowest was in Germany (3.6%), and the highest was in Egypt (14.7%;  $P = .03$  for differences among countries).

Neonatal sex distribution showed 47% were female. Median birthweight was 3300 g (IQR, 2980–3615). Highest median birthweight (3575 g) was found in Norway, although it was 100 g less in Denmark and Germany; 200 g less in Argentina, Brazil, and France; 400 g less in Democratic Republic of Congo,

**FIGURE 1**  
World Health Organization fetal growth chart: estimated fetal weight percentiles



The growth chart for estimated fetal weight is based on a longitudinal study of 1387 low-risk pregnancies from 10 countries. Under optimal living and nutritional conditions, fetal growth was not uniform but exposed a substantial dispersion, which was wider among the large fetuses than the small ones. Near term, the number of observations (*grey*) tended to be lower. From Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. *PLoS Med* 2017;14:e1002220. With permission.

Kiserud. WHO fetal growth charts. *Am J Obstet Gynecol* 2018.

Egypt, and Thailand; and 500 g less in India ( $P < .001$ ). The differences were still significant for all birthweight percentiles when adjusted for gestational age at birth:  $P = .0018$  for the 5th percentile;  $P < .001$  for the 10th, 25th, 50th, 75th, 90th, and 95th percentile.

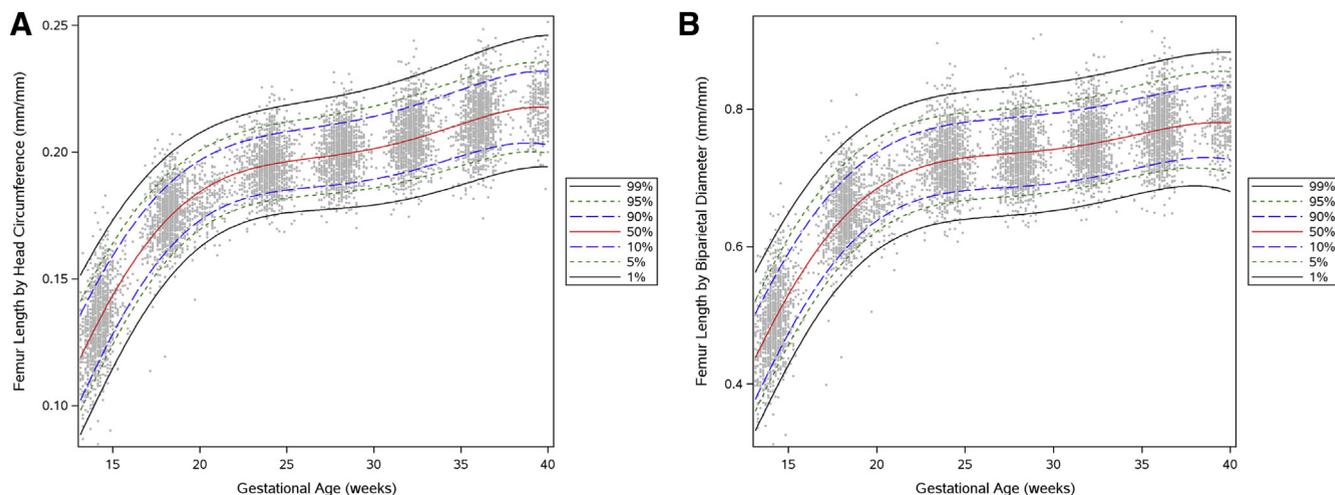
Apgar score  $< 7$  at 5 minutes occurred in 0.8% and was distributed equally among the countries.

### Maternal, Fetal, and Neonatal Complications: Exclude or Not

Maternal complications occurred in 137 pregnancies (9.9%), some having  $> 1$  condition: preeclampsia (22 pregnancies), hypertension (16 pregnancies), gestational diabetes mellitus (32 pregnancies), malaria (42 pregnancies), anemia (19 pregnancies), and others (16 pregnancies).

During pregnancy, there were 29 miscarriages, 2 medical abortions, and 3 intrauterine deaths, for a total of 34 events (2.4%) that ranged from 0% in Germany to 6.4% in Democratic Republic of Congo. The numbers of miscarriages may seem low, and the reason may be that the population that was included had no known risks. All women had first trimester scans, and participants were not included if abnormalities were diagnosed at this stage. The numbers corroborate recent Danish data.<sup>27</sup> Eight fetal malformations were identified during pregnancy (including 1 at birth). In 4 pregnancies, growth restriction had been suspected clinically; 2 women underwent Doppler examination that revealed no abnormality, and all 4 pregnancies were completed uneventfully.

FIGURE 2

**World Health Organization fetal femur length/head circumference and femur length/biparietal outer-inner diameter ratios**


The ratio of fetal **A**, femur length and head circumference or **B**, biparietal outer-inner diameter are intended for the assessment and monitoring of suspected disproportions (eg, microcephalic conditions). Particularly the femur length/biparietal outer-inner diameter ratio remains almost constant at >22 weeks of pregnancy, which is useful when gestational age is not reliably determined. From Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. *PLoS Med* 2017;14:e1002220. With permission.

Kiserud. WHO fetal growth charts. *Am J Obstet Gynecol* 2018.

Totally 83 neonates (6%) were transferred to the neonatal intensive care unit, commonly because of prematurity, respiratory distress syndrome, infections, or jaundice. There were 3 neonatal deaths; in addition to the 3 intrauterine deaths, they constitute a perinatal mortality rate of 0.4%.

The WHO study recruited and included participants in a prescriptive fashion with the intention of conditioning for optimal fetal growth. Even in a low-risk population complications can develop during the pregnancy. Some researchers would exclude these cases from the analysis, arguing that complications in pregnancy are associated with increased risk of growth deviations (eg, preeclampsia and gestational diabetes mellitus) and that the reference charts no longer represent normal growth.<sup>28</sup> Other investigators would keep them in, arguing that such complications are part of being a low-risk (not a nonrisk) population.<sup>29</sup> They would also argue that these exclusions would introduce skewness in the distribution and shift the growth charts towards being even more

“super-normal” than the population that the charts are meant to serve. Many epidemiologists would support the view that reference ranges and cut-offs should reflect the population for which they are intended. Both views have their merits. We expand on this issue under the section later. For the WHO study, we made the decision to keep these participants in the study and analyze the effect of removing or keeping them in. We ran the model for each EFW percentile with or without these cases, and there was no change in the percentiles. That may be due to low number of cases or that the conditions were mild with minimal or no effect on growth. As for the fetal conditions, they were too few to have any statistical impact anyway.

### Growth Charts Features

The WHO fetal growth study established growth charts for head circumference, biparietal diameter (outer-inner), abdominal circumference, femur length, humerus length, and EFW (Figure 1). The ratios femur length/head circumference and femur length/biparietal

diameter were added to provide screening tools when fetal body proportions are suspected to be out of range in clinical settings (Figure 2). We focused on EFW being the cornerstone of obstetric ultrasound biometry. Having recruited prescriptively to provide optimal fetal growth, one could argue that would lead to a uniform growth of the fetal population reaching their “genetic potential,” provided there are no differences in ethnic background or genetic or epigenetic regulation. Figure 1 shows otherwise; the dispersion of individual human fetal growth demonstrated here is remarkable. At 39 weeks gestation, 95% of the fetuses spread from 2612–4247 g. Such a variation, despite of uniformly optimized maternal condition, makes us speculate that it could be the result of an advantageous evolutionary strategy; variation increases collective capacity to adapt to the varied challenges on earth.

The distribution is not symmetric (Figure 1). Although there is a slightly wider dispersion at <50th percentile in the early weeks of the second trimester

(Bowley's coefficient of asymmetry,  $-0.016$ ),<sup>30</sup> the pattern inverts during the second half of pregnancy with a noticeably wider spread at  $>50$ th percentile (Bowley's coefficient,  $+0.111$ ). A possible biologic explanation for this would be that abundance in resources allows expansion in size, which is reflected in the dispersion of higher percentiles; on the other extreme, relatively limited resources do not permit such variation, and the percentiles remain denser.

### Fetal and Maternal Factors Have Graded Influence on Growth

Fetal sex difference and maternal characteristic are known to influence growth<sup>31,32</sup> and does so in this multicenter study also. Because quantile regression was applied to establish the reference ranges, each percentile was estimated separately, which provided the possibility of testing the effect of fetal sex difference on each of them. The magnitude of the effect (3.5–4.5%) justified the construction of customized reference ranges for female and male fetuses (Figure 3); the stronger effect was on the higher percentiles (Figure 4).

Maternal age influenced fetal size positively (2–3% per 10 years); the effect was strongest on the lower percentiles (Figure 4).

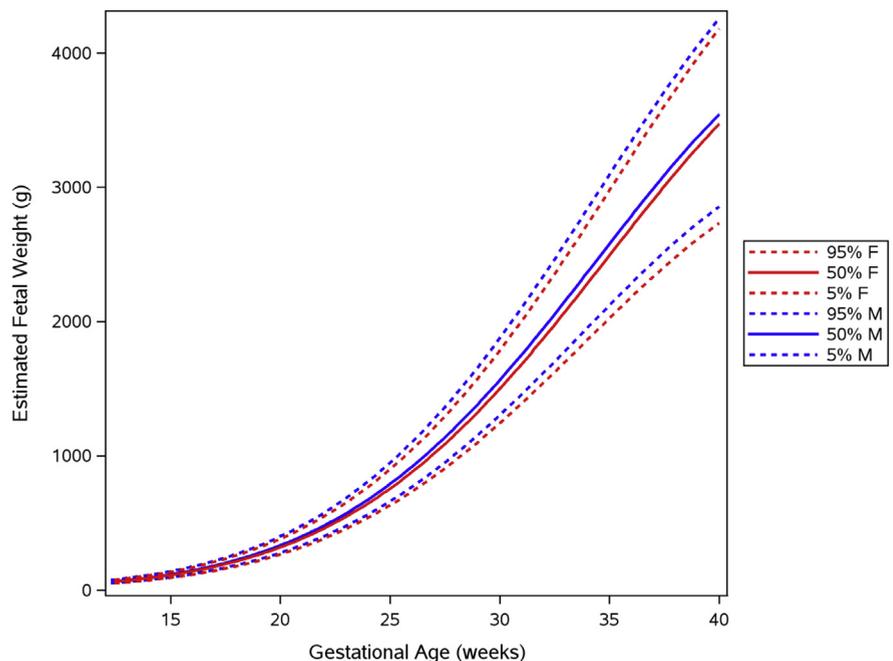
Parity ( $\geq 1$  vs 0) also had a positive effect (1–3%) but graded across the percentiles and strongest for the smaller fetuses (Figure 4). Being aware of the known relation between maternal age and parity, we controlled for this during the analysis to present their separate effects.

Maternal weight had a small but positive effect on EFW (1–1.5% per 10 kg); bear in mind that 1 of the inclusion criteria to the study was BMI 18–30 kg/m<sup>2</sup> (ie, no extreme weights). The effect of maternal weight was graded across the fetal population: the highest effect on highest percentiles (Figure 4).

Maternal height, which also had a positive effect (1–2% per 10 cm), had an opposite trend of the effect on the percentiles: the highest effect on the smallest fetuses (Figure 4).

**FIGURE 3**

### World Health Organization sex-specific growth percentiles for estimated fetal weight



The effect of fetal sex on estimated fetal weight was 3.5–4.5%, which justified separate charts. From Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. *PLoS Med* 2017;14:e1002220. With permission.

F, female; M, male.

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BMI was also considered by running the models after having substituted weight and height by BMI. BMI's effect on EFW was lower than for height and weight: 0.1% for each unit of BMI. The result might have been expected because BMI is a measure of body proportion rather than absolute resources, and the effect may be more pronounced for extreme values of BMI<sup>33</sup>; the study participants all had BMI, 18–30 kg/m<sup>2</sup>.

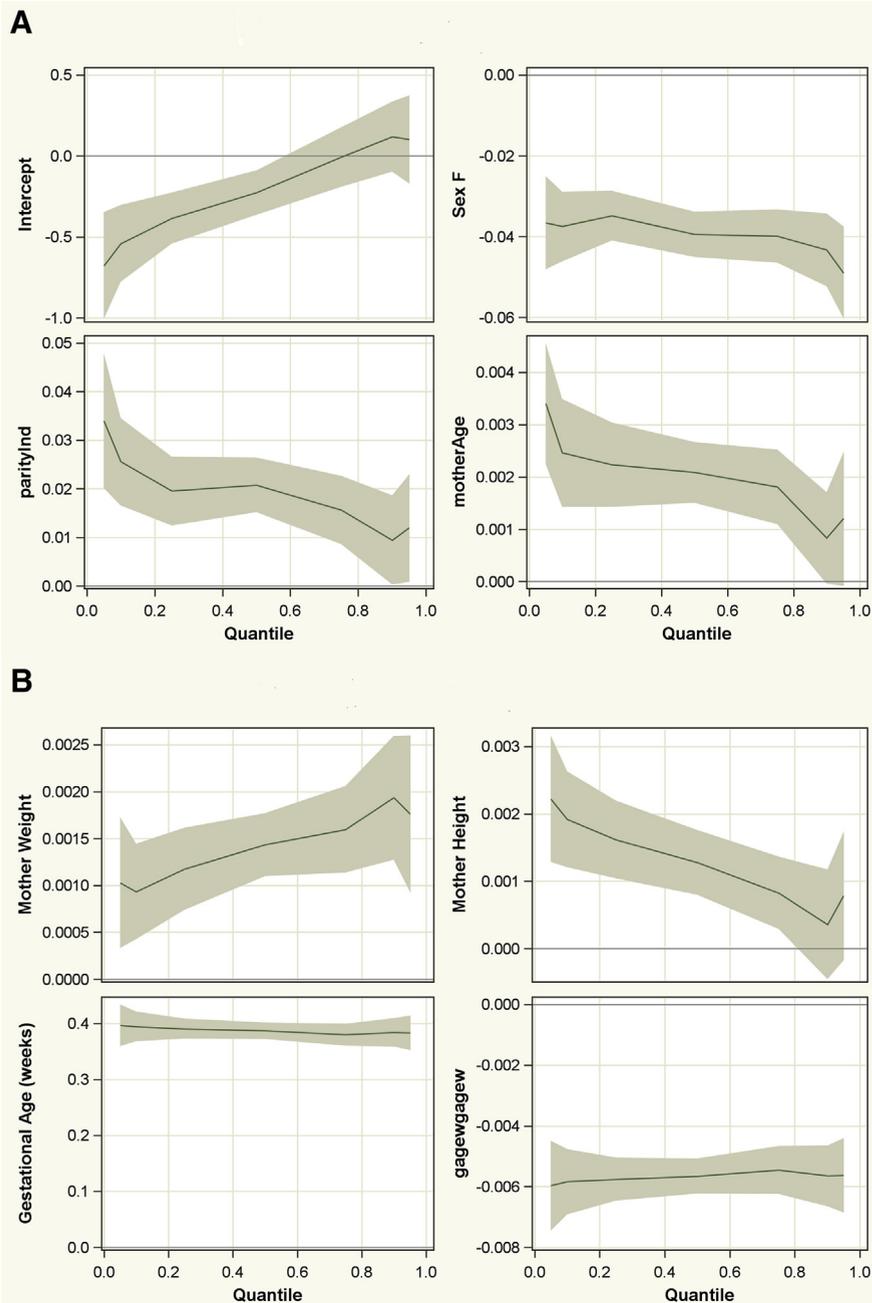
These covariates, maternal and fetal, have been examined previously.<sup>34–36</sup> The WHO study, however, has shown that the effects are not large and are not exerted equally among different EFW percentiles but may add up to be of clinical relevance. It makes any customization for individual use more complex, but statistical development, growing computer power, and more data accrual should handle it.

### Country Variation

In the WHO study, ethnic and cultural differences were represented by the classification “country.” Country influenced fetal growth significantly (Figure 5), and the variation in growth pattern is specifically visualized for the 10th, 50th and 90th percentiles in Figure 6. The variation in EFW corroborated the significant country differences in birthweight. For example, India with the lowest birthweight also had the lowest course of the 10th, 50th, and 90th percentile for EFW; maternal characteristics could explain only part of the country variation. On the other hand, other populations followed other and steeper trajectories, at times even crossing others (eg, the Norwegian; Figure 6) and signifying variations in growth trajectories. The results indicate that populations, even under optimal nutritional conditions and environment,

FIGURE 4

## Factors that influence fetal growth



**A** and **B** show how factors (green line) influenced estimated fetal weight percentiles (represented by quantiles; 0.05–0.95 quantiles correspond to 5–95 percentiles). The vertical scale shows the regression coefficients in the logarithmic scale (a difference in the logarithmic scale is a ratio in the original scale). The interpretation is thus, for example, for the effect of sex, that the female fetuses are 3.5–4.5% smaller than male fetuses. Although fetal sex had similar effect on all percentiles, it was observed to be an increasing (maternal weight) or decreasing trend between the 5th and 95th percentile (parity and maternal age and height). Also shown: intercept, gestational age and quadratic gestational age (gagewgagew). The grey zone indicates 95% confidence band.

Kiserud. WHO fetal growth charts. *Am J Obstet Gynecol* 2018.

vary and that fetal growth varies and should be considered when the WHO fetal growth charts or any growth references are applied. It is also prudent to acknowledge particularly 2 aspects of limitation: first, that the populations (or ethnic groups) that were selected for the study were urban in a world in which major groups still live in rural areas and, second, that the 10 included populations represent an extremely small proportion of the global genetic and ethnic variation. The study recruited 1 group in Egypt and another in Democratic Republic of Congo; Africa is known for a genetic diversity that exceeds the rest of the world,<sup>26</sup> and their anthropometric variation is substantial.

### Relating to Other Studies

To appreciate the practical consequences of the WHO and Intergrowth-21st percentiles for international use, their 10th and 90th percentiles for selected gestational ages have been compiled in the Table, which also includes the results of the NICHD and a Nordic single-population study.<sup>29</sup> Although not statistically tested, 10th percentile is numerically lower in the Intergrowth-21st compared with the WHO study for 28, 32, and 36 weeks gestation (−75, −164, and −208 g) and for the 90th percentile (−92, −98, and −68 g).

In Intergrowth-21st, the values of the biometric measurements were not revealed on the screen during the study, the idea being that the ultrasound operator could be biased to produce measurements that are less extreme. The WHO study exposed these measurements, and the question arises whether this could lead to skewness in the WHO study. In the WHO study, the midwives/sonographers had a long experience in clinical assessments and research. According to the protocol and ethical code, the project was committed to reveal to the woman any finding of importance to clinical treatment, and ensure that she was followed clinically. This was also in line with the routine that these midwives otherwise followed in their clinical practice, where missing a diagnosis was not a wanted outcome of the scan session, thus

conditioning a professional attitude to their measurements.

Intergrowth-21st studies introduced standards for fetal growth and birth-weight, with a similar design to the previous WHO child growth standards,<sup>37</sup> but their concept of 1 size fits all has met with critics repeatedly.<sup>38-41</sup> The NICHD fetal growth study also used the expression “standard” but acknowledged variation and established ethnic-specific curves.<sup>19</sup> During the WHO fetal growth study, these terms were discussed, and we ended with the more neutral WHO fetal growth charts acknowledging that, although these are charts that are intended for international use, variation across populations exists and has to be kept in mind when applied.

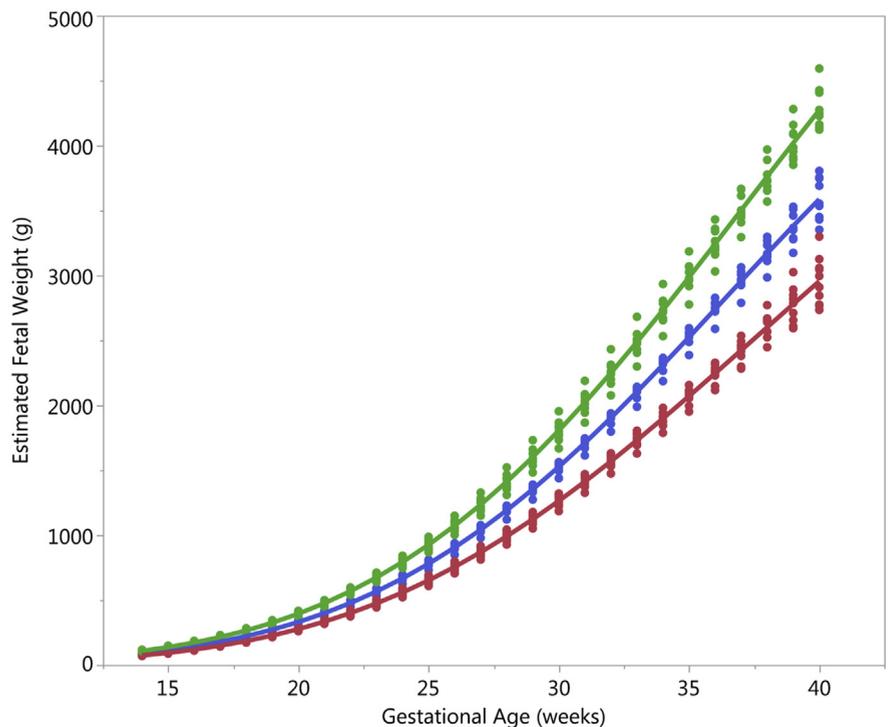
There are good reasons for a careful consideration before labeling a fetal growth chart as a standard, because it implicitly conveys a concept and a principle that this is how normal children should develop worldwide,<sup>42</sup> which is not evidenced. Also, it may stigmatize and render normal pregnancies abnormal, with consequences for management strategies.

### Different Underlying Concepts, Different Conclusions

To understand how 2 similar multinational fetal growth studies (the WHO study and Intergrowth-21st) have reached different results and conclusions, it is worthwhile to look at their underlying concepts. Intergrowth-21st had the concept that optimal fetal growth would be the same across various populations, provided maternal nutrition and condition were optimal. Thus, they designed their study to establish a single growth standard by pooling growth data from different populations. To assess degrees of likeness, they used the quotient “site-specific deviation $\pm$ 0.5 SD” (ie, [site mean—all sites mean]/SD of all sites, expressed in SD units).<sup>43</sup> Whether there was any significant population difference was not addressed. Their graphs, however, showed that Indian fetal head circumference was outside the  $-0.5$  SD site-specific deviation; on the other extreme, Italy had  $+0.5$  SD at 34–40 weeks gestation.

**FIGURE 5**

### World Health Organization estimated fetal weight percentiles: country variation



Estimated fetal weight in the World Health Organization study is shown with the 5th (red), 50th (blue) and 95th percentile (green). Lines represent fitted over-all values, and dots represent fitted percentiles for the separate countries. From Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. *PLoS Med* 2017;14:e1002220. With permission.

Kiserud. WHO fetal growth charts. *Am J Obstet Gynecol* 2018.

Further, at birth  $\geq 37$  weeks gestation, Indian neonates were 0.6 kg lighter than neonates in the United Kingdom. However, formal testing for differences was not published because it probably had not been a research aim.

The WHO study was not only designed similarly (ie, prescriptive inclusion criteria to make a single overall growth curve) but also made it an aim to test for factors that influence growth, including population differences. Thus, this study showed that significant differences existed between populations and that maternal factors influenced fetal growth.

The WHO study corroborates the NICHD study that first had tested whether there were ethnic differences and then established ethnic-specific growth curves for these populations in

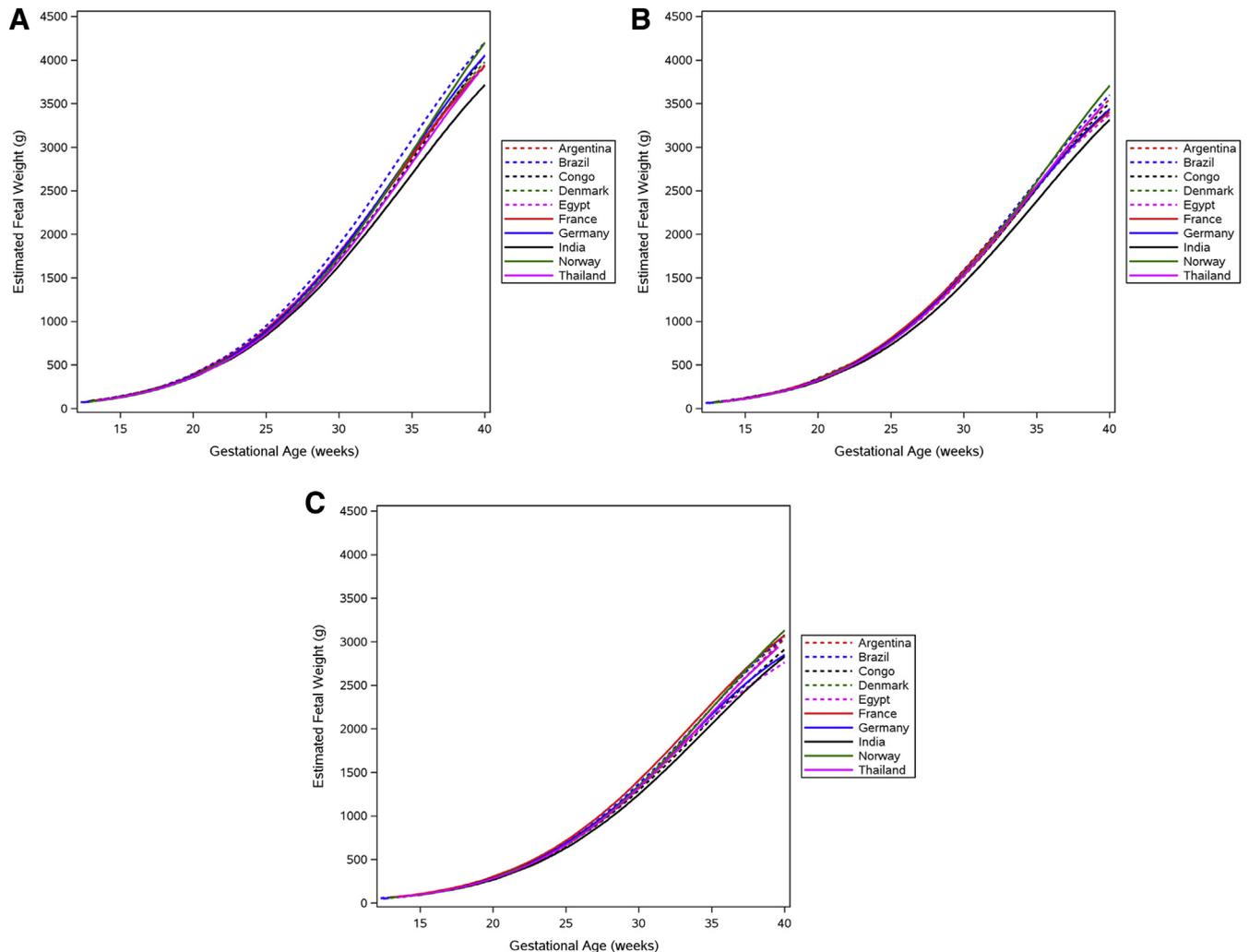
the United States.<sup>19</sup> This all shows how important research questions and aims are to the design and analyses and, in the end, to the results that are used for the conclusions. Based on the statistical power of Intergrowth-21st and what is exposed in graphs and tables, it is quite likely that an analysis would have shown significant population differences, thus bringing the 3 studies to similar conclusions, that population variation exists and is reproducible.

### Ethnicity and Variation

Ethnicity, and particularly self-reported ethnicity, is not a straight-forward characteristic of a person or population. It is more than just genetic differences because it commonly is associated with social inheritance, such as cultural and nutritional traditions, and geographic

FIGURE 6

## Country-wise development of estimated fetal weight in the World Health Organization study



The 90th percentile (A), 50th percentile (B), and 10th percentile (C) demonstrate variation of growth trajectories in estimated fetal weight among the 10 participating countries in the World Health Organization study. From Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. *PLoS Med* 2017;14:e1002220. With permission.

Kiserud. WHO fetal growth charts. *Am J Obstet Gynecol* 2018.

and environmental differences, all of which influence epigenetic settings, even to some extent conveyed in a trans-generational fashion.

The question of optimal growth and optimal size also needs answers to where and for what. These large studies have recruited participants that, to a large extent, reflect conditions and lifestyle of western urbanized women and when living in other societies of the world. However, are these conditions and the predominant sedentary lifestyle

conducted in these societies models for optimal health development? The ongoing and growing epidemic of non-communicable diseases tells a different story.<sup>3</sup>

What is apparent from all 3 studies<sup>16,17,19</sup> and previous studies<sup>29,44-46</sup> is the strikingly wide variation of human fetal growth and birthweight even when conditions are optimized.

One, it does not support the concept that equal conditions will produce equal fetal size. Rather, it creates an impression

that, under favorable nutritional and environmental conditions, the human species can afford ample variation, which is a strategy that has proved efficient in evolutionary terms, because the human species dominates on all continents. The WHO study could explain but a fraction of such variation by maternal characteristics, fetal sex, and population variation.

Two, optimal conditions and size may not be the same for an optimal life course in Alaska as in South India or

TABLE

**Estimated fetal weight from relevant studies presented with 10th and 90th percentiles for selected gestational stages**

Variable	Gestational week				
	20	24	28	32	36
10th Percentile of estimated fetal weight (g)					
United States: white <sup>a</sup>	289	583	1045	1686	2432
Democratic Republic of Congo <sup>b</sup>	288	576	1023	1624	2310
World Health Organization <sup>c</sup>	286	576	1026	1635	2352
United States: black <sup>a</sup>	286	559	985	1579	2264
Norway <sup>d</sup>	283	610	1102	1730	2411
United States: Hispanic <sup>a</sup>	279	555	987	1595	2298
United States: Asian <sup>a</sup>	275	546	978	1574	2262
Intergrowth-21st <sup>e</sup>		602	951	1473	2144
90th Percentile of estimated fetal weight (g)					
Norway <sup>d</sup>	408	833	1472	2304	3230
United States: white <sup>a</sup>	381	771	1391	2276	3368
World Health Organization <sup>c</sup>	380	765	1368	2187	3153
United States: Hispanic <sup>a</sup>	379	755	1353	2209	3245
United States: black <sup>a</sup>	376	742	1317	2135	3115
United States: Asian <sup>a</sup>	373	737	1318	2129	3111
Democratic Republic of Congo <sup>b</sup>	345	700	1277	2083	3032
Intergrowth-21st <sup>e</sup>		751	1276	2089	3089

<sup>a</sup> Buck Louis et al.<sup>19</sup>; <sup>b</sup> Landis et al.<sup>59</sup>; <sup>c</sup> Kiserud et al.<sup>16</sup>; <sup>d</sup> Johnsen et al.<sup>29</sup>; <sup>e</sup> Stirmemann et al.<sup>18</sup> The World Health Organization study, the National Institute of Child Health and Human Development study from United States, the Intergrowth-21st study, a study from the Democratic Republic of Congo, and another from Norway are listed according to descending values at 20 weeks but are not formally compared or ranked. Modified from Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. *PLoS Med* 2017;14:e1002220. With permission.

Kiserud. *WHO fetal growth charts. Am J Obstet Gynecol* 2018.

Rift Valley or rural and urban area. Probably more important, the optimal underlying profiles of metabolism and physiology will also differ. In short, this means that we need to adapt our clinical tools and assessment strategies to fit the various populations of the world optimally. One good attempt to do so is the construction of generic growth charts that are adaptable to local populations.<sup>45</sup>

Third, many societies have seen substantial development, changing environment and lifestyle, and secular changes in population anthropometrics. For example, during the period 1967–1998, birthweight at 40 weeks gestation increased by 100 g in Norway,<sup>47</sup> which indicates that reference ranges for fetal growth and birthweight need updating at intervals.

Four, in addition to the need for the adjustment of reference charts to local needs,<sup>45,48</sup> the wide variation of fetal growth within populations calls for more individualized assessment strategies<sup>49</sup> (ie, taking into account more of the information commonly available but not systematically used [eg, birthweight of siblings, maternal and paternal birthweights,<sup>50,51</sup> and growth velocities and individual growth trajectories, concepts that have been addressed in different ways]).<sup>52–55</sup> The acceptance of individual variation extends also to proportions, possibly increasing predictive capacity by adding 3-dimensional measurements of various body sections.<sup>56</sup>

### Applying Fetal Growth Charts

The recent fetal growth charts that are based on multiple populations should

be, by design, the first choice for an area where no population-specific references exist rather than previously used charts that are based on single populations from high-income societies. Further, what emanates from the recent studies and the discussion that follows them is that there is no clear indication that 1 fetal growth standard is equally applicable for all pregnancies of the world, not for clinical use and not for public health issues that include life course and health risks in adult life.

When the need comes for the improvement of clinical testing in a population, it is possible to adjust cut-off levels (level of percentile), to customize the percentiles according to fetal sex, and to take into account maternal factors. Because the presently available multinational studies represent very limited

selections of the world's population variation, it is also quite possible that population-specific growth charts may be the solution (eg, populations adapted to high altitudes or other extreme conditions).

The need for fetal growth and birth-weight reference values in the growing initiative of combating noncommunicable diseases is obvious, particularly because WHO emphasizes prevention as the best strategy.<sup>57</sup> Thus, periconception health, pregnancy development, fetal development, birth, and early infant development come into focus containing major determinants for life course and later health risks. In such a perspective, there is merit in monitoring growth beyond birth.<sup>58</sup> However, the recent results indicate that references for size must vary according to location and population for an optimized assessment. The use of 1 overall standard carries a risk of misclassification and stigmatization. ■

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# The INTERGROWTH-21<sup>st</sup> fetal growth standards: toward the global integration of pregnancy and pediatric care



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The purpose of the INTERGROWTH-21<sup>st</sup> project was to develop international, prescriptive standards for fetal growth assessed by ultrasound and fundal height, preterm postnatal growth, newborn size and body composition, maternal weight gain, and infant development at the age of 2 years. Hence, we have produced, based on World Health Organization recommendations, the first comprehensive set of international standards of optimal fetal and newborn growth that perfectly match the existing World Health Organization child growth standards. Uniquely, the same population was followed up longitudinally from 9 weeks of fetal life to 2 years of age, with growth, health, and nutritional status assessment at 2 years supporting the appropriateness of the population for construction of growth standards. The resulting package of clinical tools allows, for the first time, growth and development to be monitored from early pregnancy to infancy. The INTERGROWTH-21<sup>st</sup> fetal growth standards, which are based on observing >4500 healthy pregnancies, nested in a study of >59,000 pregnancies from populations with low rates of adverse perinatal outcomes, show how fetuses should grow—rather than the more limited objective of past references, which describe how they have grown at specific times and locations. Our work has confirmed the fundamental biological principle that variation in human growth across different populations is mostly dependent on environmental, nutritional, and socioeconomic factors. We found that when mothers' nutritional and health needs are met and there are few environmental constraints on growth, <3.5% of the total variability of skeletal growth was due to differences between populations. We propose that not recognizing the concept of optimal growth could deprive the most vulnerable mothers and their babies of optimal care, because local growth charts normalize those at highest risk for growth restriction and overweight, and can be valuable for policymakers to ensure rigorous evaluation and effective resource allocation. We strongly encourage colleagues to join efforts to provide integrated, evidence-based growth monitoring to pregnant women and their infants worldwide. Presently, there are 23.3 million infants born small for gestational age in low- to middle-income countries according to the INTERGROWTH-21<sup>st</sup> newborn size standards. We suggest that misclassification of these infants by using local charts could affect the delivery of optimal health care.

**Key words:** abdominal circumference, biparietal diameter, estimated fetal weight, femur length, fetal size, macrosomia, optimal growth, reference chart, skeletal growth, small for gestational age, socioeconomic status, standard, stunting

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## Introduction

Recent publications<sup>1-5</sup> and ensuing editorials and correspondence,<sup>6-9</sup> as well as presentations and debates at national and international meetings, have activated a controversy that goes well beyond the boundaries of obstetrics and perinatal medicine. The controversies touch upon fundamental topics in biology, genetics, politics, and human rights. Sadly, some arguments have at times been reminiscent of the historical dispute about the influence of race or ethnicity or on human head size and shape.<sup>10</sup>

There is little disagreement about the similarity of human growth across healthy populations in early pregnancy, and the applicability of international standards to estimate gestational age,<sup>2,11</sup> evaluate size at birth worldwide,<sup>12-14</sup> and monitor the growth of term newborns up to 5 years of age.<sup>15</sup> However, challenges are being made to key conceptual and factual issues relating to fetal growth monitoring in the second half of pregnancy that are preventing the introduction of integrated care across the first 1000 days of life.

Some members of the obstetric community seem to hold firmly to the view that fetal growth differences among healthy populations, specifically >14 weeks' gestation, are strongly influenced by maternal factors such as self-reported ethnicity, nationality, or political borders. This position is difficult to sustain given the strong evidence, obtained from detailed monitoring of low-risk cohorts from early pregnancy to 2 years of age, that human growth, evaluated by markers of skeletal, fat-free mass (ie, fetal crown-rump length [CRL] and head circumference [HC], birth length, HC at birth, and infant length), is very similar among low-risk populations regardless of where they live, or their race/ethnicity,<sup>16,17</sup> as demonstrated more than a decade ago by the World Health Organization (WHO) Multi-center Growth Reference Study (MGRS).<sup>18</sup>

Differences observed in perinatal health among general populations across countries are principally due to the downstream effects of environmental,

nutritional, and socioeconomic factors—frequently across generations—and this has important consequences. These are well recognized in medicine and public health, ie, a mother's ZIP code is a better indicator of her health status than her genetic code.<sup>19,20</sup> Our aim here, therefore, is to dispel these misconceptions and unsubstantiated beliefs that, if left uncorrected, could adversely affect the quality of care offered to women and their families.

## Methodological issues relevant for the screening of fetal growth abnormalities in the general pregnant population

### References vs standards

At present, clinicians around the world are using many different ultrasound charts of fetal size, based on a variety of populations and methodologies, to monitor growth. However, in a series of systematic reviews, we have shown that the majority of these charts were developed with important methodological flaws.<sup>21-23</sup>

All these charts are references rather than prescriptive standards. The distinction is critical. References describe how individuals *have grown* at a particular time and place, often decades beforehand. Prescriptive standards, on the other hand, are purposely developed using a selected, healthy population, to describe how humans *should grow* when nutritional, environmental, and health constraints on growth are minimal. They are based conceptually on the WHO 1995 recommendation that “human growth should be evaluated using international standards, describing how individuals should grow.”<sup>24</sup> Of course, results from any screening test, so also in the case of growth monitoring using a standard, then require clinical judgment to interpret findings and determine future actions.

The use of references instead of standards has important implications at individual and populations levels that impact clinical care and public health policies. To understand why, it is important to realize that the distribution of size in the general population does not constitute a standard. The prevalence of

stunting among children globally illustrates the point well, as the rate of stunting is inversely related to the level of socioeconomic status (SES).<sup>25</sup> Therefore, size charts based on the distribution of biometric measures in low and high SES populations will be very different from each other. A chart based on a low SES sample will clearly underestimate the prevalence of small for gestational age (SGA) and stunting, which are markers of social inequity.<sup>25</sup>

These differences can be illustrated when assessing the INTERGROWTH-21<sup>st</sup> project and the WHO-sponsored study by Kiserud et al,<sup>4</sup> which had completely different objectives. The former was a comprehensive evaluation of human growth and development across the first 1000 days of life, leading to the construction of fetal and preterm postnatal growth standards; it included an assessment of newborn body composition, infant feeding practices, and preterm postnatal growth, as well as postnatal growth and neurodevelopment evaluation at 2 years of age to assess the appropriateness of the complete cohort for the construction of standards (Panel 1). The INTERGROWTH-21<sup>st</sup> project<sup>26</sup> also adhered rigorously to the WHO recommendations for assessing human size and growth (see below).<sup>24</sup> In contrast, the WHO-sponsored study was hospital-based, and generated fetal growth references not standards<sup>4</sup>; the selection of the population to study, outcome measures, ultrasound equipment, and analytical strategy were different, as indeed was the lack of masking the ultrasound measures to avoid potential observer bias.

This need to differentiate standards from reference charts is not an obscure intellectual matter but a vitally important global issue with marked political and socioeconomic ramifications. How else can progress toward United Nations Sustainable Developmental Goal 3.1 (end preventable deaths of newborns and children <5 years of age) be measured, unless international standards are used to compare the health and nutritional status of infants, as was done in assessing progress toward Millennium Development Goal 1 (eradicate extreme

**PANEL 1****INTERGROWTH-21<sup>st</sup> project characteristics**

Large prospective study of 59,137 pregnant women  
 Population based: all institutions providing pregnancy and delivery care in 8 geographically limited urban areas with low rates of adverse perinatal outcomes and low pollution, domestic smoke, radiation, and other toxic substances  
 Sampling of individual women within 8 geographic areas using predefined criteria for construction of standards  
 Participants followed up to age 2 y  
 Pregnancy, neonatal anthropometry, and perinatal conditions recorded for total population (59,137 pregnant women) in 8 geographic areas using standardized procedures, identical equipment, and centrally trained staff  
 Environmental conditions evaluated using special data collection form developed in collaboration with Center for Environmental Research and Children's Health, University of California, following WHO recommendations  
 Excluded from standards only severe maternal or fetal conditions defined a priori  
 A priori data analysis plan based on WHO recommendations to construct human growth standards  
 Use of skeletal growth measures from <14 wk' gestation to age 2 y for comparisons across populations, as recommended by WHO  
 Three complementary data analysis strategies to support pooling data for construction of standards

International standards for human growth from <14 wk' gestation to age 2 y  
 International preterm postnatal growth standards as recommended by WHO  
 Preterm postnatal motor development assessment following WHO milestones

Published real-time, online data management system  
 Ultrasound equipment selected based on predefined criteria after extensive public consultation according to WHO administrative requirements  
 Ultrasound measures in triplicate and corroborated by newborn anthropometry  
 Ultrasound results masked to operators to eliminate expected result bias  
 Standardized equipment at all sites for ultrasound; maternal, newborn, and child anthropometry  
 Ultrasound machines calibrated with standard phantom  
 Published system of:
 

- Training, standardization, and certification of ultrasound operators
- Quality-control strategy for all maternal and postnatal measures
- Assessment of intraobserver and interobserver variation of ultrasound fetal biometry
- Protocols for quality control of ultrasound image review, data monitoring, and random sample remeasurement

WHO, World Health Organization.

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with no or low levels of major, known, nonmicrobiological contamination,<sup>28</sup> were selected to ensure that the study was population-based. Thus, a strategy of including delimited geographic areas where the health, educational, and nutritional needs of all the inhabitants are mostly reached is very different to that of the WHO-sponsored<sup>4</sup> and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)<sup>5</sup> fetal studies, which selected a number of convenient hospitals. This lack of population-based sampling means that the sites selected by these 2 studies would have been ineligible for the INTERGROWTH-21<sup>st</sup> project.

Healthy pregnant women with a naturally conceived singleton pregnancy, who met the individual inclusion criteria,<sup>26</sup> were identified prospectively in the INTERGROWTH-21<sup>st</sup> project. Approximately one third of the healthy women who met these criteria were enrolled in the Fetal Growth Longitudinal Study, 1 of the project's 5 studies. This is the cohort from which the fetal growth standards,<sup>1</sup> and the standards for: (1) symphysis-fundal height,<sup>29</sup> (2) gestational weight gain,<sup>30</sup> (3) early pregnancy dating,<sup>2</sup> (4) estimated fetal weight (EFW),<sup>3</sup> (5) newborn body composition,<sup>31</sup> and (6) the postnatal growth of preterm infants were derived,<sup>32</sup> as well as, in 2018, (7) fetal velocity growth and (8) neurodevelopment at 2 years of age. These tools are available as [Supplementary Material](#) for clinical use. Underlying these tools was a series of systematic reviews of current clinical practice and development of methodologies based on a deep understanding of the issues to arrive at optimal scientific analytical framework. It should be noted that there was wide heterogeneity in methods, tests, and definitions used in previous studies ([Panel 3](#)).

Women were recruited <14 weeks' gestation, and pregnancies were dated based on a certain last menstrual period, but corroborated by ultrasound measurement of the CRL.<sup>33</sup> Ultrasound scans were then performed every 5 ± 1 weeks from the initial dating scan by dedicated research staff using identical, midrange ultrasound machines at each

poverty and hunger) by showing changes in stunting rates based on the international WHO child growth standards?<sup>27</sup> Making late fetal growth charts country- or region-specific would not only make this task impossible, it risks confusing the interpretation of all other growth and health indicators across populations.

### How were the INTERGROWTH-21<sup>st</sup> populations selected?

The first step in creating prescriptive international standards of optimal fetal growth was to select free-living populations in defined geographic areas with minimal constraints on growth, and

good maternal and perinatal health outcomes. The second step was to select, from the whole population, healthy pregnant women at low risk of adverse outcomes.<sup>26</sup> This is very different to the policy of recruiting women from selected hospitals, which frequently introduces bias, because women who attend certain hospitals for pregnancy care may be different from the overall population of pregnant women—particularly when the population is served by private and public hospitals, and recruitment is from one but not the other.

In the INTERGROWTH-21<sup>st</sup> project ([Panel 2](#)), all institutions providing obstetric care in 8 delimited urban areas

study site, with rigorous training and standardization procedures,<sup>34,35</sup> quality-control measures,<sup>36</sup> and blinding of measurements.

Moreover, unlike any other longitudinal study of ultrasound in pregnancy, the infants involved in the fetal growth standards were followed up for 2 years after birth, using the same standardized methods employed in the WHO child growth standards to measure growth,<sup>18</sup> neurodevelopment, auditory processing, and sleep-wake patterns at 2 years of age.<sup>37</sup> We have recently reported that the fetal growth standards cohort remained healthy up to 2 years of age, with adequate growth and motor development assessed using WHO tools,<sup>15,38</sup> supporting its appropriateness for the construction of the international fetal and preterm postnatal growth standards.<sup>17</sup>

### Evaluating similarities in fetal growth among populations

Critics of the INTERGROWTH-21<sup>st</sup> project often misquote our conclusions by claiming we believe that all babies everywhere grow in the same way or birthweight is the same in general populations throughout the world. This is self-evidently not the case. Rather, we have demonstrated that measures of fetal and newborn skeletal growth are similar across diverse geographical settings when most of the mothers' socioeconomic, educational, nutritional, and health needs are met and environmental constraints on growth are low.<sup>16</sup>

Skeletal growth was chosen as the outcome measure to evaluate similarities in growth based on the WHO recommendation to avoid fat-based indicators, eg, abdominal circumference (AC), when comparing populations for the construction of human growth standards. This is vitally important for fetal growth screening in developed countries with an obesity epidemic, and for those developing countries in epidemiological transition.

The specific recommendation<sup>39</sup> is to use markers of skeletal or linear growth because they are: (1) mostly resistant to skewing in response to "excessive nutrition"<sup>39</sup>; (2) normally distributed (unlike

#### PANEL 2

#### Different studies of INTERGROWTH-21<sup>st</sup> project

NCSS	Demographic and pregnancy characteristics, birth length, head circumference, weight and neonatal conditions of all newborn babies from 8 geographically defined populations using identical methods and instruments
FGLS	A subgroup of NCSS: women who met individual inclusion criteria from these populations were followed up from <9 wk through to end of pregnancy; this included serial fetal ultrasound scans and newborn anthropometry and body composition
Infant Follow-Up Study	All FGLS newborns were then followed up until age 2 y for growth, health, and development
Preterm Postnatal Follow-Up Study	All preterm births in FGLS cohort that underwent detailed regular anthropometry and followed up to age of 2 y
Preterm and Impaired Fetal Growth Syndromes Study	Nested case-control study including all preterm births as well as all newborns with impaired fetal growth from NCSS

FGLS, Fetal Growth Longitudinal Study; NCSS, Newborn Cross-Sectional Study.

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fat-related indicators); (3) more precisely measurable than fat-related indicators; (4) consistent with pediatric practice worldwide as they were used by WHO to generate the WHO child growth standards; and (5) although responsive to undernutrition or infection, this is hardly relevant in our healthy populations.

The comparison to assess similarities or differences in the WHO MGRS was based on infant height.<sup>18</sup> The corresponding measure in fetuses is CRL (that can be measured reliably until 14 weeks' gestation) and length at birth; these showed remarkable similarities among sites using the 3 analytical approaches described below. It is difficult to see that large variation should exist between these 2 time points, but we assessed it; as length is not measurable (due to fetal curling) we used HC as a skeletal measure between 14 weeks of gestation and at birth.

Conversely, assessing similarities in fetal growth among populations by EFW, a composite calculation from 3 different fetal anthropometric measurements, contradicts these physiological concepts; it also adds considerable error to any estimation, especially at term. In addition, fetuses can reach the same EFW through several permutations of the equation's components, which are

clearly not comparable. The continued use in the literature of an old equation,<sup>40</sup> determined using a very small sample, adds to the confusion, especially as it includes femur length measures obtained using old ultrasound equipment, which yields different results to modern ultrasound machines.<sup>41</sup>

Many studies have shown that the 95% confidence interval of the random error associated with EFW accuracy exceeds 14% of birthweight, which is close to 400 g for the average birthweight at term. In fact, a systematic review concluded that "the size of the random errors (of EFW) remains a major obstacle to confident use in clinical practice."<sup>42</sup> Accuracy is even worse for small and large fetuses for which growth estimation is clinically more important. All these are very important issues when comparing differences in EFW values among populations, which is why it is much more logical to compare populations using the individual skeletal parameters, such as length and HC separately.

Why not to use AC alone to compare populations considering that it is associated with perinatal outcomes in late pregnancy? The response, based on the recommendation of skeletal linear growth, is that AC is a fat-/tissue-based measure equivalent to weight. Hence, if a marker of fat/tissue mass were used to

**PANEL 3****INTERGROWTH-21<sup>st</sup> international standards for monitoring growth and development from early pregnancy to 2 years of age**

<b>INTERGROWTH-21<sup>st</sup> international standards for:</b>	<b>INTERGROWTH-21<sup>st</sup> systematic review and conceptual basis supporting international standards</b>
First-trimester dating <sup>2</sup>	Systematic review of charts of pregnancy dating by fetal crown-rump length <sup>11</sup>
Late pregnancy dating <sup>63</sup>	Study design and implementation <sup>26</sup>
Fetal growth by ultrasound <sup>1</sup>	Ultrasound methodology, standardization, and quality control <sup>33-36,64,65</sup>
Estimated fetal weight by ultrasound <sup>3</sup>	Systematic review of charts of fetal size by ultrasound <sup>21</sup>
Symphysis-fundal height <sup>29</sup>	Systematic review of novel biomarkers for predicting intrauterine growth restriction and stillbirths <sup>66,67</sup> Systematic review and meta-analysis on predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction <sup>68</sup>
Phenotypic classification of SGA <sup>69</sup>	Conceptual issues on preterm birth <sup>71-73</sup>
Phenotypic classification of preterm birth <sup>70</sup>	Systematic review of novel biomarkers for prediction of spontaneous preterm birth phenotype <sup>74</sup>
Newborn size for gestational age and sex from 24 wk' gestation to term <sup>55,75</sup>	Systematic review of charts of newborn anthropometry <sup>22</sup>
Newborn body composition and weight for length standards <sup>31</sup>	Conceptual issues for preterm standards <sup>76</sup> Systematic review of preterm postnatal charts <sup>23</sup>
Preterm postnatal growth based on international feeding recommendations <sup>32</sup>	Preterm postnatal growth: new paradigm <sup>77</sup> Anthropometric protocols, standardization, and quality-control methods for international growth standards <sup>78,79</sup>
Maternal weight gain during pregnancy <sup>30</sup>	Systematic review of gestational weight gain charts <sup>80</sup>
Postnatal follow-up to age 2 y with neurodevelopmental assessment to evaluate appropriateness of population for creating growth standards <sup>17</sup>	Systematic review of differential effects of intrauterine growth restriction on childhood development <sup>81</sup> A simplified multidimensional set of neurodevelopment assessment tools <sup>37</sup>
Free e-learning training courses <sup>82,83</sup>	Evaluation of dissemination activities <sup>84,85</sup>

SGA, small for gestational age.

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compare growth across populations, it would be observed in the third trimester of pregnancy that, compared to non-overweight populations, those in the midst of the obesity epidemic have fetuses with larger AC values. This is observed in one of the NICHD publications,<sup>43</sup> which shows an increase in AC in overweight women compared to those of normal weight.

Importantly, in the context of the NICHD argument, fetal AC changes are mostly due to liver growth supported by

a small component of abdominal subcutaneous fat. It is, therefore, very difficult to understand how the different ethnic groups they studied can have differential, genetically driven, liver growth during the second part of pregnancy.

### Why outcome measures should be masked

It is a basic research principle across all biological subjects that any outcome measures being obtained, especially by medical observers,

should be masked, as prior knowledge or real-time plotting by the operator can strongly influence their measurement. Prior knowledge increases the risk of bias in favor of the hypothesis under investigation, which certainly applies to ultrasound measurements, where the operator can influence the values obtained. In the INTERGROWTH-21<sup>st</sup> project, the identical ultrasound machines used at every site were adapted to enable measurements to be taken in a blinded fashion; this has not been the case in all other fetal studies despite the well-recognized potential for bias.

### Which is the most appropriate analytical strategy?

Data from studies combining populations should be analyzed in 2 steps: first, by evaluating the similarities among sites (or ethnic groups in the case of the NICHD fetal study) and second by estimating the centiles. For the first step, we followed the WHO recommended strategy for the construction of growth standards based on 3 complementary methods after the literature was systematically reviewed.<sup>44</sup> In contrast the WHO-sponsored study on fetal growth used a *P* value-multiple testing-based strategy; while the NICHD study was designed to create separate standards for the 4 ethnic groups, so the issue of potential pooling was not assessed. In the NICHD study, judgements of differences were again based on a *P* value and although the potential clinical significance was assessed, this was done a posteriori rather than as a judgement on whether pooling should take place or not. This is another core element that differentiates these 3 publications (Panel 1).

It is obvious that statistical significance is not the same as clinical significance and that small differences, well within the measurement error of ultrasound equipment, may achieve statistical significance in a study with a large sample size. For example, in a study than included women enrolled in the NICHD study,<sup>43</sup> the median femur length was 0.8 mm longer and the median humerus

length 0.6 mm longer in 443 obese vs 2320 nonobese women (in context the lengths were 71.0 vs 70.2 mm; and 62.2 vs 61.6 mm, respectively). The differences are judged to be statistically significant because the *P* values are .01 and .03, respectively, but are of minimal clinical relevance and well within measurement error, which may in any case be higher in obese women.

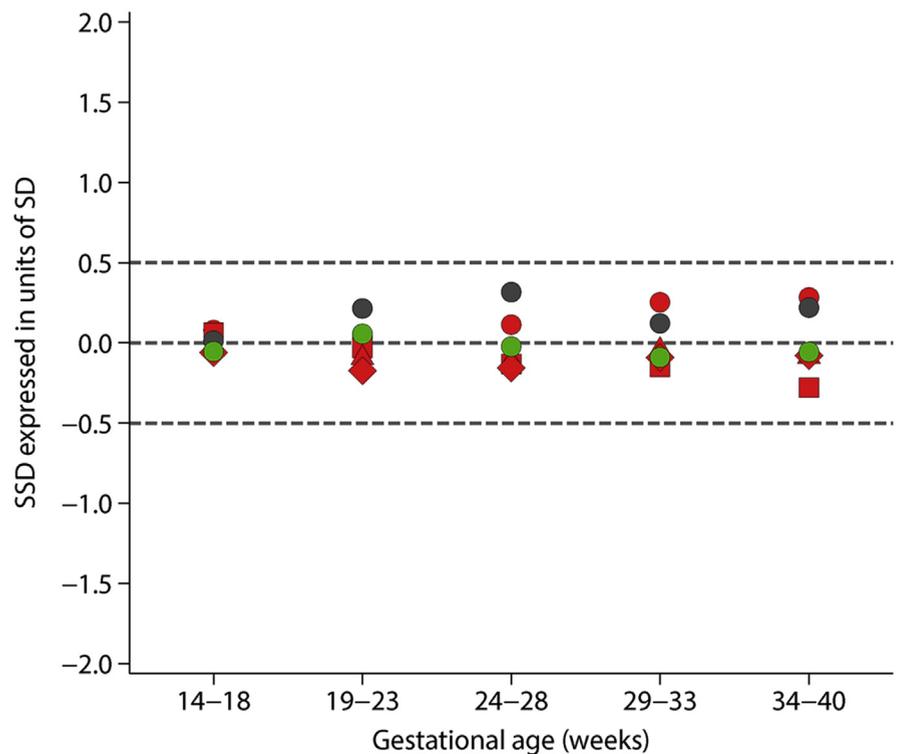
Therefore, the clinically relevant difference should be defined a priori, and *P* values have no place in deciding whether these differences are clinically meaningful. Furthermore, the use of multiple testing for comparing individual populations against each other is an irrelevance, as it was never suggested that fetuses from one site, eg, in India, should be evaluated using charts from another site, eg, in Brazil or the United States. What is recommended is to create international standards by combining data from prescriptive populations against which all samples are compared. Standardization of tools and measures is a central practice not only in biology and medicine, but also in all fields of science and even the arts.

Hence, the INTERGROWTH-21<sup>st</sup> project set up its a priori conditions on whether to pool the data sets based on the WHO internationally accepted 3-component strategy used for the WHO child growth standards. The clinically relevant difference was also defined a priori using the appropriate, recommended outcome measure for evaluating growth across populations. We are unsure why the investigators of the WHO-sponsored study, who must have been aware of the WHO expert committee recommendations, did not follow them or use even the most practical analytical method, namely sensitivity analysis. This is relevant because they advocated pooling their data, despite calling them different, without conducting a standard sensitivity analysis.<sup>4</sup>

To conduct such an evaluation, we used the SD of the all sites' combined value of fat-free measures as the denominator for the standardization process,<sup>45</sup> following WHO previous work.<sup>18</sup> For fetal growth, this involved values for both CRL and HC obtained from the

**FIGURE 1**

**Fetal HC growth in the INTERGROWTH-21<sup>st</sup>, NICHD, and WHO-sponsored studies are remarkably similar**



Standardized study discrepancy (SSD) of fitted fetal head circumference. Study-specific means were obtained as unweighted average of values from published charts (by gestational week) for 5 gestational age intervals. SSD was calculated as difference between individual study mean and mean of all studies combined, divided by Fetal Growth Longitudinal Study (FGLS) adjusted SD,<sup>7</sup> at each gestational age interval. World Health Organization–sponsored study<sup>15</sup> (gray circles); FGLS of INTERGROWTH-21<sup>st</sup><sup>20</sup> (green circles); and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development fetal growth studies<sup>19</sup>: white (red circles), black (squares), Hispanic (triangles), Asian (diamonds).

Papageorghiou. INTERGROWTH-21<sup>st</sup> fetal growth standards. *Am J Obstet Gynecol* 2018.

mean of 3 highly standardized measures of the same individual at each visit. When this protocol was applied to the INTERGROWTH-21<sup>st</sup> fetal growth data, which constituted 128 comparisons of fetal CRL and HC from early pregnancy to term, as well as birth length, only 1 value was marginally outside (standardized study discrepancy  $-0.58$ )<sup>16</sup> the primary cut-off of  $\pm 0.5$  SD, recommended by the WHO MGRS group.<sup>44</sup>

A key question is: what would the 2 recently published fetal studies' results have been had the investigators followed the same analytical strategy as the WHO MGRS group?<sup>18,44</sup> To explore this question, we have produced the matching

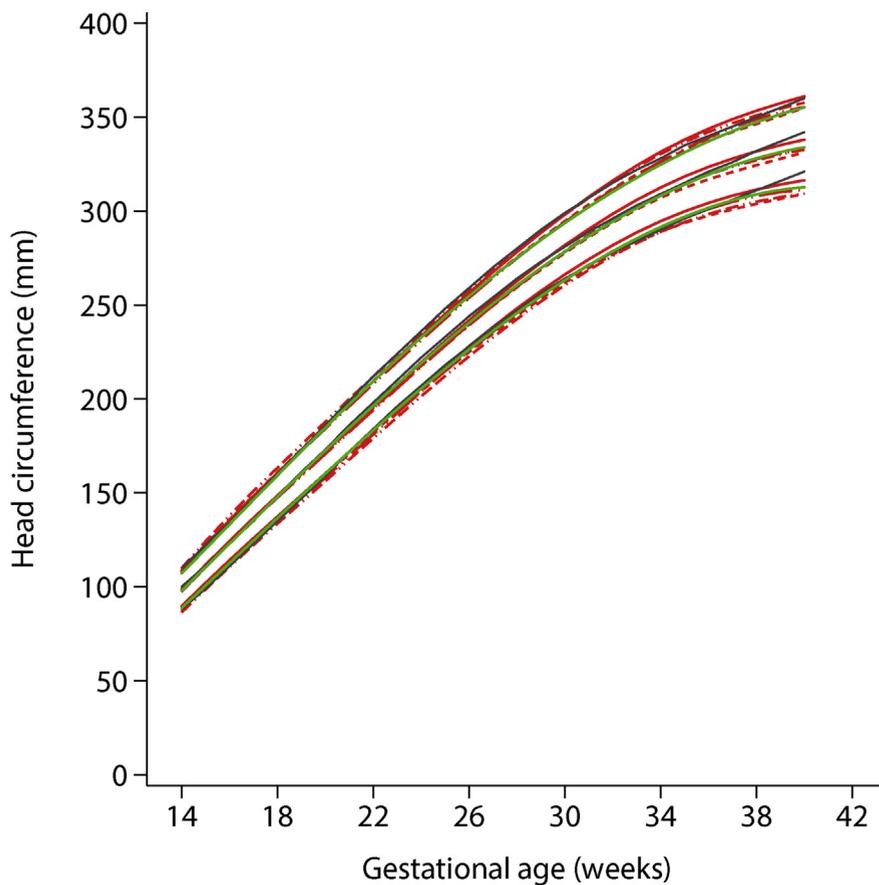
analyses, which the authors did not perform. Figure 1 shows that, when the results of the 2 studies are combined, the differences among all the study sites are well within the limits established a priori for fetal skeletal measures, in agreement with the INTERGROWTH-21<sup>st</sup> previous publications. This was to be expected because the actual 50th centile of fetal HC according to gestational age was almost identical across these populations (Figure 2).

### Race/ethnicity is not a biological factor influencing fetal growth

Several groups have suggested adjusting fetal growth charts for maternal

FIGURE 2

Comparison of INTERGROWTH-21<sup>st</sup>, NICHD, and WHO-sponsored studies show limited discrepancies in fetal HC



Comparison of fitted 5th, 50th, and 95th centiles of fetal head circumference. World Health Organization—sponsored study<sup>15</sup> (gray solid lines); Fetal Growth Longitudinal Study of INTERGROWTH-21<sup>st</sup><sup>20</sup> (green solid lines); and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development fetal growth studies<sup>19</sup>: white (solid red lines), black (dashed red lines), Hispanic (dash-dot red lines), Asian (dot-dot-dash red lines).

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characteristics, in particular self-reported race/ethnicity. However, the use of race/ethnicity is problematic in most nonisolated populations because of large ancestral admixture due to global migration, invasions, and other population movements. There are also at least 116 definitions of self-reported race/ethnicity in the biomedical literature.<sup>46</sup>

The alternative, more compelling view is that race/ethnicity is simply a social construct that represents a proxy for SES, education, and social class background, which is related to many poor health and

social outcomes, eg, stillbirth and<sup>47</sup> maternal mortality.<sup>48</sup> In the NICHD fetal study, which proposed using different charts in the United States for “non-Hispanic whites, non-Hispanic blacks, Hispanics, and Asian/Pacific islanders,” differences seen in fetal growth between these groups must be taken in the context of the enormous differences in annual family income and other SES markers such as marital status, education, and private health insurance. In addition, the fact that SES and race/ethnicity often merge is frequently ignored when making adjustments and,

in our view, presents a dangerous precedent.

There is also no scientific evidence that self-reported race/ethnicity is biologically or genetically related to fetal growth. Actually, all the genetic evidence across global populations demonstrates the opposite, ie, only a very small proportion of human linear growth is related to genetic factors. As measured in observational studies, the differences between geographic locations cannot explain >10% of the variability in human length. In addition, strong genetic evidence from a multiancestry, genomewide association study meta-analysis involving 153,781 participants identified as many as 60 genetic loci associated with birthweight (as a proxy for fetal growth) with only 15% of the variance in birthweight being captured by assays of fetal genetic variation.<sup>49</sup>

Furthermore, in any country, such as the United States, whose inhabitants often have mixed ancestral backgrounds, it is impossible to see how racial/ethnic classification could even be implemented during the course of routine antenatal care, especially as some of the groupings are hardly scientific. For example, based on US census practice, “Asian” includes Chinese, Japanese, South Indian, and Pacific Islander groups. Black American and African Americans are often grouped together, although health behaviors between African-born and American-born blacks are acknowledged to be different.<sup>50</sup> Hispanics are presumably an ethnic group of European origin with (or without) native-American mixing? In fact, the infeasibility and inaccuracy of defining race/ethnicity in contemporary multicultural settings was recently demonstrated in an Australian study,<sup>51</sup> using the gestation-related optimal weight customized charts.<sup>52</sup> In a sense, however, the impracticality is an irrelevance because racial-/ethnic-specific charts are indefensible on biological grounds.<sup>53</sup>

Interestingly, one of the quotations often used to justify having racial/ethnic fetal growth charts is from a paper by Bogin and Varela-Silva<sup>54</sup> in 2010,

although the authors themselves actually provided rather different views. They stated that “even if specific genotypes are discovered, their direct contribution to normal ethnic (so-called ‘racial’) variation in human body shape may be relatively small. At 40 weeks’ gestation, fetuses identified as African-Americans have, on average, relatively longer legs than fetuses identified as European-Americans. But the difference, as measured by (total length/CRL) is less than 1%.”<sup>54</sup> Such views and those of many other scientists accord with the belief that race/ethnicity is a social rather than a biological construct and a form of categorization that is ill-defined, especially in populations that have experienced high ancestral admixture rates.

The rationale for adjusting for other factors is similarly questionable. For example, parity (nulliparous women have on average smaller fetuses, but are also at higher risk of other features of placental insufficiency such as pre-eclampsia) or maternal weight, highly dependent on overnutrition and under-nutrition, are questionable and are not unchanging characteristics. Even characteristics that do not change within an individual’s life—such as maternal height—are highly changeable within just a few generations and therefore nutritionally dependent.

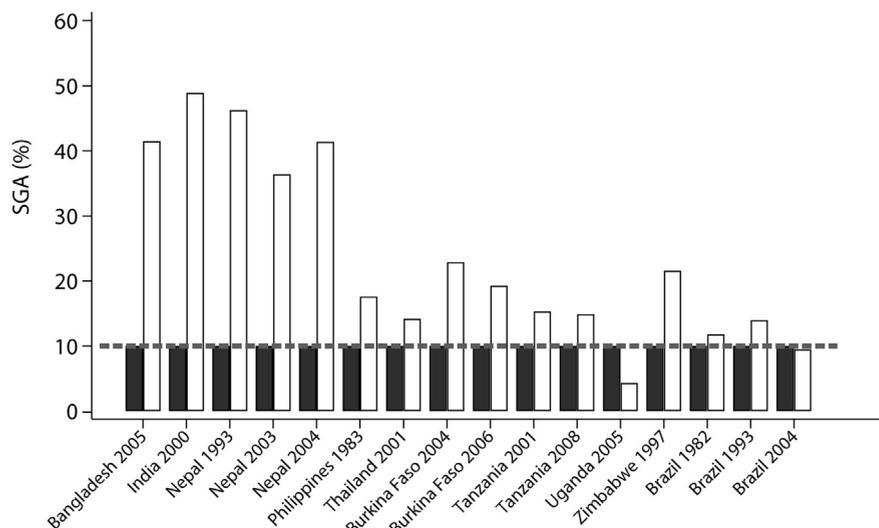
### Implications for screening in the general pregnant population: local charts vs international standards

It is suggested that fetal growth charts for EFW and common ultrasound biometric measures >14 weeks’ gestation “reveal a wide range of variation in human fetal growth across different parts of the world” with “significant differences in fetal growth between countries.”<sup>4</sup> It is hard to understand how borders between countries, often drawn on maps by colonial powers, can possibly have a biological influence on human growth, nor how heterogeneity within populations can be negated by national boundaries.

So, what happens if “population-specific high-quality reference intervals” for each population are created?<sup>4</sup> Apart

**FIGURE 3**

**Local references artificially “fix” the rate of SGA at 10%; international standards show different SGA rates as expected**



Rates of small for gestational age (SGA) from 16 prospective cohorts of newborns from 10 low- and middle-income countries. Empty columns show prevalence of SGA using INTERGROWTH-21<sup>st</sup> standards,<sup>47</sup> compared with effect of using fixed cut-off SGA rate of 10% that would result from using local reference charts (black columns). Data from Kozuki et al.<sup>56</sup>

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from the obvious hindrance of having to create hundreds of high-quality reference intervals for countries, regions, cities, villages, or hospitals, this approach is entirely fallacious. If a reference range is created for each region, by definition 10% of fetuses and newborns will be <10th centile of each local chart, and 10% will be >90th centile. Pretending that a uniform proportion of the population of fetuses across the world have the same degree of growth aberration is nonsensical and entirely at odds with differences in rates of maternal obesity, diabetes, pre-eclampsia, malnutrition, and infectious diseases. “Fixing” charts in this way would mean that no country, region, or city would have an excess of underweight or overweight babies—a concept so far removed from common sense and biological principles as to be difficult to comprehend.

This has been unequivocally demonstrated in 2 recently published reanalyses of data from low- and middle-income countries, using a birthweight <10th centile of the INTERGROWTH-21<sup>st</sup>

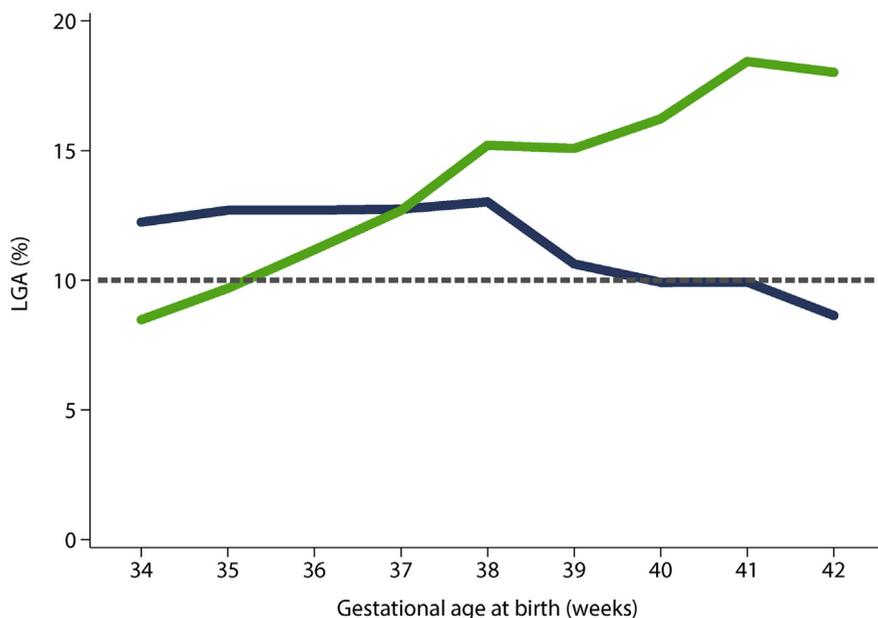
newborn size for gestational age/sex standards<sup>55</sup> as the definition of SGA. In the first study, the overall SGA prevalence was 24% among 16 birth cohorts<sup>56</sup>; in the second, the rate was 19% among 14 cohorts.<sup>12</sup> Of course, the prevalence would have been 10% had local charts been used (Figure 3).

At the other end of the health spectrum, we have previously shown that in England in 2011 through 2012 there were, as expected, 11% live singleton babies born >33 weeks’ gestation >90th centile if local charts of birthweight for gestational age are used.<sup>57</sup> However, when INTERGROWTH-21<sup>st</sup> international standards are used for the cut-off point,<sup>55</sup> the rate of overweight newborns increased to 19% overall, which matches the high prevalence of obesity in pregnant women and children in England (Figure 4).<sup>58,59</sup>

An additional practical issue specific to the WHO-sponsored reference charts, in terms of their global use for screening, is that they are sex-specific and their use presupposes prenatal sex determination. Even if we assume that the

**FIGURE 4**

**Higher rates of LGA newborns by international standards than a local reference, matching the high prevalence of overweight in the general population**



Prevalence of large for gestational age (LGA) (>90th birthweight centile) newborns in England in 2011 through 2012. Estimated prevalence of LGA using British 1990 growth reference centiles<sup>49</sup> (blue line) or INTERGROWTH-21<sup>st</sup> newborn size at birth standards<sup>47</sup> (green line). The horizontal dotted line represents the expected (by definition) 10% of newborns above the 90th centile of a local reference chart.

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determination is accurate and that parents want to know the fetal sex, the practice is banned in some countries.<sup>60</sup>

### Conclusions

The WHO child growth standards<sup>15</sup> are now used in nearly every country in the world to measure the growth of children from 0-5 years of age.<sup>61</sup> The INTERGROWTH-21<sup>st</sup> project was designed using exactly the same prescriptive approach as the WHO MGRS, ie, based on WHO recommendations regarding the construction of human growth standards.<sup>24</sup> The charts generated by the WHO MGRS and INTERGROWTH-21<sup>st</sup> project integrate perfectly so that, for the first time in history, a uniform method exists for monitoring linear growth from the “womb to classroom.”<sup>62</sup>

Many of the clinical tools derived from the same healthy cohort as the

fetal growth standards are now being used routinely around the world, eg, the preterm postnatal growth standards, which were adopted by both WHO<sup>13</sup> and the Centers for Disease Control and Prevention<sup>14</sup> in the context of the Zika epidemic. These and other standards derived from the same cohort, eg, for measuring symphysis-fundal height<sup>29</sup> and maternal weight gain,<sup>30</sup> as well as tools for estimating gestational age in early<sup>2</sup> and late<sup>63</sup> pregnancy have had >65,000 downloads from our website (data up until Nov. 21, 2017) and close to 10,000 health care professionals have been trained using INTERGROWTH-21<sup>st</sup> e-learning modules.

There is no scientific rationale for using local references instead of standards in clinical practice, and customization based on the color of a mother’s skin, the sex of her fetus, or her

nationality is unacceptable in the 21st century. Furthermore, classifying any of the 23.3 million infants born SGA in low- to middle-income countries according to the INTERGROWTH-21<sup>st</sup> newborn size standards for gestational age/sex<sup>12</sup> as normally grown by local charts could potentially deprive them of their right to better health care given that most are SGA because of impaired fetal growth due to malnutrition and/or infectious diseases. ■

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# Fetal growth standards: the NICHD fetal growth study approach in context with INTERGROWTH-21st and the World Health Organization Multicentre Growth Reference Study



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Three recently completed longitudinal cohort studies have developed intrauterine fetal growth charts, one in the United States and two international. This expert review compares and contrasts the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies, INTERGROWTH-21st and World Health Organization Multicentre Growth Reference Study conclusions in light of differences in aims, sampling frames, and analytical approaches. An area of controversy is whether a single growth reference is representative of growth, regardless of ethnic or country origin. The INTERGROWTH and World Health Organization Fetal studies used a similar approach as the World Health Organization Multicentre Growth Reference Study for infants and children, the aim of which was to create a single international reference for the best physiological growth for children aged 0–5 years. INTERGROWTH made the same assumption (ie, that there would be no differences internationally among countries or racial/ethnic groups in fetal growth when conditions were optimal). INTERGROWTH found differences in crown-rump length and head circumference among countries but interpreted the differences as not meaningful and presented a pooled standard. The World Health Organization Multicentre Growth Reference Study was designed to create a pooled reference, although they evaluated for and presented country differences, along with discussion of the implications. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Study was designed to assess whether racial/ethnic-specific fetal growth standards were needed, in recognition of the fact that fetal size is commonly estimated from dimensions (head circumference, abdominal circumference, and femur length) in which there are known differences in children and adults of differing racial/ethnic groups. A pooled standard would be derived if no racial/ethnic differences were found. Highly statistically significant racial/ethnic differences in fetal growth were found resulting in the publication of racial/ethnic-specific derived standards. Despite all 3 studies including low-risk status women, the percentiles for fetal dimensions and estimated fetal weight varied among the studies. Specifically, at 39 weeks, the 50th percentile for estimated fetal weight was 3502 g for whites, 3330 g for Hispanics, 3263 g for Asians, and 3256 g for blacks in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Study, compared with 3186 g for INTERGROWTH and 3403 g for World Health Organization Multicentre Growth Reference Study. When applying these standards to a clinical population, it is important to be aware that different percentages of small- and large-for-gestational-age fetuses will be identified. Also, it may be necessary to use more restrictive cut points, such as the 2.5th or 97.5th, for small-for-gestational-age or large-for-gestational-age fetuses, respectively. Ideally, a comparison of diagnostic accuracy, or misclassification rates, of small-for-gestational-age and large-for-gestational-age fetuses in relation to morbidity and mortality using different criteria is necessary to make recommendations and remains an important data gap. Identification of the appropriate percentile cutoffs in relation to neonatal morbidity and mortality is needed in local populations, depending on which fetal growth chart is used. On a final point, assessment of fetal growth with a one-time measurement remains standard clinical practice, despite recognition that a single measurement can indicate only size. Ultimately, it is knowledge about fetal growth in addition to other factors and clinical judgment that should trigger intervention.

**Key words:** estimated fetal weight, fetal growth, small for gestational age, ultrasound reference, ultrasound standard

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Fetal growth is monitored in pregnancies to ensure fetal well-being and to intervene in the context of maternal or fetal pathology, yet there are many challenges in distinguishing normal from abnormal growth.<sup>1-3</sup> Traditionally, cross-sectional fetal biometrics and estimated fetal weight (EFW), calculated using a formula with various combinations of fetal measurements, such as the head circumference, abdominal circumference, and femur length, are compared with reference size-for-gestational-age curves to generate a percentile, with a range of 10th to 90th percentiles often considered appropriate for gestational age.<sup>1,4</sup>

The choice in reference will therefore affect the percentage of fetuses that are identified as small or large for gestational age (SGA or LGA; often defined as <10th or ≥90th percentiles, respectively). Regarding EFW, intrauterine estimates of fetal weight by ultrasound are highly ( $r = 0.80-0.91$ ) correlated with actual birthweight, although they can differ by ≥100 g and are more inaccurate at the extremes of EFW, <2000 g and >4000 g.<sup>5</sup>

In theory then, birthweight references, whereby weight is measured directly as opposed to estimated, might seem preferable to assess fetal growth. However, birthweight-for-gestational-age reference percentiles inaccurately describe the preterm growth of fetuses who go on to deliver at term because infants who deliver preterm are more likely to be growth restricted.<sup>6,7</sup> Therefore, intrauterine references, despite the drawbacks of estimating fetal weight from ultrasound measurements, tend to be preferred to birthweight references for clinical antepartum monitoring.

The Hadlock 1991 reference<sup>8</sup> that is commonly used in the United States included 392 white women from a single center in Texas where each fetus contributed a single ultrasound, limiting the ability to determine fetal growth prospectively. Until recently, longitudinal ultrasound-based references were based on relatively small studies comprising mostly white women, although larger studies existed outside the United States.<sup>2</sup>

In light of critical data gaps about optimal fetal growth to aid clinical management of pregnant women, 3 longitudinal cohort studies were undertaken and provide new insights about contemporary fetal growth and how best to assess fetal growth: one in the United States, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies<sup>9,10</sup> and 2 international, INTERGROWTH-21st (INTERGROWTH)<sup>11,12</sup> and World Health Organization (WHO) Multicentre Growth Reference Study (WHO Fetal).<sup>13,14</sup> However, each has slightly different research aims that have an impact on the interpretation of the findings. We compare and contrast these 3 studies to aid in the application and clinical interpretation.

#### Approaches and assumptions

One of the main areas of dispute in the area of fetal and child growth is whether a single growth reference is representative of growth, regardless of ethnic or country origin. The INTERGROWTH<sup>15</sup> and the WHO Fetal<sup>16</sup> protocols started with the same premise of the WHO Multicentre Growth Reference Study (MGRS)<sup>17</sup> for infants and children, whose overarching aim was to create a single international growth reference for children aged 0–5 years.<sup>18</sup> Specifically, the WHO MGRS was predicated on the notion that infants and children of well-off parents and whose feeding met the WHO breast-feeding criteria represent optimal growth in size, and the WHO Fetal study was designed as a subsequent study to extend the WHO MGRS to the fetal period.

The INTERGROWTH and WHO Fetal studies on fetal growth started with the same assumption, that there would be no differences internationally in fetal growth when conditions were optimal. For the WHO MGRS, differences in length (0–2 years) and height (2–5 years) were evaluated among 6 countries: Brazil (South America), Ghana (Africa), India (Asia), Norway (Europe), Oman (Middle East), and the United States (North America). Without formal hypothesis testing, these differences were

interpreted as small enough to not be meaningful, so the final decision was to create 1 child growth standard.<sup>19</sup>

Additional measurements included head circumference, mid-upper-arm circumference, triceps, and subscapular skinfolds, but differences across countries in these dimensions were not tested. INTERGROWTH evaluated for differences in crown-rump length (CRL), head circumference (HC), and newborn length among countries, concluding that the differences were small enough, before pooling.<sup>20</sup> However, comparison of child growth measurements, especially for head circumference, have demonstrated wide variability across countries<sup>21</sup> so the assumption that the small fetal differences do not reflect differences that will persist and be meaningful in infancy and childhood may need to be reconsidered.

A key determinant of INTERGROWTH's decision to pool across sites was whether the standardized site difference at different gestational ages was from a somewhat arbitrary range of  $-0.5$  to  $0.5$  SD units.<sup>20</sup> Inappropriate interpretation of centiles could have resulted from pooling of sites given the allowed wide range of standardized site difference. To show this potential, our group previously calculated the probability of being below the lower limit of the standard for a particular site when the standard was constructed using data pooled across different sites for these values.<sup>22</sup> The probability of being less than the fifth centile varied according to the range of standardized site difference. Specifically, when the standardized site difference was  $0.5$ , then 3.4% of fetuses (targeted centile–pooled centile =  $5.0-1.6\%$ ) would have been misclassified as not extreme and 7.6% (targeted centile–pooled centile =  $12.6-5.0\%$ ) of fetuses would have been misclassified as extreme.

INTERGROWTH reported the magnitude of within- and between-site variation, and some of the variances reported might be highly statistically significant. Furthermore, INTERGROWTH evaluated only CRL and HC. CRL is known to not vary as much, and HC also has less

**FIGURE 1**  
Cohort profiles for the 3 studies

### NICHD



#### LOCATION

12 U.S. Sites  
New York [2], New Jersey, Delaware, Rhode Island, Massachusetts, South Carolina, Alabama, Illinois, and California [3]



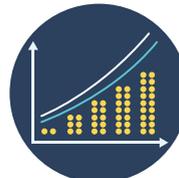
#### RACE & ETHNIC

Highly statistically significant differences in fetal growth by race/ethnicity  
Racial/ethnic-specific derived standards



#### INCLUSION/ EXCLUSION

*A priori* exclusion of pregnancy complications, preterm delivery < 37 weeks' gestation, stillbirth and fetal factors including all structural anomalies and karyotype abnormalities



#### ANALYTIC APPROACHES

Data transformation: log  
Model assumptions: linear mixed models, assuming a normal distribution of the fetal growth trajectories (after log transformation)  
Smoothing technique over gestational age: cubic splines



#### ESTIMATED FETAL WEIGHT

Calculated EFW from HC, AC and FL using the Hadlock 1985 formula<sup>26</sup>

### INTERGROWTH



#### LOCATION

8 Countries  
Brazil, China, India, Italy, Kenya, Oman, U.K. and U.S.



#### RACE & ETHNIC

One overall growth chart  
No statistical testing for differences among countries



#### INCLUSION/ EXCLUSION

Exclusion of pregnancy complications and fetal factors such as congenital anomalies and stillbirth



#### ANALYTIC APPROACHES

Data transformation: none  
Model assumptions: linear mixed models with location and scale assumptions, assuming a normal distribution of the fetal growth trajectories  
Smoothing technique over gestational age: second-degree fractional polynomials



#### ESTIMATED FETAL WEIGHT

Created a new formula<sup>12</sup> based on only HC and AC, making the comparison of EFW less meaningful

### WHO FETAL



#### LOCATION

10 Countries  
Argentina, Brazil, Democratic Republic of the Congo, Denmark, Egypt, France, Germany, India, Norway, and Thailand



#### RACE & ETHNIC

One overall growth chart  
Fetal growth showed natural variation, differing significantly between countries which largely followed ethnic distribution



#### INCLUSION/ EXCLUSION

Only optimal health inclusions  
No complication excluded (no impact on percentiles)



#### ANALYTIC APPROACHES

Data transformation: log  
Model assumptions: Quantile regression without distributional assumptions  
Smoothing technique over gestational age: polynomial functions



#### ESTIMATED FETAL WEIGHT

Calculated EFW from HC, AC and FL using the Hadlock 1985 formula<sup>26</sup>

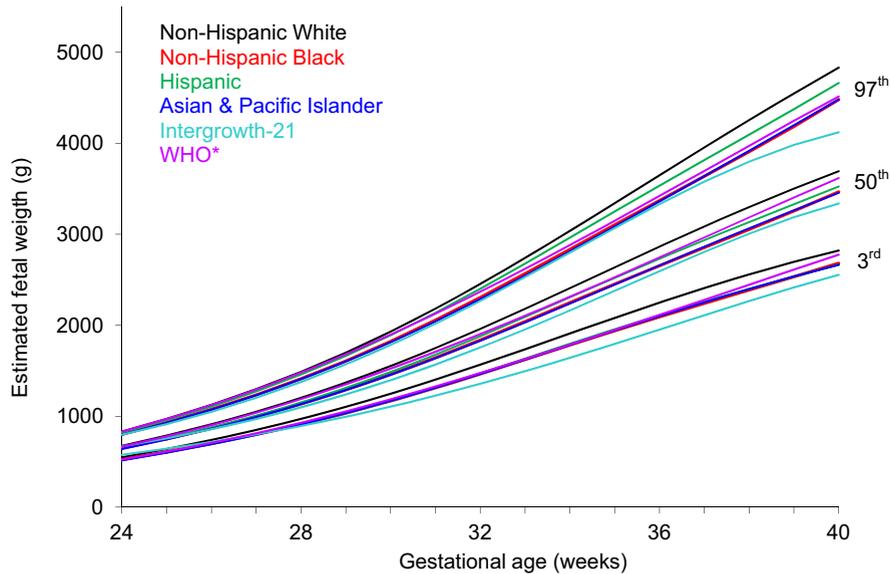
Main differences among the NICHD Fetal Growth Studies, INTERGROWTH,<sup>11,12</sup> and WHO Fetal<sup>13,14</sup> NICHD and WHO Fetal calculated EFW from HC, AC, and FL using the Hadlock 1985 formula,<sup>26</sup> while INTERGROWTH created a new formula<sup>12</sup> based on only HC and AC.

AC, abdominal length; EFW, estimated fetal weight; FL, fetal length; HC, head circumference; INTERGROWTH, INTERGROWTH-21st; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO Fetal, World Health Organization Multicentre Growth Reference Study.

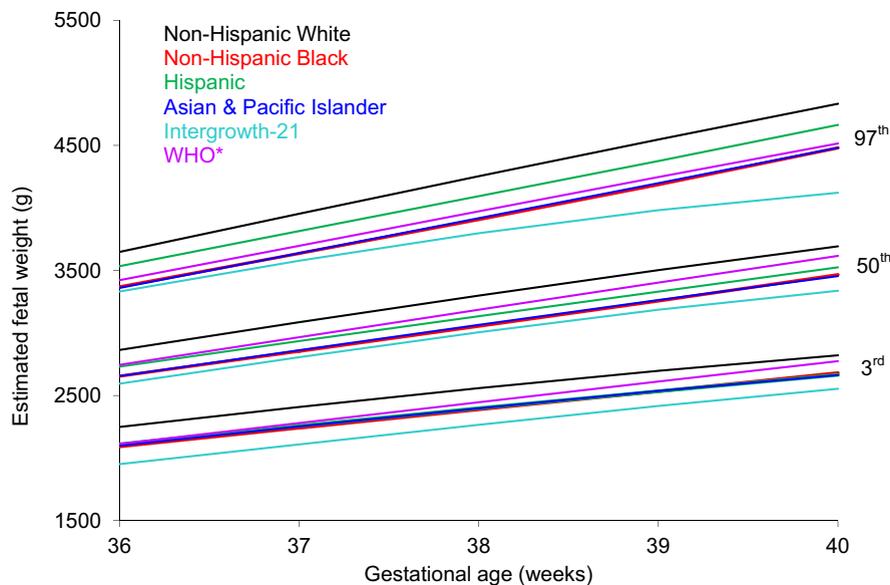
Grantz. Fetal growth charts. *Am J Obstet Gynecol* 2018.

**FIGURE 2**  
**Estimated fetal weight comparison among the 3 studies**

**A** Estimated Fetal Weight 24-40 Weeks



**B** Estimated Fetal Weight 36-40 Weeks



Distribution of the EFW by race/ethnicity and gestation, NICHD Fetal Growth Study—Singletons, INTERGROWTH-21st, and WHO Fetal for 24–40 weeks of gestation (A) and 36–40 weeks of gestation (B). Estimated third, 50th, and 97th percentiles for fetal weight by study; \*note that values are the 2.5th and 97.5th percentiles for the WHO Fetal study. Also, NICHD and WHO Fetal calculated the EFW from HC, AC, and FL using the Hadlock 1985 formula,<sup>26</sup> while INTERGROWTH created a new formula<sup>12</sup> based on only HC and AC.

AC, abdominal length; EFW, estimated fetal weight; FL, fetal length; HC, head circumference; INTERGROWTH, INTERGROWTH-21st; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO Fetal, World Health Organization Multicentre Growth Reference Study.

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variation, as demonstrated in the results below. WHO Fetal was designed to create a pooled reference, although they

evaluated for and showed country differences along with discussion of the implications.<sup>13</sup>

The primary objective of the NICHD study was also to create optimal fetal growth standards.<sup>23</sup> Unlike the 2

**TABLE 1**  
**The 50th percentiles for fetal anthropometric measurements by gestational age for the 3 studies<sup>a</sup>**

Gestational age, wks <sup>b</sup>	Estimated fetal weight (g) 50th percentiles <sup>c</sup>					
	NICHD white	NICHD Hispanic	NICHD Asian	NICHD black	INTERGROWTH	WHO Fetal
24	674	651	640	647	668	665
25	787	758	745	751	756	778
26	912	876	862	866	856	902
27	1050	1007	990	994	969	1039
28	1202	1151	1132	1134	1097	1189
29	1369	1311	1287	1289	1239	1350
30	1552	1486	1456	1459	1396	1523
31	1749	1676	1637	1642	1568	1707
32	1960	1879	1830	1837	1755	1901
33	2180	2090	2031	2040	1954	2103
34	2408	2307	2238	2247	2162	2312
35	2637	2521	2448	2452	2378	2527
36	2864	2731	2656	2654	2594	2745
37	3086	2935	2862	2854	2806	2966
38	3299	3134	3065	3054	3006	3186
39	3502	3330	3263	3256	3186	3403
40	3693	3525	3455	3466	3338	3617

INTERGROWTH, INTERGROWTH-21st; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO Fetal, World Health Organization Multicentre Growth Reference Study.

<sup>a</sup> The NICHD Fetal Growth Studies,<sup>9,10</sup> INTERGROWTH,<sup>11,12</sup> and WHO Fetal<sup>13,14</sup>; <sup>b</sup> Results were reported for the exact day (eg, 16.0 weeks) for the NICHD and WHO studies, while INTERGROWTH results were reported for completed weeks (eg, 16 weeks = 16 weeks 0 days to 16 weeks 6 days); <sup>c</sup> Note that NICHD and WHO Fetal calculated EFW from HC, AC, and FL using the Hadlock 1985 formula,<sup>26</sup> while INTERGROWTH created a new formula<sup>12</sup> based on only HC and AC.

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international studies, the NICHD study was designed to assess whether racial/ethnic fetal growth standards were needed, in recognition of the fact that because fetal size is commonly estimated from dimensions, particularly postcranial dimensions (ie, abdominal circumference [AC] and femur length [FL]), in which there are known differences in children and adults of differing racial/ethnic groups, separate standards might be necessary to capture optimal growth and more precisely estimate fetal weight.<sup>24,25</sup>

Highly statistically significant racial/ethnic differences in fetal growth were found, and by order of detection were as follows: humerus and femur lengths (beginning as early as 10 weeks), abdominal circumference (16 weeks), head circumference (21 weeks), and biparietal diameter (27 weeks) with

racial/ethnic differences continuing throughout gestation, so racial/ethnic-specific curves were derived.<sup>9</sup>

One of the continuing debates in designing and conducting an ultrasound or any physical growth study is how to select study subjects, and the terminology of reference vs standards. An ultrasound reference is a sample of pregnancies from a population and by definition contains high-risk pregnancies at risk for fetal growth restriction or overgrowth, including preexisting conditions and pregnancy complications.

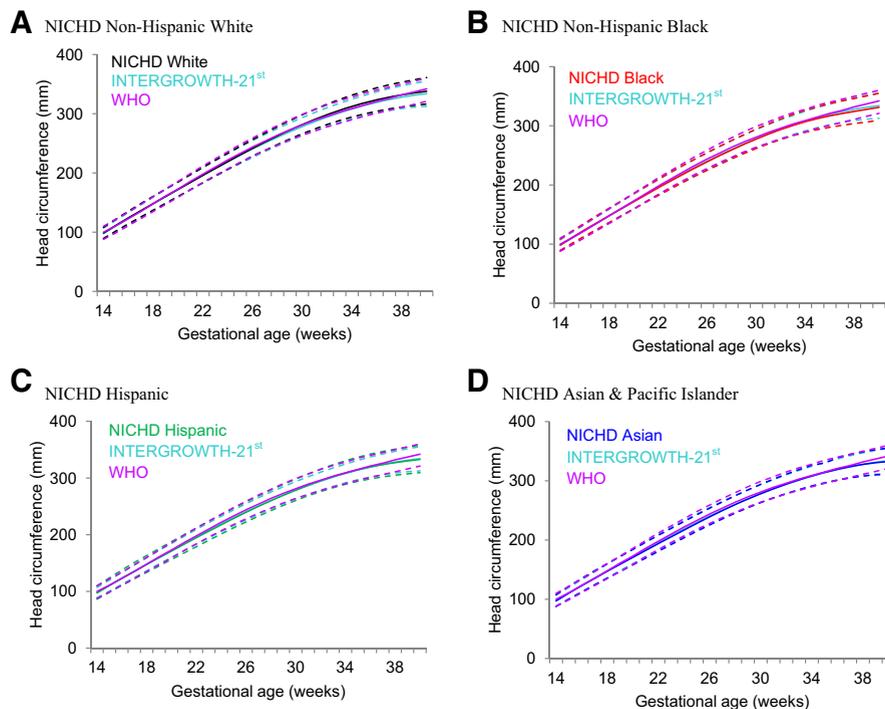
An ultrasound standard includes fetuses at low risk for growth disturbances, with the goal of describing how all fetuses should grow, as opposed to traditional reference charts that describe how some have grown at a given place and time. However, distinguishing the normal from abnormal fetal growth remains a

challenge, and the term standard in regard to fetal growth is controversial.

It is also important to note that because standards are variance restricted, their percentiles and interpretation are not the same as previous references. For example, the fifth percentile of a reference is not equivalent to the fifth percentile of a standard, in which fetuses are at lower risk for growth aberrations. It may be necessary to use more restrictive cut points, such as the 2.5th or 97.5th percentiles, for SGA or LGA, respectively.

All 3 studies selected healthy women who were positioned for optimal fetal growth and had a known last menstrual period, although the specific inclusion and exclusion criteria varied. The cohort profiles of main differences for the 3 studies are presented in Figure 1. One of the main differences was the racial/

**FIGURE 3**  
**Head circumference comparison among the 3 studies**



Distribution of head circumference, NICHD Fetal Growth Study—Singletons, INTERGROWTH-21st, and WHO Fetal. Estimated fifth, 50th, and 95th percentiles for head circumference are by race/ethnicity and gestation and study.

INTERGROWTH, INTERGROWTH-21st; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO Fetal, World Health Organization Multicentre Growth Reference Study.

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ethnic and country variation in women recruited by the 3 studies. The NICHD Study was conducted at 12 US sites (New York [2], New Jersey, Delaware, Rhode Island, Massachusetts, South Carolina, Alabama, Illinois, and California [3]), INTERGROWTH was completed in 8 countries (Brazil, China, India, Italy, Kenya, Oman, the United Kingdom, and the United States), and the WHO Fetal study in 10 countries (Argentina, Brazil, Democratic Republic of the Congo, Denmark, Egypt, France, Germany, India, Norway, and Thailand).

Another main difference was the exclusion of pregnancy complications and fetal factors such as congenital anomalies and stillbirth from the NICHD Study and INTERGROWTH, given the intention of creating standards; the NICHD defined additional a priori exclusion criteria or preterm delivery <37 weeks' gestation and karyotype

abnormalities, neither of which was excluded from INTERGROWTH. WHO Fetal did not exclude pregnancies with complications, with the rationale that they wanted their study to be more of a reference.<sup>13</sup>

The 3 studies used different statistical analytic approaches to model the fetal growth trajectories and calculate the corresponding percentiles. Both INTERGROWTH and NICHD assumed a parametric distribution of the fetal growth trajectories, under a linear mixed model, in which the methods used to create a smoothed mean trajectory differed slightly. After log transformation, the fetal growth data can be reasonably modeled by the linear mixed-effects models, assuming normally distributed random effects and error terms.

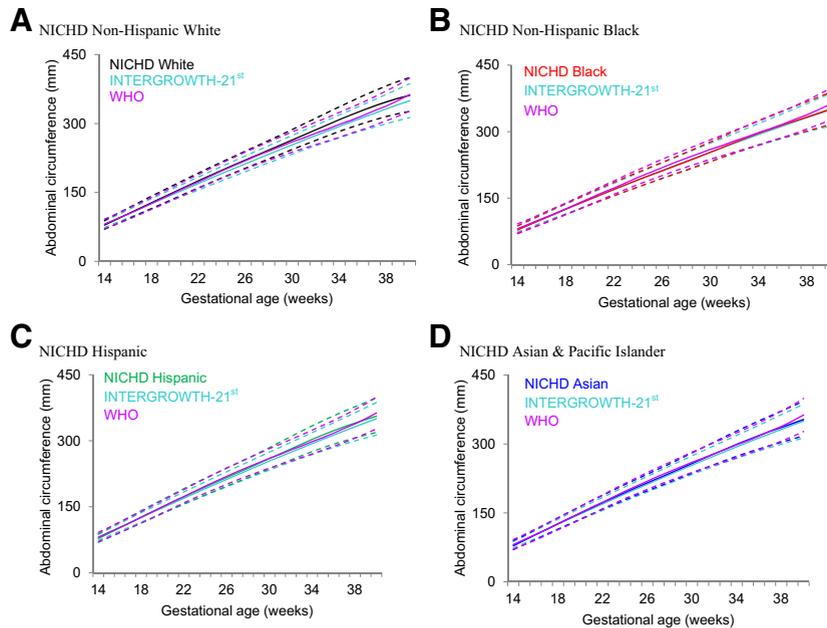
WHO Fetal used quantile regression to estimate percentiles directly and made somewhat fewer restrictive assumptions.

Despite different model assumptions and smoothing techniques, the approaches are flexible to capture the smooth fetal growth trajectories so that they should yield similar results when applied to the same fetal growth data set. In other words, any differences in results are unlikely due to the different methods used, although they have not been rigorously compared.

The analyses also adjusted for different covariates, which are not able to be summarized here because of the many analyses. For example, the WHO Fetal primary analyses did not adjust for country but secondary analyses adjusted for county and full interaction between country and gestational age.<sup>13</sup> Their EFW analyses adjusted for fetal sex, while the femur length analyses did not.

It is important to note that NICHD and WHO Fetal calculated EFW from HC, AC, and FL using the Hadlock 1985 formula,<sup>26</sup> while INTERGROWTH

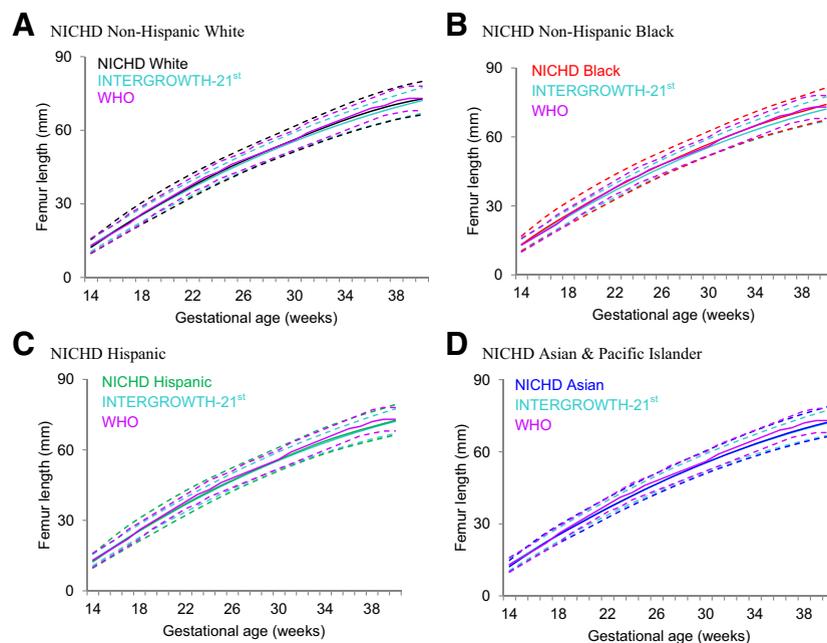
**FIGURE 4**  
Abdominal circumference comparison among the 3 studies



Distribution of head circumference, NICHD Fetal Growth Study—Singletons, INTERGROWTH-21st, and WHO Fetal. Estimated fifth, 50th, and 95th percentiles for abdominal circumference are by race/ethnicity and gestation and study.

INTERGROWTH, INTERGROWTH-21st; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO Fetal, World Health Organization Multicentre Growth Reference Study. Grantz. Fetal growth charts. *Am J Obstet Gynecol* 2018.

**FIGURE 5**  
Femur length comparison among the 3 studies



Distribution of head circumference, NICHD Fetal Growth Study—Singletons, INTERGROWTH-21st, and WHO Fetal. Estimated fifth, 50th, and 95th percentiles are for femur length by race/ethnicity and gestation and study.

INTERGROWTH, INTERGROWTH-21st; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO Fetal, World Health Organization Multicentre Growth Reference Study. Grantz. Fetal growth charts. *Am J Obstet Gynecol* 2018.

TABLE 2

The 50th percentiles for fetal anthropometric measurements by gestational age for the 3 studies<sup>a</sup>

Gestational age, wks <sup>b</sup>	Head circumference (mm) 50th percentiles					
	NICHD white	NICHD Hispanic	NICHD Asian	NICHD black	INTERGROWTH	WHO Fetal
24	219	218	217	218	219	222
25	231	229	228	229	230	233
26	242	240	239	239	241	244
27	253	250	250	250	251	254
28	263	260	260	259	260	264
29	273	270	269	269	270	273
30	282	279	278	278	278	281
31	290	287	287	286	287	289
32	299	295	295	294	294	296
33	306	303	302	301	302	303
34	313	309	308	307	308	309
35	318	315	314	312	314	315
36	324	320	320	317	319	321
37	328	324	324	321	324	326
38	332	327	328	324	328	332
39	335	330	331	328	331	337
40	338	333	333	331	334	342

INTERGROWTH, INTERGROWTH-21st; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO Fetal, World Health Organization Multicentre Growth Reference Study.

<sup>a</sup> The NICHD Fetal Growth Studies,<sup>9,10</sup> INTERGROWTH,<sup>11,12</sup> and WHO Fetal<sup>13,14</sup>; <sup>b</sup> Results were reported for the exact day (eg, 16.0 weeks) for the NICHD and WHO studies, while INTERGROWTH results were reported for completed weeks (eg, 16 weeks = 16 weeks 0 days to 16 weeks 6 days).

Grantz. Fetal growth charts. *Am J Obstet Gynecol* 2018.

created a new formula<sup>12</sup> based on only HC and AC:

INTERGROWTH: created a new

formula(based on HC and AC)<sup>12</sup>

$$\text{Log}(\text{EFW}) = 5.084820 - 54.06633 \times (\text{AC}/100)^3 - 95.80076 \times (\text{AC}/100)^3 \times \log(\text{AC}/100) + 3.136370 \times (\text{HC}/100)$$

NICHD and WHO Fetal: Hadlock 1985

(based on HC, AC, and FL)<sup>26</sup>

$$\text{Log}_{10} \text{ weight} = 1.326 - 0.00326 \text{ AC} \times \text{FL} + 0.0107 \text{ HC} + 0.0438 \text{ AC} + 0.158 \text{ FL}$$

Another slight difference among studies was the gestational ages that were included in the models to calculate EFW percentiles. Given the clinical

uncertainty associated with EFW before 15 weeks, NICHD originally did not intend to report EFW based on the actual measurements taken by sonographers between 10 and 14 weeks but to extrapolate data from the measurements taken at  $\geq 15$  weeks, but subsequently they reran the analysis using the actual measurements for EFW at 10–14 weeks and not the extrapolated data because other fetal parameters were presented for that gestational period.<sup>9</sup>

INTERGROWTH and WHO Fetal included EFW starting at 14 weeks of gestation but note that INTERGROWTH presented percentiles only starting at 22 weeks.<sup>12,13</sup> Results were reported for the exact day (eg, 16.0 weeks) for the NICHD and WHO Fetal studies, while INTERGROWTH results were reported for completed weeks (eg, 16 weeks = 16 weeks 0 days to 16 weeks 6 days).

### Study findings

EFW comparison among the 3 studies is presented in Figure 2 and Table 1 (no statistical testing was performed). EFW was plotted for the published estimated third, 50th, and 97th percentiles for INTERGROWTH and NICHD; WHO Fetal published the 2.5th and 97.5th percentiles to approximate  $\pm 2$  SD. Despite all 3 studies including women with a low-risk status, the percentiles for fetal biometrics and EFW varied among the studies.

Starting at 26 weeks of gestation and continuing through 40 weeks of gestation, the 50th percentile EFW for INTERGROWTH was smaller than the 50th percentile EFW for WHO Fetal and all racial/ethnic groups in NICHD. The 50th percentile EFW for WHO Fetal was between the NICHD EFW for white and Hispanic women. Specifically, at 39

**TABLE 3**  
**The 50th percentiles for fetal anthropometric measurements by gestational age for the 3 studies<sup>a</sup>**

Gestational age, wks <sup>b</sup>	Abdominal circumference (mm) 50th percentiles					
	NICHD white	NICHD Hispanic	NICHD Asian	NICHD black	INTERGROWTH	WHO Fetal
24	198	195	194	191	191	197
25	210	206	205	202	202	208
26	221	216	215	212	212	219
27	231	227	226	222	223	230
28	242	238	236	232	233	240
29	253	248	247	243	244	250
30	264	259	257	254	254	260
31	275	270	268	265	264	269
32	287	282	279	275	274	279
33	298	293	289	286	284	288
34	308	303	299	296	294	298
35	319	313	309	306	303	307
36	329	323	318	315	313	317
37	338	332	327	324	322	328
38	347	340	336	333	332	338
39	355	348	345	342	341	350
40	361	356	353	351	350	363

INTERGROWTH, INTERGROWTH-21st; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO Fetal, World Health Organization Multicentre Growth Reference Study.

<sup>a</sup> The NICHD Fetal Growth Studies,<sup>9,10</sup> INTERGROWTH,<sup>11,12</sup> and WHO Fetal<sup>13,14</sup>; <sup>b</sup> Results were reported for the exact day (eg, 16.0 weeks) for the NICHD and WHO Fetal studies, while INTERGROWTH results were reported for completed weeks (eg, 16 weeks = 16 weeks 0 days to 16 weeks 6 days).

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weeks, the 50th percentile for EFW was 3502 g for white, 3330 g for Hispanic, 3263 g for Asian, and 3256 g for black in the NICHD Study, compared with 3186 g for the INTERGROWTH and 3403 g for the WHO Fetal.

WHO Fetal found country-specific differences similar to NICHD findings for race/ethnicity. Quantile regression with country as a covariate, and interaction terms with gestational age, demonstrated statistically significant variation in fetal growth among countries. For example, at term the fifth percentile for Norway was 3200 g, while it was 2700 g for Egypt and 2800 g using the pooled data from all countries, differences that were also apparent in birthweight. While acknowledging these differences, WHO Fetal chose to present a pooled standard with the rationale that

the primary purpose of the study was to develop fetal standards to complement the WHO MGRS<sup>17</sup> for infants and children, aged 0–5 years.

Because differences in EFW are difficult to interpret in light of the different EFW formulas, we also compared fetal biometry among the 3 studies presented in Figures 3–5 and Tables 2–4. The differences in AC among studies paralleled that of EFW.

To directly compare the 2 EFW formulas, we used the NICHD data to calculate EFW using the Hadlock 1985 formula and INTERGROWTH formula (Figure 6). The INTERGROWTH EFW formula performed very close to the NICHD Asian racial/ethnic group but differed from the 3 other racial/ethnic groups. Additional application studies are needed in different

populations to assess whether the INTERGROWTH EFW formula outperforms the Hadlock or other EFW formulas in identifying fetuses with other signs of compromise.

We also compared the NICHD EFW standards with the Hadlock 1991 reference<sup>8</sup> that is commonly used in clinical practice in the United States (Figure 7 and Table 5). Interestingly, the NICHD white 50th percentile EFW was higher than the Hadlock reference, which also was in white women, but the other 3 NICHD racial/ethnic groups had EFW 50th percentiles lower than Hadlock. The population for Hadlock was limited to predominantly middle-class, white women without a history of maternal diseases associated with abnormal fetal growth and no congenital anomalies, so perhaps some of the differences between

TABLE 4

The 50th percentiles for fetal anthropometric measurements by gestational age for the 3 studies<sup>a</sup>

Gestational age, wks <sup>b</sup>	Femur length (mm) 50th percentiles					
	NICHD white	NICHD Hispanic	NICHD Asian	NICHD black	INTERGROWTH	WHO Fetal
24	43	42	42	43	42	43
25	45	45	44	46	44	46
26	48	47	47	48	47	48
27	50	49	49	50	49	50
28	52	52	51	53	51	52
29	54	54	53	55	53	54
30	56	56	56	57	56	56
31	58	58	58	59	58	59
32	60	60	60	61	60	61
33	62	62	61	63	61	63
34	64	64	63	65	63	65
35	66	66	65	67	65	67
36	68	67	67	68	66	69
37	69	69	68	70	68	70
38	71	70	70	71	69	72
39	72	71	71	73	71	73
40	73	73	72	74	72	73

INTERGROWTH, INTERGROWTH-21st; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO Fetal, World Health Organization Multicentre Growth Reference Study.

<sup>a</sup> The NICHD Fetal Growth Studies,<sup>9,10</sup> INTERGROWTH,<sup>11,12</sup> and WHO Fetal<sup>13,14</sup>; <sup>b</sup> Results were reported for the exact day (eg, 16.0 weeks) for the NICHD and WHO studies, while INTERGROWTH results were reported for completed weeks (eg, 16 weeks = 16 weeks 0 days to 16 weeks 6 days).

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the white women could be explained by the NICHD cohort having even more restrictions and a healthier cohort, thereby including fetuses growing under more optimal conditions. Alternatively, the NICHD cohort included overweight women (body mass index [BMI] 25.0–29.9 kg/m<sup>2</sup>) and only nonsmokers, and while body mass index was not reported by Hadlock et al,<sup>8</sup> the average BMI was lower in 1991 and smoking more common.<sup>27,28</sup> Increased maternal BMI is associated with larger birthweights, as is nonsmoking.<sup>3</sup> Nonetheless, perhaps the most important finding is that if the Hadlock 10th percentile is used to identify SGA in clinical practice, a larger percentage of fetuses from black, Hispanic, and Asian women would be labeled as SGA, while fewer fetuses from white women would be, compared with the NICHD standard.

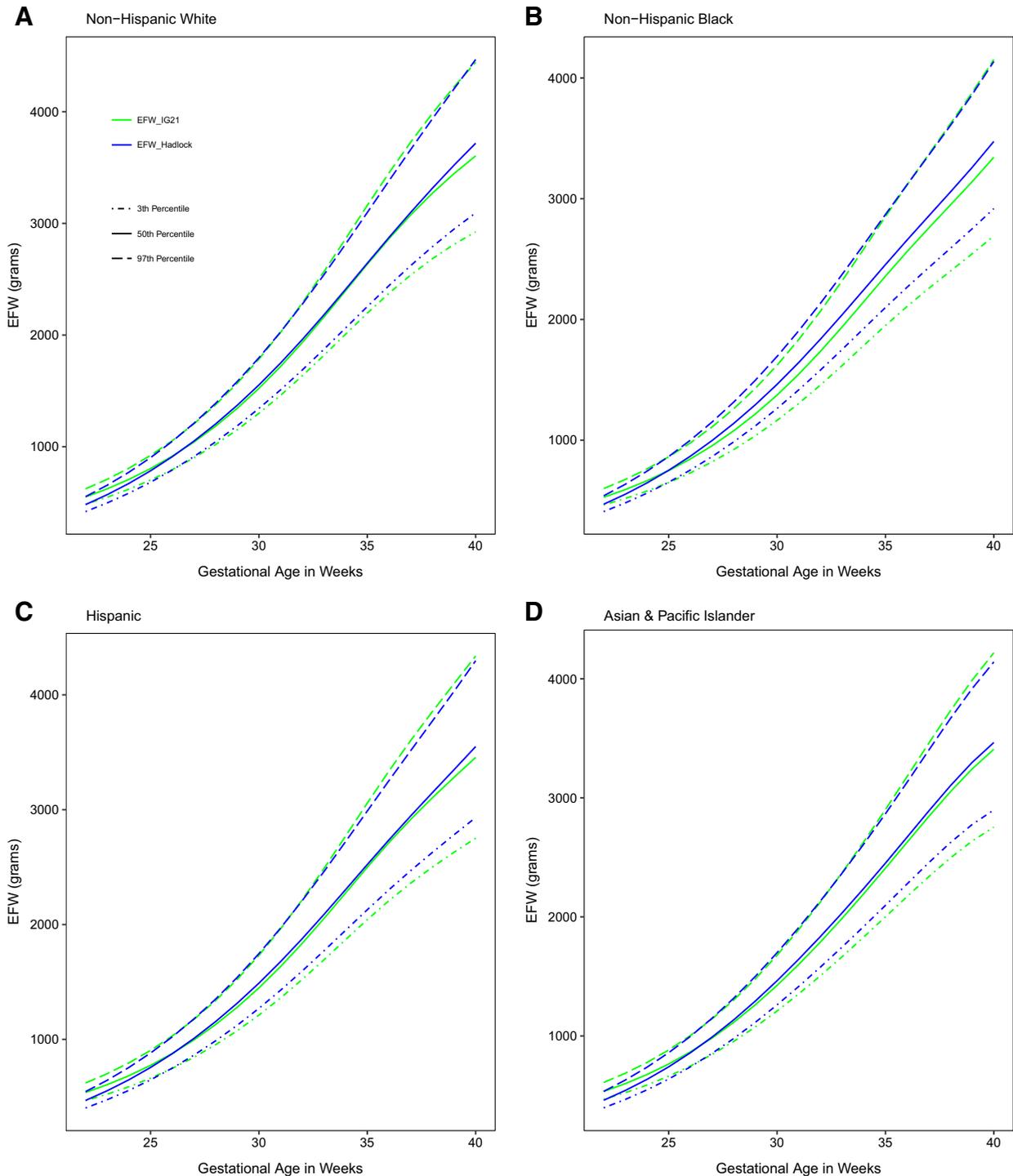
These findings are similar to the NICHD analysis, which found the percentage of fetuses classified as being below the fifth percentile for EFW when using the white standard and was substantially higher for black, Hispanic, and Asian fetuses, except for black fetuses less than 18 weeks' gestation. For example, at 35 weeks' gestation, 15%, 12%, and 14% of black, Hispanic, and Asian fetuses, respectively, would have been classified as below the fifth percentile based on the white standard.<sup>9,10</sup> Therefore, an additional 10% (15% minus 5%), 7% (12% minus 5%) and 9% (14% minus 5%) of black, Hispanic, and Asian fetuses, respectively, would be classified as extreme. Findings were also similar when a pooled standard was used. These findings are also similar to the potential for misclassification using the pooled standard in INTERGROWTH as previously demonstrated.

### Implications

Despite having extensive inclusion and exclusion criteria aimed at enrolling healthy women with uncomplicated pregnancies, allowing for optimal fetal growth, none of the 3 studies observed consistent standards for population subgroups. INTERGROWTH observed country-of-origin level differences in maternal height and weight as did WHO Fetal, while the NICHD observed both racial/ethnic differences in maternal size and fetal growth.

Collectively, these data argue for racial/ethnic fetal growth standards. This argument is supported by the fact that size and body proportion differences are known to occur across different races/ethnicities and countries for children and adults.<sup>29</sup> Mean stature for adult populations varies, and the ratio of sitting height to height, as a measure of

**FIGURE 6**  
**Comparison of estimated fetal weight formulas**



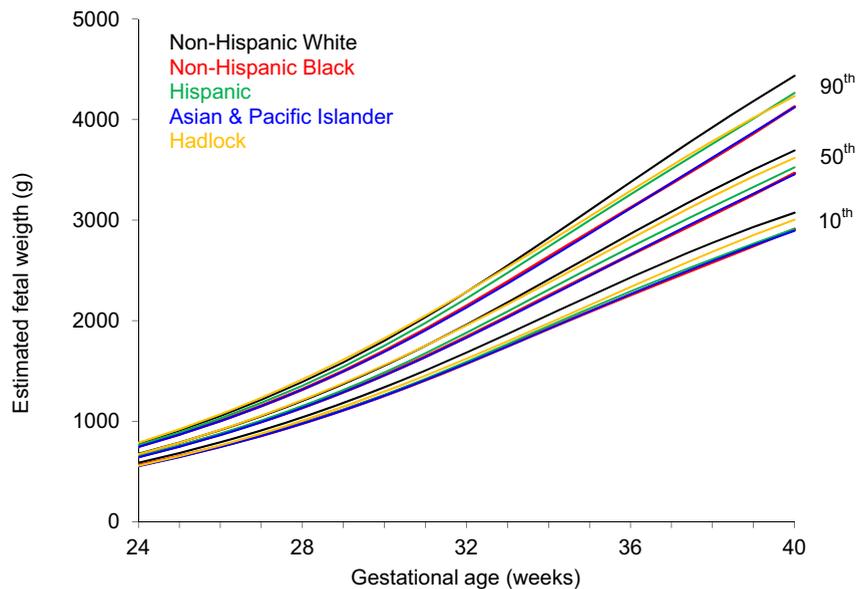
Using the NICHD Fetal Growth Study—Singleton standard data, we compared the 2 EFW formulas calculated using the Hadlock 1991 formula<sup>8</sup> from HC, AC, and FL (add reference) and INTERGROWTH formula based on HC and AC. EFW was calculated using the Hadlock formula:  $\text{Log}_{10} \text{ weight} = 1.326 - 0.00326 \text{ AC} \times \text{FL} + 0.0107 \text{ HC} + 0.0438 \text{ AC} + 0.158 \text{ FL}$  and INTERGROWTH-21<sup>st</sup> formula:  $\text{Log}(\text{EFW}) = 5.084820 - 54.06633 \times (\text{AC}/100)^3 - 95.80076 \times (\text{AC}/100)^3 \times \log(\text{AC}/100) + 3.136370 \times (\text{HC}/100)$ , and plotted across gestation.

AC, abdominal length; EFW, estimated fetal weight; FL, fetal length; HC, head circumference; INTERGROWTH, INTERGROWTH-21st; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO Fetal, World Health Organization Multicentre Growth Reference Study.

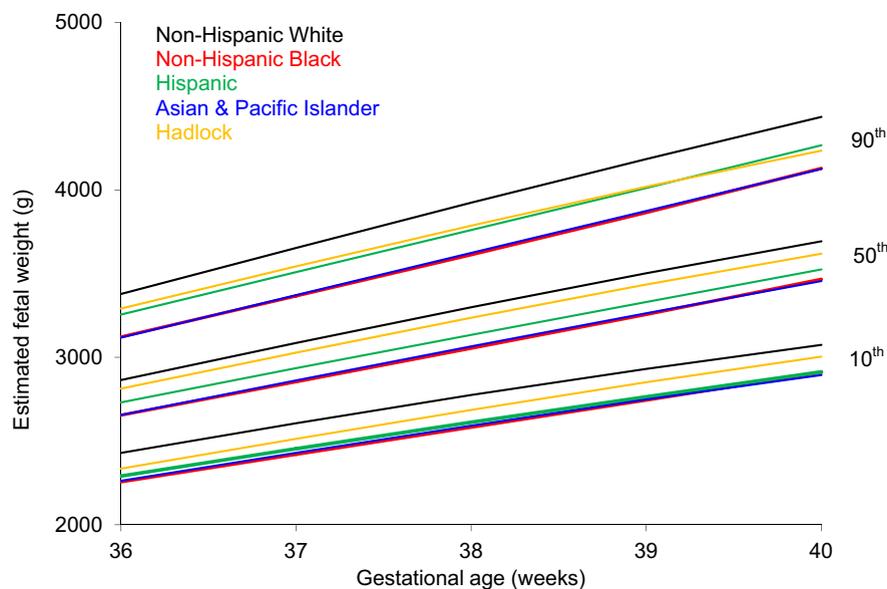
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**FIGURE 7**  
**Estimated fetal weight comparison between NICHD and Hadlock 1991**

**A** Standards for Estimated Fetal Weight 24-40 Weeks



**B** Standards for Estimated Fetal Weight 36-40 Weeks



Distribution of EFW by race/ethnicity and gestation, NICHD Fetal Growth Study—Singletons, and Hadlock 1991<sup>8</sup> for 24–40 weeks of gestation (A) and 36–40 weeks of gestation (B). Estimated third, 50th, and 97th percentiles are for fetal weight by study.

EFW, estimated fetal weight; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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body proportion, has also been shown to differ across 4 geographic areas including Australia/New Zealand/Papua New Guinea, Africa, Europe, and Asia.<sup>29</sup>

US blacks have been found to have a similar mean height compared with whites but are shorter in sitting height and longer in leg length.<sup>30</sup> Differences in body composition have also been found

among different Asian ethnic groups, in which for the same BMI, Asian Indians had the highest percentage body fat compared with Malaysians and then Chinese, all of which were higher than

**TABLE 5**  
**The 50th percentiles for estimated fetal weight by gestational age for the NICHD<sup>a</sup> and Hadlock<sup>b</sup> studies**

Gestational age, wks <sup>b</sup>	Estimated fetal weight (g) 50th percentiles				
	NICHD white	Hadlock	NICHD Hispanic	NICHD Asian	NICHD black
24	674	670	651	640	647
25	787	785	758	745	751
26	912	913	876	862	866
27	1050	1055	1007	990	994
28	1202	1210	1151	1132	1134
29	1369	1379	1311	1287	1289
30	1552	1559	1486	1456	1459
31	1749	1751	1676	1637	1642
32	1960	1953	1879	1830	1837
33	2180	2162	2090	2031	2040
34	2408	2377	2307	2238	2247
35	2637	2595	2521	2448	2452
36	2864	2813	2731	2656	2654
37	3086	3028	2935	2862	2854
38	3299	3236	3134	3065	3054
39	3502	3435	3330	3263	3256
40	3693	3619	3525	3455	3466

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

<sup>a</sup> The NICHD Fetal Growth Studies<sup>9,10</sup>; <sup>b</sup> Hadlock 1991.<sup>8</sup>

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whites.<sup>25</sup> This implies that the differences in fetal growth between the 2 international studies, INTERGROWTH and WHO Fetal, may be, to a large extent, an artifact of the international case mix (ie, maternal characteristics in the countries selected for the sample) and that, again, racial/ethnic-specific standards may improve the precision of fetal growth assessment.

In contrast to the assumption that all fetuses grow the same, INTERGROWTH found in their study of neonatal anthropometry for healthy, low-risk, term deliveries, which included 4321 neonates from the fetal growth cohort plus 20,486 newborns from a cross-sectional cohort, wide variation in birthweight and HC among the countries, consistent with differences in maternal size.<sup>31</sup> For example, birthweight ranged (mean [SD]) from 2.9 (0.4) kg in India to 3.5 (0.5) kg in the

United Kingdom and HC from 33.1 (1.1) cm to 34.5 (1.3) cm in India and the United Kingdom, respectively.

These differences in body size and proportion have been hypothesized to be explained by both environmental and genetic factors.<sup>29</sup> Using twin studies, heritability of birth size has been estimated to be up to 40%, with an intergenerational study finding that fetal genetic factors explained 31% of normal variation in birthweight and birth length, and maternal genetic factors explained 22% and 19% of normal variation in these measures, respectively.<sup>32,33</sup> Yet a complete knowledge of the determinants of fetal growth is not fully understood.<sup>33,34</sup> It has been hypothesized that the interaction of environmental influences and genetic factors on fetal growth display developmental plasticity that explain phenotypic differences in fetal growth and birthweight,

and under this paradigm, a universal fetal growth standard is elusive.<sup>35,36</sup>

In light of the many complexities underlying racial/ethnic definitions and the fact that it likely is not feasible to repeat these studies in individual populations across the world, it is important to understand how these study findings are applicable to individual populations. Ideally, a comparison of diagnostic accuracy, or misclassification rates, of SGA and LGA in relation to morbidity and mortality using different criteria is necessary to make recommendations and remains an important data gap. Identification for the appropriate percentiles is needed in local populations, depending on which standard is used.

### Conclusion

Three recently completed longitudinal observational cohort studies, NICHD,

INTERGROWTH and WHO Fetal,<sup>9-11,13,14</sup> have developed intrauterine fetal growth charts. The percentile cutpoints for SGA and LGA varied among the studies. For example, starting at 28 weeks of gestation and onward, the third percentile for INTERGROWTH was below all individual races/ethnicities in the NICHD study and the pooled sample in WHO Fetal study.

When applying these standards to pregnant women under clinical management, it is important to be aware that different percentages of SGA and LGA will be identified and that the percentiles are not interpreted in the same manner as a reference. It might be helpful to use all tools on the belt, in which a simple application could be created to calculate the percentiles (or SD scores) for comparison among the 3 charts.

Also, the assessment of fetal growth with a 1-time measurement (ie, EFW below the 10th percentile at a given gestational age) remains standard clinical practice, despite recognition that a single measurement can indicate only size. At least 2 measurements separated in time are needed to estimate a trajectory, and perhaps one of the greater contributions of these prospective studies will be the ability to estimate fetal growth velocity. Ultimately, it is knowledge about fetal growth in addition to other factors (signs of placental dysfunction or maternal complications) and clinical judgment that should trigger intervention.<sup>1</sup>

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**SUPPLEMENTAL TABLE 1****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Biparietal diameter, mm, white						
	Third	Fifth	10th	50th	90th	95th	97th
10	10.4	10.6	10.9	12.1	13.5	13.9	14.2
11	13.4	13.6	14.0	15.5	17.2	17.7	18.0
12	16.6	16.9	17.4	19.2	21.1	21.7	22.1
13	20.0	20.3	20.9	22.9	25.2	25.9	26.3
14	23.3	23.7	24.3	26.7	29.2	30.0	30.5
15	26.6	27.1	27.7	30.3	33.0	33.9	34.4
16	29.8	30.3	31.0	33.7	36.7	37.6	38.2
17	32.8	33.3	34.1	37.0	40.1	41.0	41.7
18	35.8	36.3	37.1	40.1	43.4	44.3	45.0
19	38.7	39.2	40.0	43.2	46.6	47.6	48.3
20	41.6	42.2	43.0	46.3	49.8	50.9	51.5
21	44.6	45.2	46.1	49.4	53.1	54.1	54.9
22	47.6	48.2	49.1	52.6	56.3	57.4	58.2
23	50.5	51.2	52.1	55.7	59.6	60.7	61.5
24	53.5	54.1	55.1	58.9	62.8	64.0	64.8
25	56.4	57.1	58.1	61.9	66.0	67.2	68.0
26	59.3	60.0	61.0	65.0	69.2	70.4	71.2
27	62.1	62.8	63.9	68.0	72.3	73.5	74.4
28	64.8	65.5	66.7	70.8	75.3	76.6	77.5
29	67.4	68.2	69.4	73.6	78.2	79.6	80.4
30	70.0	70.7	71.9	76.4	81.0	82.4	83.3
31	72.4	73.2	74.4	78.9	83.7	85.2	86.1
32	74.6	75.4	76.7	81.4	86.3	87.7	88.7
33	76.7	77.6	78.8	83.6	88.6	90.1	91.1
34	78.6	79.5	80.8	85.6	90.8	92.3	93.3
35	80.3	81.2	82.5	87.4	92.7	94.2	95.2
36	81.7	82.6	84.0	89.0	94.3	95.9	96.9
37	83.0	83.9	85.3	90.3	95.7	97.3	98.3
38	84.1	85.0	86.3	91.5	96.9	98.5	99.5
39	85.0	85.9	87.3	92.4	97.9	99.5	100.6
40	85.7	86.6	88.0	93.3	98.8	100.4	101.5

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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**SUPPLEMENTAL TABLE 2****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Head circumference, mm, white						
	Third	Fifth	10th	50th	90th	95th	97th
10	41.4	42.1	43.1	47.1	51.3	52.6	53.5
11	52.2	53.0	54.3	59.0	64.2	65.7	66.8
12	63.9	64.9	66.3	71.9	77.9	79.6	80.8
13	76.1	77.2	78.9	85.1	91.9	93.9	95.3
14	88.4	89.6	91.5	98.5	106.0	108.2	109.7
15	100.7	102.0	104.0	111.6	119.7	122.1	123.7
16	112.7	114.1	116.3	124.3	132.9	135.4	137.1
17	124.4	125.8	128.1	136.6	145.6	148.2	150.0
18	135.8	137.3	139.7	148.5	157.8	160.6	162.4
19	147.1	148.7	151.2	160.3	169.9	172.7	174.6
20	158.6	160.3	162.8	172.2	182.1	185.0	186.9
21	170.2	171.9	174.5	184.1	194.2	197.2	199.2
22	181.7	183.5	186.2	196.0	206.4	209.4	211.4
23	193.2	195.0	197.7	207.8	218.4	221.5	223.5
24	204.4	206.3	209.1	219.4	230.2	233.4	235.5
25	215.4	217.3	220.2	230.8	241.8	245.1	247.2
26	226.1	228.0	231.0	241.8	253.1	256.4	258.6
27	236.3	238.3	241.3	252.5	264.1	267.5	269.7
28	246.1	248.1	251.3	262.7	274.7	278.2	280.5
29	255.3	257.4	260.7	272.5	284.8	288.4	290.8
30	264.0	266.2	269.5	281.8	294.5	298.2	300.7
31	272.1	274.3	277.8	290.4	303.7	307.5	310.0
32	279.5	281.8	285.4	298.5	312.2	316.2	318.8
33	286.2	288.6	292.3	305.9	320.1	324.2	326.9
34	292.1	294.6	298.5	312.5	327.2	331.5	334.3
35	297.3	299.8	303.8	318.4	333.6	338.0	341.0
36	301.7	304.3	308.5	323.5	339.2	343.8	346.9
37	305.4	308.2	312.4	327.9	344.2	348.9	352.1
38	308.6	311.4	315.8	331.8	348.5	353.4	356.7
39	311.2	314.1	318.6	335.1	352.4	357.4	360.8
40	313.4	316.4	321.0	338.0	355.8	361.1	364.5

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 3****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Abdominal circumference, mm, white						
	Third	Fifth	10th	50th	90th	95th	97th
10	30.5	31.1	32.1	35.8	40.0	41.3	42.1
11	38.8	39.6	40.8	45.4	50.5	52.0	53.0
12	48.1	49.0	50.4	55.9	61.9	63.8	65.0
13	58.1	59.2	60.9	67.2	74.2	76.3	77.7
14	68.7	69.9	71.8	79.0	86.9	89.3	90.9
15	79.7	81.0	83.2	91.2	99.9	102.6	104.3
16	90.8	92.3	94.7	103.4	112.9	115.8	117.7
17	102.0	103.6	106.2	115.6	125.8	128.9	131.0
18	113.2	114.9	117.6	127.7	138.6	141.8	144.0
19	124.4	126.2	129.1	139.7	151.2	154.6	156.9
20	135.6	137.6	140.6	151.7	163.7	167.3	169.7
21	146.8	148.9	152.0	163.6	176.2	179.9	182.4
22	157.9	160.0	163.3	175.4	188.4	192.3	194.8
23	168.9	171.0	174.4	187.0	200.5	204.5	207.1
24	179.6	181.8	185.4	198.4	212.3	216.4	219.2
25	190.1	192.4	196.1	209.6	224.0	228.2	231.0
26	200.4	202.8	206.6	220.6	235.5	239.9	242.8
27	210.5	213.0	217.0	231.4	246.9	251.5	254.5
28	220.5	223.1	227.2	242.3	258.4	263.1	266.3
29	230.5	233.2	237.5	253.2	270.0	274.9	278.2
30	240.5	243.4	247.8	264.3	281.8	287.0	290.4
31	250.5	253.5	258.2	275.4	293.8	299.3	302.9
32	260.3	263.4	268.4	286.5	305.9	311.6	315.4
33	269.9	273.2	278.4	297.5	318.0	324.0	328.0
34	279.2	282.7	288.1	308.3	329.9	336.3	340.5
35	288.0	291.7	297.5	318.8	341.6	348.3	352.8
36	296.4	300.2	306.3	328.8	352.9	360.1	364.8
37	304.0	308.1	314.5	338.2	363.7	371.2	376.2
38	310.9	315.2	321.9	346.9	373.8	381.8	387.0
39	316.8	321.4	328.4	354.7	383.0	391.4	397.0
40	321.7	326.4	333.8	361.4	391.2	400.1	406.0

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 4****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Femur length, mm, white						
	Third	Fifth	10th	50th	90th	95th	97th
10	1.7	1.8	1.9	2.4	3.0	3.2	3.3
11	2.9	3.1	3.2	4.0	5.0	5.3	5.5
12	4.7	4.9	5.1	6.3	7.7	8.2	8.5
13	6.9	7.1	7.5	9.1	11.0	11.6	12.0
14	9.5	9.8	10.3	12.3	14.8	15.5	16.0
15	12.4	12.8	13.4	15.8	18.7	19.6	20.2
16	15.3	15.8	16.5	19.3	22.5	23.5	24.2
17	18.3	18.8	19.6	22.6	26.1	27.2	28.0
18	21.1	21.7	22.5	25.7	29.5	30.6	31.4
19	23.9	24.5	25.4	28.7	32.6	33.7	34.5
20	26.7	27.3	28.2	31.7	35.6	36.8	37.5
21	29.5	30.1	31.0	34.6	38.5	39.7	40.5
22	32.3	32.9	33.8	37.4	41.3	42.5	43.3
23	35.0	35.6	36.5	40.1	44.0	45.2	46.0
24	37.5	38.2	39.1	42.7	46.6	47.8	48.5
25	40.0	40.6	41.6	45.2	49.1	50.2	51.0
26	42.3	43.0	43.9	47.5	51.4	52.6	53.4
27	44.6	45.2	46.2	49.8	53.7	54.9	55.7
28	46.7	47.3	48.3	52.0	56.0	57.2	57.9
29	48.7	49.3	50.4	54.1	58.2	59.4	60.2
30	50.6	51.3	52.4	56.3	60.4	61.7	62.5
31	52.5	53.2	54.3	58.4	62.7	64.0	64.8
32	54.4	55.1	56.2	60.4	64.9	66.2	67.1
33	56.1	56.9	58.1	62.4	67.0	68.4	69.3
34	57.8	58.6	59.8	64.3	69.1	70.5	71.4
35	59.4	60.2	61.5	66.1	71.0	72.5	73.4
36	60.9	61.7	63.0	67.7	72.8	74.3	75.3
37	62.3	63.1	64.4	69.3	74.5	76.0	77.0
38	63.5	64.4	65.7	70.6	75.9	77.5	78.5
39	64.6	65.4	66.8	71.8	77.2	78.8	79.9
40	65.4	66.3	67.7	72.8	78.3	79.9	81.0

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

## SUPPLEMENTAL TABLE 5

## Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies

Gestational age, wks	Humerus length, mm, white						
	Third	Fifth	10th	50th	90th	95th	97th
10	1.8	1.9	2.0	2.5	3.1	3.3	3.4
11	3.2	3.3	3.5	4.2	5.2	5.5	5.7
12	5.0	5.2	5.5	6.6	8.0	8.5	8.8
13	7.4	7.6	8.0	9.6	11.5	12.1	12.5
14	10.1	10.4	10.9	12.9	15.3	16.0	16.5
15	13.0	13.3	14.0	16.3	19.1	20.0	20.6
16	15.9	16.3	17.0	19.7	22.8	23.8	24.5
17	18.6	19.1	19.9	22.8	26.2	27.2	27.9
18	21.2	21.7	22.5	25.6	29.1	30.2	30.9
19	23.7	24.2	25.0	28.2	31.8	32.9	33.6
20	26.1	26.6	27.5	30.8	34.4	35.5	36.2
21	28.5	29.1	29.9	33.2	36.9	38.0	38.7
22	30.9	31.4	32.3	35.6	39.2	40.3	41.1
23	33.1	33.7	34.6	37.9	41.5	42.6	43.3
24	35.3	35.9	36.7	40.0	43.6	44.7	45.4
25	37.3	37.9	38.8	42.1	45.7	46.8	47.5
26	39.3	39.8	40.7	44.0	47.6	48.7	49.4
27	41.1	41.6	42.5	45.9	49.5	50.6	51.3
28	42.8	43.4	44.3	47.6	51.3	52.4	53.1
29	44.4	45.0	45.9	49.4	53.1	54.2	54.9
30	45.9	46.5	47.5	51.0	54.8	55.9	56.7
31	47.4	48.0	49.0	52.6	56.5	57.7	58.4
32	48.8	49.5	50.5	54.2	58.2	59.4	60.2
33	50.2	50.9	51.9	55.7	59.8	61.1	61.9
34	51.5	52.2	53.2	57.2	61.4	62.7	63.5
35	52.7	53.4	54.5	58.6	62.9	64.2	65.1
36	53.9	54.6	55.8	59.9	64.4	65.7	66.6
37	55.0	55.7	56.9	61.1	65.7	67.0	67.9
38	56.0	56.7	57.9	62.2	66.9	68.3	69.2
39	56.8	57.6	58.8	63.2	67.9	69.3	70.2
40	57.4	58.2	59.4	63.9	68.7	70.2	71.1

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. Fetal growth charts. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 6****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Head circumference/abdominal circumference, white						
	Third	Fifth	10th	50th	90th	95th	97th
10	1.219	1.231	1.250	1.317	1.388	1.409	1.422
11	1.209	1.220	1.238	1.304	1.373	1.393	1.406
12	1.194	1.206	1.223	1.287	1.354	1.374	1.387
13	1.177	1.188	1.205	1.267	1.333	1.352	1.365
14	1.158	1.168	1.185	1.246	1.310	1.329	1.341
15	1.138	1.148	1.165	1.224	1.286	1.305	1.317
16	1.118	1.128	1.144	1.202	1.263	1.281	1.293
17	1.099	1.109	1.125	1.182	1.241	1.259	1.270
18	1.083	1.092	1.108	1.163	1.222	1.239	1.250
19	1.068	1.078	1.093	1.148	1.205	1.222	1.233
20	1.057	1.066	1.081	1.135	1.192	1.209	1.220
21	1.047	1.057	1.072	1.126	1.182	1.199	1.210
22	1.040	1.049	1.064	1.118	1.174	1.191	1.202
23	1.034	1.043	1.058	1.112	1.168	1.185	1.196
24	1.028	1.037	1.052	1.106	1.163	1.180	1.190
25	1.023	1.032	1.047	1.101	1.158	1.175	1.186
26	1.017	1.027	1.042	1.096	1.154	1.171	1.182
27	1.011	1.021	1.036	1.091	1.149	1.166	1.177
28	1.004	1.013	1.029	1.084	1.143	1.160	1.171
29	0.995	1.004	1.020	1.076	1.135	1.152	1.164
30	0.984	0.994	1.009	1.066	1.126	1.143	1.155
31	0.972	0.982	0.997	1.055	1.115	1.133	1.144
32	0.958	0.968	0.984	1.042	1.103	1.121	1.133
33	0.944	0.954	0.970	1.028	1.090	1.109	1.121
34	0.928	0.938	0.955	1.014	1.077	1.095	1.108
35	0.912	0.922	0.939	0.999	1.063	1.082	1.094
36	0.896	0.906	0.923	0.984	1.049	1.068	1.081
37	0.880	0.890	0.907	0.969	1.036	1.055	1.068
38	0.865	0.876	0.893	0.956	1.024	1.044	1.057
39	0.851	0.862	0.880	0.945	1.014	1.035	1.048
40	0.839	0.851	0.869	0.935	1.007	1.029	1.043

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 7****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Biparietal diameter, mm, black						
	Third	Fifth	10th	50th	90th	95th	97th
10	10.3	10.5	10.8	11.9	13.3	13.7	13.9
11	13.3	13.5	13.9	15.4	17.0	17.5	17.8
12	16.5	16.8	17.3	19.1	21.0	21.6	22.0
13	19.9	20.3	20.8	22.8	25.1	25.7	26.2
14	23.3	23.7	24.3	26.6	29.1	29.8	30.3
15	26.5	27.0	27.6	30.2	32.9	33.7	34.3
16	29.7	30.1	30.9	33.6	36.5	37.4	38.0
17	32.7	33.1	33.9	36.8	39.9	40.8	41.5
18	35.6	36.1	36.9	39.9	43.2	44.2	44.8
19	38.5	39.0	39.9	43.0	46.5	47.5	48.1
20	41.4	42.0	42.9	46.2	49.7	50.8	51.5
21	44.4	45.0	45.9	49.3	53.0	54.1	54.8
22	47.3	47.9	48.9	52.5	56.3	57.4	58.2
23	50.2	50.8	51.8	55.5	59.5	60.7	61.5
24	53.1	53.7	54.8	58.6	62.7	63.9	64.7
25	55.9	56.6	57.6	61.6	65.8	67.0	67.9
26	58.6	59.3	60.4	64.5	68.8	70.1	71.0
27	61.3	62.0	63.1	67.3	71.8	73.1	74.0
28	63.8	64.6	65.8	70.1	74.7	76.1	77.0
29	66.4	67.1	68.3	72.8	77.5	78.9	79.9
30	68.8	69.6	70.8	75.4	80.2	81.7	82.6
31	71.0	71.8	73.1	77.8	82.8	84.3	85.3
32	73.1	74.0	75.3	80.1	85.2	86.7	87.7
33	75.0	75.9	77.2	82.1	87.4	88.9	89.9
34	76.7	77.6	79.0	84.0	89.3	90.8	91.9
35	78.2	79.1	80.4	85.5	90.9	92.5	93.6
36	79.4	80.3	81.7	86.8	92.3	93.9	95.0
37	80.5	81.4	82.8	88.0	93.5	95.2	96.2
38	81.4	82.3	83.8	89.1	94.7	96.3	97.4
39	82.4	83.3	84.7	90.1	95.8	97.4	98.5
40	83.3	84.2	85.7	91.2	97.0	98.7	99.8

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 8****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Head circumference, mm, black						
	Third	Fifth	10th	50th	90th	95th	97th
10	40.6	41.2	42.2	46.1	50.3	51.6	52.4
11	51.7	52.5	53.7	58.4	63.6	65.1	66.1
12	63.6	64.5	66.0	71.6	77.6	79.4	80.6
13	75.9	77.0	78.7	85.1	92.0	94.0	95.4
14	88.3	89.5	91.4	98.5	106.2	108.5	110.0
15	100.5	101.8	103.9	111.6	120.0	122.4	124.1
16	112.3	113.7	116.0	124.2	133.1	135.7	137.5
17	123.7	125.3	127.6	136.4	145.7	148.5	150.3
18	135.0	136.6	139.1	148.2	157.9	160.8	162.7
19	146.3	148.0	150.6	160.0	170.1	173.1	175.0
20	157.7	159.4	162.1	171.9	182.3	185.3	187.3
21	169.1	170.9	173.6	183.7	194.3	197.4	199.5
22	180.4	182.2	185.0	195.3	206.2	209.4	211.5
23	191.5	193.3	196.2	206.8	217.9	221.2	223.3
24	202.3	204.2	207.2	218.0	229.3	232.7	234.8
25	212.8	214.8	217.8	228.9	240.4	243.8	246.1
26	223.0	225.0	228.1	239.4	251.2	254.7	257.0
27	232.8	234.8	238.0	249.6	261.7	265.2	267.5
28	242.2	244.3	247.5	259.4	271.7	275.4	277.7
29	251.1	253.3	256.6	268.8	281.5	285.2	287.6
30	259.6	261.8	265.2	277.7	290.8	294.6	297.1
31	267.4	269.7	273.2	286.1	299.6	303.5	306.1
32	274.6	276.9	280.6	293.9	307.8	311.9	314.6
33	280.9	283.4	287.2	300.9	315.3	319.5	322.3
34	286.5	289.0	292.9	307.1	322.0	326.3	329.2
35	291.1	293.7	297.7	312.4	327.8	332.3	335.2
36	294.9	297.6	301.7	316.9	332.8	337.5	340.5
37	298.1	300.9	305.2	320.8	337.3	342.1	345.3
38	300.9	303.8	308.2	324.4	341.4	346.4	349.7
39	303.5	306.5	311.1	327.8	345.4	350.6	354.0
40	306.1	309.2	313.9	331.3	349.7	355.1	358.6

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Grantz. Fetal growth charts. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 9****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Abdominal circumference, mm, black						
	Third	Fifth	10th	50th	90th	95th	97th
10	30.8	31.4	32.4	35.9	39.7	40.9	41.7
11	39.2	39.9	41.1	45.3	50.0	51.4	52.4
12	48.5	49.3	50.6	55.7	61.2	62.9	64.0
13	58.4	59.4	60.9	66.8	73.1	75.1	76.3
14	68.8	69.9	71.6	78.2	85.5	87.6	89.0
15	79.4	80.7	82.6	89.9	97.9	100.3	101.9
16	90.1	91.5	93.7	101.7	110.4	113.0	114.7
17	100.9	102.3	104.7	113.3	122.7	125.5	127.3
18	111.5	113.1	115.6	124.9	134.8	137.8	139.8
19	122.2	123.9	126.6	136.4	146.9	150.1	152.2
20	132.8	134.6	137.4	147.8	158.9	162.2	164.4
21	143.2	145.1	148.1	159.0	170.7	174.2	176.5
22	153.5	155.4	158.5	170.0	182.3	185.9	188.3
23	163.4	165.5	168.8	180.8	193.6	197.4	199.9
24	173.1	175.3	178.7	191.3	204.7	208.7	211.4
25	182.6	184.9	188.5	201.6	215.7	219.9	222.6
26	191.9	194.3	198.1	211.8	226.6	230.9	233.8
27	201.2	203.7	207.6	222.0	237.5	242.0	245.1
28	210.4	213.0	217.2	232.3	248.5	253.3	256.5
29	219.8	222.6	226.9	242.8	259.9	264.9	268.3
30	229.4	232.3	236.8	253.6	271.6	276.9	280.4
31	239.0	242.1	246.8	264.5	283.5	289.1	292.8
32	248.5	251.7	256.8	275.4	295.4	301.3	305.3
33	257.8	261.2	266.5	286.1	307.2	313.4	317.6
34	266.6	270.2	275.8	296.4	318.6	325.2	329.5
35	274.9	278.6	284.5	306.1	329.4	336.4	340.9
36	282.7	286.6	292.7	315.4	339.8	347.1	351.9
37	290.1	294.2	300.6	324.3	349.9	357.5	362.5
38	297.3	301.6	308.3	333.1	359.9	367.9	373.1
39	304.6	309.1	316.0	342.0	370.1	378.5	384.0
40	312.0	316.7	324.0	351.3	380.9	389.7	395.6

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 10****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Femur length, mm, black						
	Third	Fifth	10th	50th	90th	95th	97th
10	1.7	1.8	1.9	2.4	3.1	3.3	3.4
11	3.1	3.2	3.4	4.2	5.3	5.7	5.9
12	4.9	5.1	5.4	6.7	8.3	8.8	9.2
13	7.3	7.6	8.0	9.8	12.0	12.7	13.1
14	10.0	10.4	10.9	13.2	16.0	16.9	17.4
15	12.9	13.3	14.0	16.8	20.0	21.1	21.8
16	15.8	16.3	17.1	20.2	23.9	25.1	25.8
17	18.6	19.2	20.0	23.4	27.4	28.7	29.5
18	21.3	21.9	22.8	26.4	30.6	31.9	32.8
19	24.0	24.6	25.6	29.4	33.7	35.0	35.9
20	26.7	27.4	28.4	32.3	36.7	38.0	38.9
21	29.5	30.1	31.2	35.1	39.6	40.9	41.8
22	32.2	32.8	33.9	37.9	42.3	43.7	44.6
23	34.8	35.5	36.6	40.6	45.0	46.3	47.2
24	37.4	38.1	39.2	43.2	47.6	48.9	49.8
25	39.9	40.6	41.7	45.6	50.0	51.3	52.2
26	42.3	43.0	44.1	48.0	52.3	53.6	54.5
27	44.6	45.3	46.4	50.3	54.6	55.9	56.7
28	46.8	47.5	48.6	52.5	56.8	58.1	58.9
29	49.0	49.7	50.7	54.7	59.0	60.3	61.1
30	51.1	51.8	52.9	56.9	61.2	62.5	63.4
31	53.1	53.8	54.9	59.0	63.4	64.7	65.6
32	55.0	55.7	56.9	61.1	65.6	66.9	67.8
33	56.8	57.6	58.7	63.0	67.7	69.0	69.9
34	58.5	59.3	60.5	64.9	69.6	71.0	72.0
35	60.0	60.8	62.1	66.6	71.5	72.9	73.9
36	61.4	62.2	63.5	68.2	73.2	74.7	75.6
37	62.8	63.6	64.9	69.7	74.8	76.3	77.3
38	64.0	64.9	66.2	71.1	76.4	77.9	79.0
39	65.3	66.2	67.5	72.6	78.0	79.6	80.6
40	66.5	67.4	68.8	74.1	79.7	81.4	82.5

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 11****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Humerus length, mm, black						
	Third	Fifth	10th	50th	90th	95th	97th
10	2.0	2.1	2.2	2.6	3.1	3.2	3.3
11	3.6	3.7	3.9	4.5	5.3	5.6	5.7
12	5.7	5.9	6.1	7.1	8.3	8.6	8.9
13	8.3	8.6	8.9	10.3	11.8	12.3	12.6
14	11.3	11.6	12.0	13.7	15.7	16.3	16.7
15	14.4	14.7	15.2	17.2	19.5	20.2	20.7
16	17.3	17.7	18.3	20.6	23.1	23.9	24.4
17	20.1	20.5	21.1	23.6	26.3	27.1	27.7
18	22.6	23.1	23.7	26.3	29.2	30.0	30.6
19	25.1	25.5	26.2	28.9	31.9	32.8	33.4
20	27.5	28.0	28.7	31.5	34.5	35.4	36.0
21	29.8	30.3	31.1	33.9	37.0	38.0	38.6
22	32.0	32.5	33.3	36.3	39.5	40.4	41.1
23	34.2	34.7	35.5	38.5	41.8	42.8	43.5
24	36.1	36.7	37.5	40.7	44.0	45.1	45.7
25	38.0	38.6	39.4	42.7	46.2	47.2	47.9
26	39.7	40.3	41.2	44.6	48.2	49.3	50.0
27	41.4	42.0	42.9	46.4	50.1	51.2	52.0
28	42.9	43.6	44.5	48.1	52.0	53.2	53.9
29	44.4	45.1	46.1	49.8	53.9	55.1	55.9
30	45.9	46.6	47.6	51.5	55.7	56.9	57.8
31	47.4	48.1	49.2	53.2	57.5	58.8	59.6
32	48.8	49.5	50.6	54.7	59.2	60.5	61.4
33	50.1	50.9	52.0	56.2	60.8	62.2	63.1
34	51.4	52.2	53.3	57.7	62.3	63.7	64.7
35	52.6	53.3	54.5	59.0	63.7	65.2	66.1
36	53.7	54.5	55.7	60.2	65.0	66.5	67.5
37	54.8	55.5	56.8	61.4	66.3	67.8	68.8
38	55.8	56.6	57.9	62.6	67.7	69.2	70.2
39	56.9	57.8	59.1	63.9	69.1	70.7	71.7
40	58.1	59.0	60.3	65.4	70.9	72.5	73.6

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 12****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Head circumference/abdominal circumference, black						
	Third	Fifth	10th	50th	90th	95th	97th
10	1.182	1.195	1.215	1.291	1.372	1.395	1.411
11	1.183	1.196	1.217	1.291	1.371	1.394	1.409
12	1.178	1.191	1.211	1.285	1.363	1.386	1.401
13	1.167	1.180	1.200	1.273	1.350	1.372	1.387
14	1.153	1.166	1.185	1.257	1.332	1.355	1.369
15	1.137	1.149	1.169	1.239	1.313	1.335	1.350
16	1.120	1.132	1.151	1.220	1.293	1.315	1.329
17	1.104	1.116	1.134	1.202	1.274	1.295	1.309
18	1.089	1.101	1.119	1.186	1.257	1.278	1.292
19	1.077	1.088	1.107	1.173	1.244	1.265	1.278
20	1.067	1.079	1.097	1.163	1.233	1.254	1.268
21	1.060	1.071	1.089	1.155	1.226	1.246	1.260
22	1.053	1.065	1.083	1.149	1.219	1.240	1.254
23	1.048	1.060	1.078	1.144	1.215	1.235	1.249
24	1.043	1.055	1.073	1.140	1.210	1.231	1.245
25	1.038	1.050	1.068	1.135	1.206	1.227	1.241
26	1.033	1.045	1.063	1.130	1.201	1.223	1.236
27	1.026	1.038	1.056	1.124	1.196	1.217	1.231
28	1.018	1.030	1.048	1.116	1.188	1.210	1.224
29	1.008	1.020	1.038	1.106	1.179	1.200	1.214
30	0.996	1.008	1.026	1.095	1.167	1.189	1.203
31	0.982	0.994	1.013	1.081	1.154	1.176	1.190
32	0.968	0.980	0.998	1.067	1.140	1.162	1.176
33	0.952	0.964	0.983	1.052	1.125	1.147	1.161
34	0.937	0.949	0.967	1.036	1.110	1.131	1.146
35	0.921	0.933	0.951	1.020	1.094	1.116	1.130
36	0.905	0.917	0.935	1.005	1.079	1.101	1.115
37	0.889	0.901	0.919	0.989	1.064	1.086	1.101
38	0.873	0.885	0.904	0.974	1.049	1.072	1.087
39	0.857	0.869	0.888	0.959	1.035	1.058	1.073
40	0.841	0.854	0.873	0.945	1.022	1.045	1.060

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**SUPPLEMENTAL TABLE 13****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Biparietal diameter, mm, Hispanic						
	Third	Fifth	10th	50th	90th	95th	97th
10	10.2	10.4	10.7	12.0	13.5	13.9	14.2
11	13.1	13.3	13.8	15.4	17.1	17.7	18.0
12	16.2	16.5	17.0	18.9	21.1	21.7	22.1
13	19.5	19.8	20.4	22.6	25.1	25.8	26.3
14	22.7	23.2	23.8	26.3	29.1	29.9	30.4
15	26.0	26.4	27.2	29.9	32.9	33.8	34.4
16	29.1	29.6	30.4	33.3	36.6	37.5	38.2
17	32.1	32.6	33.4	36.6	40.0	41.0	41.7
18	35.0	35.5	36.4	39.7	43.3	44.4	45.1
19	37.8	38.4	39.4	42.8	46.5	47.6	48.4
20	40.8	41.4	42.3	45.9	49.8	50.9	51.7
21	43.7	44.4	45.4	49.1	53.1	54.2	55.0
22	46.7	47.4	48.4	52.2	56.3	57.5	58.4
23	49.7	50.4	51.4	55.3	59.6	60.8	61.7
24	52.6	53.3	54.4	58.5	62.8	64.1	64.9
25	55.6	56.3	57.4	61.5	65.9	67.3	68.1
26	58.4	59.1	60.3	64.5	69.0	70.4	71.3
27	61.2	62.0	63.1	67.5	72.1	73.4	74.3
28	63.9	64.7	65.9	70.3	75.0	76.4	77.3
29	66.5	67.3	68.5	73.0	77.8	79.3	80.2
30	69.0	69.8	71.0	75.7	80.6	82.0	83.0
31	71.3	72.2	73.4	78.1	83.1	84.6	85.6
32	73.5	74.4	75.7	80.4	85.5	87.0	88.0
33	75.5	76.4	77.7	82.6	87.8	89.3	90.3
34	77.3	78.2	79.5	84.5	89.8	91.3	92.3
35	78.8	79.7	81.1	86.1	91.5	93.1	94.1
36	80.2	81.1	82.5	87.6	93.0	94.6	95.7
37	81.3	82.2	83.6	88.8	94.4	96.0	97.1
38	82.4	83.3	84.7	90.0	95.6	97.3	98.4
39	83.3	84.3	85.7	91.1	96.8	98.5	99.6
40	84.3	85.3	86.8	92.2	98.0	99.8	100.9

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 14****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Head circumference, mm, Hispanic						
	Third	Fifth	10th	50th	90th	95th	97th
10	38.7	39.5	40.7	45.5	50.8	52.4	53.5
11	49.2	50.2	51.7	57.5	64.0	65.9	67.2
12	60.7	61.8	63.6	70.5	78.0	80.3	81.8
13	72.7	74.0	76.1	83.9	92.5	95.1	96.8
14	84.9	86.4	88.7	97.4	106.9	109.8	111.7
15	97.0	98.6	101.2	110.6	121.0	124.1	126.2
16	108.9	110.6	113.3	123.5	134.5	137.8	140.0
17	120.4	122.2	125.1	135.8	147.4	150.9	153.2
18	131.7	133.6	136.6	147.7	159.8	163.3	165.7
19	142.9	144.9	148.0	159.5	171.9	175.6	178.0
20	154.2	156.2	159.4	171.3	184.0	187.8	190.2
21	165.6	167.7	170.9	183.1	196.1	199.9	202.4
22	176.9	179.0	182.4	194.8	208.0	211.9	214.5
23	188.1	190.3	193.8	206.4	219.8	223.8	226.4
24	199.2	201.4	204.9	217.7	231.3	235.4	238.0
25	209.9	212.2	215.8	228.8	242.6	246.7	249.4
26	220.4	222.7	226.3	239.6	253.6	257.7	260.4
27	230.5	232.8	236.5	250.0	264.2	268.4	271.1
28	240.1	242.5	246.3	260.0	274.4	278.7	281.4
29	249.3	251.8	255.6	269.5	284.3	288.6	291.4
30	258.0	260.5	264.4	278.7	293.7	298.1	301.0
31	266.1	268.6	272.6	287.2	302.6	307.1	310.1
32	273.5	276.1	280.2	295.2	310.9	315.6	318.6
33	280.2	282.9	287.1	302.5	318.6	323.4	326.5
34	286.1	288.9	293.2	309.0	325.6	330.4	333.6
35	291.2	294.1	298.5	314.6	331.7	336.7	339.9
36	295.5	298.4	302.9	319.5	337.0	342.1	345.5
37	299.0	302.0	306.6	323.6	341.6	346.8	350.3
38	301.9	305.0	309.7	327.1	345.5	350.9	354.4
39	304.3	307.4	312.3	330.1	348.9	354.5	358.1
40	306.2	309.4	314.4	332.7	352.0	357.7	361.4

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 15****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Abdominal circumference, mm, Hispanic						
	Third	Fifth	10th	50th	90th	95th	97th
10	30.5	31.2	32.2	35.9	40.1	41.3	42.2
11	38.7	39.4	40.6	45.2	50.3	51.8	52.8
12	47.7	48.6	50.1	55.5	61.5	63.4	64.6
13	57.5	58.5	60.2	66.6	73.6	75.7	77.1
14	67.8	69.0	70.9	78.2	86.2	88.6	90.2
15	78.5	79.8	82.0	90.1	99.1	101.8	103.5
16	89.3	90.8	93.2	102.2	112.0	115.0	116.9
17	100.2	101.9	104.5	114.2	124.9	128.1	130.2
18	111.1	112.9	115.7	126.2	137.6	141.0	143.3
19	121.9	123.8	126.8	138.0	150.2	153.8	156.2
20	132.8	134.8	138.0	149.8	162.6	166.4	169.0
21	143.5	145.6	149.0	161.4	174.9	178.9	181.6
22	154.0	156.3	159.8	172.8	186.9	191.1	193.9
23	164.4	166.7	170.4	184.0	198.7	203.1	206.0
24	174.5	177.0	180.8	195.0	210.2	214.8	217.8
25	184.5	187.0	191.0	205.7	221.6	226.3	229.4
26	194.2	196.9	201.0	216.3	232.8	237.7	240.9
27	203.9	206.6	211.0	226.9	244.0	249.1	252.4
28	213.5	216.4	220.9	237.5	255.3	260.5	264.0
29	223.3	226.3	231.0	248.2	266.8	272.3	275.9
30	233.2	236.3	241.2	259.3	278.7	284.4	288.2
31	243.1	246.4	251.5	270.4	290.8	296.8	300.8
32	253.0	256.4	261.8	281.6	303.0	309.3	313.5
33	262.5	266.1	271.8	292.6	315.0	321.7	326.1
34	271.7	275.5	281.4	303.2	326.8	333.8	338.5
35	280.2	284.2	290.4	313.3	338.1	345.4	350.3
36	288.0	292.2	298.7	322.7	348.8	356.5	361.6
37	295.2	299.6	306.4	331.6	358.9	367.1	372.5
38	301.9	306.4	313.6	340.0	368.7	377.2	382.9
39	308.1	312.9	320.3	348.0	378.1	387.1	393.1
40	313.9	318.9	326.7	355.8	387.5	397.0	403.3

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 16****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Femur length, mm, Hispanic						
	Third	Fifth	10th	50th	90th	95th	97th
10	1.7	1.7	1.9	2.4	3.0	3.2	3.4
11	2.9	3.0	3.2	4.0	5.1	5.4	5.6
12	4.6	4.8	5.1	6.3	7.9	8.3	8.7
13	6.8	7.1	7.5	9.2	11.2	11.9	12.3
14	9.4	9.7	10.2	12.4	15.0	15.8	16.4
15	12.2	12.6	13.2	15.8	18.9	19.9	20.6
16	15.0	15.5	16.3	19.2	22.8	23.9	24.6
17	17.9	18.4	19.2	22.5	26.3	27.6	28.4
18	20.6	21.2	22.1	25.6	29.6	30.9	31.7
19	23.3	23.9	24.9	28.5	32.7	34.0	34.9
20	26.1	26.7	27.7	31.4	35.7	37.0	37.9
21	28.9	29.5	30.5	34.3	38.6	39.9	40.8
22	31.6	32.2	33.2	37.1	41.4	42.7	43.5
23	34.3	34.9	35.9	39.8	44.0	45.3	46.1
24	36.9	37.5	38.5	42.3	46.5	47.8	48.6
25	39.4	40.0	41.0	44.8	48.9	50.1	51.0
26	41.7	42.4	43.4	47.1	51.2	52.4	53.2
27	44.0	44.7	45.7	49.4	53.4	54.6	55.4
28	46.2	46.9	47.9	51.6	55.5	56.7	57.5
29	48.3	49.0	50.0	53.7	57.7	58.9	59.7
30	50.4	51.1	52.1	55.8	59.9	61.1	61.9
31	52.4	53.1	54.1	58.0	62.1	63.3	64.1
32	54.3	55.0	56.1	60.0	64.2	65.4	66.3
33	56.1	56.8	57.9	62.0	66.3	67.6	68.4
34	57.8	58.5	59.6	63.8	68.2	69.6	70.4
35	59.3	60.0	61.2	65.5	70.1	71.4	72.3
36	60.7	61.4	62.6	67.0	71.7	73.1	74.0
37	61.9	62.7	63.9	68.5	73.3	74.7	75.7
38	63.1	63.9	65.2	69.8	74.8	76.2	77.2
39	64.3	65.1	66.4	71.2	76.2	77.7	78.7
40	65.5	66.3	67.6	72.5	77.8	79.3	80.4

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 17****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Humerus length, mm, Hispanic						
	Third	Fifth	10th	50th	90th	95th	97th
10	1.7	1.8	1.9	2.4	3.0	3.2	3.3
11	3.1	3.2	3.4	4.2	5.1	5.5	5.7
12	4.9	5.1	5.4	6.6	8.1	8.5	8.8
13	7.3	7.5	8.0	9.6	11.6	12.2	12.6
14	10.0	10.3	10.9	12.9	15.4	16.2	16.8
15	12.9	13.3	13.9	16.4	19.3	20.2	20.9
16	15.7	16.1	16.9	19.7	23.0	24.0	24.7
17	18.4	18.9	19.7	22.7	26.2	27.3	28.0
18	20.9	21.4	22.2	25.4	29.1	30.2	30.9
19	23.3	23.8	24.7	28.0	31.7	32.8	33.6
20	25.7	26.3	27.1	30.5	34.2	35.3	36.1
21	28.1	28.7	29.5	32.9	36.6	37.8	38.5
22	30.4	31.0	31.9	35.2	39.0	40.1	40.8
23	32.7	33.2	34.1	37.5	41.2	42.3	43.0
24	34.8	35.4	36.3	39.6	43.3	44.4	45.1
25	36.9	37.4	38.3	41.6	45.2	46.3	47.0
26	38.8	39.4	40.2	43.6	47.1	48.2	48.9
27	40.6	41.2	42.1	45.4	49.0	50.0	50.7
28	42.3	42.9	43.8	47.1	50.7	51.8	52.5
29	43.9	44.5	45.4	48.8	52.5	53.6	54.3
30	45.4	46.0	47.0	50.4	54.2	55.3	56.0
31	46.9	47.5	48.5	52.0	55.9	57.0	57.8
32	48.2	48.9	49.9	53.6	57.5	58.7	59.5
33	49.5	50.2	51.2	55.0	59.1	60.3	61.1
34	50.8	51.5	52.5	56.4	60.6	61.9	62.7
35	51.9	52.6	53.7	57.7	62.1	63.3	64.2
36	53.0	53.7	54.8	58.9	63.4	64.7	65.6
37	54.0	54.7	55.9	60.1	64.6	66.0	66.9
38	54.9	55.7	56.8	61.1	65.8	67.2	68.1
39	55.8	56.6	57.8	62.2	66.9	68.3	69.2
40	56.6	57.4	58.6	63.1	68.0	69.4	70.4

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 18****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Head circumference/abdominal circumference, Hispanic						
	Third	Fifth	10th	50th	90th	95th	97th
10	1.142	1.158	1.184	1.278	1.379	1.409	1.429
11	1.148	1.163	1.188	1.278	1.375	1.404	1.424
12	1.146	1.161	1.184	1.272	1.365	1.393	1.412
13	1.138	1.153	1.176	1.260	1.350	1.377	1.394
14	1.127	1.141	1.163	1.244	1.331	1.356	1.373
15	1.113	1.127	1.148	1.226	1.309	1.333	1.350
16	1.098	1.111	1.132	1.206	1.286	1.310	1.325
17	1.083	1.096	1.115	1.187	1.264	1.287	1.301
18	1.069	1.081	1.100	1.170	1.244	1.265	1.280
19	1.057	1.069	1.088	1.155	1.227	1.248	1.262
20	1.048	1.060	1.078	1.143	1.213	1.234	1.247
21	1.041	1.052	1.070	1.134	1.203	1.223	1.236
22	1.035	1.046	1.064	1.127	1.195	1.215	1.228
23	1.031	1.042	1.059	1.122	1.188	1.208	1.221
24	1.026	1.037	1.054	1.117	1.183	1.203	1.216
25	1.022	1.033	1.050	1.112	1.179	1.198	1.211
26	1.017	1.028	1.045	1.108	1.174	1.194	1.206
27	1.011	1.022	1.039	1.102	1.169	1.188	1.201
28	1.003	1.014	1.031	1.095	1.162	1.182	1.195
29	0.993	1.004	1.022	1.086	1.154	1.174	1.187
30	0.981	0.992	1.010	1.074	1.143	1.163	1.177
31	0.968	0.979	0.997	1.062	1.131	1.152	1.165
32	0.953	0.964	0.982	1.048	1.118	1.139	1.153
33	0.937	0.949	0.967	1.034	1.105	1.126	1.140
34	0.921	0.933	0.951	1.019	1.091	1.113	1.127
35	0.905	0.917	0.936	1.004	1.078	1.100	1.114
36	0.890	0.902	0.920	0.990	1.065	1.087	1.102
37	0.874	0.886	0.905	0.976	1.052	1.075	1.090
38	0.859	0.871	0.891	0.963	1.041	1.064	1.079
39	0.844	0.857	0.877	0.950	1.030	1.053	1.069
40	0.830	0.842	0.863	0.938	1.019	1.044	1.060

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 19****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Biparietal diameter, mm, Asian						
	Third	Fifth	10th	50th	90th	95th	97th
10	10.0	10.2	10.5	11.8	13.3	13.8	14.1
11	12.9	13.2	13.6	15.2	17.0	17.6	17.9
12	16.1	16.4	16.9	18.9	21.0	21.7	22.1
13	19.4	19.8	20.4	22.6	25.1	25.9	26.4
14	22.8	23.2	23.9	26.4	29.2	30.1	30.6
15	26.1	26.6	27.3	30.1	33.1	34.1	34.7
16	29.3	29.8	30.6	33.6	36.9	37.8	38.5
17	32.4	32.9	33.7	36.9	40.3	41.4	42.1
18	35.3	35.8	36.7	40.0	43.6	44.7	45.4
19	38.1	38.7	39.6	43.1	46.8	47.9	48.6
20	41.0	41.6	42.6	46.1	49.9	51.1	51.8
21	44.0	44.6	45.6	49.2	53.1	54.3	55.1
22	47.0	47.6	48.6	52.3	56.4	57.6	58.4
23	49.9	50.6	51.6	55.5	59.6	60.8	61.6
24	52.9	53.6	54.7	58.6	62.8	64.1	64.9
25	55.9	56.6	57.7	61.7	66.0	67.3	68.1
26	58.8	59.5	60.6	64.7	69.1	70.4	71.3
27	61.6	62.4	63.5	67.7	72.2	73.5	74.3
28	64.4	65.1	66.3	70.6	75.1	76.5	77.3
29	67.0	67.8	69.0	73.3	78.0	79.3	80.2
30	69.5	70.3	71.5	76.0	80.7	82.1	83.0
31	71.9	72.7	73.9	78.5	83.3	84.7	85.6
32	74.1	74.9	76.2	80.8	85.7	87.2	88.1
33	76.2	77.0	78.3	83.0	88.0	89.5	90.4
34	78.0	78.9	80.2	85.0	90.1	91.6	92.6
35	79.7	80.6	81.9	86.8	92.0	93.5	94.5
36	81.2	82.1	83.5	88.5	93.7	95.3	96.3
37	82.6	83.5	84.8	89.9	95.3	96.8	97.9
38	83.7	84.6	86.0	91.1	96.6	98.2	99.2
39	84.6	85.5	87.0	92.1	97.7	99.3	100.3
40	85.3	86.2	87.7	93.0	98.6	100.2	101.3

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 20****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Head circumference, mm, Asian						
	Third	Fifth	10th	50th	90th	95th	97th
10	39.9	40.6	41.7	45.9	50.4	51.8	52.7
11	50.6	51.5	52.8	57.8	63.3	64.9	66.0
12	62.2	63.2	64.8	70.6	77.0	78.9	80.2
13	74.3	75.4	77.2	83.9	91.1	93.3	94.7
14	86.6	87.9	89.9	97.3	105.3	107.7	109.3
15	98.9	100.3	102.5	110.5	119.2	121.8	123.5
16	110.9	112.4	114.7	123.3	132.6	135.3	137.1
17	122.6	124.2	126.6	135.6	145.3	148.1	150.0
18	133.9	135.6	138.1	147.5	157.4	160.4	162.3
19	145.1	146.8	149.4	159.0	169.3	172.3	174.3
20	156.4	158.1	160.8	170.7	181.1	184.2	186.2
21	167.8	169.6	172.3	182.4	193.0	196.1	198.1
22	179.3	181.1	183.9	194.0	204.8	208.0	210.0
23	190.7	192.5	195.3	205.7	216.6	219.7	221.8
24	201.9	203.8	206.6	217.1	228.1	231.3	233.5
25	212.9	214.8	217.7	228.3	239.5	242.7	244.9
26	223.6	225.5	228.4	239.2	250.5	253.8	256.0
27	233.8	235.8	238.8	249.7	261.2	264.5	266.7
28	243.6	245.6	248.6	259.8	271.5	274.9	277.1
29	252.8	254.8	257.9	269.3	281.3	284.7	287.0
30	261.3	263.4	266.6	278.3	290.6	294.1	296.5
31	269.2	271.3	274.7	286.7	299.3	303.0	305.4
32	276.4	278.6	282.1	294.5	307.5	311.3	313.8
33	282.9	285.2	288.8	301.7	315.2	319.1	321.7
34	288.8	291.2	294.9	308.3	322.3	326.4	329.0
35	294.0	296.5	300.3	314.2	328.8	333.0	335.8
36	298.5	301.1	305.0	319.5	334.7	339.1	342.0
37	302.3	304.9	309.0	324.1	339.8	344.4	347.5
38	305.2	308.0	312.2	327.8	344.2	349.0	352.1
39	307.3	310.1	314.5	330.7	347.7	352.7	355.9
40	308.3	311.3	315.9	332.6	350.3	355.4	358.8

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

## SUPPLEMENTAL TABLE 21

## Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies

Gestational age, wks	Abdominal circumference, mm, Asian						
	Third	Fifth	10th	50th	90th	95th	97th
10	30.9	31.5	32.4	36.0	40.0	41.2	42.0
11	39.2	39.9	41.1	45.4	50.1	51.6	52.5
12	48.4	49.2	50.6	55.7	61.3	63.0	64.1
13	58.3	59.3	60.9	66.8	73.3	75.2	76.5
14	68.8	70.0	71.8	78.4	85.7	87.9	89.4
15	79.7	81.0	83.0	90.4	98.5	100.9	102.5
16	90.8	92.2	94.3	102.5	111.3	113.9	115.6
17	101.8	103.3	105.7	114.5	123.9	126.8	128.6
18	112.9	114.5	117.0	126.3	136.4	139.4	141.4
19	123.8	125.5	128.1	138.0	148.7	151.8	153.9
20	134.6	136.4	139.2	149.6	160.8	164.1	166.3
21	145.3	147.2	150.2	161.1	172.8	176.3	178.6
22	155.9	157.9	161.0	172.4	184.6	188.2	190.6
23	166.2	168.3	171.5	183.4	196.2	200.0	202.5
24	176.3	178.4	181.8	194.3	207.6	211.5	214.1
25	186.1	188.4	191.9	204.9	218.8	222.9	225.6
26	195.7	198.1	201.8	215.4	229.9	234.2	237.0
27	205.2	207.6	211.5	225.8	241.0	245.5	248.4
28	214.5	217.1	221.2	236.1	252.1	256.8	259.9
29	223.9	226.7	230.9	246.7	263.4	268.4	271.7
30	233.4	236.3	240.8	257.3	275.0	280.3	283.7
31	242.8	245.8	250.5	268.0	286.7	292.3	295.9
32	252.0	255.2	260.2	278.7	298.5	304.3	308.2
33	260.9	264.3	269.6	289.1	310.1	316.3	320.4
34	269.5	273.1	278.7	299.3	321.4	328.0	332.3
35	277.6	281.4	287.3	309.0	332.4	339.3	343.9
36	285.2	289.2	295.4	318.3	342.9	350.3	355.1
37	292.4	296.6	303.1	327.2	353.2	360.9	366.0
38	299.4	303.7	310.6	335.9	363.2	371.4	376.8
39	306.2	310.7	317.9	344.5	373.4	382.0	387.7
40	312.9	317.7	325.2	353.3	383.8	392.9	398.9

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. Fetal growth charts. *Am J Obstet Gynecol* 2018.

## SUPPLEMENTAL TABLE 22

## Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies

Gestational age, wks	Femur length, mm, Asian						
	Third	Fifth	10th	50th	90th	95th	97th
10	1.6	1.7	1.8	2.2	2.6	2.8	2.9
11	2.9	3.0	3.2	3.8	4.6	4.8	5.0
12	4.7	4.9	5.1	6.1	7.2	7.6	7.8
13	7.0	7.3	7.6	8.9	10.5	11.0	11.3
14	9.8	10.0	10.5	12.2	14.2	14.8	15.3
15	12.7	13.1	13.6	15.7	18.1	18.8	19.3
16	15.7	16.1	16.8	19.1	21.9	22.7	23.3
17	18.7	19.1	19.8	22.4	25.4	26.3	26.9
18	21.4	21.9	22.6	25.4	28.5	29.5	30.1
19	24.1	24.6	25.3	28.2	31.5	32.4	33.1
20	26.7	27.2	28.0	31.0	34.3	35.3	36.0
21	29.4	29.9	30.7	33.8	37.1	38.1	38.8
22	32.1	32.6	33.4	36.5	39.9	40.9	41.5
23	34.7	35.2	36.0	39.1	42.5	43.6	44.2
24	37.2	37.7	38.6	41.7	45.1	46.2	46.8
25	39.6	40.2	41.0	44.2	47.7	48.7	49.4
26	42.0	42.5	43.4	46.6	50.1	51.2	51.8
27	44.2	44.8	45.7	49.0	52.5	53.5	54.2
28	46.3	46.9	47.8	51.2	54.8	55.9	56.6
29	48.4	49.0	49.9	53.4	57.1	58.2	58.9
30	50.4	51.0	51.9	55.5	59.3	60.4	61.1
31	52.3	52.9	53.9	57.5	61.4	62.6	63.4
32	54.1	54.7	55.7	59.5	63.5	64.7	65.5
33	55.8	56.5	57.5	61.4	65.6	66.8	67.6
34	57.5	58.1	59.2	63.2	67.5	68.8	69.6
35	59.0	59.8	60.9	65.0	69.4	70.7	71.5
36	60.6	61.3	62.4	66.7	71.2	72.5	73.4
37	62.0	62.7	63.9	68.3	72.9	74.2	75.1
38	63.3	64.1	65.3	69.7	74.5	75.9	76.8
39	64.5	65.3	66.6	71.1	76.0	77.4	78.3
40	65.6	66.4	67.7	72.4	77.4	78.9	79.9

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

## SUPPLEMENTAL TABLE 23

## Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies

Gestational age, wks	Humerus length, mm, Asian						
	Third	Fifth	10th	50th	90th	95th	97th
10	1.8	1.8	1.9	2.3	2.8	3.0	3.1
11	3.2	3.3	3.4	4.1	4.8	5.1	5.2
12	5.1	5.2	5.5	6.4	7.6	7.9	8.2
13	7.5	7.7	8.1	9.4	10.9	11.4	11.7
14	10.3	10.6	11.0	12.7	14.6	15.2	15.6
15	13.3	13.6	14.1	16.1	18.4	19.1	19.6
16	16.2	16.6	17.2	19.4	22.0	22.8	23.3
17	19.0	19.4	20.0	22.5	25.3	26.1	26.7
18	21.5	22.0	22.6	25.2	28.1	29.0	29.5
19	23.9	24.3	25.0	27.7	30.6	31.5	32.1
20	26.2	26.6	27.4	30.0	33.0	33.9	34.5
21	28.5	28.9	29.7	32.4	35.4	36.3	36.9
22	30.7	31.2	31.9	34.7	37.7	38.6	39.2
23	32.9	33.4	34.1	36.9	39.9	40.8	41.4
24	35.0	35.5	36.3	39.1	42.1	43.0	43.6
25	37.0	37.5	38.3	41.2	44.2	45.2	45.8
26	38.9	39.4	40.2	43.1	46.3	47.2	47.8
27	40.6	41.2	42.0	45.0	48.3	49.2	49.9
28	42.3	42.8	43.7	46.8	50.1	51.1	51.8
29	43.8	44.4	45.3	48.5	52.0	53.0	53.7
30	45.3	45.8	46.8	50.1	53.7	54.8	55.5
31	46.6	47.2	48.2	51.6	55.4	56.5	57.2
32	47.9	48.5	49.5	53.1	57.0	58.2	58.9
33	49.1	49.8	50.8	54.5	58.6	59.7	60.5
34	50.3	51.0	52.0	55.9	60.1	61.3	62.1
35	51.5	52.2	53.3	57.3	61.5	62.8	63.6
36	52.7	53.4	54.5	58.6	63.0	64.3	65.1
37	53.8	54.5	55.6	59.8	64.3	65.6	66.5
38	54.8	55.5	56.7	60.9	65.5	66.9	67.8
39	55.7	56.4	57.6	61.9	66.6	68.0	68.9
40	56.4	57.1	58.3	62.7	67.5	68.9	69.8

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. Fetal growth charts. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 24****Race/ethnic-specific percentiles for fetal anthropometric measurements by gestational age, NICHD fetal growth studies**

Gestational age, wks	Head circumference/abdominal circumference, Asian						
	Third	Fifth	10th	50th	90th	95th	97th
10	1.198	1.209	1.227	1.293	1.362	1.382	1.395
11	1.192	1.203	1.221	1.284	1.350	1.370	1.383
12	1.181	1.192	1.209	1.271	1.336	1.355	1.368
13	1.167	1.178	1.194	1.255	1.319	1.338	1.351
14	1.150	1.161	1.177	1.238	1.301	1.319	1.332
15	1.132	1.143	1.159	1.219	1.281	1.300	1.312
16	1.115	1.125	1.141	1.200	1.262	1.280	1.292
17	1.098	1.108	1.124	1.182	1.243	1.261	1.273
18	1.082	1.092	1.108	1.166	1.226	1.244	1.256
19	1.068	1.078	1.094	1.152	1.212	1.230	1.242
20	1.057	1.068	1.083	1.141	1.201	1.219	1.231
21	1.049	1.059	1.075	1.133	1.194	1.211	1.223
22	1.042	1.053	1.069	1.127	1.188	1.206	1.218
23	1.037	1.047	1.063	1.122	1.184	1.202	1.214
24	1.032	1.043	1.059	1.118	1.181	1.199	1.211
25	1.028	1.038	1.055	1.115	1.178	1.197	1.209
26	1.023	1.033	1.050	1.111	1.175	1.194	1.207
27	1.017	1.028	1.044	1.106	1.171	1.191	1.203
28	1.009	1.020	1.037	1.100	1.166	1.185	1.198
29	1.000	1.011	1.028	1.091	1.159	1.178	1.191
30	0.989	1.000	1.017	1.081	1.149	1.169	1.182
31	0.976	0.987	1.005	1.069	1.138	1.158	1.172
32	0.962	0.974	0.991	1.057	1.126	1.147	1.160
33	0.948	0.959	0.977	1.043	1.114	1.135	1.148
34	0.933	0.945	0.963	1.030	1.101	1.123	1.136
35	0.919	0.931	0.949	1.017	1.089	1.111	1.125
36	0.905	0.916	0.935	1.004	1.077	1.099	1.114
37	0.890	0.902	0.921	0.990	1.065	1.087	1.102
38	0.874	0.886	0.905	0.976	1.052	1.075	1.090
39	0.857	0.870	0.889	0.960	1.038	1.061	1.076
40	0.839	0.851	0.871	0.943	1.022	1.046	1.061

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Grantz. *Fetal growth charts. Am J Obstet Gynecol* 2018.

## SUPPLEMENTAL TABLE 25

## Race/ethnic-specific percentiles for estimated fetal weight by gestational age, NICHD fetal growth studies

Gestational age, wks	Estimated fetal weight, g, white						
	Third	Fifth	10th	50th	90th	95th	97th
10	29	30	31	36	41	43	44
11	36	37	38	44	51	53	54
12	45	46	48	55	63	66	68
13	56	58	60	69	80	83	85
14	71	73	76	88	101	105	108
15	90	93	96	111	127	133	136
16	114	117	122	140	161	167	172
17	143	147	153	176	202	211	216
18	179	184	191	220	253	263	270
19	222	227	237	272	313	325	334
20	271	278	289	333	383	398	409
21	328	336	350	403	464	482	495
22	393	403	419	483	556	578	593
3	466	478	497	573	660	687	705
24	547	562	585	674	777	808	830
25	638	655	682	787	907	944	970
26	739	758	790	912	1052	1096	1125
27	849	872	908	1050	1213	1263	1297
28	970	997	1039	1202	1390	1449	1488
29	1103	1133	1181	1369	1586	1653	1699
30	1247	1282	1337	1552	1801	1878	1930
31	1402	1441	1504	1749	2034	2123	2182
32	1566	1610	1682	1960	2284	2385	2453
33	1736	1786	1866	2180	2547	2662	2739
34	1909	1965	2055	2408	2821	2950	3037
35	2081	2144	2244	2637	3099	3244	3342
36	2248	2318	2429	2864	3378	3539	3648
37	2408	2484	2606	3086	3653	3832	3953
38	2559	2642	2774	3299	3923	4120	4254
39	2697	2787	2931	3502	4184	4401	4547
40	2821	2918	3074	3693	4436	4673	4833

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Estimated fetal weight was calculated from head circumference, abdominal circumference, and femur length using the Hadlock 1985 formula (Hadlock<sup>26</sup>). Reproduced, with permission, from Buck Louis and Grewal J.<sup>10</sup>

Grantz. Fetal growth charts. *Am J Obstet Gynecol* 2018.

SUPPLEMENTAL TABLE 26

## Race/ethnic-specific percentiles for estimated fetal weight by gestational age, NICHD fetal growth studies

Gestational age, wks	Estimated fetal weight, g, black						
	Third	Fifth	10th	50th	90th	95th	97th
10	29	30	31	36	41	43	44
11	36	37	39	44	51	53	55
12	46	47	49	56	64	67	69
13	57	59	61	71	81	84	87
14	73	75	78	89	103	107	110
15	92	94	98	113	130	135	138
16	115	118	123	142	163	170	174
17	144	148	154	177	204	213	218
18	179	184	191	220	254	264	271
19	220	225	235	270	311	324	333
20	266	273	285	328	378	394	404
21	320	328	342	394	455	474	486
22	380	390	406	469	541	564	579
23	448	460	479	553	639	665	683
24	523	537	560	647	748	779	800
25	606	623	649	751	869	906	930
26	699	718	748	866	1003	1046	1075
27	800	822	857	994	1152	1201	1234
28	912	937	977	1134	1316	1373	1411
29	1034	1063	1110	1289	1498	1563	1607
30	1168	1201	1254	1459	1697	1772	1822
31	1313	1350	1410	1642	1914	1998	2055
32	1465	1507	1575	1837	2144	2240	2304
33	1623	1670	1746	2040	2385	2493	2566
34	1782	1835	1919	2247	2632	2752	2833
35	1939	1997	2089	2452	2878	3012	3102
36	2091	2155	2256	2654	3122	3270	3369
37	2240	2309	2420	2854	3366	3527	3636
38	2387	2462	2582	3054	3612	3788	3907
39	2533	2614	2744	3256	3864	4056	4186
40	2681	2769	2910	3466	4128	4338	4480

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Estimated fetal weight was calculated from head circumference, abdominal circumference, and femur length using the Hadlock 1985 formula (Hadlock<sup>26</sup>). Reproduced, with permission, from Buck Louis and Grewal J.<sup>10</sup>

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## SUPPLEMENTAL TABLE 27

## Race/ethnic-specific percentiles for estimated fetal weight by gestational age, NICHD fetal growth studies

Gestational age, wks	Estimated fetal weight, g, Hispanic						
	Third	Fifth	10th	50th	90th	95th	97th
10	28	29	30	35	41	42	44
11	35	36	38	44	50	53	54
12	44	45	47	55	63	66	68
13	55	57	59	69	80	83	86
14	70	72	75	87	101	105	108
15	88	90	94	110	128	133	137
16	111	114	119	138	161	168	173
17	139	143	149	174	202	211	217
18	173	178	186	216	252	263	271
19	213	219	229	267	311	325	334
20	260	267	279	325	380	397	408
21	313	322	336	393	458	479	493
22	373	384	401	469	548	572	589
23	441	454	474	555	649	678	698
24	517	532	556	651	761	796	820
25	601	618	647	758	887	928	955
26	694	714	747	876	1027	1074	1106
27	796	820	858	1007	1182	1236	1273
28	909	936	980	1151	1352	1416	1458
29	1033	1064	1114	1311	1542	1614	1663
30	1169	1204	1262	1486	1750	1833	1889
31	1315	1356	1421	1676	1977	2072	2136
32	1471	1517	1590	1879	2220	2327	2400
33	1632	1684	1766	2090	2474	2596	2677
34	1795	1853	1945	2307	2736	2872	2963
35	1956	2019	2121	2521	2998	3148	3250
36	2110	2179	2291	2731	3255	3422	3534
37	2257	2333	2454	2935	3509	3691	3815
38	2398	2480	2612	3134	3760	3959	4094
39	2534	2622	2764	3330	4011	4228	4375
40	2665	2760	2913	3525	4266	4503	4664

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Estimated fetal weight was calculated from head circumference, abdominal circumference, and femur length using the Hadlock 1985 formula (Hadlock<sup>26</sup>). Reproduced, with permission, from Buck Louis and Grewal.<sup>10</sup>

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**SUPPLEMENTAL TABLE 28****Race/ethnic-specific percentiles for estimated fetal weight by gestational age, NICHD fetal growth studies**

Gestational age, wks	Estimated fetal weight, g, Asian						
	Third	Fifth	10th	50th	90th	95th	97th
10	27	28	29	34	40	41	43
11	34	35	36	43	50	52	54
12	43	44	46	54	63	66	68
13	55	56	59	68	80	83	86
14	69	71	74	87	101	106	109
15	87	90	94	109	128	133	137
16	110	113	118	138	160	167	172
17	137	141	148	172	200	209	215
18	171	176	183	214	249	260	267
19	210	216	226	263	306	319	328
20	256	264	275	320	372	388	399
21	309	318	332	386	448	468	481
22	370	380	396	461	535	558	574
23	438	450	469	545	633	660	679
24	514	528	551	640	743	775	796
25	599	615	642	745	865	902	927
26	693	712	742	862	1000	1043	1072
27	796	818	853	990	1149	1199	1232
28	910	935	975	1132	1314	1370	1408
29	1034	1063	1108	1287	1494	1559	1602
30	1168	1201	1253	1456	1691	1765	1814
31	1312	1349	1408	1637	1904	1987	2043
32	1464	1506	1572	1830	2130	2224	2287
33	1622	1668	1743	2031	2368	2473	2544
34	1783	1834	1917	2238	2614	2732	2811
35	1943	2000	2091	2448	2865	2996	3084
36	2099	2162	2263	2656	3118	3262	3360
37	2252	2320	2430	2862	3371	3530	3638
38	2397	2472	2592	3065	3623	3799	3918
39	2536	2617	2748	3263	3874	4067	4198
40	2664	2753	2894	3455	4125	4337	4481

Estimated fetal weight was calculated from head circumference, abdominal circumference, and femur length using the Hadlock 1985 formula (Hadlock<sup>26</sup>). Reproduced, with permission, from Buck Louis and Grewal J.<sup>10</sup>

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# Individualized growth assessment: conceptual framework and practical implementation for the evaluation of fetal growth and neonatal growth outcome



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Fetal growth abnormalities can pose significant consequences on perinatal morbidity and mortality of nonanomalous fetuses. The most widely accepted definition of fetal growth restriction is an estimated fetal weight less than the 10th percentile for gestational age according to population-based criteria. However, these criteria do not account for the growth potential of an individual fetus, nor do they effectively separate constitutionally small fetuses from ones that are malnourished. Furthermore, conventional approaches typically evaluate estimated fetal weight at a single time point, rather than using serial scans, to evaluate growth. This article provides a conceptual framework for the individualized growth assessment of a fetus/neonate based on measuring second-trimester growth velocity of fetal size parameters to estimate growth potential. These estimates specify size models that generate individualized third-trimester size trajectories and predict birth characteristics. Comparisons of measured and predicted values are used to separate normally growing fetuses from those with growth abnormalities. This can be accomplished with individual anatomical parameters or sets of parameters. A practical and freely available software (Individualized Growth Assessment Program) has been developed to allow implementation of this approach for clinical and research purposes.

**Key words:** customized fetal growth, individualized growth assessment, Individualized Growth Assessment Program, Rossavik growth model, second trimester, third trimester, ultrasound

Beginning in the early 1800s, routine weighing of newborns began in British lying-in hospitals, with some American maternity hospitals following by midcentury.<sup>1</sup> By 1900, birthweight was the most common quantitative measure available for evaluating

individual fetal growth, although it is actually a measure of size.<sup>2</sup> This availability of birthweight led to its use in establishing relationships between obstetrical, pediatric, and neuro-behavioral variables beginning in the late 1940s.<sup>1</sup>

Birthweight as the surrogate for fetal growth was described in the classic paper of Battaglia and Lubchenco,<sup>3</sup> which introduced the classification system still in use today. This system categorizes neonates with birthweights below the 10th percentile for gestational age as small for gestational age (SGA), those with birth weights between the 10th and 90th percentiles as appropriate for gestational age (AGA), and those above the 90th percentile as large for gestational age (LGA).<sup>3-12</sup> These category boundaries were justified only by the observation that 10th percentile values were similar in different studies.<sup>3</sup> However, this system provided a means for relating size and preterm birth to neonatal mortality.<sup>13-16</sup>

Given this focus on birthweight as an indicator of fetal growth, it is not surprising that with the introduction of ultrasound into obstetrical practice in the 1970s, estimating fetal weight (because it cannot be measured directly) became a primary subject for investigation.<sup>17-24</sup> This has led to the development of numerous formulas for estimating fetal weight.<sup>25-40</sup>

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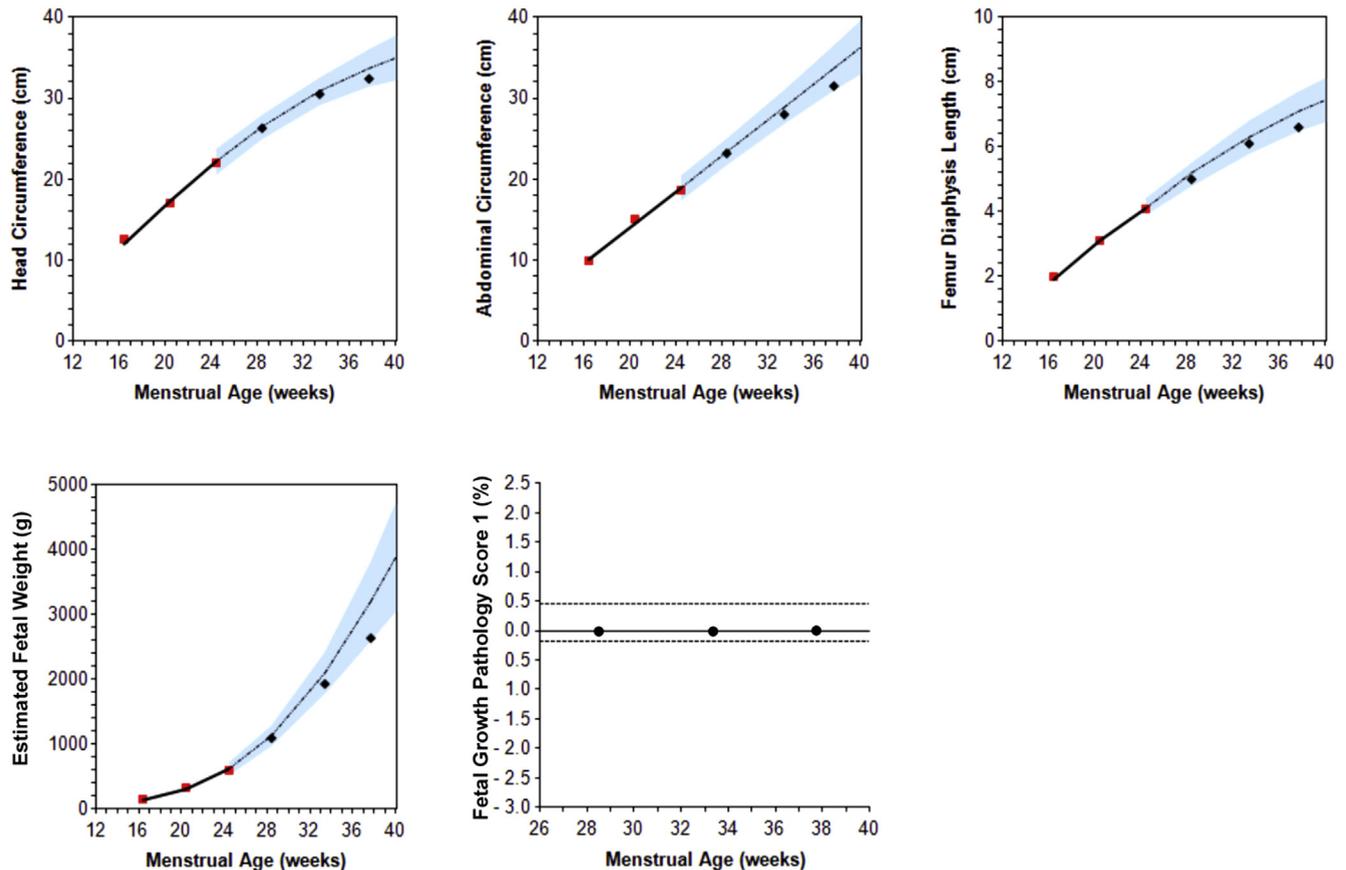
The authors report no conflict of interest.

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**FIGURE 1**  
**Normal prenatal growth in newborn considered small for gestational age**

**Individualized Fetal Growth Assessment Summary**



This small-for-gestational-age newborn had a birthweight of 2490 g at 39.1 weeks, which is at the fourth percentile according to the Intergrowth-21st standard. The growth summary for this individual included head circumference, abdominal circumference, femur diaphysis length, and estimated fetal weight. The estimated fetal weight is calculated using biparietal diameter, head circumference, abdominal circumference, and femur diaphysis length. FGPS1 values (head circumference, abdominal circumference, femur diaphysis length, and estimated weight) are plotted in the lower-right-hand panel. All of these values are equal to zero, indicating no growth pathology. The 2 horizontal dashed lines define reference range boundaries for the +FGPS1 (upper) and -FGPS1 (lower) values. All 3 growth potential realization index values were normal (neonatal assessment screen not shown): (weight: 83.0%; head circumference: [100.2%]; and crown heel length: 94.5%) with an average pathological growth potential realization index of 0.0%. Apgar scores were 9 of 9 at birth. The infant was discharged from the low-risk nursery at 4 days following delivery. This case illustrates that even small newborns can grow normally during the prenatal period, and this process can be verified using individualized growth assessment. The finding of normal interval growth in a small fetus, based on growth potential, may provide useful information for guiding decisions about the number and frequency of antenatal surveillance tests, delivery timing, and/or postnatal therapeutic interventions (eg, postnatal nutritional supplementation). However, optimal application of these individualized results will require additional clinical investigation.

FGPS1, fetal growth pathology score 1.

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A principal objective of this work has been to predict the SGA-AGA-LGA status of the neonate. Successful predictions would have allowed the utilization of associations between birthweight categories and perinatal complications and/or long-term

neurobehavioral development. However, conventional approaches utilizing comparisons of an individual to his/her appropriate size group have not been able to reliably predict birthweight categorizations.<sup>41,42</sup> It is now time to think differently about how fetal

and neonatal growth should be evaluated.

**The importance of velocity in the assessment of fetal growth**

Growth is defined as a change in body dimensions over time. The physical

**TABLE 1**  
**Second-trimester growth velocities as estimators of fetal growth potential**

Characteristics of second-trimester growth velocities<sup>a</sup>

Direct measures of change in size with time (growth)

Empirical measurements reflecting both known and unknown growth determinants

Can be measured when fetal nutritional requirements are low

Constant during the second trimester

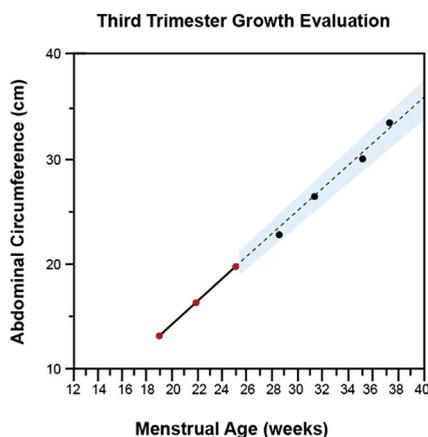
Specify growth models that accurately predict third-trimester size trajectories and birth characteristics in fetuses/neonates with normal growth

<sup>a</sup> Characteristics of second-trimester growth velocities support their use as anatomical parameter growth potential estimates.<sup>83</sup>

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parameter that describes growth is velocity (the general formula for velocity is distance divided by time interval).

**FIGURE 2**  
**Second- and third-trimester abdominal circumference by individualized growth assessment**



Individualized size trajectory is specified by the second-trimester abdominal circumference growth velocity. First, data points (red dots) are used to determine the slope (growth velocity) of the solid line. Next, the predicted third trimester trajectory (dashed line) is generated by a model derived from the second-trimester growth velocity. The black dots represent subsequent measurements superimposed on the predicted line. The shaded area is the abdominal circumference reference range obtained from fetuses with normal neonatal growth outcomes.<sup>89,90</sup>

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Obstetricians studying fetal growth often refer to this measurement as growth velocity.<sup>43,44</sup> Several studies have characterized the growth velocities of different parameters (eg, abdominal circumference, estimated fetal weight),<sup>45-52</sup> and this was largely pioneered by the studies of Owen and colleagues.<sup>43,44,53-60</sup>

Accumulating evidence suggests that abnormal fetal growth velocity of the abdominal circumference is associated with perinatal morbidity, in both SGA and LGA infants.<sup>61,62</sup> The most recent evidence in support of this comes from a large, prospective cohort study of unselected nulliparous women with a single viable gestation who underwent a dating ultrasound examination (typically at 10–14 weeks) and then subsequent examinations at 20, 28, and 36 weeks of gestation.<sup>62,63</sup>

Among SGA neonates with an estimated fetal weight (EFW) less than the 10th percentile, those with an abdominal circumference velocity at the lowest decile (ie, abnormal) were at an increased risk for neonatal morbidity (risk ratio [RR], 3.9; 95% confidence interval [CI], 1.9–8.1) when compared with those with a normal abdominal circumference growth velocity.<sup>62</sup>

Neonatal morbidity was defined as a 5 minute Apgar <7, cord blood pH <7.1, base deficit <10 mmol/L, or admission to the neonatal unit at term. Adverse outcomes were defined as stillbirth, term neonatal death, hypoxic ischemic encephalopathy, use of inotropes, mechanical ventilation, or metabolic acidosis. These results provide

compelling evidence that growth deceleration is more important than smallness in the prediction of neonatal morbidity.

The importance of this information is strengthened by the fact that about 70% of fetuses diagnosed as SGA did not have an abnormal abdominal circumference growth velocity. It is interesting that suboptimal growth velocity of the abdominal circumference was associated with adverse neonatal outcome, while the results of umbilical or uterine artery Doppler velocimetry were not.<sup>62</sup>

The importance of growth velocity is not limited to fetal growth restriction. Indeed, in a different study, Sovio et al<sup>61</sup> evaluated 117 LGA infants (birthweight greater than the 90th percentile). The sensitivity of estimated fetal weight in the detection of neonatal LGA was 38% (67 of 177). Importantly, in LGA fetuses with increased abdominal circumference growth velocity, there was a doubling in the risk of any neonatal morbidity (RR, 2.0, 95% CI, 1.1–3.6;  $P = .04$ ) and greater than 6-fold risk of severe adverse neonatal outcome (RR, 6.5; 95% CI, 2.0–21.1;  $P = .01$ ).<sup>61</sup>

Neonatal morbidity was defined as a 5 minute Apgar <7, cord blood pH <7.1, base deficit <10 mmol/L, or admission to the neonatal unit at term. Adverse outcomes were defined as stillbirth, term neonatal death, hypoxic ischemic encephalopathy, use of inotropes, mechanical ventilation, or metabolic acidosis. Sonographic LGA was associated with a 10-fold risk and the combination of LGA and top decile of abdominal circumference growth velocity was associated with a greater than 20-fold risk. The associations remained very similar after adjustments for preexisting diabetes and gestational diabetes.<sup>61</sup>

Therefore, in light of these observations, an emerging body of evidence has coalesced to support the importance of evaluating fetal growth velocity.<sup>45-52,64</sup> What is measured clinically, and their associated standards, has focused on detecting smallness or largeness at birth (SGA or LGA). Recent standards generated by various groups that have studied fetal size longitudinally<sup>24,33,65</sup> have not provided data on fetal growth velocity

and its relationship with neonatal morbidity at the time of this publication.

Such velocity standards are expected to be forthcoming. Yet they reflect population standards rather than individualized growth standards for a particular fetus/neonate.<sup>24,33,65,66</sup> The method that we describe herein uses fetal growth velocity that is personalized for an individual fetus/neonate. This is possible by generating a mathematical model based on an early trajectory of growth, which allows estimation of growth potential.

This article provides the conceptual framework for the individualized growth assessment of the fetus/neonate coupled with a practical and freely available software that allows implementation of this method for clinical and research purposes.

### The optimal assessment of fetal/neonatal growth

We propose that an optimal method should address a few simple clinical criteria whose validity can be easily verified by any clinician in his/her medical practice:

- All patients are different and must be evaluated on an individualized basis.
- Medical conditions evolve over time, and therefore, serial evaluations are needed.
- Abnormalities manifest themselves differently among individuals, so a set of tests is required for proper evaluation.

Application of these fundamental principles can be used to specify a fetal/neonatal growth evaluation system with the following characteristics:

- (1) *Estimation of growth potential.* Fetal growth restriction is generally defined as a failure to achieve such potential<sup>67,68</sup> (the opposite applies to macrosomia). However, the student of this subject will note that after such statement is made, very few authors have attempted to measure growth potential. Individualized assessment of fetal growth and neonatal growth outcome requires knowing what values a

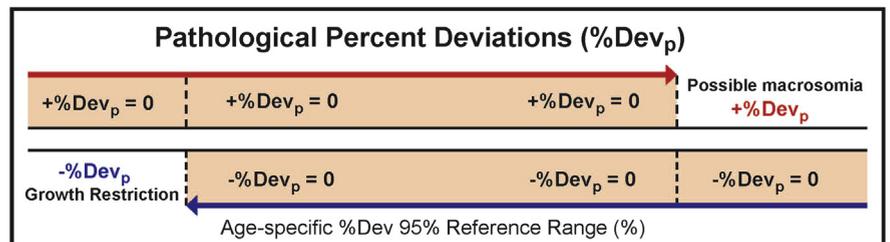
**FIGURE 3**

### Fetal growth evaluation using %Dev and %Dev<sub>p</sub>



### Percent Deviation (%Dev)

$$\% \text{ Dev} = \left( \frac{\text{measured parameter} - \text{predicted parameter}}{\text{predicted parameter}} \right) \times 100$$



The calculation of %Dev and its associated %Dev<sub>p</sub> are defined in the figure. The %Dev compares the measured and predicted parameter values. Pathological percent deviations can be positive (upper row, possible macrosomia) or negative (lower row, fetal growth restriction). The %Dev<sub>p</sub> quantifies growth pathology by indicating how far the %Dev is outside its age-specific reference range (located between the vertical dashed lines). The categories within the shaded area were assigned a value of zero because they provide no information on the growth pathology being studied.<sup>82</sup>

%Dev, percent deviation; %Dev<sub>p</sub>, pathological percent deviation.

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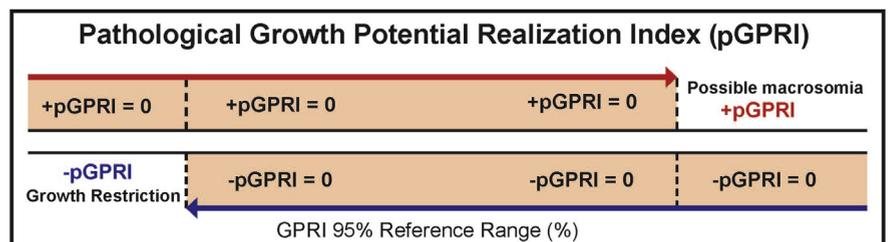
**FIGURE 4**

### Neonatal growth evaluation using GPRI and pGPRI



### Growth Potential Realization Index (GPRI)

$$\text{GPRI} = \left( \frac{\text{measured birth parameter}}{\text{predicted birth parameter}} \right) \times 100$$



The calculation of GPRI and its associated pGPRI are defined in the figure. The GPRI compares the measured and predicted birth characteristic values. Pathological GPRI can be positive (upper row, possible macrosomia) or negative (lower row, fetal growth restriction). The pGPRI quantifies neonatal growth pathology by indicating how far the GPRI is outside its reference range. The categories within the shaded area were assigned a value of zero because they provide no information on the growth pathology being studied.<sup>82</sup>

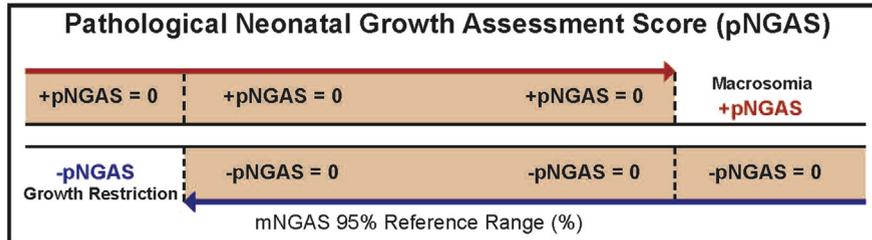
GPRI, Growth Potential Realization Index; pGPRI, pathological growth potential realization index.

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**FIGURE 5**  
**Neonatal growth outcomes using mNGAS and pNGAS**

### Modified Neonatal Growth Assessment Score (mNGAS)

$$m_3NGAS_{s1} = 0.660 (GPRI_{WT}) + 0.602 (GPRI_{THC}) + 0.394 (GPRI_{AC}) + 0.159 (GPRI_{CHL}) + 0.146 (GPRI_{HC})$$



This figure demonstrates how the mNGAS and its associated pNGAS are calculated. The mNGAS provides a composite measure of neonatal growth outcome based on 5 weighted GPRI values. The weights give the importance of specific GPRI values in separating growth-restricted, normal, and macrosomic neonates. The pNGAS quantifies growth outcome pathology by indicating how far the mNGAS is beyond its reference range (determined in neonates with normal growth outcomes). The categories within the *shaded area* were assigned a value of zero because they provide no information on the growth pathology being studied.

*GPRI*, growth potential realization index; *mNGAS*, modified neonatal growth assessment score; *pNGAS*, pathological modified neonatal growth assessment score.

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growth parameter should have had at different time points in a specific case. The optimal evaluation system should provide a method for estimating growth potential, applicable to all growth parameters (eg, head circumference, abdominal circumference, weight, etc) in individual fetuses.

- (2) *Determination of individualized growth standards.* To assess growth status serially during pregnancy, individual standards for all pertinent parameters must be available for each specific fetus/neonate. The optimal evaluation system should provide a set of expected third-trimester trajectories (derived from growth potential estimates) that are age and anatomical parameter specific (eg, abdominal circumference, head circumference).
- (3) *Definition of a set of growth parameters.* Variability in how growth abnormalities manifest themselves

in different fetuses/neonates necessitates the use of a set of growth parameters, not a single parameter. For example, a growth disorder may affect differently the abdominal circumference, head circumference, and femur diaphysis length. Therefore, it is necessary to evaluate multiple parameters and then develop a method for combining measurements to create composite indicators of growth status to facilitate communication among clinicians.

#### Fetal growth assessment methods

*Conventional fetal growth assessment.* Conventional methods of fetal growth assessment compare measurements of single anatomical parameter (usually estimated weight or abdominal circumference prenatally, birthweight postnatally) to population standards.<sup>24,33,34,65,66,69-73</sup> However, no information on individual growth

potential is available in such assessments and the variability because of differences in growth potential is part of normal variability.

It is generally assumed that population-based percentile lines are the expected trajectories of normally growing fetuses. Yet this assumption produces significantly larger prediction errors than trajectories derived from individual growth potential estimates in the same fetuses.<sup>74</sup> Several investigators have described improvement in the prediction of adverse outcomes by customizing birthweight percentiles<sup>70,75-80</sup> and several papers in this issue of the Journal describe customization in detail as well as the pros and cons of this approach. Customization differs from individualized assessment in that it is carried out with only weight and known maternal determinants of growth. Individualized assessment uses multiple anatomical parameters and empirical measures of growth potential, which reflect both known and unknown growth determinants.

Because only 1 parameter is generally used in clinical medicine to monitor growth (eg, abdominal circumference or estimated fetal weight), any abnormality sparing this parameter would not be detected.<sup>81</sup> There is evidence that individualized growth assessment (IGA) can distinguish normally growing small fetuses/neonates from those that have true growth restriction.<sup>82</sup> For example, it is noteworthy that 42% (53 of 126) of SGA singletons diagnosed using conventional methods were actually growing normally, based on prenatal and postnatal individualized growth assessments (see the following paragraph for a complete description of IGA)<sup>82</sup> (Figure 1).

#### Individualized growth assessment

A method that assesses fetal growth potential, an unmet need in our discipline, is individualized growth assessment. This method establishes standards for each anatomical parameter in a fetus or neonate (an individual is its own control) and identifies growth pathology as deviations from these standards, using

either a single parameter or a set of parameters.

*Concepts of normal fetal/neonatal growth assessment using individualized growth assessment.*

(1) *Fetal growth potential.* In contrast to conventional methods, individualized growth assessment obtains empirical estimates of growth potential for all measured anatomical parameters in an individual fetus. We have proposed that fetal growth potential can be estimated by calculating second-trimester growth velocities for the reasons listed in Table 1.<sup>83</sup> Because second-trimester fetal growth is quite linear (or can be linearized by mathematical transformation),<sup>83,84</sup> growth velocities for all measurements can be determined using linear regression. Growth potential estimates obtained from these empirically determined growth velocities reflect all known and unknown determinants of growth operating in the second trimester. Because second-trimester growth can be evaluated based on several parameters, there is more than 1 growth potential [one for each growth parameter].

To be valid representatives of inherent growth potential, velocity measurements must be obtained in the absence of fetal growth pathology. Typically this occurs in the early second trimester. Optimal implementation of IGA requires at least 2 sets of fetal biometric measurements between 14 and 28 weeks, with an interval of at least 2–3 weeks during a period of normal growth. Ultrasound examinations can be performed at any time within this timeframe. It should be emphasized that the earlier the examination is performed, the less likely that a fetal growth disorder has begun that could alter model specification.

(2) *Fetal growth start point.* Human biological studies indicate that an individual starts as a single cell and through embryogenesis becomes an organism with 7500 named parts.<sup>85</sup> These embryonic biometric parameters can be detected for the first time at different points in development.<sup>86</sup> For any anatomical structure, its duration of growth cannot begin until it exists. The use of menstrual age to assess fetal age

**FIGURE 6**  
Examples of how to calculate mPGAS

### Modified Prenatal Growth Assessment Scores (mPGAS)

		Menstrual Age (wks)				
		30	32	34	37	
HC	-%Dev <sub>p</sub> (%)					<b>Example 1</b> <b>ANATOMIC PARAMETER PGAS (apPGAS)</b> $-acPGAS = (0.0 - 4.7 + 0.0 - 5.0) \div 4 = -2.4\%$
AC		0.0	-4.7	0.0	-5.0	
FDL						
EFW						
		30	32	34	37	
HC	-%Dev <sub>p</sub> (%)		0.0			<b>Example 2</b> <b>INDIVIDUAL COMPOSITE PGAS (icPGAS)</b> $-icPGAS = (0.0 - 4.7 + 0.0 - 5.1) \div 4 = -2.5\%$
AC			-4.7			
FDL			0.0			
EFW			-5.1			

This figure illustrates the calculation of 2 different types (example 1: multiple time points for a single anatomical parameter, and example 2: multiple anatomical parameters at a single time point) of modified prenatal growth assessment scores. The pathological percent deviation values for 4 size parameters (HC, AC, FDL, EFW) were obtained in serial examinations at 30, 32, 34, and 37 weeks (menstrual age). Example 1: The  $- \%Dev_p$  values for AC at different menstrual ages were averaged to give the  $-acPGAS$  that quantifies AC growth pathology in the third trimester. For this fetus, the  $-acPGAS$  is  $-2.4\%$ , which indicates growth restriction. Example 2: The  $- \%Dev_p$  values at 1 time point (32 weeks) for HC, AC, FDL and EFW were averaged to give a composite parameter ( $-icPGAS$ ) that quantifies overall growth pathology at 32 weeks.<sup>94</sup> For this fetus, the  $-icPGAS$  is  $-2.5\%$ , which indicates growth restriction at 32 weeks.

AC, abdominal circumference;  $-acPGAS$ , negative abdominal circumference PGAS;  $\%Dev_p$ , pathological percent deviation;  $- \%Dev_p$ , negative pathological percent deviation; EFW, estimated fetal weight; FDL, femur diaphysis length; HC, head circumference; icPGAS, individual composite prenatal growth assessment score; mPGAS, modified prenatal growth assessment scores.

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instead of duration of growth creates a challenge because growth of anatomical parameters cannot start 2 weeks before there is a fertilized zygote. Therefore, defining duration of growth requires determination of a start point,<sup>84</sup> which is the point at which an anatomical parameter can first be identified (see the Glossary for Start Point determination). (3) *Modeling of fetal size.* Individualized growth assessment uses a mathematical function  $[P = c(t)^{k+st}]$  developed by Ivar Rossavik to model fetal growth.<sup>87</sup> The model defines the relationship between the size of an anatomical parameter and the duration of fetal growth. This relationship is specified by coefficients c, k, and s. Because this function is closely related to fractional polynomials,<sup>88</sup> there

is great flexibility in fitting individual size trajectories.<sup>87</sup>

This particular mathematical function has been compared with population percentile lines and conditional probability methods for generating individualized fetal growth trajectories and found to be more accurate.<sup>82</sup> The model coefficients are likely to have biological meaning, c being related to the growth potential, k related to the anatomical characteristics of the parameter being measured, and s related to a growth controller, such as the insulin-like growth factor system<sup>89</sup> (for more details about the method and calculation of the coefficients, see the Glossary).

(4) *Size model specification.* Model specification requires obtaining

**TABLE 2**  
**Specific fetal growth pathology parameters**

Trimester	Parameter name	Abbreviation	Description and use
Second	Abnormal growth velocity score	AGVS	Difference between the reference range boundary and the measurement; classifies growth velocities as abnormally high or low and gives abnormality magnitudes.
Third	Pathological percent deviation	%Dev <sub>p</sub>	Difference between the reference range boundary and the measurement (Figure 2). <sup>94</sup> This parameter provides a measure of growth pathology for individual anatomic parameters at specified time points.
	Anatomical parameter prenatal growth assessment score	apPGAS	Average pathological percent deviation for a single anatomic parameter during the third trimester. <sup>94</sup> This score provides a measure of growth pathology during the third trimester for individual anatomical parameters.
	Individual composite prenatal growth assessment score	icPGAS	Average pathological percent deviation for a set of anatomical parameters at a specific time point. <sup>94</sup> This score provides a way to evaluate growth abnormalities that manifest themselves differently among fetuses.
	Fetal growth pathology score	FGPS	Average pathologic percent deviation for all available anatomical measurements at specific time points in the third trimester (Figure 6). <sup>82</sup> The FGPS measures growth pathology found in the third trimester using all anatomical parameters and time points.

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estimates of the coefficients  $c$ ,  $k$ , and  $s$ .<sup>89</sup> These coefficient estimates can be obtained from linear relationships between the growth velocity and  $c$  as well as between  $c$  and  $s$ . The coefficient  $k$  can be considered a constant<sup>90</sup> (see the [Glossary](#) for more details).

(5) *Third-trimester size trajectories*. To generate third-trimester size trajectories for each individual fetus, size

models specified from second-trimester growth velocities are used (Figure 2).<sup>89,90</sup> These size trajectories represent individualized size standards because they are derived from estimates of growth potential in the fetus being studied (each fetus is its own control). They indicate what the size of a specific parameter should be if the fetus is growing normally, as is

assumed to be the case in the second trimester.

Predicted values for measured anatomical parameters can be directly calculated from their respective size models. For estimated parameters (eg, estimated fetal weight), size models for all of the directly measured parameters used to estimate the desired parameter can give predicted values at any given time point. This set of predicted values is then mathematically transformed into the predicted value for the parameter using an estimation function.<sup>21</sup>

Deviations from the predicted trajectory reflect differences between predicted and measured average growth rates for intervals starting at the beginning of the third trimester to any subsequent time point. These IGA concepts have been verified in 4 previous studies.<sup>89,91-93</sup>

(6) *Individualized size standards: comparison of measured and predicted values*. With IGA, new measurements are not compared with group standards but to what the measurement should have been if growth was normal for a specific fetus. The statistic carrying this comparison information is the percent deviation (Figure 3), the difference between the measured and expected values expressed as a percentage of the predicted value.<sup>84,89</sup>

**TABLE 3**  
**Specific neonatal growth pathology parameters**

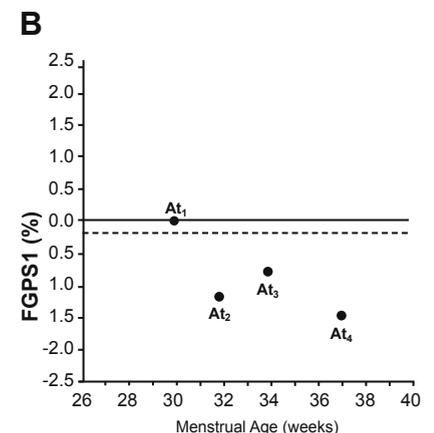
Parameter name	Abbreviation	Description and use
Pathological growth potential realization index	pGPRI	Difference between the reference range boundary and the measurement for a single anatomic parameter (Figure 3). <sup>82</sup> This outcome parameter can be used to detect abnormal growth outcomes that express themselves differently in different individuals. <sup>82,95,98</sup>
Average pathological growth potential realization index	apGPRI	Average pGPRI value for a set of anatomical parameters. This composite parameter provides a comprehensive measure of neonatal growth pathology.
Pathological modified neonatal growth assessment score	pNGAS	Difference between the reference range boundary and the modified neonatal growth assessment score measurement (Figure 4). <sup>89</sup> The pNGAS provides a comprehensive assessment of neonatal growth outcome based on multiple anatomical parameters weighted for their importance in detecting abnormal growth outcomes.

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**FIGURE 7**  
**FGPS (data calculation with corresponding plot)**

**A** **Fetal Growth Pathology Score (FGPS1)**

Menstrual age (weeks)	30	32	34	37
Negative Pathological Percent Deviation (-%Dev <sub>p</sub> )				
HC	0.0	0.0	0.0	0.0
AC	0.0	-4.7	0.0	-5.0
FDL	0.0	0.0	0.0	0.0
EWT	0.0	-5.1	-0.4	-8.8
FGPS1 <sub>At1</sub> = 0.0%				
HC	0.0	0.0	0.0	0.0
AC	0.0	-4.7	0.0	-5.0
FDL	0.0	0.0	0.0	0.0
EWT	0.0	-5.1	-0.4	-8.8
FGPS1 <sub>At2</sub> = -1.23%				
HC	0.0	0.0	0.0	0.0
AC	0.0	-4.7	0.0	-5.0
FDL	0.0	0.0	0.0	0.0
EWT	0.0	-5.1	-0.4	-8.8
FGPS1 <sub>At3</sub> = -0.85%				
HC	0.0	0.0	0.0	0.0
AC	0.0	-4.7	0.0	-5.0
FDL	0.0	0.0	0.0	0.0
EWT	0.0	-5.1	-0.4	-8.8
FGPS1 <sub>At4</sub> = -1.53%				



This score represents the degree of growth pathology in the third trimester. In this example, 4 size parameters (head circumference, abdominal circumference, femur diaphysis length, estimated fetal weight) are being used to evaluate fetal growth at 30, 32, 34, and 37 weeks (menstrual age). The cumulative moving average of the  $-\%Dev_p$  values for these specific size parameters is designated the FGPS 1.<sup>82</sup> A, As follows:

- All  $-\%Dev_p$  values available at 30 weeks (At1, all anatomical parameters at time point 1 included) (*gray shaded area*) were averaged to give the FGPS1, which was 0% (interpreted as normal growth).
- This process was repeated at 32 weeks (At2), which included all measurements available (*gray shaded area*, at both 30 and 32 weeks). The values were averaged to give the FGPS1 value of  $-1.23\%$ . This signifies that growth restriction has occurred.
- This process was repeated at 34 weeks (At3), which included all measurements available (*gray shaded area*, at 30, 32, and 34 weeks). The values were averaged to give the FGPS1 value of  $-0.85\%$ . This signifies that growth has improved.
- This process was repeated at 37 weeks (At4), which included all measurements available (*gray shaded area*, at 30, 32, 34, and 37 weeks). The values were averaged to give the FGPS1 value of  $-1.53\%$ . This signifies that growth restriction has worsened.
- All negative pathological percent deviations represent growth pathology (*red font*).

B, Serial calculations of the FGPS1 (At1, At2, At3, At4) for a single fetus in the third trimester are presented in the plot. The four scores correspond to the data shown in Figure 6A. The *horizontal dashed line* represents the lower boundary of the negative FGPS1 reference range.

AC, abdominal circumference;  $\%Dev_p$ , pathological percent deviation; EFW, estimated fetal weight; FDL, femur diaphysis length; FGPS, fetal growth pathology score; HC, head circumference.

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Percent deviations from normally growing fetuses contain random variability because of measurement errors, modeling errors, and intrinsic

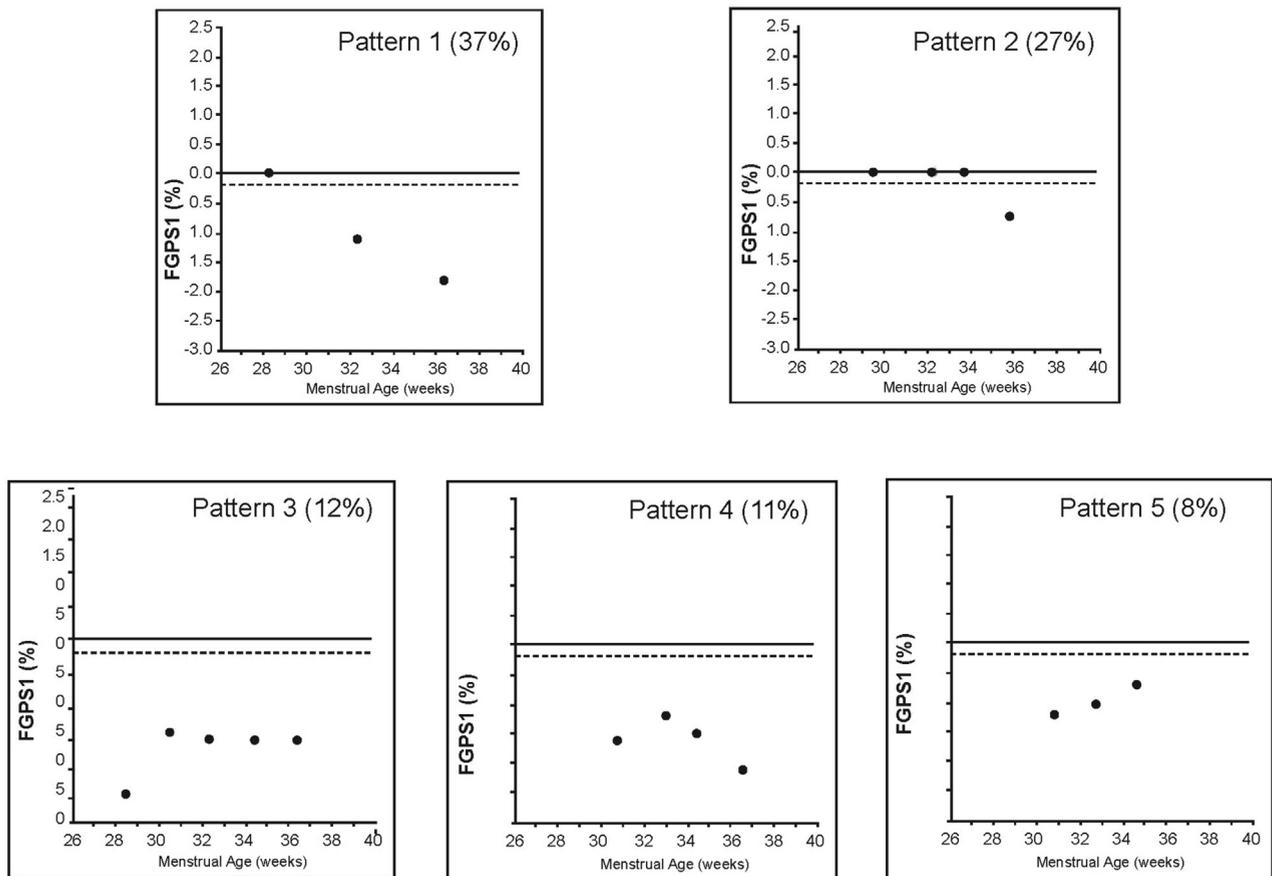
biological control variability, the latter probably related to factors affecting an individual's ability to follow a specified trajectory. However, these variability

sources have only a small effect as indicated by the narrow reference ranges of the percent deviations in fetuses with normal neonatal growth

FIGURE 8

## Patterns of fetal growth restriction during third trimester using FGPS

## FGPS1 Pattern Types



Different third-trimester patterns of the FGPS1 were observed in 73 small-for-gestational age fetuses with confirmed postnatal growth restriction. Each fetus had an abnormal third trimester: FGPS1 and an abnormal average pathological growth potential realization index value as a neonate. Seventy of the 73 cases (95%) could be classified into 1 of 5 patterns that are distinct, few in number, seen repeatedly, and have plausible biological interpretations.<sup>101</sup> FGPS1 values are plotted for individual fetuses as a function of menstrual age (*black dots*).

- Pattern 1. There is a constant decline in the FGPS1 with advancing menstrual age. This pattern was observed in 37% of small-for-gestational-age fetuses (27 of 73).
- Pattern 2. This fetus had several FGPS1 values of zero, indicating that the fetus was following its own expected growth trajectory. However, fetal growth restriction developed at the last examination (36 weeks). This pattern was observed in 27% of small-for-gestational-age fetuses (20 of 73).
- Pattern 3. There was an initially very low FGPS1 that leveled off and remained approximately constant in subsequent third-trimester examinations. This pattern was observed in 12% of small-for-gestational-age fetuses (9 of 73).
- Pattern 4. After an initial low FGPS1, there was evidence of recovery followed by subsequent worsening of the growth restriction process. This pattern was observed in 11% of small-for-gestational-age fetuses (8 of 73).
- Pattern 5. The initial low FGPS1 was followed by a continuous regression toward normal during the latter part of the third trimester. This pattern was observed in 8% of small-for-gestational-age fetuses (6 of 73).

FGPS1, fetal growth pathology score 1.

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**FIGURE 9**  
Individualized Growth Assessment Program



This freely available software uses individualized growth assessment to evaluate changes in fetal size parameters over time by comparing current and expected size trajectories. Actual measurements are compared with third-trimester size predictions, based on second-trimester size models that have been previously established for the individual fetus (each fetus being its own control). iGAP can be found at <https://igap.research.bcm.edu>.

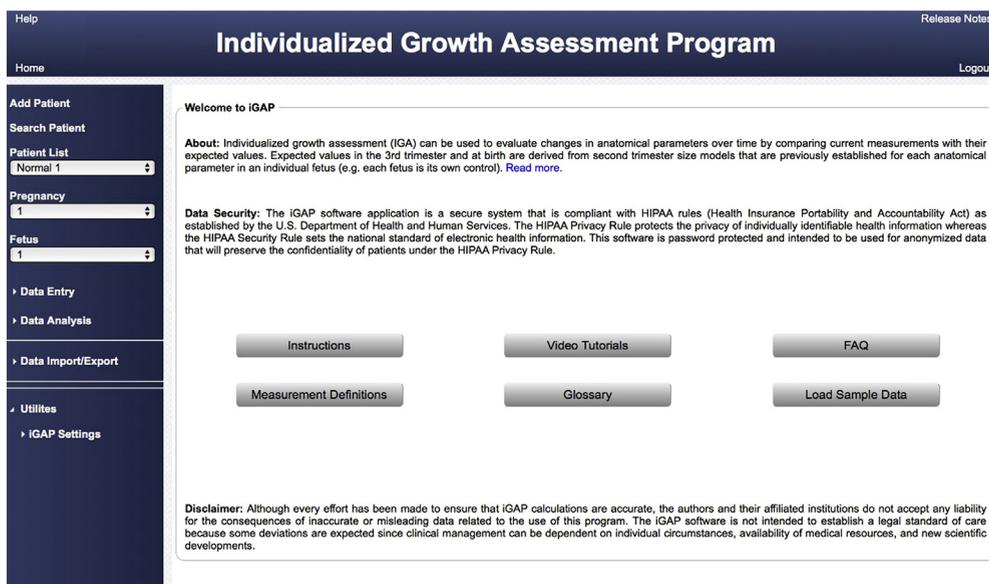
iGAP, Individualized Growth Assessment Program.

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outcomes.<sup>89</sup> Furthermore, percent deviations are independent of differences in growth potential and trajectory shapes and have been shown to be proportional to the difference in expected and measured average third-trimester growth velocities<sup>84</sup>. Therefore, they are true measures of growth (not size), and values for different anatomical parameters can be combined to create composite growth measures.<sup>94</sup>

(7) *Prediction of anatomical birth characteristics.* Because birth is just the endpoint of the third-trimester size trajectory, the expected size of any anatomical parameter at birth (if prenatal and postnatal measurements are available) can be obtained with the appropriate fetal parameter-specific size model obtained during pregnancy. However, this requires selection of a birth age, and empirical studies have shown that fetuses delivering after 38 weeks (menstrual age) demonstrate

**FIGURE 10**  
iGAP home page screen



This page allows the user to navigate between instructions, measurement definitions, video tutorials, glossary of terms, and frequently asked questions. Patient selection is made on this page. The main functions of iGAP are listed under Data Entry and Data Analysis (left-hand side of screen).

iGAP, Individualized Growth Assessment Program.

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**FIGURE 11**  
Parameter selection screen

The screenshot shows the 'Parameter Selection' screen of the Individualized Growth Assessment Program. The interface is divided into a left sidebar, a top header, and a main content area.

**Header:** 'Individualized Growth Assessment Program' with 'Help', 'Release Notes', 'Home', and 'Logout' links.

**Left Sidebar:** Contains navigation options: 'Add Patient', 'Search Patient', 'Patient List' (with a dropdown for 'Normal 1'), 'Pregnancy' (with a dropdown for '1'), 'Fetus' (with a dropdown for '1'), 'Data Entry', 'Data Analysis' (with sub-options: 'Parameter Selection' (highlighted), 'Processed Fetal Data', 'Second Trimester Model Specification', 'Model Validation / Second Trimester Growth Evaluation', 'Growth Summary', 'Third Trimester Growth Evaluation', 'Graphs', 'Neonatal Growth Assessment'), 'Data Import/Export', and 'Utilites' (with sub-option: 'IGAP Settings').

**Main Content Area:**

- Parameter Selection:** A section with a 'Summary' table.
 

Patient ID	Normal 1	Final EDD	09/20/2006
Pregnancy	1	Fetus	1
- Buttons:** A row of six buttons: 'Profile Diameter Selection', 'Weight Estimation Selection', 'mPGAS Selection', 'Normal Growth Limit Selection', 'Process Fetal Data', and 'Change Selections'.
- Profile Diameter Selection for Weight Estimation:** A section with a heading 'What are Profile Diameters and how are they used?' and a question 'Would you like to use these procedures to calculate the profile diameters?' with radio buttons for 'Yes' and 'No'. Below this is a 'Please note:' section stating: 'If Yes, then iGAP will calculate the profile diameters (and Cubes). If No, then iGAP will continue processing without these profile diameter values.'

The user must select a combination of 4 parameters: profile diameter selection, weight estimation selection, mPGAS selection, and normal growth limit selection. Once this set of parameters is selected by the user, IGA analysis is initiated by clicking on Processed Fetal Data.

iGA, individualized growth assessment; mPGAS, modified prenatal growth assessment scores.

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minimal growth after 38 weeks, which we have designated as growth cessation in cases with normal neonatal growth outcomes.<sup>95</sup> Therefore, IGA uses the actual birth age for deliveries at or before 38 weeks, menstrual age, and 38 weeks, menstrual age, for deliveries after 38 weeks.

Individualized growth assessment does not compare measured birth characteristics with group standards but rather to what these measurements should have been if growth in the designated fetus was normal. The statistic carrying this comparison information is the growth potential realization index (GPRI) (Figure 4),

defined as the ratio of the measured value to the predicted value multiplied by 100 [ideal value = 100%].<sup>95,96</sup>

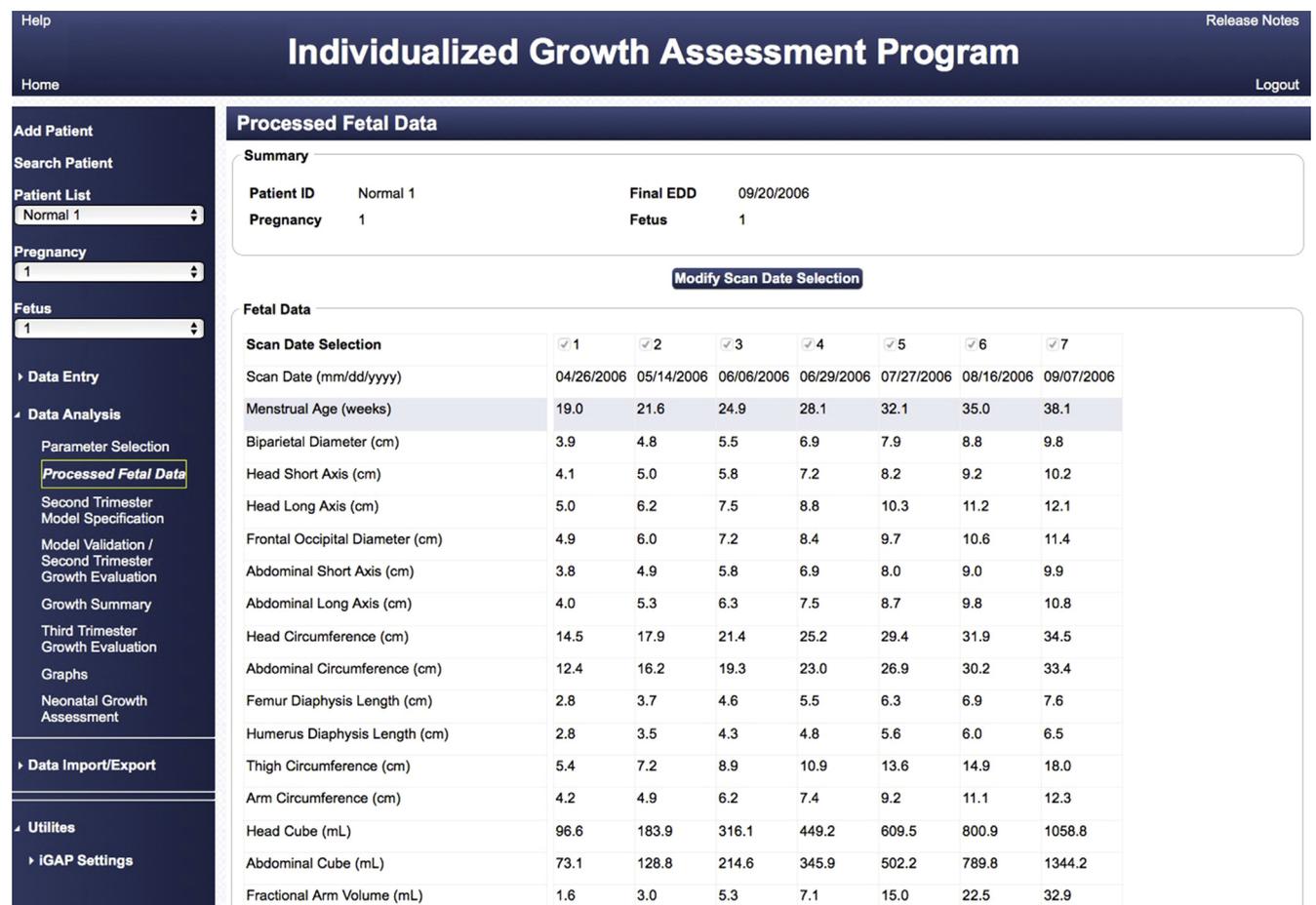
For some anatomical parameters, there are systematic measurement errors because of differences in the prenatal and postnatal measurement procedures (eg, prenatal abdominal circumference vs neonatal abdominal circumference; predicted birthweight vs measured birthweight).<sup>97</sup> The predicted values for these parameters are corrected for such systematic measurement errors before GPRI calculation.<sup>95,97</sup> GPRI values have been shown to be proportional to the difference between the expected and

measured average third-trimester growth velocities so are measures of growth, not size.<sup>84</sup>

Past studies indicate that GPRI values are independent of differences in growth potential, age at delivery, growth cessation, and systematic measurement errors.<sup>84,95-97</sup> Neonatal growth outcome evaluations, provided by GPRI values, are not dependent on third-trimester growth information.

(8) *Modified neonatal growth assessment score (mNGAS)*. A more comprehensive neonatal growth outcome parameter utilizing several GPRI values is the mNGAS<sup>81</sup> (Figure 5). This score is calculated from a linear function of

**FIGURE 12**  
Processed fetal data screen



This screen summarizes ultrasound data for several fetal size parameters at each scan date and menstrual age.

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weighted GPRI values for weight, thigh circumference, abdominal circumference, head circumference, and crown-heel length. The weighting factors were obtained using principal components analysis and indicate the relative importance of each anatomical parameter in separating growth-restricted, normal, and macrosomic neonates. Such a separation has been made with an accuracy of 96.9%.<sup>81</sup>

*Concepts of abnormal fetal/neonatal growth assessment.*

(1) *Detection and quantification of growth abnormalities.* The primary objective of IGA is to identify normal and abnormal fetal/neonatal growth

outcomes. Accordingly, measurements outside the parameter- and age-specific 95% range for fetuses/neonates<sup>89</sup> is considered abnormal, even if the clinical neonatal outcomes are apparently normal.

The magnitude of a growth abnormality is expressed by the difference between the measurement and the upper, or lower, boundary of the reference range. Because the 4 fundamental measures of growth are the second-trimester growth velocity, the percent deviation, the GPRI, and the mNGAS, these differences have been given the following designations:

- Abnormal growth velocity score (AGVS).<sup>83</sup>

- Pathological percent deviation (% Dev<sub>p</sub>) (Figure 3).<sup>82</sup>
- Pathological GPRI (pGPRI) (Figure 4).<sup>82,98</sup>
- Pathological mNGAS (pNGAS) (Figures 5 and 6).

Positive and negative values denote those above and below the reference range, respectively. Measurements within their reference ranges are assigned a difference value of zero because they do not signify a growth abnormality.<sup>82,99,100</sup>

(2) *Specific growth pathology parameters.* Individualized growth assessment evaluates growth abnormalities using specific growth parameters in the second and third trimesters (Table 2) and at birth (Table 3).

FIGURE 13

## Model validation/second-trimester growth evaluation screen

Help Release Notes

**Individualized Growth Assessment Program**

Home Logout

---

**Model Validation / Second Trimester Growth Evaluation** Print Preview

**Summary**

Patient ID Normal 1 Final EDD 09/20/2006 Red Text (H) : Value above normal range  
 Pregnancy 1 Fetus 1 Black Text : Value within normal range  
Blue Text (L) : Value below normal range

**Model Validation**

**More Information** What is the Abnormal Growth Velocity Score?

Size Model Performance				2nd Trimester Growth Abnormalities		
Parameter	Start Point (wks)	2nd Trimester Growth Velocity (cm/wk)	28 Weeks' Prediction (cm or mL)	Parameter	Abnormal Growth Velocity Score	
					High (cm/wk)	Low (cm/wk)
BPD	4.2	0.27	6.5	BPD	0.00	0.00
HC	6.4	1.16	25.1	HC	0.00	0.00
AC	8.1	1.16	23.0	AC	0.00	0.00
FDL	9.6	0.30	5.4	FDL	0.00	0.00
HDL	7.9	0.25	5.0	HDL	0.00	0.00
ThC	9.7	0.59	10.8	ThC	0.00	0.00
ArmC	6.9	0.34	7.4	ArmC	0.00	0.00
Hcube*	6.7	0.38	467.4	Hcube*	0.00	0.00
Acube*	5.2	0.31	373.9	Acube*	0.00	0.00
AVol*	6.9	0.10	8.9	AVol*	0.00	0.00
TVol*	9.2	0.15	21.6	TVol*	0.00	0.00

Hover on number to obtain Reference Range for Start Point or 2<sup>nd</sup> Trimester Growth Velocity.  
 \* Unit is mL. Growth velocities for these anatomical parameters are for the cube roots of the actual measurements.

On the left-hand side, data for start point, second-trimester growth velocity, and the model prediction at 28 weeks are presented. Such data are used to detect abnormal values that would result in poor model performance. The right side of the screen depicts the growth velocity measurements compared with their respective reference ranges and calculation of the abnormal growth velocity scores.

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- (1) Second trimester.
  - Abnormal growth velocity scores (AGVS).
- (2) Third trimester.
  - Pathological percent deviation (%Dev<sub>p</sub>).
  - Anatomical parameter prenatal growth assessment score (apPGAS).
  - Individual composite prenatal growth assessment score (icPGAS).
  - Fetal growth pathology score (FGPS) (Figures 7 and 8).
- (3) At birth.
  - Pathological growth potential realization index (pGPRI).
  - Average pathological growth potential realization index.
  - Pathological modified neonatal growth assessment score (pNAS).

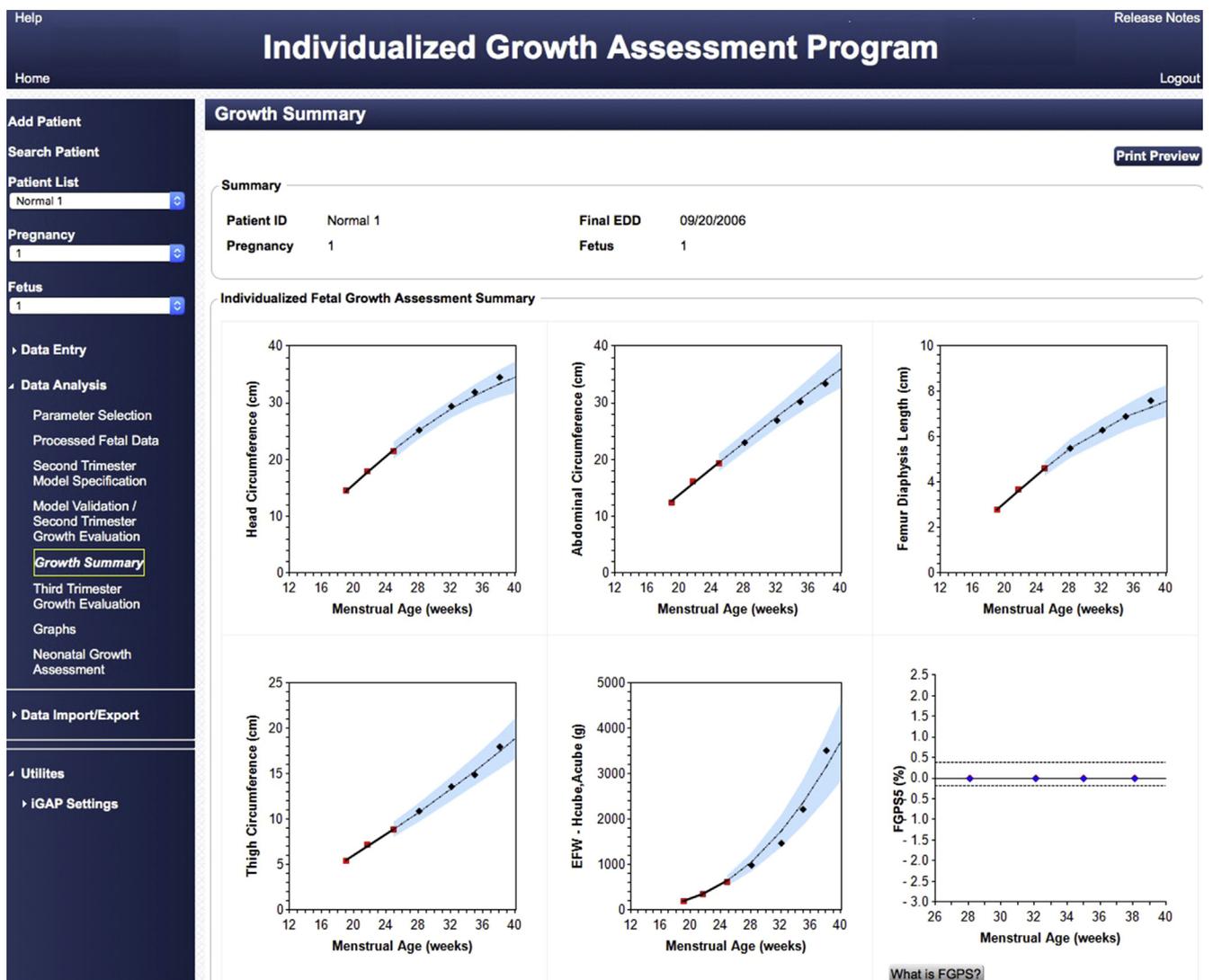
#### Concordance between fetal and neonatal growth evaluations

Individualized growth assessment has the ability to evaluate third-trimester growth and neonatal growth outcomes separately. However, the anatomical parameters evaluated and sources of error are not the same in these 2 assessment periods. Some parameters have to be estimated (eg, prenatal: measured and predicted weight; neonatal: predicted

weight and predicted crown-heel length), while others are directly measured. Therefore, it is very unlikely that third-trimester and neonatal growth assessments will agree by chance.

If the same wrong classification (eg, normal vs abnormal) is made, this would require that all sources of error operate in such a way as to cancel each other out so that the same wrong answer is obtained. This possibility is so remote that we consider concordance between individualized third-trimester and neonatal growth evaluations provides the strongest evidence for the presence or absence of growth pathology.

**FIGURE 14**  
Growth summary screen



Several size parameters are summarized for an individual fetus (in this example, the fetus is normally grown). Red dots indicate the measurements used to calculate second-trimester growth velocities. Rossavik models generate expected size trajectories, and actual measurements (black dots) are superimposed on each curve for different size parameters (eg, head circumference). The blue shaded areas represent the range of normal variation based on fetal growth in pregnancies with confirmed normal neonatal growth outcomes. The graph in the lower-right corner presents the FGPS, calculated at different time points in the third trimester. For this fetus, the dots are on the zero line because there is no growth pathology present.

FGPS, fetal growth pathology score.

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### Limitations of individualized growth assessment

This method of fetal growth assessment requires a series of longitudinal biometric measurements. At least 2 measurements for each anatomical parameter in the second trimester (14–28 weeks) with an interval of at

least 2–3 weeks are required. If a fetal growth disorder has already occurred within this window of time, it can alter the estimates of growth potential and compromise model performance. Such situations can be detected by calculating the AGVS, as described earlier in this article and prior publications: this

statistic is calculated by the Individualized Growth Assessment Program (iGAP) software.

Currently there have been no IGA studies related to the following: (1) physiological abnormalities, (2) clinical management, or (3) prediction of perinatal complications or adverse

**FIGURE 15**  
**Growth abnormalities/mPGAS screen**

▼ **Growth Abnormalities**

Modified Prenatal Growth Assessment Score (mPGAS)

What is mPGAS?

mPGAS Definitions

What is FGPS?

MA weeks	Anatomical Parameters					Growth Abnormalities	
	+ihcPGAS %	+iacPGAS %	+ifdlPGAS %	+ithcPGAS %	+iewtPGAS %	+ic1aPGAS %	+FGPS5 %
28.1	0.00	0.00	0.00	0.00	0.00	0.00	0.00
32.1	0.00	0.00	0.00	0.00	0.00	0.00	0.00
35.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
38.1	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<b>+apPGAS</b>	0.00	0.00	0.00	0.00	0.00	<b>+c1aPGAS</b>	0.00

MA weeks	Anatomical Parameters					Growth Abnormalities	
	-ihcPGAS %	-iacPGAS %	-ifdlPGAS %	-ithcPGAS %	-iewtPGAS %	-ic1aPGAS %	-FGPS5 %
28.1	0.00	0.00	0.00	0.00	0.00	0.00	0.00
32.1	0.00	0.00	0.00	0.00	0.00	0.00	0.00
35.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
38.1	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<b>-apPGAS</b>	0.00	0.00	0.00	0.00	0.00	<b>-c1aPGAS</b>	0.00

Hover on the column or row labels for more information.

The table shows the positive (upper panel) and negative (lower panel) individual PGAS values (percentage) for each individual anatomical parameter at each time point in the third trimester. The average values (apPGAS) for the third trimester are shown in the *gray shaded area* in 2 rows. The 2 columns in the *gray shaded area* present the individual composite PGAS values (percentage) and the FGPS calculated at each time point. For this fetus, all measured values were zero, indicating that this was a normally growing fetus.

apPGAS, anatomical parameter prenatal growth assessment score; FGPS, fetal growth pathology scores; mPGAS, modified prenatal growth assessment score.

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long-term neurobehavioral development. Therefore, the iGAP implementation of IGA cannot provide all the tools needed for the clinical care of fetuses with growth abnormalities. However, the software could be introduced as a secondary assessment of fetuses at risk for growth restriction. No studies of its use in macrosomia are presently available.

**Practical implementation of individualized growth assessment in clinical obstetrics software**

In 2016, a freely available Internet-based software application (iGAP) developed by our team was introduced to allow personalized analyses of fetal growth based on IGA principles. For a given pregnancy, iGAP software (Figure 9) provides a comparison of measured and predicted third-trimester measurements using each fetus as its own control.

The growth analysis tools of iGAP are compatible with multiple computer platforms (Windows, Mac, or Linux) and current Internet browsers. More information about the Health Insurance Portability and Accountability Act, data security, and technical specifications of iGAP are available at the software website (<https://igap.research.bcm.edu/>). Once a software registration request has been received, the new user will receive a confirmatory e-mail with sign-on instructions generally within no more than 1 business day.

All parameters described in this article, including the model for fetal growth, model coefficients, predicted size trajectories, and the indices used to assess fetal/neonatal growth are available in iGAP. The program includes easy-to-follow instructions, video tutorials, measurement definitions, glossary of

terms, and frequently asked questions (Figure 10).

Readers are encouraged to review 3 training videos that have been prepared on the iGAP website to review basic concepts about individualized growth assessment (17 minutes, 6 seconds), explain how iGAP software is used on a normally growing fetus (12 minutes, 7 seconds), and demonstrate how it can be used to assess abnormal growth (10 minutes, 45 seconds).

Specifically, iGAP provides data analysis templates for the following:

- Parameter selection: provides a choice of parameters for IGA including weight estimation procedure, modified prenatal growth assessment score, and normal growth limit (Figure 11).
- Processed fetal data: presents the biometric data to be analyzed (Figure 12).

**FIGURE 16**  
Neonatal growth assessment screen

**Individualized Growth Assessment Program**

Neonatal Growth Assessment

Summary

Patient ID: Normal 1      Final EDD: 09/20/2006  
 Pregnancy: 1      Fetus: 1

Date of birth: 09/12/2006      Birth Age: 38.9 weeks      Last-scan-to-delivery interval: 0.8 weeks

Basic

Study date: 09/15/2006

Neonatal Parameter	Measured	Correction Factor	Predicted	GPRI (%)	Growth Abnormalities	
					+pGPRI (%)	-pGPRI (%)
Weight (g)	3454	1.000	3135	110.2	0.00	0.00
Head Circumference (cm)	34.0	1.000	33.4	101.9	0.00	0.00
Abdominal Circumference (cm)	30.5	0.897	30.4	100.4	0.00	0.00
Thigh Circumference (cm)	16.0	0.883	15.4	103.9	0.00	0.00
Crown Heel Length (cm)	51.0	1.000	49.8	102.4	0.00	0.00
<b>Average</b>					0.00	0.00

Calculate neonatal predicted values at

Growth Cessation Age       Birth Age      **Change**

m <sub>3</sub> NGAS <sub>51</sub>	mNGAS (%)	Pathological NGAS	
		+pNGAS (%)	-pNGAS (%)
	206	0	0

The measured and predicted values for neonatal birth characteristics and their associated GPRI values are presented for the anatomical parameters measured postnatally. The GPRI values are compared with their reference ranges and the pGPRI values calculated. The predicted values depend on the gestational age at delivery being used, which can be selected in the lower-left-hand corner (growth cessation age, birth age). The averages for pGPRI values (*gray shaded row*) are presented below the pGPRI columns. If appropriate data are available, the mNGAS is presented in the lower-right-hand corner of the screen. The mNGAS is compared with its reference range to give the pNGAS. The measures of pathology (pGPRI, average pGPRI, pNGAS) are all zero in this example, indicating normal neonatal growth outcome.

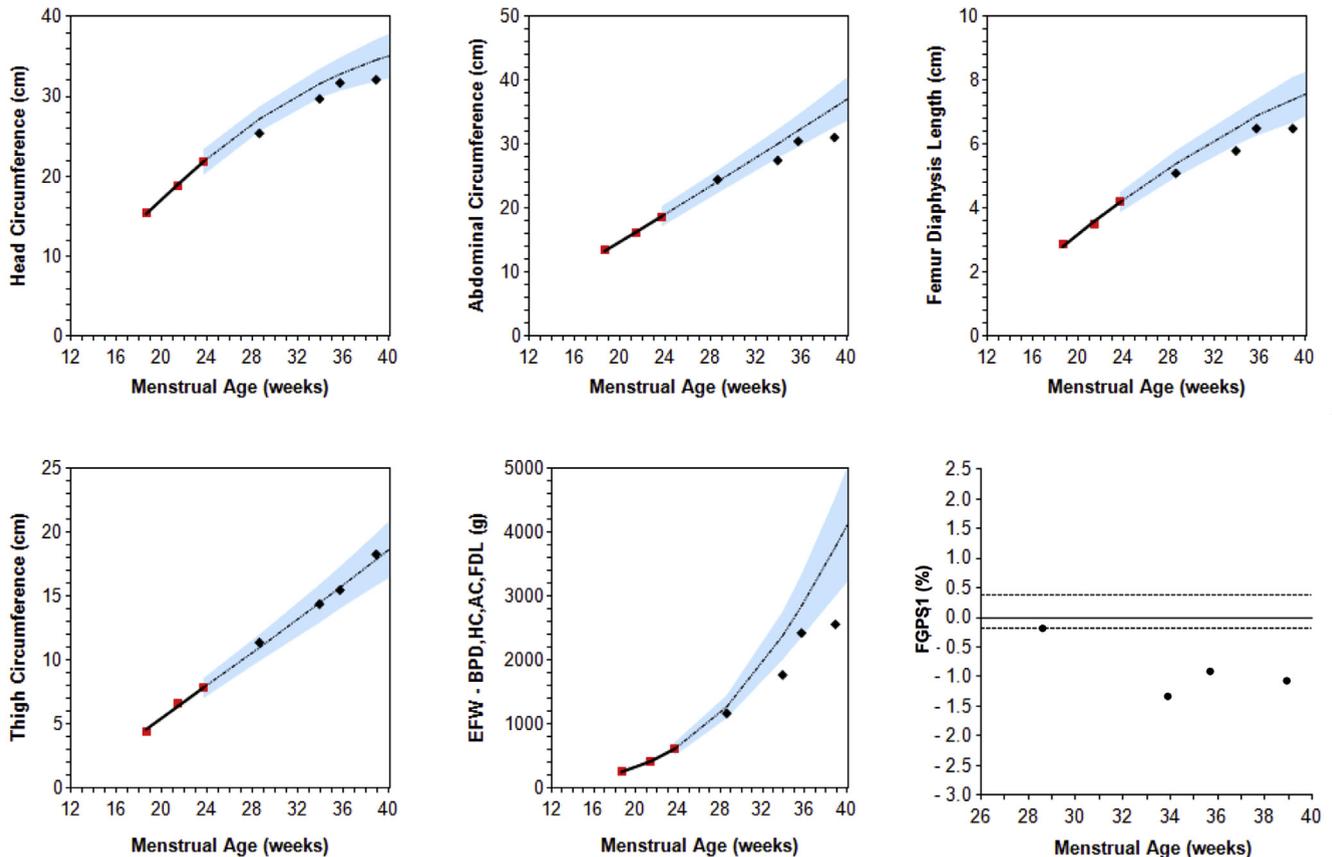
GPRI, growth potential realization index; mNGAS, modified neonatal growth assessment score; pGPRI, pathological GPRI; pNGAS, pathological neonatal growth assessment score.

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- Second-trimester model specification: to determine the model coefficients that allow generation of predicted growth trajectories.
- Model validation: to evaluate characteristics of growth start points and second-trimester growth velocities as well as the ability of the model to predict a normal value at 28 weeks) (Figure 13).
- Second-trimester growth evaluation: to compare growth velocities with their reference ranges (Figure 13).
- Growth summary: plots of individual anatomical parameter size trajectories and the FGPS (Figure 14).
- Third-trimester growth evaluation: tables that give percent deviations, PGAS, and FGPS at different time points in the third trimester for each anatomical parameter (Figure 15).
- Anatomical parameter graph display (eg, head circumference): provides the results of IGA analysis in graphic form for each anatomical parameter.
- Neonatal growth assessment: table that gives the predicted and measured birth characteristics as well as growth potential realization indices for all

**FIGURE 17**  
Fetal growth restriction example

Individualized Fetal Growth Assessment Summary



Growth assessments are graphically summarized in an individual fetus for head circumference, abdominal circumference, femur diaphysis length, thigh circumference, and estimated fetal weight. The fetal weight estimation procedure utilizes biparietal diameter, head circumference, abdominal circumference, and femur diaphysis length. All parameters show abnormal values (*black dots* below *blue shaded reference ranges*) except for thigh circumference (lower left panel). FGPS7 values incorporate 5 anatomical parameters (lower right panel). Two *horizontal dashed lines* define the reference range boundaries for the +FGPS7 (upper) and -FGPS7 (lower) values. This graph shows an initial borderline value (*black dot*) followed by 3 persistently low values, indicating growth restriction after 34 weeks. The neonate had a birthweight of 2305 g at 39.0 weeks' gestation (less than the third percentile based on Intergrowth-21st standard). The analysis indicated abnormally low GPRI values for 4 of 5 neonatal parameters (weight, 71.1%; head circumference, 93.8%; thigh circumference, 82.0%; and crown heel length, 91.0%) with a substantially negative average pathological GPRI of  $-3.82$ , confirming growth restriction (neonatal assessment screen not shown). In this case, the antenatal suspicion of fetal growth restriction was confirmed by postnatal findings based on individualized growth assessment.

FGPS7, fetal growth pathology score 7; GPRI, growth potential realization.

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anatomical parameters measured. pGPRIs and their average are also presented. If appropriate data are available, the mNGAS is calculated (Figure 16).

The user can interactively select which second-trimester measurements are used to specify size models. Recently the implementation of IGA for the detection

of late-onset fetal growth restriction (using iGAP software) was independently validated by Simcox et al<sup>93</sup> in a longitudinal prospective cohort study of 115 pregnancies. An evaluation of fetal growth restriction using iGAP is demonstrated in Figure 17.

Unlike conventional methods to assess fetal growth, iGAP provides a means to easily interpret complex information

(eg, repeated biometric measurements and multiple composite anatomical parameters). For a given fetus/neonate, the advantages of iGAP include the following: (1) estimation of growth potential using multiple anatomical parameters, (2) prediction of future growth, (3) identifying evolutionary patterns of fetal growth pathology during the third trimester, and (4) accurate

classification of growth outcome in the neonate.

### Conclusions

Individualized growth assessment provides a comprehensive method for identifying third-trimester fetal and/or neonatal growth abnormalities based on an individual's growth potential. The clinical use of individualized growth assessment to characterize abnormal growth and its relationships to physiological changes, perinatal complications, and long-term disabilities warrants further study. Earlier detection and improved monitoring of pathological growth processes provide clinicians with valuable information to determine the optimal frequency of antenatal testing or implementation of timely therapeutic interventions. ■

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### Glossary of terms

**Abnormal growth velocity score (AGVS).** Measured second-trimester growth velocities for each anatomical parameter (eg, abdominal circumference, femur diaphysis length) are compared with their appropriate reference ranges. Measurements within these ranges are assigned AGVS values of zero because no growth abnormality is present. For measurements above or below their respective reference ranges, the AGVS values are the differences between the measurements and the appropriate anatomical parameter-specific reference ranges.

**Anatomical parameter prenatal growth assessment score (apPGAS).** This type of prenatal growth assessment score measures the growth pathology in individual growth parameters (eg, head circumference) during the third trimester. It is the average of pathological percent deviation (%Dev<sub>p</sub>) values obtained at all third-trimester time points.

**Anatomical parameter (P).** This is a fetal biometric parameter that can be 1-, 2- and 3-dimensional and is used to characterize different aspects of normal fetal growth and to detect growth abnormalities. Examples include biparietal diameter (1 dimensional), abdominal profile area (2 dimensional), and fractional limb volume (3 dimensional).

**Coefficient c and coefficient c\*.** These coefficients of the Rossavik model are strongly related to second-trimester growth velocity. They are thought to represent known and unknown controllers of normal fetal growth. Coefficient c is determined by regression analysis; if this regression analysis is carried out using a fixed value of k, coefficient c is now designated as coefficient c\*.

**Coefficient k.** This coefficient represents the characteristics (including dimensionality) of the anatomical parameter being measured. It is considered to be constant from fetus to fetus for a given anatomical measurement and has values that have been determined in fetuses with normal neonatal growth outcomes.

**Coefficient s and coefficient s\*.** These coefficients of the Rossavik model represent factors that control fetal growth. Their major effect is observed at the end of the third trimester. Coefficient s is determined by regression analysis; if this regression analysis is carried out using a fixed value of k, coefficient s is now designated as coefficient s\*.

**Estimated coefficient c\* (estimated c\*).** Second-trimester growth velocities (slopes) for anatomical parameters have very strong linear relationships with the coefficient c values of Rossavik size functions fitted to sets of second- and third-trimester anatomical measurements. Therefore, linear functions relating the coefficient c\* to the slope can be used to obtain estimates of the coefficient c\* [estimated c\* = b<sub>0</sub> + b<sub>1</sub> slope]. This concept is implemented in the iGAP software.

**Estimated coefficient predicted s\* (estimated predicted s\*).** Coefficient s\* values have significant linear relationships with coefficient c\* values when Rossavik growth models are fitted to sets of second- and third-trimester anatomical measurements. Estimates of predicted s\* can be obtained using functions relating s\* to c\* (estimated predicted s\* = c<sub>0</sub> + c<sub>1</sub> [estimated c\*]).

**Fetal growth pathology score (FGPS).** This score provides a quantitative measure of growth pathology and addresses a number of confounding variables present in longitudinal growth studies. The FGPS represents the average of available positive or negative pathological percent deviations [%Dev<sub>p</sub>] at the end of each ultrasound examination in the third-trimester (cumulative moving average) (see [Figure 7](#)). The FGPS can be used to detect growth abnormalities; estimate the onset, duration, and magnitude of pathological growth processes; and identify different growth abnormality patterns.

**Fetal weight estimation.** Fetal weight cannot be measured directly using ultrasound technology. Weight estimates are obtained from single anatomical measurements or a set of anatomical measurements. Predicted values for each anatomical parameter are obtained using the appropriate second-trimester—specified Rossavik size model. A predicted weight estimate is calculated using these predicted values and the weight estimation function. The measured weight estimate is calculated using the age-specific ultrasound measurements themselves and the same function.

**Fractional polynomials.** Fractional polynomials are a class of mathematical functions that have power values that are not limited to whole numbers. This property gives these functions great flexibility in modeling fetal size data.

**Individual composite prenatal growth assessment score (icPGAS).** This type of prenatal growth assessment score measures growth pathology at a single time point in the third trimester. It is the average of the pathological percent deviation (%Dev<sub>p</sub>) values obtained at a specific time point for a set of anatomical parameters used to evaluate different aspects of fetal growth (eg, head circumference, abdominal circumference, femur diaphysis length, estimated fetal weight).

**Individualized growth assessment (IGA).** A method for the evaluation of fetal growth and neonatal growth outcome in which each fetus is its own control, based on estimates of individual growth potentials. Third-trimester growth measurements and birth characteristics are compared with their predicted values obtained using size models specified in the second trimester.

**Individualized Growth Assessment Program (iGAP).** This Internet-based software implements the concepts of individualized growth assessment for clinical use or research. The application is freely available at <https://igap.research.bcm.edu/>.

**Individualized size trajectories.** Third-trimester predicted values for an anatomical parameter constitute its expected size trajectory in a given fetus. It is specific for that fetus and is unaffected by biological differences between fetuses. Only the second-trimester growth velocity and random modeling/measurement errors alter its shape. If second-trimester growth is normal, it is the most appropriate standard for evaluating subsequent third-trimester measurements.

**Modified prenatal growth assessment score (+PGAS, −PGAS).** The PGAS is a composite size parameter that averages pathological percent deviations (%Dev<sub>p</sub>) obtained in the third trimester. Macrosomia is evaluated using +PGAS values, whereas growth restriction is evaluated using −PGAS values. Serial calculations of +PGAS and −PGAS provide a quantitative means for characterizing third-trimester growth pathology.

**Modified prenatal growth assessment score reference ranges.** Age-specific reference ranges [95%] for modified prenatal growth assessment scores have been determined during the third trimester in fetuses with normal neonatal growth outcomes. Values outside the appropriate ranges are considered to be abnormal and indicative of a growth disorder.

**Percent Deviations (%Dev).** This statistic is used to compare third-trimester anatomical measurements to their predicted values: %Dev = [(measured value − predicted value)/predicted value] × 100]. The ideal value for a percent deviation is zero. Once all anatomical measurements are converted to percent deviations, they are in a common form that can be combined to form composite size parameters.

**Pathological percent deviation (%Dev<sub>p</sub>).** Pathological percent deviation is the part of the percent deviation above the upper limit (+p% Dev) or below the lower limit (−p%Dev) of its age-specific reference range. Percent deviations within the reference range are assigned % Dev<sub>p</sub> values of zero because no pathology was found. Pathological percent deviations quantify the magnitude of the growth pathology.

**Rossavik size model.** This is an equation that was empirically derived and is used to characterize fetal growth. The formula is the following:

$$P = c(t)^{k+s(t)}$$

P is the anatomical parameter

c, k, and s are the model coefficients (meaning and method of calculation are explained in this *Glossary*)

t is the duration of growth, which is menstrual age — start point

The size model can be specified for different parameters (eg, abdominal circumference, femur diaphysis length, biparietal diameter, estimated fetal weight, etc). It is derived from growth velocity measurements calculated using at least 2 ultrasound examinations in the second trimester of pregnancy, separated by at least 2–3 weeks.

- *Second-trimester Rossavik size model specification.* This size model can be specified if values for coefficients c, k, and s are known.
  - Coefficient k is a known constant whose value depends on the characteristics of the anatomical parameter being measured.
  - An estimate of coefficient c\* can be obtained from the slope of the second-trimester growth curve (growth velocity).
  - Predicted s\* values (used as estimates of coefficient s\*) can be obtained from estimates of coefficient c\* derived from second-trimester slopes.

The precise method for calculating these coefficients is available.<sup>89</sup> Moreover, the Individualized Growth Assessment Program calculates these coefficients based on the results of ultrasound examinations, obviating the need for clinicians to perform manual calculations using regression analysis.

**Second-trimester growth velocity (slope).** In the second trimester, the growth of all fetal biometric parameters, which are unidimensional (eg, abdominal circumference, femur diaphysis length, biparietal diameter, etc), is linear. It is believed that such linearity of growth in the second trimester is due to the fact that fetal nutritional requirements are easily met. This concept can be extended to 2- and 3-dimensional parameters by appropriate mathematical transformation of the data. The Individualized Growth Assessment Program performs these calculations automatically.

**Start Point (SP).** Growth of a given anatomical parameter can begin only when it first appears in embryological development (start point). Start points for anatomical parameters in a given fetus are determined by extrapolating the straight lines fitted to second-trimester measurements back to the point at which the lines cross the time (menstrual age) axis. It may be necessary to transform the measurements prior to fitting to use linear functions (eg, cube root of fractional thigh volume or square root of abdominal profile area).

**Third-trimester predicted values.** Second-trimester—specified Rossavik size models can be used to calculate predicted values for anatomical parameters at any time point in the third trimester. Usually the time points chosen are those for which sonographic measurements of the anatomical parameter are available.

**Time variable (t).** The time variable  $t$  in the Rossavik size model represents the duration of growth for a measured anatomical parameter. It is defined as menstrual age at the time of measurement minus the start point [ $t = \text{menstrual age} - \text{start point}$ ]. This time variable is necessary because the usual measure of fetal age (menstrual age) defines a time period that begins 2 weeks before conception.

#### *Neonatal growth evaluation*

**Fetal growth cessation.** Anatomical parameters of normally growing fetuses typically show minimal change in size at the end of the third trimester. For this reason, birth characteristics need to be predicted at the growth cessation age, not the birth age, after 38 weeks.

**Growth potential realization index (GPRI).** The GPRI indicates neonatal growth outcome for an individual anatomical parameter and is the ratio of the measured birth characteristic (mBC) to the predicted birth characteristic (prBC) as follows:

$$\text{GPRI} = (\text{mBC}/\text{prBC}) \times 100$$

Interpreting birth characteristic values are affected by several confounding variables including the following: (1) individual growth potential, (2) age at delivery, and (3) reference range to which they are compared. The prBC is derived from an estimate of the individual's growth potential and is predicted at the birth age or the growth cessation age as appropriate. GPRI standards are derived from neonates with known normal growth outcomes. The GPRI calculation transforms birth characteristic values into a common form, allowing direct comparisons and use in combinations to create composite growth outcome variables.

**Growth potential realization index correction factor.** Systematic birth characteristic prediction errors have been found for some anatomical parameters. These prediction errors can be corrected for by multiplying the predicted birth characteristic by a correction factor. The correction factor can be calculated using the following formula: correction factor =  $1 - (\text{systematic birth characteristic prediction error}/100)$ .

**Growth potential realization index (GPRI) reference range.** The ideal value for all GPRI values is 100%. In neonates with normal growth outcomes, the mean GPRI for all anatomical parameters was very close to 100%. In such neonates, the GPRI 95% ranges varied from 94–106% (crown-heel length) to 83–117% (weight).<sup>95</sup>

**Modified neonatal growth assessment score (mNGAS).** The mNGAS is a composite neonatal growth outcome parameter developed using a principal components analysis. This statistical procedure determines weighing factors for five GPRI:  $\text{mNGAS} = a_{\text{WT}} (\text{GPRI}_{\text{WT}}) + a_{\text{THC}} (\text{GPRI}_{\text{THC}}) + a_{\text{AC}} (\text{GPRI}_{\text{AC}}) + a_{\text{CHL}} (\text{GPRI}_{\text{CHL}}) + a_{\text{HC}} (\text{GPRI}_{\text{HC}})$ . The subscripts refer to the anatomical parameter, such as weight, thigh circumference, abdominal circumference, crown-heel length, head circumference). Coefficient values indicate the importance of a GPRI in separating different types of neonates (eg, growth restricted, normal, macrosomic). These 3 types of neonates have been separated with an accuracy of 96.9% in previous studies.<sup>81</sup>

**Pathological growth potential realization index (pGPRI).** Analogous to the pathological percent deviation, the pGPRI is the part of the GPRI above (+pGPRI) or below (−pGPRI) the 95% GPRI reference range and is obtained by subtraction. GPRI values within their reference ranges are assigned a pGPRI value of zero because no growth pathology is evident. The average of the −pGPRI values is a measure of growth restriction magnitude. Values greater than −0.69% are currently considered abnormal. There are insufficient data to determine whether the average +pGPRI is a measure of the degree of macrosomia.

**Prediction of birth characteristics.** Second-trimester—specified Rossavik growth models can generate predicted birth characteristics for any selected age if a time variable having the following form is used:  $t = (\text{menstrual age} - \text{start point})$ . These predicted values are calculated in essentially the same way as those used to evaluate fetal growth during the third trimester. Actual birth age is used for deliveries up to 38 weeks, menstrual age, and the growth cessation age after 38 weeks.

## OBSTETRICS

# A new customized fetal growth standard for African American women: the PRB/NICHD Detroit study



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**BACKGROUND:** The assessment of fetal growth disorders requires a standard. Current nomograms for the assessment of fetal growth in African American women have been derived either from neonatal (rather than fetal) biometry data or have not been customized for maternal ethnicity, weight, height, and parity and fetal sex.

**OBJECTIVE:** We sought to (1) develop a new customized fetal growth standard for African American mothers; and (2) compare such a standard to 3 existing standards for the classification of fetuses as small (SGA) or large (LGA) for gestational age.

**STUDY DESIGN:** A retrospective cohort study included 4183 women (4001 African American and 182 Caucasian) from the Detroit metropolitan area who underwent ultrasound examinations between 14-40 weeks of gestation (the median number of scans per pregnancy was 5, interquartile range 3-7) and for whom relevant covariate data were available. Longitudinal quantile regression was used to build models defining the “normal” estimated fetal weight (EFW) centiles for gestational age in African American women, adjusted for maternal height, weight, and parity and fetal sex, and excluding pathologic factors with a significant effect on fetal weight. The resulting Perinatology Research Branch/*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (hereinafter, PRB/NICHD) growth standard was compared to 3 other existing standards—the customized gestation-related optimal weight (GROW) standard; the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (hereinafter, NICHD) African American standard; and the multinational World Health Organization (WHO) standard—utilized to screen fetuses for SGA (<10th centile) or LGA (>90th centile) based on the last available ultrasound examination for each pregnancy.

**RESULTS:** First, the mean birthweight at 40 weeks was 133 g higher for neonates born to Caucasian than to African American mothers and 150 g higher for male than female neonates; maternal weight, height, and parity had a positive effect on birthweight. Second, analysis of longitudinal EFW revealed the following features of fetal growth: (1) all weight centiles were

about 2% higher for male than for female fetuses; (2) maternal height had a positive effect on EFW, with larger fetuses being affected more (2% increase in the 95th centile of weight for each 10-cm increase in height); and (3) maternal weight and parity had a positive effect on EFW that increased with gestation and varied among the weight centiles. Third, the screen-positive rate for SGA was 7.2% for the NICHD African American standard, 12.3% for the GROW standard, 13% for the WHO standard customized by fetal sex, and 14.4% for the PRB/NICHD customized standard. For all standards, the screen-positive rate for SGA was at least 2-fold higher among fetuses delivered preterm than at term. Fourth, the screen-positive rate for LGA was 8.7% for the GROW standard, 9.2% for the PRB/NICHD customized standard, 10.8% for the WHO standard customized by fetal sex, and 12.3% for the NICHD African American standard. Finally, the highest overall agreement among standards was between the GROW and PRB/NICHD customized standards (Cohen’s interrater agreement,  $\kappa = 0.85$ ).

**CONCLUSION:** We developed a novel customized PRB/NICHD fetal growth standard from fetal data in an African American population without assuming proportionality of the effects of covariates, and without assuming that these effects are equal on all centiles of weight; we also provide an easy-to-use centile calculator. This standard classified more fetuses as being at risk for SGA compared to existing standards, especially among fetuses delivered preterm, but classified about the same number of LGA. The comparison among the 4 growth standards also revealed that the most important factor determining agreement among standards is whether they account for the same factors known to affect fetal growth.

**Key words:** comparison of fetal growth standards, customized fetal growth standards, ethnic differences, fetal biometry, fetal growth restriction, fetal sex, large for gestational age, maternal height, maternal weight, parity, quantile regression, small for gestational age

## Introduction

Growth is a time-dependent change of bodily dimensions.<sup>1</sup> The human fetus grows at a particularly rapid rate,<sup>2,3</sup> and this is important because a principle of developmental biology is that organisms are more susceptible to injury during

periods of fast growth.<sup>4</sup> Birthweight has been used extensively as a parameter to characterize the appropriateness of fetal growth<sup>5</sup> and, to date, remains the most frequently used index to assess size as a proxy to growth. Therefore, in clinical practice, many obstetricians rely on the assessment of sonographic estimation of fetal weight to evaluate fetal size and growth.<sup>6-12</sup> Although the terms “fetal size” and “fetal growth” are not synonymous, there is a relationship between

the two, and this is why “fetal size charts” have been referred to as “fetal growth charts.”

Fetal weight is estimated from ultrasound measurements of fetal biometric parameters (eg, biparietal diameter [BPD], abdominal circumference [AC], femur length [FL], and head circumference [HC]) using 1 of many mathematical formulas.<sup>13-16</sup> One widely used equation for estimated fetal weight (EFW) is that proposed by Hadlock et al,<sup>14</sup> which

includes HC, AC, and FL. Assessment of the appropriateness of fetal size is performed by comparing the observed EFW to a standard. Yet, which standard should be used is a subject of debate.

One issue is whether the same standard, referred to as “population-based,” should be used for all fetuses,<sup>16</sup> or whether the standard should be customized for physiologic and constitutional factors known to affect neonatal size at birth<sup>17-19</sup> as well as EFW.<sup>20,21</sup>

One of the most widely used population-based growth charts was proposed by Hadlock et al<sup>22</sup> based on data collected from 392 Caucasian women in the United States. The same investigators suggested using the 10th and 90th centiles of the EFW to evaluate fetal size and growth—adopting the concepts of Battaglia and Lubchenco,<sup>5</sup> who classified neonates with a birthweight <10th centile as small for gestational age (SGA) and those >90th centile as large for gestational age (LGA). However, fetuses with an EFW <10th or >90th centile are a heterogeneous group: some SGA fetuses have growth deceleration, and others are constitutionally small. Growth-restricted fetuses are those that have deviated from their growth potential, unlike those who are constitutionally small. Similar concepts apply to LGA fetuses, which could either experience fetal growth acceleration or be constitutionally large.<sup>23</sup>

To address the need for distinguishing between constitutionally small or large fetuses and those affected by growth disorders, Gardosi et al<sup>17,18</sup> proposed to customize the chart of Hadlock et al<sup>22</sup> by shifting the normal EFW centiles proportionally up or down so that the mean weight at 40 weeks matches “term optimal weight.” Term optimal weight is personalized for each fetus based on maternal ethnicity, height, weight, and parity and fetal sex, and excludes pathological factors known to affect birthweight, such as smoking. This approach, referred to as gestation-related optimal weight (GROW), derives customization coefficients for nonpathologic maternal characteristics and fetal sex by analyzing birthweight data in local populations.<sup>19,24,25</sup>

Other approaches to the customization of growth charts include the individualized growth assessment<sup>26-28</sup> that assumes all relevant factors that determine the growth potential of a fetus are captured in the rate of growth during the second trimester. The importance of considering longitudinal measurements to derive fetus-specific growth velocity was also highlighted by Sovio et al,<sup>29</sup> who found that the SGA fetuses identified based on the chart of Hadlock et al<sup>22</sup> were at risk for neonatal morbidity only if their fetal AC growth velocity was in the lowest decile.<sup>29,30</sup>

Although several studies suggest that estimates for the association between adverse neonatal outcomes and abnormal birthweight are higher for customized than noncustomized (population-based) standards,<sup>31-37</sup> recent initiatives undertaken to develop growth standards proposed either population-based or only partially customized standards. For example, the INTERGROWTH-21st study<sup>16,38-40</sup> proposed a one-size-fits-all standard derived from a multiethnic population. By contrast, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) fetal growth studies<sup>21</sup> reported standards specific to 4 different ethnic-racial groups (non-Hispanic White, Hispanic, African American, and Asian),<sup>21</sup> yet customization by factors other than race was not provided. Recently, a study sponsored by the World Health Organization (WHO)<sup>20,41</sup> proposed a multiethnic growth standard customized only by fetal sex, despite the observation that other factors (eg, country of origin, maternal age, height, and parity) had independent effects on EFW. Of interest, by using quantile regression to model EFW data (an approach that does not rely on assuming normal distribution of the data), the investigators reported that the effects of several factors (eg, maternal height and weight, fetal sex) were graded among the centiles of weight distribution. For example, maternal weight had a higher effect on larger fetuses than on smaller fetuses.<sup>20</sup>

The most widely adopted customization approach is that of Gardosi

et al,<sup>18</sup> which is based on birthweight data and assumes that the effects of covariates are proportional during gestation (eg, fetuses of parous mothers will have a higher EFW than those of nulliparous mothers by the same proportion at all gestational ages). However, the assumption of proportionality has not been tested thus far using longitudinal fetal data. Our study is based on a cohort of pregnant women who attended our center in Detroit, MI, where the predominant ethnic group is African American based on self-reporting. The objectives of this study were to (1) develop a new customized fetal growth standard for African American women; and (2) compare the standard derived from our population to 3 existing standards for the classification of fetuses as SGA and LGA.

## Materials and Methods

### Study population

This retrospective longitudinal cohort study was conducted at the Center for Advanced Obstetrical Care and Research of the Perinatology Research Branch (PRB), NICHD, National Institutes of Health, US Department of Health and Human Services. The Center is housed at Hutzel Women’s Hospital in partnership with the Wayne State University School of Medicine in Detroit, MI. All patients included in this study provided written informed consent for ultrasound examinations and were enrolled in research protocols approved by the Human Investigation Committee of Wayne State University and the Institutional Review Board of NICHD.

From 2002 through 2016, 4681 pregnant women were enrolled and had ultrasound examinations performed by a maternal-fetal specialist or a senior sonographer with >3 years of experience who performs a minimum of 300 ultrasound scans per year. More than 95% of women were actually enrolled from 2006 through 2015, at an average enrollment of 445 per year, which represents about 25% of the yearly enrollment at our clinic. Women self-reported as African American, 4239 (90.6%); Caucasian, 197 (4.2%); Hispanic, 31 (0.7%); Asian, 31 (0.7%); and 183 (3.9%) either as other or

unknown race or ethnicity. African American and Caucasian women were included in this study, regardless of pregnancy outcome, if they met the following criteria: (1) age 18-40 years; and (2) had at least 1 ultrasound examination performed between 14-40 weeks of gestation with available measurements of the AC, HC, FL, BPD, and gestational age at each examination. Of the 4143 African American and 188 Caucasian women who met these inclusion criteria, 4 were excluded because of outlier fetal biometric measurements, and 144 (3.3%) were excluded because of missing data on maternal weight, height, and parity or fetal sex, resulting in 4001 African American and 182 Caucasian women (Supplementary Figure 1).

### Ultrasound examinations

Ultrasound studies were performed using the General Electric Voluson Expert and Voluson E8 (GE Healthcare, Milwaukee, WI) ultrasound systems and 5- to 2-MHz probes. Biometric measurements were obtained using methods previously described by Chitty et al<sup>42-44</sup> and Altman and Chitty,<sup>45</sup> which are consistent with recommendations of the International Society of Ultrasound in Obstetrics and Gynecology<sup>46</sup> and the American Institute of Ultrasound in Medicine.<sup>47</sup> Fetal biometric parameters included: (1) BPD (outer edge to inner edge of the calvarium); (2) HC (ellipse around the outside of the calvarium); (3) AC (ellipse placed at the outer surface of the skin); and (4) FL (calipers placed at the ends of the ossified diaphysis). EFW was computed from the AC, HC, and FL measurements using the formula of Hadlock et al<sup>14</sup> to enable direct comparison to previous standards. The indices of proportionality (HC/AC, FL/AC, and BPD/FL) were also determined. The median number of ultrasound examinations per pregnancy was 5 (interquartile range [IQR] 4-7). Gestational age was determined based on the last menstrual period and validated during the first ultrasound examination either by crown-rump length or BPD measurement.

### Statistical analysis

#### Effect of covariates on birthweight

We used multilinear regression with backward elimination as described by Gardosi and Francis<sup>19</sup> to assess the effect of covariates on birthweight at 40 weeks of gestation (280 days). The birthweight of neonates born  $\geq 37$  gestational weeks was regressed on self-reported ethnicity, height and weight, parity, fetal sex, and gestational age at delivery as well as the following pathologic factors: extremely low or high body mass index (BMI) (defined as  $<20.5$  kg/m<sup>2</sup> or  $>40.5$  kg/m<sup>2</sup>, respectively), smoking status, gestational diabetes mellitus, hypertension, preeclampsia, and fetal anomalies. A *P* value  $<.05$  was considered significant.

#### Development of a customized (PRB/NICHD) fetal growth standard for African American women

We used penalized fixed-effects quantile regression models<sup>48,49</sup> to fit individual centiles (5th, 10th, 50th, 90th, and 95th) of the distributions of fetal biometric parameters, indices of proportionality, and EFW as a function of gestational age. We relied on Bayesian information criteria recommended by Lee et al<sup>50</sup> to determine the “shrinkage parameter” of the fetus-specific fixed effects. The resulting population-level centiles (ie, noncustomized, and representing the entire study population) were superimposed on the raw data for visualization purposes and compared to other noncustomized standards, such as the NICHD African American standard<sup>21</sup> and the WHO standard noncustomized by fetal sex.

To determine the effect of covariates on fetal weight centiles, additional covariates were considered for inclusion in the quantile regression models and retained if significant: maternal height, weight, and parity; fetal sex; extremely low or high BMI; smoking status; diabetes; hypertension; preeclampsia; preterm delivery; fetal anomalies; and, importantly, interaction terms between these covariates and gestational age. The 5th, 10th,

50th, 90th, and 95th centiles of EFW were derived from a model that had the same terms but eventually different coefficients for each centile curve. The EFW data were first log transformed; therefore, each covariate without a significant interaction with gestational age had a constant proportional effect on a given EFW centile throughout gestation. The effects of covariates were reported as a percentage of change in estimated weight.

Although fitting of the quantile regression models involved EFW data from all pregnancies regardless of outcome, the prediction of customized normal centiles from the quantile regression models was based only on the contribution of nonpathologic factors that affect growth. This is in keeping with the concept proposed by Gardosi et al.<sup>18</sup>

All statistical analyses were conducted using the R statistical language and environment ([www.r-project.org](http://www.r-project.org)), including the *rqpd* package for longitudinal quantile regression, available from R-Forge (<https://r-forge.r-project.org>). Centiles for the customized GROW standard were obtained using the bulk centile calculator version 6.7.8\_US from the authors' website (<https://www.gestation.net/>).

## Results

### Maternal characteristics

For the group of 4001 African American women, the median maternal age, height, and weight were 23 (IQR 20-27) years, 163 (IQR 157-168) cm, and 73 (IQR 61-91) kg, respectively. There were 632 women (15.8%) who delivered preterm ( $<37$  weeks of gestation), and 1457 (36%) were nulliparous.

For the group of 182 Caucasian women, the median maternal age, height, and weight were 26 (IQR 22-30) years, 163 (IQR 157-168) cm, and 68 (IQR 59-84) kg, respectively. There were 29 women (15.9%) who delivered preterm, and 67 (37%) were nulliparous.

### Factors affecting birthweight of neonates delivered at term

Neonatal data were analyzed from 3368 African American and 152 Caucasian women who delivered at term and had

**TABLE 1**  
**Effect of covariates on birthweight in women with term delivery**

Variable	Birthweight, g		P value
	Coefficient	SE	
Intercept	3223	16.3	<.001
GA from 40 wk			
Linear	144	10.3	<.001
Quadratic	-15	6.0	.02
Cubic	3	2.7	.36
Sex			
Male	150	13.3	<.001
Race			
Caucasian	133	32.9	<.001
Maternal height (from 163 cm) <sup>a</sup>	78	10.6	<.001
Maternal weight (from 64 kg) <sup>b</sup>	25	5.1	<.001
Parity			
Para 1	58	16.6	<.001
Para 2	96	19.6	<.001
Para 3	85	20.5	<.001
Low BMI (<20.5 kg/m <sup>2</sup> )	-81	25.4	.001
High BMI (>40.4 kg/m <sup>2</sup> )	-40	32.1	.21
Smoking	-92	17.2	<.001
Diabetes	247	35.1	<.001

Analysis involved data from 3368 African American and 152 Caucasian women who delivered at term and had available birthweight data. In the regression model ( $R^2 = 0.28$ ), intercept (3223 g) represents mean birthweight at 40 wk (280 d) of GA for a nulliparous African American mother, having a height of 163 cm, weighing 64 kg at first visit, nonsmoking, and without diabetes; 10th/90th centiles of BMI in African American women in the study population were used to define abnormally low and high BMI, respectively.

BMI, body mass index; GA, gestational age.

<sup>a</sup> Effect is estimated for 10-cm increments in maternal height; <sup>b</sup> Effect is estimated for 10-kg increments in maternal weight.

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available birthweight data. **Table 1** shows the results of multilinear regression of birthweight on gestational age at delivery, maternal weight, height, and parity and fetal sex, as well as pathologic risk factors: extremely low or high BMI, smoking, and diabetes. All of these variables explained 28% of the variance in birthweight at term ( $R^2 = 0.28$ ).

The mean birthweight at 40 weeks (280 days) was 3223 g for a female fetus born to a nulliparous African American mother having a height of 163 cm, weighing 64 kg at the first visit, nonsmoking, and without diabetes (**Table 1**). Such a combination of

maternal weight and height for the reference pregnancy was used to enable direct comparisons to previously reported effects on birthweight in a different US population.<sup>19</sup> Independent of all other factors listed in **Table 1**, mean birthweight was higher for male fetuses (by 150 g), Caucasian mothers (by 133 g), and parous women (58 g, 96 g, and 85 g for parity 1, 2, and  $\geq 3$ , respectively). An additional 10 cm in maternal height increased birthweight by 78 g, and an additional 10 kg of maternal weight was associated with a 25-g increase in birthweight. Such increments in maternal height and weight were chosen to enable comparison to a previous study.<sup>20</sup>

A low BMI (<10th percentile, 20.5 kg/m<sup>2</sup>) was associated with an 81-g decrease in mean birthweight, whereas a high BMI (>90th percentile, 40.4 kg/m<sup>2</sup>) had a negative effect on the mean birthweight that did not reach statistical significance (40 g,  $P = .21$ ). Smoking was associated with a 92-g decrease in mean birthweight, while diabetes was associated with a 247-g increase in mean birthweight. Preeclampsia, gestational hypertension, and fetal anomalies were considered as pathologic covariates, but they did not have a significant effect on term birthweight (all  $P > .05$ ) and were not included in the regression model (**Table 1**). Neonates with congenital anomalies had a lower mean birthweight (71-g difference); however, this was not significant, probably due to the low prevalence of congenital anomalies in our cohort (1.8%). Although more prevalent, preeclampsia (4.8%) and gestational hypertension (13.1%) had a smaller magnitude of effect; hence, they were also nonsignificant in this analysis.

### Customized fetal growth standard for the African American population in Detroit, MI

Given the ethnic differences in EFW reported in the NICHD study<sup>21</sup> and in birthweight data reported herein, combined with the limited number of Caucasian women in our study population, we decided to focus on developing a customized fetal growth standard for African American women. Non-customized centiles (5th, 10th, 50th, 90th, and 95th) of fetal biometric parameters, EFW, and indices of proportionality for all 4001 African American women (regardless of clinical outcome) are shown in **Supplementary Figure 2**. The centile curves in **Supplementary Figure 2** can be considered a local reference since about 10% of data points are </>10th/90th centiles and no pathologic factors were excluded. The local reference for EFW was superimposed onto the noncustomized NICHD African American and WHO standards (**Supplementary Figure 3**). While the 10th, 50th, and 90th EFW centile curves for our local reference were systematically lower than those of

the WHO standard, the variability in estimated weight at 40 weeks (distance between the 10<sup>th</sup> and 90<sup>th</sup> centiles) were similar. By contrast, the 10<sup>th</sup> centile of the NICHD standard was lower (especially close to term), the 50<sup>th</sup> centile was about the same, and the 90<sup>th</sup> centile was higher than that of our local reference (Supplementary Figure 3).

To define a customized EFW chart that corresponds to normal growth, we fitted quantile regression models that included maternal height, weight, and parity and fetal sex, while accounting for and excluding the contribution of pathologic factors with significant effect on at least 1 of the weight centiles: extremely low or high BMI, smoking, diabetes, preterm delivery, and fetal anomalies (Supplementary Table). Figure 1 shows the effects of nonpathologic covariates on the predicted normal fetal weight centiles (10<sup>th</sup>, 50<sup>th</sup>, and 90<sup>th</sup>). In Figure 1, the EFW standard used as the baseline (continuous lines) corresponds to a female fetus of a nulliparous African American mother, who is 163 cm in height and 64 kg in weight. Since the effects (derived from quantile regression models described in the Supplementary Table) may vary with gestational age for some covariates, these effects are presented at 2 gestational ages (30 and 40 weeks) in Table 2 and can be summarized as follows:

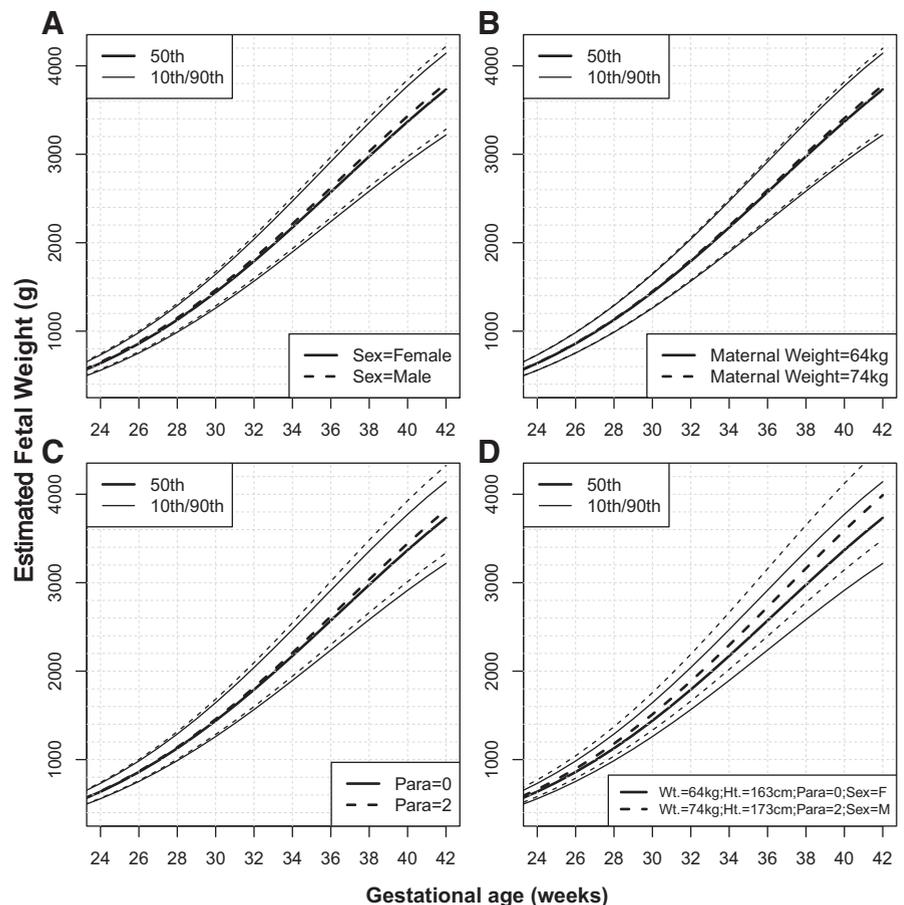
### Fetal sex

The EFW of male fetuses was about 2% higher than that of female fetuses, independent of all other factors listed in Table 2. This effect was similar among all centiles of the distribution that were evaluated (5<sup>th</sup>, 10<sup>th</sup>, 50<sup>th</sup>, 90<sup>th</sup>, and 95<sup>th</sup>). Since no interaction was found between fetal sex and gestational age, customization by fetal sex involves a proportional increase of the entire chart (all centile curves) by about 2% for male fetuses (Figure 1, A, and Table 2).

### Maternal height

This covariate had a significant effect on all centiles of EFW, yet the effect was higher for the most extreme centiles. The 95<sup>th</sup> EFW centile increased by about 2% for each additional 10 cm of maternal height while the 5<sup>th</sup> centile increased by

**FIGURE 1**  
Effect of covariates on fetal growth in African American women



Unless otherwise stated, continuous lines represent the estimated fetal weight median and 10<sup>th</sup>/90<sup>th</sup> centiles for a female (F) fetus born at term to a nulliparous African American mother with a height (Ht) of 163 cm and a weight (Wt) of 64 kg at the first visit. Interrupted lines show how the chart would change for: **A**, male (M) fetus; **B**, additional 10 kg of maternal Wt; **C**, mother in her third pregnancy (parity = 2); and **D**, combination of factors (additional 10 kg in maternal Wt, additional 10 cm Ht, parity of 2, and M fetus).

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about 1%. The interaction between maternal height and gestational age was not significant; therefore, customization by maternal height involved a proportional shift of the EFW chart for taller mothers, with higher centile curves being shifted more than the lower centiles (Table 2).

### Maternal weight

For women with a BMI between the 10<sup>th</sup> and 90<sup>th</sup> percentiles of the population, the effect of maternal weight on all centiles of EFW at 40 weeks was up to a 1.4% increase for each additional 10 kg

in maternal weight. However, since the interaction between maternal weight and gestational age was significant for all centiles, the effect of maternal weight increased with gestational age, being about twice as high at 40 weeks as it was at 30 weeks of gestation (Figure 1, B, and Table 2).

### Parity

Fetuses of parous women had a higher EFW than those of nulliparous women, although the magnitude of such an effect varied among centiles and changed with gestational age. For example, compared

**TABLE 2**  
**Effect of covariates on estimated fetal weight at 30 and 40 weeks of gestation**

	EFW (g) at 30 wk					EFW (g) at 40 wk				
	5th	10th	50th	90th	95th	5th	10th	50th	90th	95th
	1206	1260	1440	1643	1716	2777	2914	3369	3773	3902
Effect (% change)										
Fetal sex (male)	2.3 <sup>a</sup>	2 <sup>a</sup>	1.9 <sup>a</sup>	1.9 <sup>a</sup>	2.4 <sup>a</sup>	2.3 <sup>a</sup>	2 <sup>a</sup>	1.9 <sup>a</sup>	1.9 <sup>a</sup>	2.4 <sup>a</sup>
Maternal height (10 cm)	0.9 <sup>a</sup>	1.0 <sup>a</sup>	1.2 <sup>a</sup>	1.8 <sup>a</sup>	1.9 <sup>a</sup>	0.9 <sup>a</sup>	1.0 <sup>a</sup>	1.2 <sup>a</sup>	1.8 <sup>a</sup>	1.9 <sup>a</sup>
Maternal weight (10 kg)	0.6 <sup>a</sup>	0.7 <sup>a</sup>	0.6 <sup>a</sup>	0.6 <sup>a</sup>	0.6 <sup>a</sup>	1.4 <sup>a</sup>	1.4 <sup>a</sup>	1.1 <sup>a</sup>	1.2 <sup>a</sup>	1.1 <sup>a</sup>
Para 1	0.1	0.8 <sup>a</sup>	0.5 <sup>a</sup>	1.1 <sup>a</sup>	0	1.1	2.1 <sup>a</sup>	0.7	2.4 <sup>a</sup>	0.7
Para 2	1.4 <sup>a</sup>	1.9 <sup>a</sup>	1.2 <sup>a</sup>	2.4 <sup>a</sup>	1.4 <sup>a</sup>	3.4 <sup>a</sup>	3.4 <sup>a</sup>	2.2 <sup>a</sup>	4.1 <sup>a</sup>	3.0 <sup>a</sup>
Para 3	1.0	0.9	1.5 <sup>a</sup>	2.3 <sup>a</sup>	1.8 <sup>a</sup>	1.1	0.2	2.4 <sup>a</sup>	4.0 <sup>a</sup>	3.7 <sup>a</sup>
BMI <20.5	1.6	0.8	-1.4 <sup>a</sup>	-2.0 <sup>a</sup>	-2.2 <sup>a</sup>	1.6 <sup>a</sup>	0.8	-1.4 <sup>a</sup>	-2.0 <sup>a</sup>	-2.2 <sup>a</sup>
BMI >40.4	-1.4	-1.3	-0.9 <sup>a</sup>	-0.2	1.0	-5.3 <sup>a</sup>	-4.6 <sup>a</sup>	-3.3 <sup>a</sup>	-1.7	0.2
Smoking (yes)	-3.6 <sup>a</sup>	-2.8 <sup>a</sup>	-2.1 <sup>a</sup>	-2.5 <sup>a</sup>	-2.5 <sup>a</sup>	-7.8 <sup>a</sup>	-5.5 <sup>a</sup>	-3.2 <sup>a</sup>	-3.5 <sup>a</sup>	-2.4 <sup>a</sup>
Diabetes	5.4 <sup>a</sup>	4.6 <sup>a</sup>	3.4 <sup>a</sup>	3.7 <sup>a</sup>	3.1 <sup>a</sup>	6.5 <sup>a</sup>	5.6 <sup>a</sup>	4.2 <sup>a</sup>	4.6 <sup>a</sup>	4.5 <sup>a</sup>
Preterm delivery	-12.0 <sup>a</sup>	-9.8 <sup>a</sup>	-2.8 <sup>a</sup>	0.3	1.3	-14.5 <sup>a</sup>	-11.9 <sup>a</sup>	-3.5 <sup>a</sup>	-0.7	1.3
Fetal anomalies	-5.1 <sup>a</sup>	-3.7 <sup>a</sup>	-2 <sup>a</sup>	-0.8	0.8	-5.1 <sup>a</sup>	-3.7 <sup>a</sup>	-2 <sup>a</sup>	-0.8	0.8

Top panel shows EFW centiles at 30 wk (left) and 40 wk (right) of gestation for a female fetus of a nulliparous African American mother, having a height of 163 cm, weighing 64 kg at the first visit, nonsmoking, and without diabetes. Middle and bottom panels display the effects of nonpathologic and pathologic covariates, respectively. Effects are expressed as percentage change in weight. Positive values correspond to an increase while negative values correspond to a decrease in EFW centiles. For example, the effect of fetal sex (male vs female) is associated with about a 2% increase in EFW, and this effect is the same at 30 and 40 wk gestation and affects all centiles similarly. By contrast, maternal height has a stronger positive effect at higher EFW centiles, and this effect does not depend on gestation. Positive effect of additional 10 kg in maternal weight (with normal BMI range) is about twice as large at 40 wk as at 30 wk for all centiles.

BMI, body mass index; EFW, estimated fetal weight.

<sup>a</sup> Significant effects ( $P < .05$ ).

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to nulliparous women, the 90th centile of EFW for women in their third pregnancy (parity = 2) was 4.1% higher at 40 weeks but only 2.4% higher at 30 weeks of gestation (Figure 1, C, and Table 2).

Figure 1, D, illustrates the combined effect of change in multiple covariates on the normal growth chart of African American women. For example, at 40 weeks of gestation, the 90th centile of EFW for a male fetus of a mother in her third pregnancy (para = 2), who is 173 cm tall and weighs 74 kg, is 9% higher (4122 g) than for a female fetus of a nulliparous mother who is 10 cm shorter and weighs 10 kg less (3773 g).

The effects of pathologic factors on EFW were higher than those of nonpathologic variables, and such effects also varied across gestation and among

the centiles (Table 2). The effect of maternal complications that led to a preterm delivery was associated with a 12% reduction in the 5th centile of EFW at 30 weeks, and with a 5.3% and a 7.8% reduction at 40 weeks for women with a high BMI and those who smoked, respectively.

The equations describing the PRB/NICHD customized chart are provided in Supplementary Table along with an example of the calculation of centiles. In addition, we provide a user-friendly spreadsheet calculator, available from the authors' website (<http://bioinformaticsprb.med.wayne.edu/>). This tool allows: (1) interactive exploration of the effect of covariates on the growth chart; (2) obtaining the customized centile corresponding to an observed EFW value (determined from AC, HC,

and FL measurements) for a given gestational age; and (3) printing of the entire customized chart for a given pregnancy.

### Comparison of fetal growth standards for classifying fetuses as SGA or LGA

Our next objective was to determine how different fetal growth standards affect the classification of pregnancies as being at risk for either an SGA or LGA fetus. Therefore, we applied 4 different growth standards, including the PRB/NICHD standard developed herein, to classify fetuses of 4001 African American women based on the observed EFW at the last available ultrasound examination. The median gestational age at the last examination was 36.0 (IQR 33-38) weeks. We determined the overall

TABLE 3

## Percentage of unselected pregnancies predicted at risk of a small- (&lt;10th) or large- (&gt;90th) for-gestational-age neonate by different standards

	Fetuses classified as SGA <10th, %			Fetuses classified as LGA >90th, %		
	Preterm	Term	All	Preterm	Term	All
NICHD AA	17.6 (14.7–20.8)	5.3 (4.6–6.1)	7.2 (6.4–8.1)	13 (10.5–15.9)	12.2 (11.2–13.4)	12.3 (11.4–13.4)
WHO	24.2 (21–27.8)	10 (9–11)	12.2 (11.2–13.3)	10.6 (8.4–13.3)	10 (9–11.1)	10.1 (9.2–11.1)
WHO by sex	24.5 (21.3–28.1)	10.8 (9.8–11.9)	13 (12–14.1)	11.9 (9.5–14.7)	10.6 (9.6–11.7)	10.8 (9.8–11.8)
GROW	26.3 (22.9–29.9)	9.7 (8.7–10.7)	12.3 (11.3–13.4)	7.8 (5.8–10.2)	8.9 (7.9–9.9)	8.7 (7.9–9.6)
PRB/NICHD AA	29 (25.5–32.7)	11.6 (10.6–12.8)	14.4 (13.3–15.5)	8.9 (6.8–11.4)	9.2 (8.3–10.3)	9.2 (8.3–10.1)

Standards compared are the NICHD AA, WHO with or without customization by fetal sex, customized GROW, and PRB/NICHD customized for AA women. Analysis of SGA and LGA is based on the last available scan of each pregnancy; median gestational age at the last scan is 36.0 (interquartile range 33–38) wk. Proportion (95% confidence intervals) of fetuses classified as SGA or LGA was determined for pregnancies delivered preterm (<37 wk), at term, and overall.

AA, African American; GROW, gestation-related optimal weight; LGA, large for gestational age; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development/National Institutes of Health; PRB, Perinatology Research Branch; SGA, small for gestational age; WHO, World Health Organization.

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proportions of fetuses that screened positive for SGA or LGA, but also separately for women with a term or a preterm delivery (Table 3).

The percentage of fetuses classified as SGA (<10th centile) was as follows: (1) NICHD African American standard, 7.2%; (2) GROW standard, 12.3%; (3) WHO standard, 12.2% (13% if customized by fetal sex); and (4) PRB/NICHD standard, 14.4%. All fetal growth standards except the NICHD African American standard classified more SGA fetuses than the expected 10% cut-off.

The proportion of fetuses classified as SGA was 2- to 3-fold higher among women who delivered preterm compared to those who delivered at term, depending upon the standard used. The rate of SGA among fetuses delivered preterm was as follows: NICHD African American standard, 17.6%; WHO standard, 24.2% (24.5% if customized by fetal sex); GROW standard, 26.3%; and PRB/NICHD standard, 29%.

To illustrate the similarity among the 4 different standards, we constructed a Venn diagram to represent the number of fetuses classified as SGA by each combination of standards (Figure 2, A). All fetuses identified as SGA by the NICHD African American standard were also identified by at least 2 other standards. Of note, the WHO standard

classified 71 fetuses as SGA that were not identified as such by any other standard. The highest agreement among standards, as assessed by Cohen's kappa coefficient, occurred between the PRB/NICHD and GROW standards ( $kappa = 0.84$ ), followed by the PRB/NICHD standard and the WHO standard customized by fetal sex ( $kappa = 0.79$ ). On the other hand, the lowest agreement, although still substantial,<sup>51</sup> was between the NICHD African American and PRB/NICHD standards ( $kappa = 0.63$ ).

The percentage of fetuses classified as LGA was: (1) GROW, 8.7%; (2) PRB/NICHD customized, 9.2%; (3) WHO, 10.1% (10.8% if customized by fetal sex); and (4) NICHD African American standards, 12.3%. Of note, the LGA rates for the GROW and NICHD African American standards were significantly lower or higher than the expected 10% cut-off, respectively (Table 3).

Unlike the rate of SGA, the rate of LGA was similar between fetuses delivered preterm or at term, for all fetal growth standards (Table 3).

The agreement among the different standards for LGA classification can be visualized in the Venn diagram in Figure 2, B. The PRB/NICHD and GROW standards were in high agreement ( $kappa = 0.85$ ), and the same was true for the WHO standard customized by fetal sex and NICHD African

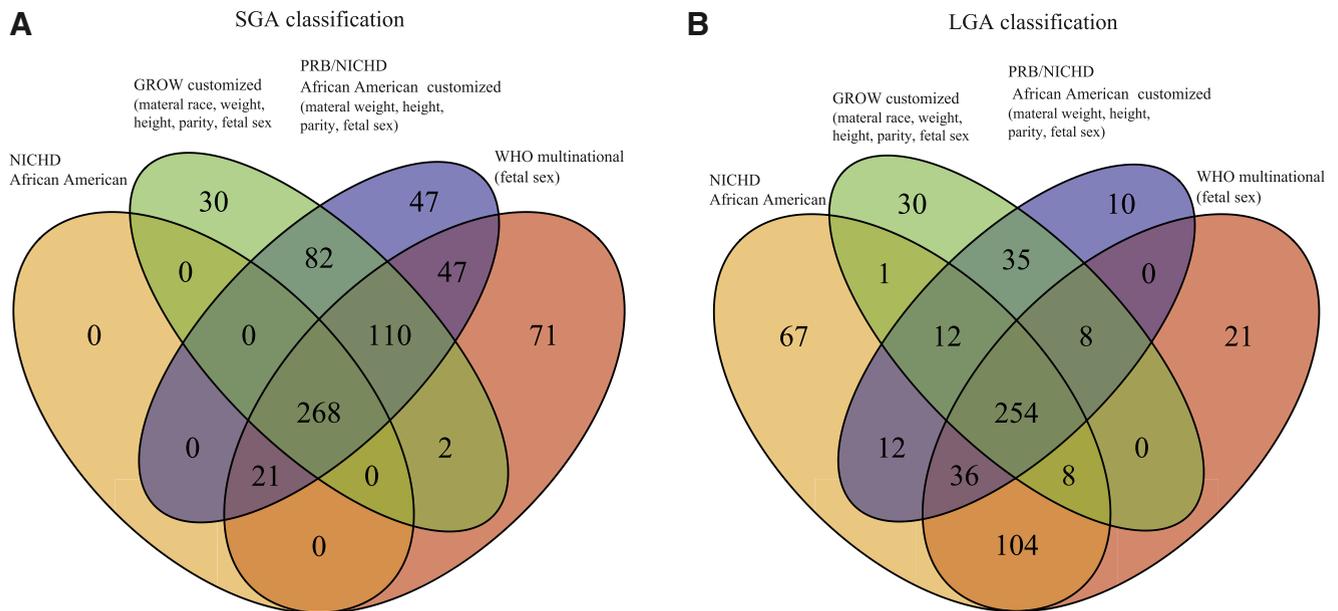
American standards ( $kappa = 0.85$ ). Even the least similar pair of standards (NICHD African American and GROW) was still in substantial agreement for the LGA classification ( $kappa = 0.61$ ).

## Comment

The principal findings of the study are as follows. First, the birthweight of a term neonate is affected by maternal ethnicity, weight, height, and parity and fetal sex. Second, longitudinal fetal weight analysis revealed the following features of fetal growth: (1) all weight centiles were about 2% higher for male than for female fetuses; (2) maternal height had a positive effect on fetal weight, with larger fetuses being affected more (2% increase in the 95th centile of weight for each 10-cm increase in height); and (3) maternal weight and parity had positive effects on fetal weight that increased with gestation and varied among the weight centiles. Third, the rate of SGA was 7.2% for the NICHD African American standard, 12.3% for the GROW standard, 13% for the WHO standard customized by fetal sex, and 14.4% for the PRB/NICHD customized standard herein. For all standards, the proportion of SGA was at least 2-fold higher among fetuses delivered preterm than at term. Fourth, the rate of LGA was 8.7% for the GROW standard,

FIGURE 2

## Agreement among standards for small (SGA)- and large (LGA)-for-gestational-age screening



Fetuses of African American (AA) women were classified as A, SGA (<10th) or B, LGA (>90th) based on the last available scan before delivery using 4 standards: the NICHD AA, the WHO customized by fetal sex, the customized GROW, and the customized PRB/NICHD AA. For SGA classification, the highest agreement among standards, as assessed by Cohen's kappa coefficient, occurred between PRB/NICHD AA and GROW ( $kappa = 0.84$ ), followed by PRB/NICHD AA and WHO customized by fetal sex ( $kappa = 0.79$ ), while the least agreement was indicated between NICHD AA and PRB/NICHD AA ( $kappa = 0.63$ ). For LGA classification, the highest agreement among standards occurred between PRB/NICHD AA and GROW and also between WHO customized by fetal sex and NICHD AA (both pairs,  $kappa = 0.85$ ).

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9.2% for the PRB/NICHD customized standard, 10.8% for the WHO standard customized by fetal sex, and 12.3% for the NICHD African American standard. Finally, the highest agreement among any 2 standards was between the GROW and PRB/NICHD standards for both SGA and LGA classifications (Cohen's interrater agreement  $kappa = 0.85$ ).

### Factors affecting birthweight in term neonates

We found that the mean birthweight of a female neonate born at 40 weeks to a reference African American mother (nulliparous, 163 cm tall, and weighing 64 kg) was 3223 g, which is similar to the 3226 g reported by Gardosi and Francis<sup>19</sup> in a US population. The effects of several nonpathologic and pathologic factors on birthweight were also similar between these 2 studies, such as 150 vs

132 g for fetal sex, 133 vs 161 g difference between Caucasian and African American women, and 247 vs 241 g for diabetes. Although consistent in terms of significance and direction of effect, the magnitude of effect of other covariates was somewhat lower in this study compared to those reported by Gardosi and Francis.<sup>19</sup> The negative effect of a high BMI (>90th centile) on birthweight in the current study was similar to the one reported by Gardosi and Francis<sup>19</sup> (40 vs 63.4 g), but it did not reach statistical significance. One reason for differences in the magnitude of effect for some covariates is that the US population in the study by Gardosi and Francis<sup>19</sup> was composed mostly of women of European origin, while this study was composed of mostly African American women.

Ethnic differences in fetal biometric parameters were also recently assessed by

other investigators for women with a low-risk pregnancy.<sup>21</sup> The difference in mean birthweight between African American and Caucasian women at term in the study herein was about one-half (133 g) compared to that reported in the NICHD study (246 g).<sup>21</sup> Possible explanations for this discrepancy are differences in population characteristics and the covariates accounted for in each analysis.

### One-size-fits-all vs customized fetal growth standards

There is controversy as to whether a population-based or a customized chart should be used to screen fetuses as being at risk for SGA or LGA. SGA fetuses are at increased risk for fetal death and adverse neonatal outcomes (eg, cesarean delivery for nonreassuring fetal heart rate status, neonatal death, and admission to a neonatal intensive care

unit).<sup>35,52-55</sup> Although other customization methods exist, such as the individualized growth assessment,<sup>26-28</sup> the GROW approach of Gardosi et al<sup>18</sup> is the most widely adopted customized standard and has been applied to several populations, including a mostly Caucasian population in the United States.<sup>19,24,25</sup> The same authors reported that customization of fetal growth improved the detection of small fetuses at risk for fetal death and adverse neonatal outcomes, such as neonatal death and a low 5-minute Apgar score.<sup>56</sup> However, previous comparisons between customized and population-based growth charts for the detection of fetuses at risk for adverse outcome yielded conflicting results.<sup>10,53,54,57-70</sup> A recent meta-analysis<sup>71</sup> reported that the odds ratios of the association between adverse pregnancy outcomes (eg, perinatal mortality and neonatal intensive care unit admission) and abnormal birthweight were higher for the customized GROW standard compared to the noncustomized standards, although the difference was not statistically significant. Reaching a consensus regarding which type of fetal growth standards should be implemented in clinical care remains an important question, as it has a direct effect on patient management and care.

### Development of a customized fetal growth standard for the African American population

Previous fetal growth standards were derived from fetal biometric data by excluding patients who developed complications during the current pregnancy<sup>21</sup> and/or those with certain risk factors, such as an abnormal BMI, smoking, and adverse perinatal outcomes in previous pregnancies.<sup>20,21</sup>

Our approach was to adjust for the presence of pathology in the current pregnancy while assessing the effects of nonpathologic factors on fetal growth. The effects of pathologic variables included in the quantile regression models do not contribute to defining the normal fetal weight chart (eg, the chart will not be lowered because of a risk

factor, eg, smoking), but the additional data from patients with pathologic factors increased the power to dissect the effect of nonpathologic covariates on fetal growth and helped to better calibrate the model so as to distinguish normal from abnormal growth.

Of interest, all variables that had a significant effect on birthweight of neonates delivered at term (Table 1) also had a significant effect on EFW in the longitudinal analysis (Table 2 and Supplementary Table). This is important because it increases confidence that these variables are indeed needed to define the fetal growth potential, since birthweight data are more reliable than EFW data. In addition, although a high BMI (>90th centile) was not associated with a significant decrease in term birthweight (Table 2), it had a negative effect on the lower centiles of EFW. The 5th and 10th centiles of weight at 40 weeks were about 4.6% lower for women with a BMI >40.4; hence, this group of women are at higher risk of delivering an SGA neonate contrary to other observations.<sup>72</sup> Similarly, although the negative effect of fetal anomalies on birthweight of neonates delivered at term was not significant, fetal anomalies were associated with up to a 5% reduction in the median, 10th centile, and 5th centile of EFW (Table 2).

While our approach is conceptually similar to Gardosi et al,<sup>18,19</sup> the customization parameters in our study were based directly on EFW data rather than on birthweight. Moreover, instead of assuming that each covariate has a proportionally constant effect on EFW at each gestational age, we tested for the first time and found significant interactions between parity as well as maternal weight and gestational age (Figure 1 and Table 2). Testing for these interactions would not have been feasible using cross-sectional birthweight data. Additionally, similar to the study by WHO,<sup>20</sup> we used quantile regression to determine the effect of covariates on each centile of the distribution, rather than assessing the effect on mean fetal weight and

assuming a normal distribution of weight around the mean value at each gestational age. Growth chart customization by differentially adjusting the centile curves according to the specific contribution and timing of each factor is novel. Such differences in both study design and analytical approach are reflected in our new customized fetal growth standard and impact the number of fetuses that will screen positive for SGA or LGA as well as who those fetuses are.

### SGA and LGA screening rates using different fetal growth standards

The newly developed PRB/NICHD customized growth standard was compared to 3 existing standards: GROW,<sup>19</sup> WHO with and without adjustment by fetal sex,<sup>20</sup> and NICHD African American.<sup>21</sup> A comparison to the INTERGROWTH-21st standard<sup>16</sup> was not performed due to differences in the ultrasound protocols that were previously noted<sup>73</sup> (eg, the BPD was measured from the outer to the outer, while we measured from the outer to the inner, borders of the parietal bones) and also due to the different EFW formula used in the INTERGROWTH-21st standard. Among the 4 standards compared in this study, there were significant differences in the fraction of fetuses classified as SGA (<10th centile) based on the last available ultrasound examination for each pregnancy. The proportion of fetuses that screened positive for SGA in a certain population is determined, in part, by the burden of pregnancy complications present in the population that are related to growth restriction. Indeed, since 15.8% of the African American women in the current study population delivered preterm, it is not surprising that most standards classified significantly more fetuses as SGA (<10th centile) than the expected 10%. For fetuses delivered preterm, the SGA screen-positive rate was significantly >10% for all standards, with the GROW and PRB/NICHD customized standards classifying 26.3% and 29% of the preterm population as being at risk, respectively. This finding is consistent

with previous reports showing that SGA fetuses are at an increased risk of a preterm delivery.<sup>74,75</sup> The rate of fetuses classified as SGA (<10th centile) in women who delivered at term was close to 10% for the WHO and GROW standards, and significantly >10% for the PRB/NICHD (11.6%) and lower for the NICHD African American (5.3%) standards. The fact that the 10th centile of the NICHD African American standard is low for our population, and hence it screens positive for fewer SGA fetuses than expected (7.2%), can also be understood from [Supplementary Figure 3](#), where the 10th centile curve of the NICHD standard is lower than the corresponding centile of the local reference, especially after 37 weeks of gestation. However, the customized PRB/NICHD standard is built excluding the contribution of fetuses with risk factors associated with lower weight (eg, preterm delivery), thus the 10th centile of the PRB/NICHD standard is higher than the 10th centile of the local reference shown in [Supplementary Figure 3](#), therefore classifying 14.4% of fetuses as SGA.

Only the NICHD African American standard classified significantly more fetuses as LGA (12.3%) than the reference cut-off of 10%, which, combined with a lower than expected rate of SGA, suggests that this standard is low for our patient population. The GROW standard identified significantly less than expected (8.7%), while the PRB/NICHD standard identified 9.2% of fetuses as LGA. Since this was an unselected population, it is reasonable to assume that not all fetuses reached their growth potential; hence, standards classifying slightly less fetuses as LGA are actually tracking the growth potential of fetuses rather than being miscalibrated.

In addition to comparing the SGA and LGA screening rates among the 4 growth standards, we provided complementary information regarding the agreement among the standards in terms of which fetuses are at risk. Using Venn diagrams ([Figure 2](#)) and

interrater agreement statistics for all pairs of standards, we found that the 2 fully customized standards (GROW and PRB/NICHD) were the most similar, reaching an interrater agreement  $\kappa$  of about 0.85 for both SGA and LGA classifications. Considering the multiple differences in the design of the 4 standards compared herein, such as the population on which they were based (homogenous vs multiethnic), the type of data they were derived from (birthweight vs fetal weight), the analytical assumptions they relied on, and the factors these standards were customized for (ethnicity or fetal sex only vs fully customized), this study suggests that customization by the same set of covariates is key for the reproducibility of growth assessment.

### Research and clinical implications

This study confirms previous observations that maternal ethnicity, height, weight, and parity and fetal sex are factors affecting birthweight and/or fetal growth;<sup>76-78</sup> hence, they should be considered when defining fetal growth potential.<sup>72,79</sup> Customization of growth charts is commonly performed by assuming a proportionally constant effect of covariates during gestation, and we found that, indeed, this assumption holds for genetically determined (fetal sex) or transmissible (height) traits. However, the effects of maternal weight and parity are proportionally graded with gestational age. Additionally, the effects of maternal height and parity in African American women were graded among the different centiles of EFW. The customization approach proposed herein can be applied to other populations as well, provided that ultrasound data and relevant covariate information are available. An easy-to-use implementation of the PRB/NICHD customized growth chart for African American women is freely available from the authors' website (<http://bioinformaticsprb.med.wayne.edu/>).

The higher similarity of the two fully customized standards compared to the

similarity between the two partially customized standards suggests that the use of customized charts is more likely to lead to reproducible growth assessment across studies.

Depending on the standard used, the rate of fetuses that screened positive for SGA can vary by a factor of 2 in a given population. The use of fully customized standards in high-risk populations may identify more fetuses as being at risk for growth restriction. However, comparing how the in utero SGA and LGA screening based on different standards relates to an SGA or LGA diagnosis at birth and to adverse pregnancy outcomes was outside the scope of the current study. Of note, the ability of ultrasound-based EFW to predict actual birthweight was described previously.<sup>14,29,73</sup> For example, in a blinded study conducted in a low-risk population, Sovio et al<sup>29</sup> reported that an EFW <10th centile at 36 weeks of gestation correctly identified 57% of fetuses (sensitivity) that were destined to have a birthweight <10th centile, with a specificity of 95%. In their study, a non-customized EFW standard was used for screening while the gold standard for SGA was based on a fetal sex-customized birthweight reference.<sup>29</sup>

### Strengths and limitations

We conducted the largest longitudinal fetal growth study in an African American population to date. Additional strengths of our study are that all patients were enrolled at a single ultrasound unit and that a consistent protocol was implemented to acquire ultrasound data. Moreover, the large sample size combined with advanced analytical approaches allowed the development of customized fetal growth centiles for an African American population under less-restrictive analytical assumptions than before. Although a possible limitation is that the ultrasound examinations studied herein were not scheduled at fixed gestational-age time points (as was the case for other fetal growth studies), the average number of scans (5) still compares favorably to previous reports.

## Conclusion

We report herein the largest longitudinal fetal growth study of pregnant women self-reported as African American. We found that the effects of maternal weight and parity on EFW increase with gestational age and that maternal height and parity affect small or large fetuses differently. The PRB/NICHD customized growth chart was designed to account for these features of fetal growth. This standard classified more fetuses as being SGA (14.4%) than other standards, especially among fetuses delivered preterm. Moreover, this standard classified as LGA about the same fraction of fetuses as expected (10%). The comparison among the 4 growth standards considered herein revealed that the most important factor determining the agreement among standards is whether they account for the same factors known to affect fetal growth. ■

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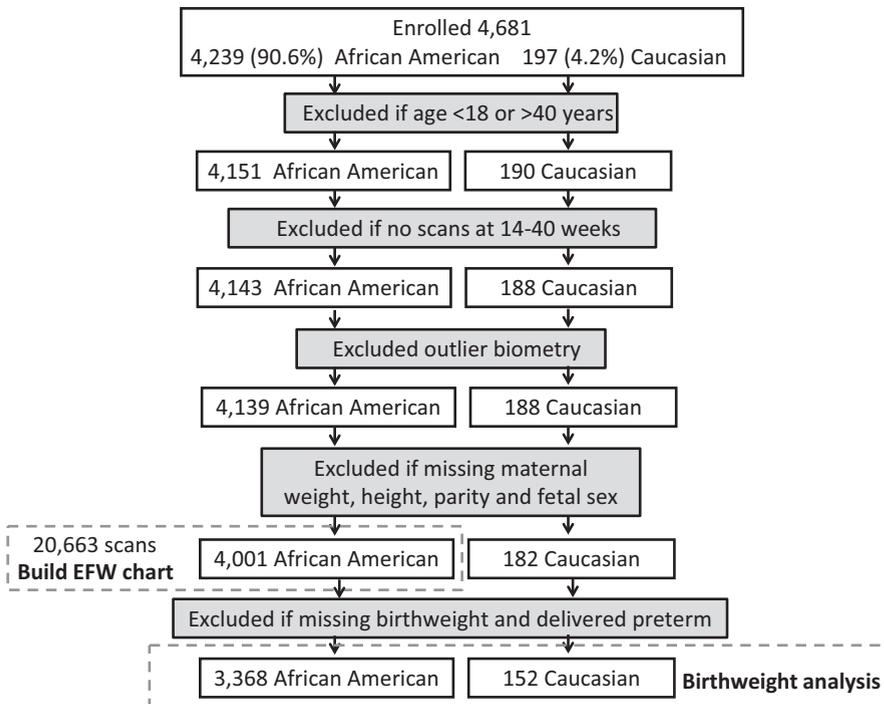
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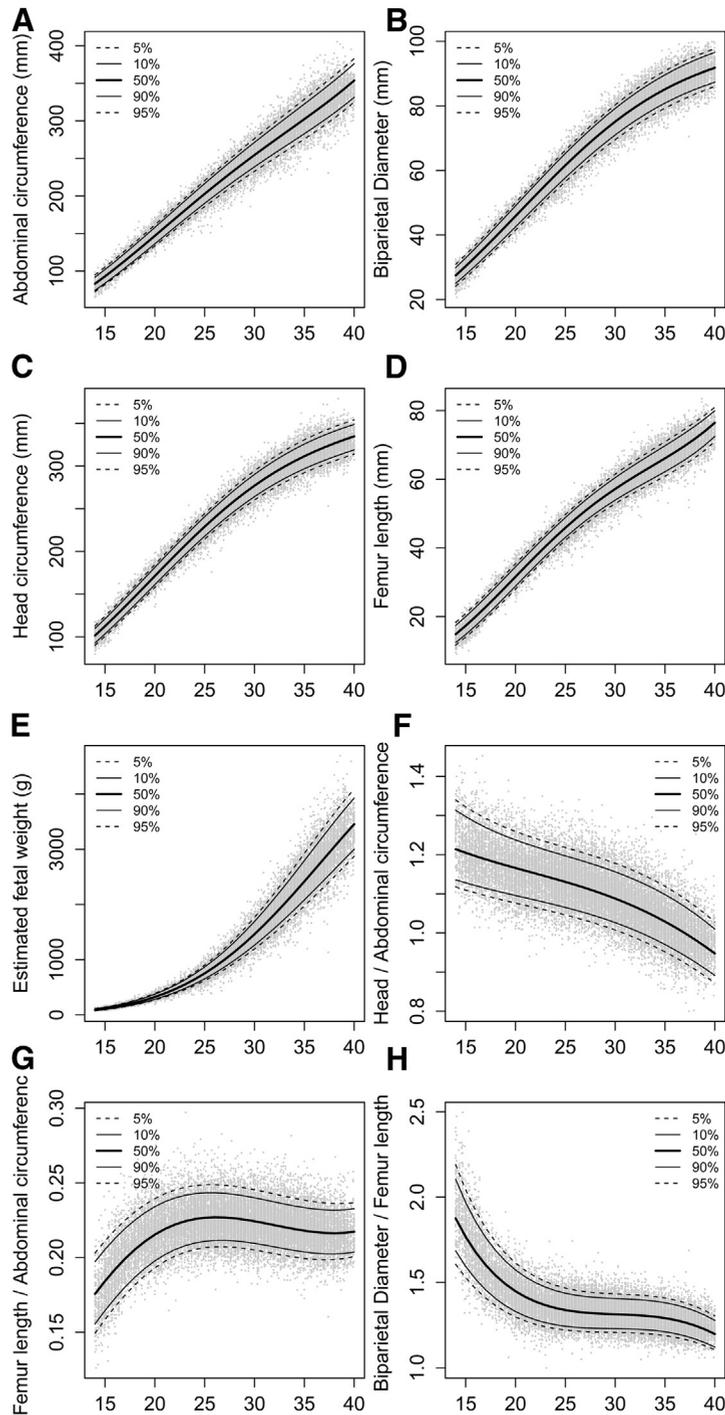
**SUPPLEMENTARY FIGURE 1**  
**Patient selection flowchart**


Of the 4681 women enrolled in the study, only the most prevalent ethnic groups, African American (AA) (4239, 90.6%) and Caucasian (197, 4.2%), were considered for inclusion in the analysis. Patients were excluded if maternal age was unknown or if maternal age was <18 or >40 years. Patients were also excluded if they did not undergo an ultrasound scan between 14-40 weeks of gestation. Scans were discarded if they had outlier biometric values, resulting in a dataset of 4139 AA and 188 Caucasian women with at least 1 valid scan. An additional 144 women were excluded because of missing maternal weight, height, and parity, and fetal sex information, leading to a dataset of 4001 AA and 182 Caucasian women. Data from the 4001 AA women (20,663 ultrasound scans) were used to build the customized estimated fetal weight chart. The effect of covariates, including maternal race, on birthweight was assessed using data from the subset of 3368 AA and 152 Caucasian women with an available birthweight and who delivered at term.

Tarca et al. Fetal growth charts for African American women. *Am J Obstet Gynecol* 2018.

## SUPPLEMENTARY FIGURE 2

## Noncustomized fetal biometry and estimated fetal weight centiles in an unselected population of African American (AA) women

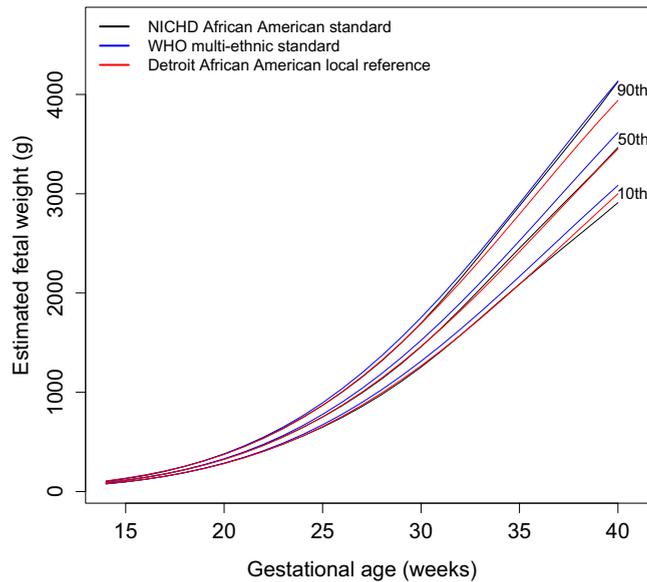


Centiles (5th, 10th, 50th, 90th, and 95th) of fetal biometry, proportionality ratios, and estimated fetal weight determined using penalized quantile regression in an unselected population of AA women.

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## SUPPLEMENTARY FIGURE 3

## Comparison of the estimated fetal weight local reference to the NICHD African American (AA) and WHO standards



Centiles (10th, 50th, and 90th) of estimated fetal weight derived from all 4001 women in this study (also shown in [Supplementary Figure 2](#)) superimposed onto the same centiles of NICHD AA and WHO noncustomized standards.

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## SUPPLEMENTARY TABLE

## Longitudinal analysis of estimated fetal weight

Variable	Coefficient					Pvalue				
	5th	10th	50th	90th	95th	5th	10th	50th	90th	95th
Intercept	7.929	7.977	8.122	8.236	8.269	<.001	<.001	<.001	<.001	<.001
t	0.5549	0.5486	0.5652	0.5253	0.4912	<.001	<.001	<.001	<.001	<.001
t <sup>2</sup>	-0.2506	-0.2668	-0.2643	-0.2944	-0.3280	<.001	<.001	<.001	<.001	<.001
t <sup>3</sup>	0.0284	0.0227	0.0205	0.0115	0.0021	<.001	<.001	<.001	.023	.705
Ht	0.0089	0.0096	0.0119	0.0178	0.0184	.006	<.001	<.001	<.001	<.001
Wt	0.0136	0.0137	0.0114	0.0123	0.0110	<.001	<.001	<.001	<.001	<.001
t × Wt	0.0073	0.0072	0.0050	0.0059	0.0049	<.001	<.001	<.001	<.001	.002
Para 1	0.0107	0.0212	0.0071	0.0235	0.0073	.367	.002	.154	<.001	.368
Para 2	0.0335	0.0330	0.0218	0.0400	0.0295	.002	<.001	<.001	<.001	.003
Para ≥3	0.0109	0.0020	0.0238	0.0395	0.0368	.402	.849	<.001	<.001	<.001
t × Para 1	0.0101	0.0129	0.0018	0.0131	0.0075	.212	.012	.636	.008	.237
t × Para 2	0.0193	0.0139	0.0100	0.0161	0.0155	.021	.038	.014	.003	.029
t × Para ≥3	0.0008	-0.0066	0.0087	0.0171	0.0194	.937	.38	.05	.008	.01
Sex (male)	0.0230	0.0199	0.0184	0.0185	0.0239	<.001	<.001	<.001	<.001	<.001
BMI <20.5	0.0160	0.0081	-0.0136	-0.0207	-0.0226	.032	.083	<.001	<.001	<.001
BMI >40.4	-0.0545	-0.0471	-0.0332	-0.0168	0.0018	<.001	<.001	<.001	.223	.925
Smoking (yes)	-0.0807	-0.0571	-0.0321	-0.0356	-0.0242	<.001	<.001	<.001	<.001	.007
Diabetes	0.0634	0.0543	0.0408	0.0447	0.0436	<.001	<.001	<.001	<.001	.002
Preterm delivery	-0.1562	-0.1262	-0.0361	-0.0065	0.0126	<.001	<.001	<.001	.448	.158
Fetal anomalies	-0.0520	-0.0376	-0.0207	-0.0076	0.0084	.002	.002	.015	.369	.605
t × BMI >40.4	-0.0403	-0.0343	-0.0238	-0.0143	-0.0079	<.001	.001	<.001	.111	.496
t × Smoking	-0.0441	-0.0286	-0.0111	-0.0106	0.0007	<.001	<.001	.002	.055	.919
t <sup>2</sup> × Diabetes	-0.0104	-0.0094	-0.0072	-0.0085	-0.0132	.024	.02	.013	.006	.003
t <sup>2</sup> × Preterm delivery	0.0286	0.0230	0.0081	0.0038	-0.0001	<.001	<.001	<.001	.208	.979

Quantile regression coefficients (left) and *P* values (right) for different centiles of log-estimated fetal weight. Customized estimated fetal weight centiles that exclude the effect of pathologies (PRB/NICHD standard) can be obtained by multiplying the coefficients of nonpathologic covariates (top panel) with corresponding predictors, summing terms, and exponentiating results. Coefficients for pathologic variables (extremely low or high BMI, smoking, diabetes, preterm delivery, and fetal anomalies) are also shown, but they are not to be used in predicting centiles. Analysis is centered at 40 wk of gestation for a female fetus of a nulliparous African American mother, having a height of 163 cm and weighing 64 kg at the first visit. *t* is the gestational age in wk from 40 wk scaled by 10. *Ht* is maternal height in cm from 163 cm scaled by 10. *Wt* is maternal weight in kg from 64 kg scaled by 10. For example, the 10<sup>th</sup> centile at 30 wk of gestation for a male fetus of an African American mother weighing 74 kg, 173 cm tall, and in her third pregnancy (parity = 2) can be calculated as:  $\exp(7.977 + 0.5486 \times t - 0.2668 \times t^2 + 0.0227 \times t^3 + 0.0096 \times Ht + 0.0137 \times Wt + 0.0072 \times t \times Wt + 0.033 \times para2 + 0.0139 \times t \times para2 + 0.0199 \times sex) = 1331$  g, where:  $t = (30 - 40)/10 = -1$ ;  $Ht = (173 - 163)/10 = 1$ ;  $Wt = (74 - 64)/10 = 1$ ;  $para2 = 1$  and  $sex = 1$ .

BMI, body mass index.

Tarca et al. Fetal growth chart for African American women. *Am J Obstet Gynecol* 2018.

## OBSTETRICS

# Customized vs INTERGROWTH-21<sup>st</sup> standards for the assessment of birthweight and stillbirth risk at term



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**BACKGROUND:** Fetal growth abnormalities are linked to stillbirth and other adverse pregnancy outcomes, and use of the correct birthweight standard is essential for accurate assessment of growth status and perinatal risk.

**OBJECTIVE:** Two competing, conceptually opposite birthweight standards are currently being implemented internationally: customized gestation-related optimal weight (GROW) and INTERGROWTH-21<sup>st</sup>. We wanted to compare their performance when applied to a multiethnic international cohort, and evaluate their usefulness in the assessment of stillbirth risk at term.

**STUDY DESIGN:** We analyzed routinely collected maternity data from 10 countries with a total of 1.25 million term pregnancies in their respective main ethnic groups. The 2 standards were applied to determine small for gestational age (SGA) and large for gestational age (LGA) rates, with associated relative risk and population-attributable risk of stillbirth. The customized standard (GROW) was based on the term optimal weight adjusted for maternal height, weight, parity, and ethnic origin, while INTERGROWTH-21<sup>st</sup> was a fixed standard derived from a multiethnic cohort of low-risk pregnancies.

**RESULTS:** The customized standard showed an average SGA rate of 10.5% (range 10.1–12.7) and LGA rate of 9.5% (range 7.3–9.9) for the set of cohorts. In contrast, there was a wide variation in SGA and LGA rates with INTERGROWTH-21<sup>st</sup>, with an average SGA rate of 4.4% (range 3.1–16.8) and LGA rate of 20.6% (range 5.1–27.5). This variation in

INTERGROWTH-21<sup>st</sup> SGA and LGA rates was correlated closely ( $R = \pm 0.98$ ) to the birthweights predicted for the 10 country cohorts by the customized method to derive term optimal weight, suggesting that they were mostly due to physiological variation in birthweight. Of the 10.5% of cases defined as SGA according to the customized standard, 4.3% were also SGA by INTERGROWTH-21<sup>st</sup> and had a relative risk of 3.5 (95% confidence interval, 3.1–4.1) for stillbirth. A further 6.3% (60% of the whole customized SGA) were not SGA by INTERGROWTH-21<sup>st</sup>, and had a relative risk of 1.9 (95% confidence interval, 3.1–4.1) for stillbirth. An additional 0.2% of cases were SGA by INTERGROWTH-21<sup>st</sup> only, and had no increased risk of stillbirth. At the other end, customized assessment classified 9.5% of births as large for gestational age, most of which (9.0%) were also LGA by the INTERGROWTH-21<sup>st</sup> standard. INTERGROWTH-21<sup>st</sup> identified a further 11.6% as LGA, which, however, had a reduced risk of stillbirth (relative risk, 0.6; 95% confidence interval, 0.5–0.7).

**CONCLUSION:** Customized assessment resulted in increased identification of small for gestational age and stillbirth risk, while the wide variation in SGA rates using the INTERGROWTH-21<sup>st</sup> standard appeared to mostly reflect differences in physiological pregnancy characteristics in the 10 maternity populations.

**Key words:** birthweight, customized growth charts GROW, epidemiology, ethnicity, fetal growth, INTERGROWTH-21<sup>st</sup>, large for gestational age, pregnancy risk, small for gestational age, stillbirth

## Introduction

Fetal growth restriction and low birthweight are closely linked to risk of stillbirth and other indicators of adverse perinatal outcome. As these associations have become ever clearer, the focus has shifted to prevention, which requires adequate tools and standards.

Many reference curves and tables have been produced in various settings for the assessment of fetal growth and birthweight. They can vary because of the methods used, the quality of the data they originated from, and whether they were based on longitudinal or cross-sectional, fetal, or neonatal data. They also vary with the physiological and pathological characteristics of the

population. Therefore, an approach that has gained traction in recent years is not to base reference curves on the whole population, but to set a standard that seeks to represent the optimal growth and birthweight that can be achieved in the absence of any complications, and that therefore should be better able to detect abnormalities in fetal growth.

Such a standard has been developed as the computer-generated customized GROW chart, which uses coefficients derived from large birthweight databases to predict optimal growth for each mother in each pregnancy.<sup>1,2</sup> Physiological variables such as ethnic origin, maternal size, and parity are adjusted for, and the standard is set at a level that is free from pathology, so that the effect adverse influences such as smoking, hypertension, or diabetes, are better recognized. Because the construction of the standard combines a term optimal

weight (TOW) with a proportionality fetal weight curve for all gestations, the same chart can be used for the assessment of fetal growth as well as birthweight. Customized charts have been shown to be internationally applicable,<sup>3–8</sup> are recommended by the Royal College of Obstetricians and Gynecologists,<sup>9</sup> and are now increasingly in clinical and international research use. The GROW (Gestation Related Optimal Weight) application has recently been updated with additional coefficients to represent over 100 ethnic or country-of-origin groups.

An alternative approach to derive a standard is that taken by the INTERGROWTH-21<sup>st</sup> (IG21) project, which selected low-risk, well-nourished mothers with uncomplicated pregnancies. Data were combined from cohorts in 8 countries to produce a single, prescriptive, multiethnic standard for

birthweight<sup>10,11</sup> and fetal growth<sup>12,13</sup> to be used universally. The recently published World Health Organization fetal growth project,<sup>14</sup> based on data from 10 countries, used similar methodology, but concluded that there were significant differences between populations in maternal characteristics that affected growth. Similarly, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies<sup>15</sup> and other studies<sup>16-18</sup> demonstrated ethnic differences in fetal growth in low-risk pregnancies. Nevertheless, the IG21 standards are being actively promoted and have begun to be implemented in many settings.

We therefore set out to compare the IG21 birthweight standard with the individually customized (GROW) standard in an international cohort based on maternity datasets from 10 countries, to assess how well they were able to associate birthweight with stillbirth risk. We focused our analysis on term data, as preterm birthweight ought to be assessed with a fetal rather than a neonatal weight standard in light of the known associations between prematurity and fetal growth restriction.<sup>19-21</sup>

## Materials and Methods

### Data source

The Perinatal Institute administers the Gestation Network ([www.gestation.net](http://www.gestation.net)), which is a portal for provision of free software tools including customized centile calculators for local, national, and international use. The applications contain coefficients for adjustment of the growth and weight standard according to maternal characteristics, derived from anonymized databases submitted from clinicians and researchers who wish to have an application suitable for their own local population. To date, datasets from 23 countries have been received totaling 3.2 million births. Based on this database, the first global customized centile calculator was recently released, which can adjust for over 100 ethnic groups or countries of origin as well as the mother's height, weight and parity, and the sex of the baby.

**TABLE 1**

**Exclusions from original data submitted from 10 countries (2,140,543) resulting in cohort used in this study (1,251,289)**

	Excluded, n	Remaining, n	Remaining, %
Congenital anomalies and multiple pregnancies	57,322	2,083,221	97.3
Missing or invalid gestational age or birthweight	41,581	2,041,640	95.4
Preterm deliveries (<259 d)	121,676	1,919,964	89.7
Minority ethnic group or missing ethnic origin data	490,406	1,429,558	66.8
Missing or invalid sex or maternal height, weight or parity	178,269	1,251,289	58.5

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Ten of these Gestation Network data sets, totaling 2,140,543 cases, also contained stillbirth as a pregnancy outcome and represented the overall cohort used in this analysis. The origins of the data ranged from hospital-based collections to wider population-based registers, and included, in alphabetical order, datasets from Bhutan (national referral hospital), China (randomly selected births from 150 hospitals), Germany (State of Hesse birth register), India (large private tertiary maternity hospital in Hyderabad), Ireland (6 hospitals in the Perinatal Ireland network), The Netherlands (96 independent Dutch midwifery practices), Slovenia (national perinatal information system), Sweden (national medical birth registry), United Kingdom (83 maternity hospitals within the national growth assessment protocol (GAP) program), and United States (14 hospitals in the Washington State Obstetrics Clinical Outcome Assessment Program). The collaborators providing the data are listed under the Acknowledgment. All data were fully anonymized before receipt, and no institutional review board approval was required for this study.

Each dataset originated in settings with established routine ultrasound dating scans and these had been used to calculate gestational age at birth unless not available, in which case the last menstrual period was used. Maternal height and weight was measured at the beginning of pregnancy and ethnicity was recorded according to mother-declared ethnic origin or country of birth. Multiple

pregnancies, congenital anomalies, and preterm births (<37 weeks) were excluded and only the predominant ethnic group from each country was included in the analysis, with complete data on maternal and pregnancy variables required for customized adjustment. This resulted in a study cohort of 1,251,289 cases. The stepwise exclusions are summarized in Table 1.

### Standards for calculating centiles

Small for gestational age (SGA) was defined as <10th, and large for gestational age (LGA) as >90th weight for gestational age centile, according to 2 methods:

1. Customized centiles were determined using the global centile calculator, entering the birthweight and gestational age at delivery, sex of the neonate, and information about maternal height, early pregnancy weight, parity (as it was at beginning of pregnancy), and ethnic origin. Coefficients for all predominant ethnic groups and associated maternal variables were available within the global centile calculator (GROW v.8.0.1).
2. IG21 centiles were based on the published IG21 neonatal weight-for-gestational age standard<sup>10</sup> and included birthweight and gestational age at delivery as well as adjustment for neonatal sex.

Centiles for stillborn babies were also calculated according to the above

**TABLE 2**  
**Characteristics of 10 country cohorts**

	No.	All 1,251,289	Bhutan 2779	China 27,383	Germany 292,227	India 6436	Ireland 10,124	Netherlands 191,345	Slovenia 127,067	Sweden 275,924	United Kingdom 289,381	United States 28,623
Maternal height, cm	Mean (SD)	166.8 (6.5)	154.8 (5.8)	160.5 (4.8)	167.3 (6.2)	158.3 (6.0)	164.2 (6.3)	170.4 (6.3)	166.7 (5.9)	166.8 (5.8)	165.0 (6.3)	165.7 (6.7)
	Median (IQR)	167 (8)	155 (7)	160 (5)	168 (8)	157 (7)	164 (8)	170 (9)	167 (7)	167 (8)	165 (8)	165 (10)
Maternal weight, g	Mean (SD)	68.3 (14.6)	54.6 (7.2)	56.1 (9.1)	68.6 (14.9)	62.2 (11.6)	69.1 (14)	69.5 (13.3)	64.7 (12.2)	65.6 (11.2)	72.5 (17.2)	70.4 (16.7)
	Median (IQR)	65 (17)	54 (8)	55 (10)	65 (16)	61 (15)	67 (16)	67 (15)	62 (14)	64 (13)	69 (21)	66 (18)
Body mass index	Mean (SD)	24.5 (5.0)	22.8 (3.0)	21.8 (3.3)	24.5 (5.0)	24.8 (4.4)	25.6 (5.0)	23.9 (4.3)	23.3 (4.2)	23.6 (3.8)	26.6 (6.0)	25.7 (6.0)
	Median (IQR)	23.4 (5.5)	22.5 (3.7)	21.2 (3.9)	23.3 (5.4)	24.3 (5.7)	24.6 (5.8)	23.0 (4.9)	22.3 (4.6)	22.8 (4.2)	25.3 (7.5)	24.1 (6.6)
Nullipara	%	44.1	49.1	63.6	42.2	55.4	42.9	49.1	49.1	40.0	41.9	46.9
Sex male	%	51.0	52.2	53.0	50.9	50.9	51.5	51.0	51.2	51.0	50.8	50.7
Gestational age	Mean (SD)	278.9 (8.5)	278.4 (8.6)	276.1 (7.1)	277.6 (8.2)	273.2 (7.7)	279.5 (8.5)	279.8 (8.3)	278.8 (7.6)	280.8 (8.8)	278.5 (8.8)	277.8 (7.7)
	Median (IQR)	280.0 (12.0)	280.1 (12.5)	276.7 (9.9)	278.8 (12.4)	273.4 (12.4)	280.6 (12.7)	281 (11.9)	280.2 (10.3)	281.6 (12.1)	279.5 (12.5)	278.1 (10.4)
Birthweight, g	Mean (SD)	3497.6 (477.6)	3209.7 (455.4)	3360.7 (411.6)	3433.6 (452.4)	3055.5 (420.8)	3514.2 (485)	3542.0 (482.9)	3453.0 (441.8)	3623.0 (484.7)	3457.5 (484.6)	3502.0 (457.4)
	Median (IQR)	3490 (623)	3200 (600)	3350 (500)	3425 (600)	3040 (550)	3510 (625)	3530 (640)	3450 (580)	3610 (640)	3450 (625)	3490 (599)
Stillbirths	Frequency	1667	12	53	252	11	12	159	143	374	632	19
	Rate/1000	1.3	4.3	1.9	0.9	1.7	1.2	0.8	1.1	1.4	2.2	0.7
TOW1 standardized <sup>a</sup>	280 d	3434.6	3469.5	3575.4	3397.5	3292.4	3477.4	3391.2	3442.9	3524.6	3393.6	3491.5
TOW2 adjusted <sup>b</sup>	Median gestation	3561.0	3280.3	3428.1	3489.0	3209.3	3657.9	3610.3	3524.0	3679.1	3525.2	3551.5
GROW—SGA	%	10.5	11.6	11.3	10.1	11.3	12.7	10.7	10.7	10.7	10.5	11.1
GROW—LGA	%	9.5	8.5	8.8	9.9	8.7	7.3	9.4	9.3	9.3	9.6	9.1
IG21—SGA	%	4.4	14.4	4.7	4.9	16.8	4.9	4.2	4.5	3.1	5.0	3.5
IG21—LGA	%	20.6	7.1	13.2	17.3	5.1	21.7	22.9	16.7	27.5	18.6	21.1

GROW, gestation-related optimal weight; IG21, INTERGROWTH-21<sup>st</sup> birthweight standard; IQR, interquartile range; LGA, large for gestational age; SGA, small for gestational age; TOW, term optimal weight.

<sup>a</sup> Adjusted for para 0, height 163 cm, weight 64 kg, sex averaged, delivery at 280 d; <sup>b</sup> Adjusted for average parity, height and weight, sex averaged, delivery at median gestation.

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methods, but with 2 days deducted from the gestational age at delivery, as an approximation of the gestational age at the time of intrauterine demise.<sup>22-24</sup>

SGA and LGA numbers, rates, and relative risk (RR) of stillbirths were presented according to the GROW and IG21 methods, as well as in subgroups according to whether they overlapped, ie, the birthweight was SGA or LGA by both standards, or was SGA or LGA by GROW or IG21 only.

## Analysis

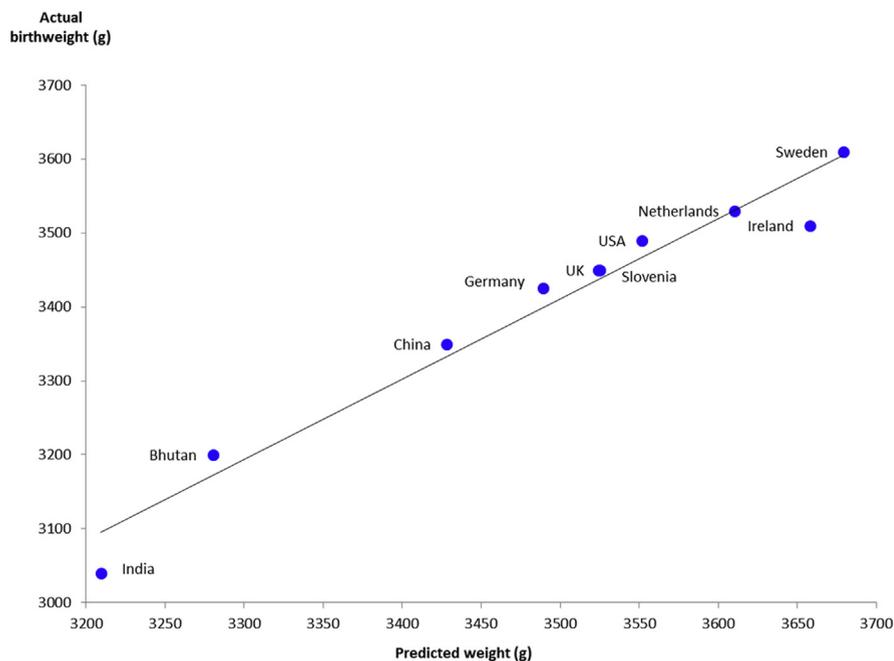
Statistical analyses were performed using software programs Excel (2016; Microsoft, Redmond, WA) and Stata (Version 14.2; StataCorp, College Station, TX). A descriptive table was constructed including data from each of the 10 country cohorts, showing mean, SD, median, and interquartile range for birthweight; gestation; and maternal height, weight, and body mass index (BMI), as well as listing gender, parity, and stillbirths rates. The multiple regression-derived ethnic constants were based on median gestation at delivery, and expressed as term optimal weight TOW in 2 ways: TOW1 adjusted to 280 days and standardized for maternal characteristics (para 0, height 163 cm, weight 64 kg, sex averaged, delivery at 280 days); and TOW2 adjusted for average maternal characteristics within that group, and at the respective median gestational age. RR with 95% confidence intervals (CI) and population attributable risk values were calculated.

To assess how IG21 standards relate to birthweight variation in the 10 country cohorts, IG21 SGA and LGA rates were compared with the predicted weight (TOW2) adjusted for average maternal height, weight, parity, and sex, and controlled for gestational age at delivery. Bivariate statistics included scatter plots, line of best fit, and correlation coefficient (R), and significance of *P* values was based on a *t* statistic under the null hypothesis that there was no correlation between the variables under investigation.

## Results

Details of the 10 datasets are listed in Table 2. Averages with measures of

**FIGURE 1**  
Predicted customized vs actual birthweight averages in 10 country cohorts



Predicted birthweight was customized for average maternal height, weight, parity and sex, and controlled for gestational age at delivery.  $R = 0.9787$ ;  $P < .01$ .

UK, United Kingdom, USA, United States.

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dispersion are provided to illustrate the wide variation in maternal characteristics between country cohorts. Maternal height ranged from 155-170 cm, early pregnancy weight from 54-69 kg, median gestational age at delivery from 273-282 days, and median birthweight from 3040-3610 g.

Also shown is the ethnic group-based TOW predicted for a standard size mother in her first pregnancy at 280 days (TOW1), and the predicted weight adjusted for the average maternal height, weight, and parity and the median length of pregnancy in that cohort (TOW2). The correlation between predicted and actual mean birthweights for the 10 country cohorts was high:  $R = 0.979$  (Figure 1).

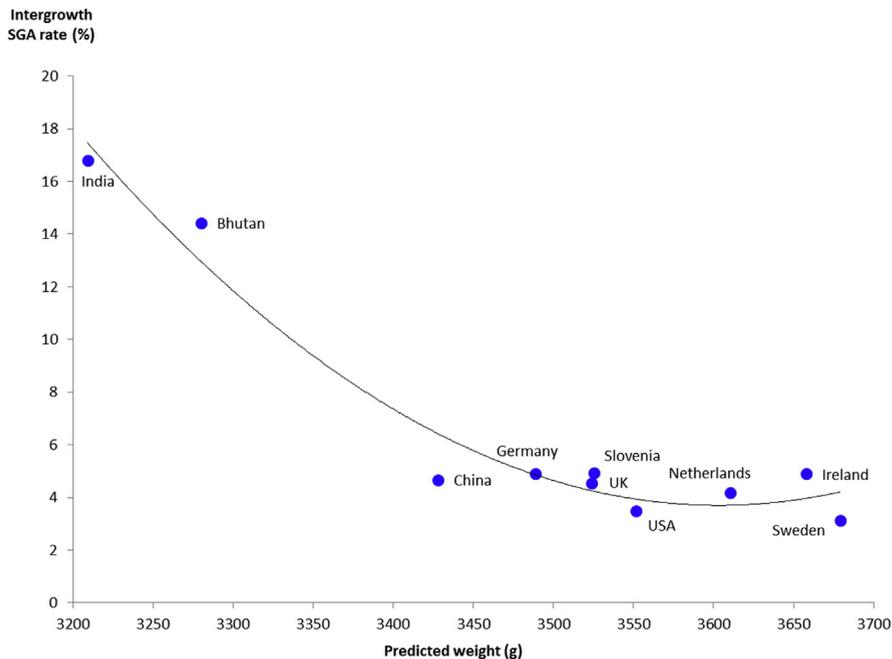
Table 2 also shows the variation between cohorts in SGA and LGA rates according to the customized GROW and the IG21 methods of assessment. Average GROW SGA rate was 10.5% with a range of 10.1-12.7, while LGA

averaged 9.5% with a range of 7.3-9.9. In contrast, average IG21 values were lower for SGA: 4.4%, ranging from 3.1-16.8, while average LGA rates were much higher: 20.6%, with a range of 5.1-27.5.

In Figures 2 and 3, the adjusted TOW constants (TOW2) for each of the 10 country cohorts are plotted against the IG21 SGA and LGA rates, respectively. The relationship with IG21 SGA rates (Figure 2) is curvilinear, with the 2 cohorts with the lowest predicted weights assigned very high SGA rates of 16.8 (India) and 14.4 (Bhutan). For LGA (Figure 3), there is a direct, linear relationship between the predicted weight and IG21-determined LGA rates. These significant correlations suggest that the varying proportions of cases identified as SGA or LGA with IG21 merely reflect normal variation in birthweight between these country cohorts.

Tables 3 and 4 detail the association between stillbirths and SGA and LGA.

**FIGURE 2**  
**Predicted customized birthweight vs INTERGROWTH-21<sup>st</sup> SGA rate**



Predicted birthweight customized for average maternal height, weight, parity and sex, and controlled for gestational age at delivery.  $R = 0.9789$ ;  $P < .01$ .

UK, United Kingdom, USA, United States.

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The highest RR for stillbirth (3.5; 95% CI, 3.1–4.1) was observed for babies SGA by both standards. IG21 adds only another 2087 SGA cases including 3 stillbirths, which do not represent an elevated stillbirth risk. In contrast, using GROW, a further 60% of births (78,703 of 131,950) are categorized as SGA and add another 185 (45%) to the 226 stillbirths identified by both methods, with RR 1.9 (95% CI, 1.6–2.2).

At the other end of the spectrum, being LGA by both standards was not associated with stillbirth (RR, 0.9; 95% CI, 0.8–1.1) and according to GROW there were another 6792/118,954 or 5.7% LGA with 13 stillbirths and no effect on risk. IG21 however classified a further 56.5% (145,570 of 257,732) as LGA but these cases had in fact a lower RR for stillbirth.

## Comment

This is, to our knowledge, the first multinational comparison of the IG21

and customized birthweight standards. It shows firstly that using IG21, there are wide differences in SGA and LGA rates across the 10 cohorts studied, ranging from 3.1–16.8% for SGA and 5.1–27.5% for LGA rates. As Figures 2 and 3 show, these values are strongly correlated with the TOW calculated by GROW for each cohort, suggesting that IG21 SGA and LGA rates vary mostly due to physiological differences between different populations.

For example, the high IG21 SGA rate for India (16.8%) (Table 2) most likely represents physiological variation due to ethnic origin and small maternal size, as the data represent a mostly middle-class Indian population that has a GROW SGA rate of just 11.3%. GROW centiles adjust only between normal BMI limits; for example if a mother's BMI is 17, the GROW software will limit downward adjustment to 18.5 when calculating the predicted term weight. This means that GROW adjustments do not extend to

birthweights that might reflect under-nutrition. The IG21 SGA rate is high because physiological maternal characteristics are not taken into account, and the correlation with the GROW TOW confirms that IG21 SGA is mostly dictated by physiological variation. Furthermore, this exaggerated IG21 SGA rate does not correspond to the stillbirth rate, which was not elevated in this predominantly middle-class maternity population receiving high standard of care.

GROW centiles applied to the population cohorts had an overall narrower range of values (SGA 10.1–12.7, LGA 7.3–9.9) than that obtained with IG-21. The actual SGA (<10th centile) rate tends to be above 10%, as in any maternity population it is more likely that fetuses do not fulfill their predicted growth potential due to pathological influences than exceed it. The overall SGA rate tends to be higher if the cohort includes preterm deliveries due to their association with growth restriction,<sup>20</sup> or if they are derived from high-risk referral centers with an elevated risk level for fetal growth problems and associated perinatal morbidities. None of the cohorts showed a GROW SGA rate as low as the average 4.4% displayed by the IG21 standard.

Our findings are consistent with that of Anderson and colleagues,<sup>25</sup> who also compared the IG21 birthweight standard with customized GROW centiles, applying them to their Auckland database. The authors reported similarly low SGA rates with IG21, and substantial variation within their main ethnic groups, which did not reflect pathological outcomes.

Lee and colleagues<sup>26</sup> recently applied the IG21 standard to the Child Health Epidemiology Reference Group (CHERG) dataset of 14 birth cohorts from low- and middle-income countries, and reported SGA rates ranging from 5% or 6% in Eastern Asia and Northern Africa, to 34% in India. While countries in South Asia and sub-Saharan Africa had high SGA rates as well as high neonatal mortality rates, causality was not demonstrated, and the association was contradicted by other countries or

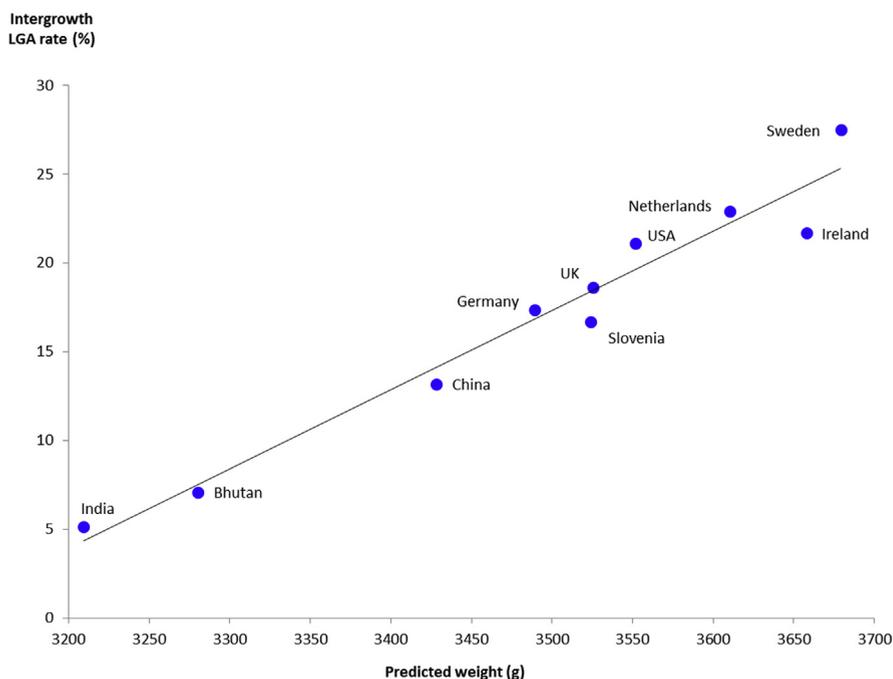
regions with elevated mortality risk that had low SGA rates according to IG21.

Misclassification with a one-size-fits-all model that does not adjust for physiological variation can have considerable unwanted clinical effects. Antenatal overdiagnosis of SGA may lead to unnecessary investigations, intervention, and anxiety for babies with appropriate growth and size for their population. At the same time, with the falsely low IG21 SGA rate, many at-risk babies will go unrecognized because they are being classified as not <10th centile, and we have shown this to be the case in 60% of the at-risk population (Table 3). Postnatally, babies falsely considered SGA may receive unnecessary supplementary feeding to compensate for an imagined deficit. The wrong standard may result in misdirection of available resources in the target population, and a loss of focus on identifying babies truly at risk.

A weakness of this study is that we had only stillbirth as recorded outcome measure in these 10 cohorts, which is not the only relevant outcome measure to assess fetal growth abnormalities. In particular, LGA babies may have complications such as shoulder dystocia and associated morbidities due to birth trauma. There have, however, been several studies with such outcome data that compared customized and population-based centiles for macrosomia and found the customized definition of LGA to be superior and able to identify an additional group in the population that is also at risk of complications.<sup>27-29</sup> A standard such as IG21 that consistently classifies >20% of cases as LGA is likely to lead to excessive maternal anxiety and unnecessary interventions.

Inclusion of LGA in our analysis allowed a look at both ends of the spectrum. It shows that the low IG21 SGA rate is accompanied by a high LGA rate, indicating that the standard not only ignores physiological variation but is overall too low for this population. According to the published IG21 formula,<sup>10</sup> the predicted weight at 40 weeks is 3380 g (boys) and 3260 g (girls), while the optimal 40.0-week weight predicted by the customized standard for this

**FIGURE 3**  
Predicted customized birthweight vs INTERGROWTH-21<sup>st</sup> LGA rate



Predicted birthweight customized for average maternal height, weight, parity and sex, and controlled for gestational age at delivery.  $R = 0.9775$ ;  $P < .01$ .

UK, United Kingdom, USA, United States, LGA, large for gestational age.

Francis et al. Customized vs INTERGROWTH-21<sup>st</sup> standard for birthweight. *Am J Obstet Gynecol* 2018.

cohort (3561 g) as well as the actual weight reached (3490 g) were substantially higher.

The datasets we studied recorded birthweight and not fetal weight and had

the benefit of being routinely collected, whereas fetal weight measurements at term are likely to represent a smaller, selected population that had indications for ultrasound scans. Nevertheless, our

**TABLE 3**  
SGA by GROW and INTERGROWTH 21<sup>st</sup> and stillbirth risk

SGA	SGA by GROW	SGA by IG21	
Classified as SGA, n (%)	131,950 (10.5)	55334 (4.4)	
Stillbirths, n (/1000)	411 (3.1)	229 (4.1)	
	SGA by GROW only	SGA by both standards	SGA by IG21 only
Classified as SGA, n (%)	78,703 (6.3)	53,247 (4.3)	2087 (0.2)
Stillbirths, n (/1000)	185 (2.4)	226 (4.2)	3 (1.4)
Relative risk (95% CI)	<b>1.9</b> (1.6–2.2)	<b>3.5</b> (3.1–4.1)	1.1 (0.4–3.4)
Population attributable risk %	5.1	9.7	0.0

Total N = 1,251,289.

CI, confidence interval; GROW, gestation-related optimal weight; IG21, INTERGROWTH-21<sup>st</sup> birthweight standard; SGA, small for gestational age.

Statistically significant relative risk values are shown in bold.

Francis et al. Customized vs INTERGROWTH-21<sup>st</sup> standard for birthweight. *Am J Obstet Gynecol* 2018.

**TABLE 4**  
**LGA by GROW and INTERGROWTH-21<sup>st</sup> and stillbirth risk**

LGA	LGA by GROW	LGA by IG21	
Classified as LGA, n (%)	118,954 (9.5)	257,732 (20.6)	
Stillbirths, n (/1000)	149 (1.3)	262 (1.0)	
	LGA by GROW only	LGA by both standards	LGA by IG21 only
Classified as LGA, n (%)	6792 (0.5)	112,162 (9.0)	145,570 (11.6)
Stillbirths, n (/1000)	13 (1.9)	136 (1.2)	126 (0.9)
Relative risk (95% CI)	1.4 (0.8–2.5)	0.9 (0.8–1.1)	<b>0.6 (0.5–0.7)</b>
Population attributable risk, %	0.2	–0.9	–4.6

Total N = 1,251,289.

CI, confidence interval; GROW, gestation-related optimal weight; IG21, INTERGROWTH-21<sup>st</sup> birthweight standard; LGA, large for gestational age.

Statistically significant relative risk value is shown in bold.

Francis et al. Customized vs INTERGROWTH-21<sup>st</sup> standard for birthweight. *Am J Obstet Gynecol* 2018.

findings here are also relevant for the IG21 fetal weight standard,<sup>13</sup> which is being proffered for international use under the same one-size-fits-all assumption. The equivalent 40-week value of the IG21 fetal growth formula<sup>13</sup> is 3338 g and is therefore also unlikely to represent growth curves that are suitable for this multicountry cohort.

Our results confirm doubts about the one-size-fits-all approach<sup>30</sup> and improve our understanding of the reported difficulties in local implementation of IG21 fetal and neonatal standards in various environments.<sup>25,31,32</sup> We demonstrate the substantial variation in maternal and physiological pregnancy characteristics across population cohorts, and present evidence that the varied SGA and LGA rates using the IG21 formula mostly reflect physiological variation, which blunts the standard's ability to identify pathology. Finally, we have shown that GROW as a globally applicable but individually adjustable standard improves the strength of association with stillbirth as an adverse outcome, and identifies 60% more SGA cases at increased risk. ■

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# Fetal growth velocity and body proportion in the assessment of growth



Liran Hirsch, MD; Nir Melamed, MD, MSc

Fetal growth restriction implies failure of a fetus to meet its growth potential and is associated with increased perinatal mortality and morbidity. Therefore, antenatal detection of fetal growth restriction is of major importance in an attempt to deliver improved clinical outcomes. The most commonly used approach towards screening for fetal growth restriction is by means of sonographic fetal weight estimation, to detect fetuses small for gestational age, defined by an estimated fetal weight <10th percentile for gestational age. However, the predictive accuracy of this approach is limited both by suboptimal detection rate (as it may overlook non-small-for-gestational-age growth-restricted fetuses) and by a high false-positive rate (as most small-for-gestational-age fetuses are not growth restricted). Here, we review 2 strategies that may improve the diagnostic accuracy of sonographic fetal biometry for fetal growth restriction. The first strategy involves serial ultrasound evaluations of fetal biometry. The information obtained through these serial assessments can be interpreted using several different approaches including fetal growth velocity, conditional percentiles, projection-based methods, and individualized growth assessment that can be viewed as mathematical techniques to quantify any decrease in estimated fetal weight percentile, a phenomenon that many care providers assess and monitor routinely in a qualitative manner. This strategy appears promising in high-risk pregnancies where it seems to improve the detection of growth-restricted fetuses at increased risk of adverse perinatal outcomes and, at the same time, decrease the risk of falsely diagnosing healthy constitutionally small-for-gestational-age fetuses as growth restricted. Further studies are needed to determine the utility of this strategy in low-risk pregnancies as well as to optimize its performance by determining the optimal timing and interval between exams. The second strategy refers to the use of fetal body proportions to classify fetuses as either symmetric or asymmetric using 1 of several ratios; these include the head circumference to abdominal circumference ratio, transverse cerebellar diameter to abdominal circumference ratio, and femur length to abdominal circumference ratio. Although these ratios are associated with small for gestational age at birth and with adverse perinatal outcomes, their predictive accuracy is too low for clinical practice. Furthermore, these associations become questionable when other, potentially more specific measures such as umbilical artery Doppler are being used. Furthermore, these ratios are of limited use in determining the etiology underlying fetal smallness. It is possible that the use of the 2 gestational-age-independent ratios (transverse cerebellar diameter to abdominal circumference and femur length to abdominal circumference) may have a role in the detection of mild-moderate fetal growth restriction in pregnancies without adequate dating. In addition, despite their limited predictive accuracy, these ratios may become abnormal early in the course of fetal growth restriction and may therefore identify pregnancies that may benefit from closer monitoring of fetal growth.

**Key words:** conditional percentiles, growth, individualized growth, serial, velocity

## Background

The term “fetal growth restriction” (FGR) implies failure of a fetus to meet its growth potential. However, given the difficulty in determining the growth potential of the individual fetus, the definition of FGR is challenging and is often based on a combination of measures of fetal size and abnormal Doppler studies.<sup>1-5</sup>

FGR is associated with excess perinatal mortality and morbidity.<sup>6-11</sup> Accordingly, improved detection of FGR has been identified as 1 of the top-10 interventions needed to reduce the global burden of stillbirth.<sup>12</sup> Although various tools are available to screen for FGR, including maternal obstetric history<sup>13,14</sup> and serum markers,<sup>15-21</sup> the most commonly screening approach is

through sonographic fetal weight estimation to detect fetuses that are small for gestational age (SGA), defined empirically as an estimated fetal weight (EFW) <10th percentile for gestational age.<sup>22-26</sup> This approach, however, has a high false-positive rate for FGR, as the majority of SGA fetuses are healthy constitutionally small fetuses rather than growth restricted.<sup>25</sup> Furthermore,

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the detection rate of this approach is also limited given that it may overlook those fetuses with impaired growth even though EFW still remains >10th percentile.<sup>27</sup> Thus, additional measures, mindful of the need to identify failure to achieve individual growth potential, are needed to establish effective screening for FGR.

In the current article we will review 2 strategies that may improve the diagnostic accuracy of sonographic fetal biometry for FGR: (1) use of serial ultrasound evaluations to assess fetal growth; and (2) assessment of fetal body proportions.

### The use of serial ultrasound evaluations to assess fetal growth

One strategy to improve the diagnosis of FGR is through the use of serial ultrasound evaluations. This approach is intuitive and emphasizes the idea that FGR should be viewed as a process rather than a point event. Indeed, the validity of this concept has already been established in infants, where it was shown that growth velocity is more predictive of size later in life than any single cross-sectional measurement of infant size.<sup>28</sup> However, the optimal approach to interpret the information obtained from serial measurements of the same fetus remains unclear.

### Interpretation of serial sonographic assessments of fetal biometry

Several approaches are available for the interpretation of serial measurements of fetal biometry including fetal growth velocity, conditional percentiles, projection-based methods, and individualized growth assessment (IGA).

**Fetal growth velocity.** Fetal growth velocity is defined as the change in fetal size between 2 time points during gestation.<sup>29,30</sup> This approach can be applied to the change in either a specific fetal biometric index (eg, abdominal circumference [AC] or biparietal diameter [BPD]) or in EFW, and is usually expressed as change in absolute value of the biometric index per time unit (eg, mm/wk or g/d) or as a change

in z-score (ie, the value of the biometric index normalized for gestational age) per time unit (known as z-velocity) (Figure 1, A).<sup>31</sup>

Several standards for fetal growth velocity have been published.<sup>29,32-36</sup> The methodology used to generate growth velocity standards differs considerably between studies, and can be grossly divided into 2 types. The first and most commonly used methodology, often referred to as “average growth velocity,” is based on direct measurement of fetal size on  $\geq 2$  time points along gestation. The average growth velocity is calculated by dividing the difference in fetal size by the time interval between the 2 time points. In the case of  $>2$  sets of measurements, the average growth velocity can be calculated using linear regression. Obviously, this approach is based on the assumption that fetal growth is linear throughout the time interval being studied. For example, Guihard-Costa et al<sup>34</sup> used a set of cross-sectional and longitudinal data to calculate the growth velocity rate of 3 biometric indices within individual 3-week intervals between 7-40 weeks. Subsequently, Bertino et al<sup>36</sup> used 2-stage linear model to generate growth velocity standards for 5 biometric indices based on 6- or 10-week intervals. Owen et al,<sup>29</sup> in a longitudinal study of 274 low-risk women, calculated the mean growth velocity for several biometric indices and EFW across 4-week intervals, and used a quadratic equation to model the mean and SD of the growth velocity of the various indices and EFW across these intervals. Others used cross-sectional data to generate growth velocity standards based on the difference between birthweight and the median EFW at 20 weeks,<sup>32</sup> and between sonographic AC at 36-20 weeks of gestation.<sup>33</sup>

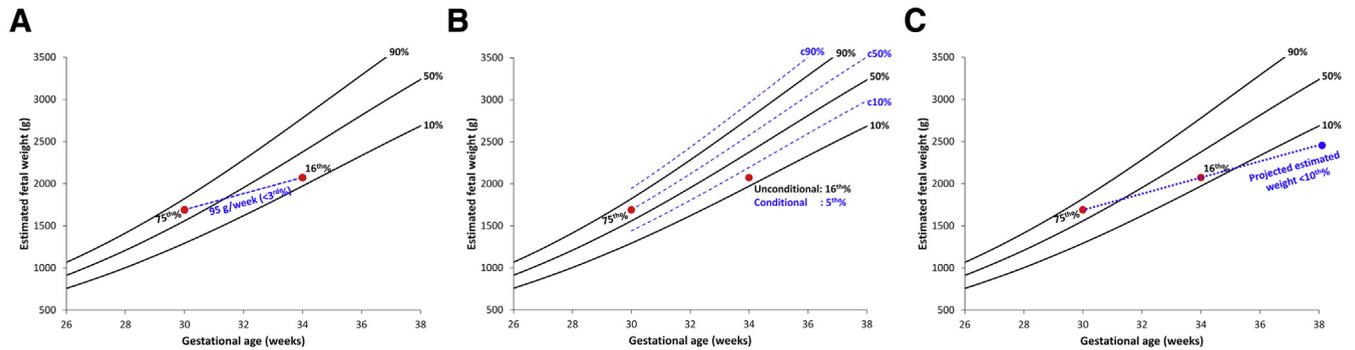
The second methodological approach for the calculation of fetal growth velocity is known as “instantaneous growth velocity” and was used by Deter and Harist<sup>35</sup> in a longitudinal study of 20 fetuses. In that study, the authors generated growth velocity standards for BPD, head circumference (HC), AC, and

femur length (FL) based on the Rossavik growth model, which describes the change of the individual biometric index as a function of gestational age using the following function:  $I = c(t)^{k+s(t)}$  (where I represents the individual biometric index; t represents gestational age; and c, k, and s are the model coefficients). The instantaneous growth velocity was calculated using the first derivative of the Rossavik growth model by gestational age (dI/dt), which provides the instantaneous growth velocity at gestational age t. This approach may be more accurate for the generation of growth velocity standards since, in contrast to the average growth velocity approach, it is not limited by the assumption that fetal growth is linear within a given time interval.

**Conditional percentiles.** An alternative approach towards the interpretation of serial measurements of fetal biometry is through the calculation of conditional percentiles.<sup>37-42</sup> The underlying concept is that the calculation of EFW percentile takes into account (or is conditioned on) previous weight estimation of the same fetus earlier in pregnancy. Thus, the first weight estimation (or the conditioning scan) is used to adjust the standard growth curve to the expected growth trajectory of the individual fetus, and the EFW percentile at the time of the subsequent exam is determined based on this new adjusted curve, which is narrower and shifted toward the initial percentile compared with the original standard growth curve (Figure 1, B). This approach is based on multilevel modeling that takes into account the variability in growth within and between fetuses.<sup>37,39</sup>

**Projection-based methods.** Projection-based methods use linear mixed-effects models to predict EFW at a later point in gestation based on  $\geq 2$  observations of EFW and are a way to combine size and velocity information (since both the start value as well as rate of growth over time are factored into the projection).<sup>43,44</sup> A projected EFW below a fixed cut-off (eg, 5th or 10th percentile for gestational age) can then

**FIGURE 1**  
Serial ultrasound can improve the detection rate for fetal growth restriction



**A**, “Fetal growth velocity” is defined as difference in estimated fetal weight (EFW) between 2 time points during gestation divided by difference in corresponding gestational ages. In current example, EFW was 1692 g at 30 weeks and 2074 g at 34 weeks, translating to growth velocity of 95 g/wk, which is less than third percentile of expected growth velocity.<sup>29</sup> Thus, assessment of growth velocity in current case identified suboptimal growth suggestive of FGR despite fact that EFW at 34 weeks was >10th percentile for gestational age. See [Appendix](#) for detailed description of calculation of growth velocity percentile. **B**, Conditional percentiles involve customization of EFW reference according to first EFW observation, and EFW percentile at time of subsequent exams is determined based on these new adjusted curves, which are narrower and shifted toward initial centile compared with original reference curves. In current example, EFW at 30 weeks was consistent with 75th percentile for gestational age. Therefore, expected growth trajectory for this individual fetus is expected to be along 75th percentile and as result, adjusted growth curve for this fetus (dashed blue lines) is narrower and shifted upwards compared with original reference curves (solid black lines). Subsequent EFW at 34 weeks is consistent with 5th percentile for gestational age according to adjusted curves (conditional percentile), which is suggestive of FGR, diagnosis that might have been overlooked if conventional (unconditional) percentiles according to original references curves are used (16th percentile in current example). c10%, c50%, and c90% represent 10th, 50th, and 90th conditional percentiles, respectively. **C**, Projection-based methods use linear mixed effects models to predict EFW at later point in gestation based on  $\geq 2$  observations of EFW. In current example, projected EFW at 38 weeks based on 2 weight estimations at 30 and 34 weeks is <10th percentile for gestational age. Thus, use of projected EFW in current case identified fetus potentially growth restricted despite fact that EFW at 34 weeks was >10th percentile for gestational age.

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be used as a positive screen for FGR ([Figure 1, C](#)).

*Individualized growth assessment.* With this approach, fetal size assessments during the third trimester are interpreted by calculating the degree to which they deviate from the expected growth curve of the same individual fetus, a curve that is based on 2 sonographic assessments performed <26 weeks of gestation (ie, presumably prior to the onset of any pathologic factor that may affect fetal growth).<sup>45,46</sup>

The approaches described above can be simply viewed as mathematical techniques to quantify any decrease in fetal weight percentile, a phenomenon that is associated with adverse perinatal outcome<sup>47</sup> that most care providers assess and monitor routinely in a qualitative manner. Thus, for a fetus

experiencing slowing in growth, the decline in growth can be expressed by low growth velocity ([Figure 1, A](#)); by an adjusted EFW (conditional) percentile that is shifted downwards to reflect the lower-than-expected interval growth ([Figure 1, B](#)); or by a projected EFW that is below a fixed cut-off. These approaches may improve the detection rate for FGR because they are capable of detecting fetuses experiencing suboptimal interval growth, even if EFW is >10th percentile for gestational age ([Figure 1](#)). Furthermore, approaches such as fetal growth velocity and conditional percentiles may decrease the false-positive rate for the diagnosis of FGR by identifying SGA fetuses likely to be constitutionally small rather than growth restricted ([Figure 2](#)). However, it should be emphasized that the interpretation of the measured fetal growth

velocity (ie, determining whether it is within normal range, eg, whether it is greater than third percentile of the expected growth velocity for gestational age) is not as straightforward as the calculation of fetal size percentiles and requires information on the mean and SD of growth velocity for the gestational age interval of interest. An example of such calculation is demonstrated in the [Appendix](#). In addition, the use of these approaches requires better understanding of several methodological aspects and limitations of these tools.

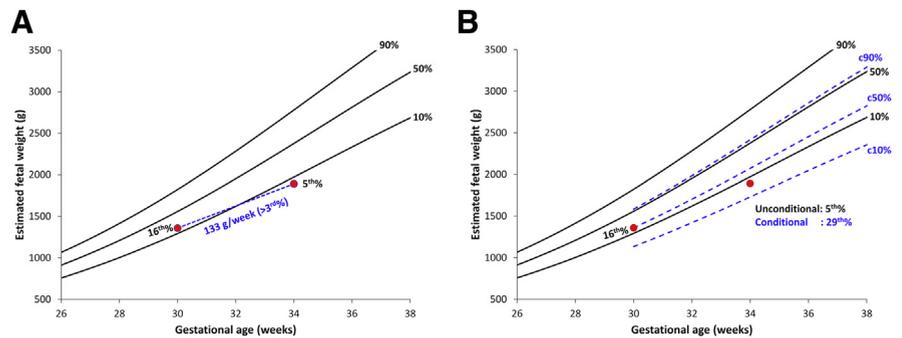
#### Methodological aspects and limitations related to the interpretation of serial sonographic assessments of fetal biometry

One important methodological consideration relates to the number and spacing of ultrasound measurements, as well as to

the timing of the first (baseline, or conditioning) ultrasound evaluation that is used to condition the calculation of the subsequent fetal size percentile. With regard to the number of ultrasound measurements, based on the regression to mean principle, it is reasonable to assume that the accuracy of approaches such as projection-based methods and IGA will improve with the number of ultrasound measurements. However, increasing the number of ultrasound exams has important implications in terms of time, resources, and cost. The second consideration relates to the spacing or interval between ultrasound exams. Although the ideal spacing remains to be determined, it is clear that a very short interval may increase the risk of error due to the higher ratio between the random measurement error and the expected interval growth (ie, greater noise-to-signal ratio). Indeed, Owen et al,<sup>48</sup> in a study on the predictive accuracy of growth velocity of fetal abdominal area, reported that the ideal intermeasurements interval for calculation of growth velocity is 4 or 6 weeks rather than 2 weeks. However, it should be emphasized that growth velocity calculations are based on the assumption of linear growth between the 2 given time points being assessed. While this assumption may be true for short intervals or in certain parts of the growth curves, it may not apply for wider intervals.<sup>35,49</sup> The third consideration relates to the timing of scans. Based on the rationale underlying these approaches, the first (or conditioning) ultrasound should reflect the true growth potential of the fetus and should therefore be performed prior to the onset of any pathologic factors that may impair fetal growth (Figure 3). Otherwise, in cases where the conditioning scan is performed after the onset of pathologic factors that decrease fetal growth (Figure 3), the use of growth velocity or conditional percentiles may underestimate the true fetal growth potential and may fail to detect FGR. However the ideal timing of the conditioning scan remains unclear given evidence that, in cases of FGR, growth alterations can be seen as early as 11-14 weeks,<sup>50</sup> which means that in some cases even the 18- to 22-week anatomy scan

FIGURE 2

### Serial ultrasound can decrease the risk of false diagnosis of fetal growth restriction



**A**, In current example, estimated fetal weight (EFW) was 1360 g at 30 weeks and 1892 g at 34 weeks, translating to growth velocity of 133 g/wk, which is normal.<sup>29</sup> Although EFW percentile at 34 weeks was <10th percentile and may raise concern of FGR, presence of normal growth velocity suggests that diagnosis of constitutionally small-for-gestational-age fetus is more likely. **B**, Same can be achieved with use of conditional percentiles. Given that EFW at 30 weeks was consistent with 16th percentile for gestational age, adjusted growth curve for this fetus (dashed blue lines) is narrower and shifted downwards compared with original reference curves (solid black lines). As result, subsequent EFW at 34 weeks was consistent with 29th percentile for gestational age according to adjusted curves (conditional percentile), thus avoiding misdiagnosis of this fetus as growth restricted based on conventional (unconditional) percentiles according to original reference curves (5th percentile in current example). c10%, c50%, and c90% represent 10th, 50th, and 90th conditional percentiles, respectively.

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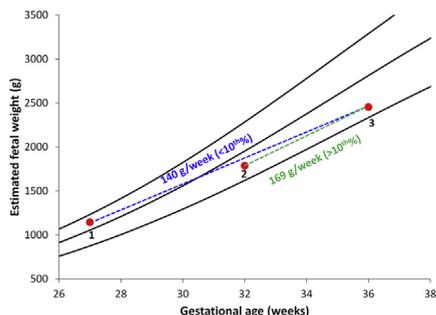
might be already too late to be used as the conditioning scan.

Another important consideration when using any of these approaches is that even a slight overestimation or underestimation of fetal size at the time of the first (conditioning) ultrasound exam would have a considerable effect on the expected growth trajectory of the individual fetus, which in turn may result in overdiagnosis or underdiagnosis of FGR, respectively. Such overestimation or underestimation of fetal size at the time of the conditioning scan is not unlikely given the considerable random error associated with fetal biometry,<sup>26,51</sup> the potential for systematic error (eg, due to changes in measurement techniques or technology),<sup>52</sup> and the considerable interobserver measurement variation that was found in a recent study to be as high as 5%, 9%, and 11% for HC, AC, and FL, respectively.<sup>53</sup> The risk of overestimation or underestimation of fetal growth trajectory may be even greater in studies that use EFW as the predictor

variable (as compared with an individual biometric index) given that a composite variable such as EFW may amplify the measurement error associated with each of its components.

One additional potential limitation of the growth velocity approach is that this approach does not account for the regression to the mean principle. Regression to the mean is the statistical phenomenon that a variable with an extreme value on its first measurement will tend to be closer to the mean (ie, to the center of the distribution) when it is measured again. The manifestation of this phenomenon in the case of serial ultrasound measurement of fetal size is that when the first measurement of EFW is considerably lower than average (eg, EFW is at the 5th percentile for gestational age at the first ultrasound measurement), the EFW percentile of the same fetus at the time of the subsequent measurement several weeks later will tend to be higher on average and closer to the mean (ie, closer to the 50th

**FIGURE 3**  
Effect of timing of first ultrasound scan on assessment of growth velocity and conditional percentiles



Ideally, when growth velocity or conditional percentiles are being used, first (conditioning) scan should reflect true growth potential of fetus and should therefore be performed prior to onset of any pathologic factors that may impair fetal growth (measurement 1). In cases where conditioning scan is performed after onset of pathologic factors that compromise fetal growth (measurement 2), use of growth velocity or conditional percentiles may underestimate true fetal growth potential and may fail to detect fetal growth restriction (FGR). In current example, when first scan is done early in gestation (measurement 1, 27 weeks), growth velocity (calculated between measurements 1 and 3 at 36 weeks, blue line) is abnormally low, suggesting diagnosis of FGR even though estimated fetal weight percentile at 36 weeks is >10th percentile. Alternatively, if measurement 2 (at 32 weeks) had been used as conditioning scan, fetal growth velocity (between measurements 2 and 3, green line) would be interpreted as normal, thereby failing to detect FGR.

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percentile) compared with the first EFW (Figure 4, blue dots). Such a tendency will not be observed in cases in which the first EFW is close to the mean (50th percentile) (Figure 4, green dots). Similarly, in a fetus with a high EFW percentile at the time of the first measurement (eg, 95th percentile for gestational age), the subsequent EFW percentile of the same fetus several weeks later will tend to be lower on average and closer to the mean compared with the first EFW (Figure 4, red dots). A detailed

discussion of the reasons for this phenomenon is beyond the scope of the current article, but in general this phenomenon can be attributed to the random error of EFW (eg, due to measurement error).<sup>54</sup> This phenomenon can result in a considerable bias when it comes to the assessment of growth velocity since fetuses with a low EFW percentile in the first measurement will display on average a higher growth rate compared with fetuses with an average EFW at the time of the first measurement, while fetuses with a high EFW percentile in the first measurement will display on average a lower growth rate compared with fetuses with an average EFW at the time of the first measurement, merely due to this statistical phenomenon (Figure 4). Thus, studies that focus on fetal growth velocity should recognize this potential for bias and account for it.

#### Evidence regarding the benefit of serial ultrasound assessments of fetal biometry

Although the concept of serial ultrasound assessment to assess fetal growth is appealing, the evidence that this strategy significantly improves the diagnostic accuracy for FGR is conflicting. Some studies demonstrate that serial assessments of fetal growth improved the detection of FGR and adverse perinatal outcomes in comparison with single (cross-sectional) sonographic evaluation of fetal size,<sup>41,48,55-61</sup> while others reported that single measurements performed either as well as<sup>43,62,63</sup> or even better<sup>42,64</sup> than serial ultrasound assessments of fetal biometry. The conflicting findings may be attributed to differences between studies with regard to the methodological aspects of the interpretation serial ultrasound data (as described above), the choice of predictor variable (eg, fetal AC, abdominal area, or EFW), and the choice of outcome measures used to diagnose FGR (newborn size [eg, birthweight <10th percentile, low ponderal index] or adverse perinatal outcomes).

Another key difference between studies is the study population. Available

data suggest that the performance of growth velocity and conditional percentiles vary considerably based on whether it is applied to low risk (or unselected) populations or to women at high risk of FGR. We will therefore review current evidence separately for low-risk and high-risk pregnancies.

*Performance of serial ultrasound assessment in low-risk population.* Owen et al<sup>48,56,57,59,60</sup> reported on the performance of fetal growth velocity using the same cohort of 274 low-risk women described above. Growth velocity of fetal abdominal area between 32-36 weeks was superior to a single measurement of fetal abdominal area at 36 weeks of gestation in the prediction of cesarean delivery for fetal distress (odds ratio [OR], 5.1; 95% confidence interval [CI], 1.7-17.3 vs OR, 2.3; 95% CI, 0.8-6.5) and admission to a neonatal unit,<sup>56</sup> and was predictive of FGR based on anthropometric assessment of the newborn (positive likelihood ratio 10.4 [95% CI, 3.9-26] for low skinfold thickness and positive likelihood ratio 9.5 [95% CI, 4.6-19] for low ponderal index).<sup>57</sup> Similarly, Pedersen et al<sup>61</sup> evaluated the association between conditional percentiles of BPD in the second trimester (which were conditioned on the BPD percentile in the first trimester) and adverse perinatal outcome in an unselected population of 7642 women with a singleton pregnancy. Conditional BPD percentiles <10th and 2.5th percentiles were associated with perinatal mortality (OR, 16.0 [95% CI, 2.9-88.7] and OR, 7.3 [95% CI, 2.4-22.2], respectively), while such an association was not observed for conventional (unconditional) BPD percentile in the second trimester.

By contrast, other studies reported no or only little benefit for serial ultrasound assessments. Hutcheon et al<sup>62</sup> reported that the use of conditional birthweight percentiles (which were conditioned on EFW at 32-33 weeks of gestation) did not improve the prediction of adverse perinatal outcomes compared with conventional (unconditional) birthweight percentile in an unselected population. Similarly, conditional birthweight

percentiles (which were conditioned on EFW at 25 weeks of gestation) had minimal contribution to that achieved with conventional (unconditional) birthweight percentiles in the prediction of anthropometric characteristics at 5 years of age.<sup>63</sup> It should be noted, however, that these latter studies used birthweight conditional percentiles rather than EFW conditional percentile as was originally described by others.<sup>29</sup>

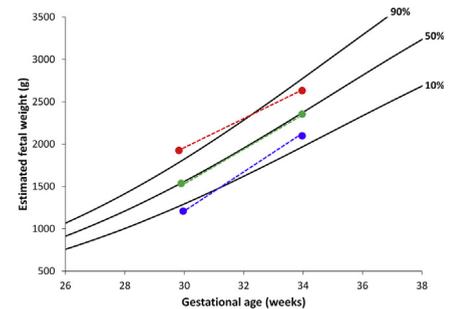
In another recent study, Tarca et al<sup>43</sup> compared serial vs single ultrasound evaluations of fetal biometry in predicting SGA and large for gestational age at birth (birthweight <5th percentile and >95th percentile for gestational age, respectively) using a prospective cohort of 3971 low-risk women.<sup>43</sup> The authors found that serial ultrasound evaluations (which were interpreted through the calculation of the projected EFW at 40 weeks) did not improve the prediction of SGA compared with a conventional EFW percentile at the time of the last ultrasound assessment. Similarly, Caradeux et al<sup>42</sup> assessed the accuracy of serial ultrasound assessments of fetal biometry in the second trimester (21 weeks) and third trimester (32 weeks), interpreted as AC growth velocity and AC conditional percentiles, in predicting SGA (defined as birthweight <10th percentile according to customized standards) and late FGR (defined as birthweight less than third percentile; or birthweight <10th percentile plus abnormal Doppler within 1 week before birth) in a cohort of 2696 unselected singletons pregnancies. The predictive value of AC growth velocity and AC conditional percentiles was lower than that achieved with a single measurement of AC percentile in the third trimester (area under the curve [AUC], 0.63 [95% CI, 0.59–0.66]; AUC, 0.56 [95% CI, 0.53–0.60]; and AUC, 0.81 [95% CI, 0.79–0.84] for the prediction of SGA, respectively). It should be emphasized, however, that the outcome variables in these 2 latter studies were measure of size (SGA and FGR) rather than adverse perinatal outcomes. As such, it is actually not surprising that such outcome measures would be better predicted by similar measures of size (eg, conventional EFW

percentile or AC percentile) at the time of the last ultrasound exam than by measures of fetal growth (eg, longitudinal projection of EFW, AC growth velocity, or AC conditional percentiles), constituting a self-fulfilled prophecy (Figure 5).<sup>42</sup> Instead, we believe that studies assessing the benefit of measures of fetal growth using serial ultrasound evaluations (compared with cross-sectional measures of fetal size) should focus on the prediction of adverse perinatal outcomes rather than measures of size at birth. This is based on the rationale underlying the use of measures of fetal growth, which is to improve the predictive accuracy for FGR through: (1) increasing the detection of normal-size (non-SGA) growth-restricted fetuses; and (2) decreasing the false-positive diagnosis of FGR in cases of constitutional healthy SGA fetuses. In both scenarios, fetal size percentile at the time of last ultrasound is expected to be more predictive of SGA at birth while measures of fetal growth are expected to be more predictive of FGR and adverse perinatal outcome (Figure 5).

*Performance of serial ultrasound assessment in high-risk population.* In contrast to the conflicting results in low-risk pregnancies, most studies in women at high-risk for FGR suggest a beneficial role for serial measures of fetal growth in the prediction of adverse perinatal outcomes attributable to FGR.<sup>41,55,58,65,66</sup>

The definition of “high risk” varied between studies and included the presence of vascular risk factors (eg, preexisting hypertension, smoking),<sup>41,58</sup> late maternal age,<sup>58</sup> history of pregnancies complicated by FGR or preeclampsia,<sup>41,58</sup> or EFW <10th or 5th percentile in the current pregnancy.<sup>41,65</sup> de Jong et al<sup>58</sup> assessed fetal growth velocity during the 6-week period prior to birth in 200 pregnancies at high risk of FGR and found fetal growth velocity to be predictive of adverse perinatal outcome: fetal growth velocity was significantly lower among fetuses requiring operative delivery for fetal distress (20.9 g/d) or admission to neonatal intensive care unit (20.3 g/d) compared with those with a

**FIGURE 4**  
Risk of bias in assessment of fetal growth velocity due to regression to mean phenomenon



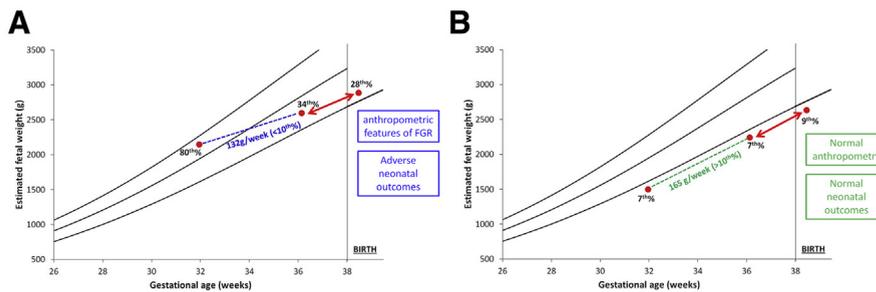
Regression to mean phenomenon and potential risk of bias attributed to this phenomenon when assessing fetal growth velocity. In cases when first measurement of estimated fetal weight (EFW) is considerably lower than average (eg, at 5th percentile for gestational age, blue dot at 30 weeks), subsequent EFW percentile of same fetus at 34 weeks will tend to be on average higher and closer to mean (ie, closer to 50th percentile) compared with first EFW (blue dot at 34 weeks). Such tendency will not be observed in cases in which first EFW is close to mean (green dots at 30 and 34 weeks). Similarly, in fetus with high EFW percentile at time of first measurement (eg, 95th percentile for gestational age, red dot at 30 weeks), subsequent EFW of same fetus at 34 weeks will tend to be on average lower and closer to mean compared with first EFW (red dot at 34 weeks). Thus, fetuses with low EFW percentile in first measurement will display on average higher growth rate (blue dashed line) compared with fetuses with average EFW at time of first measurement (green dashed line), while fetuses with high EFW percentile in first measurement will display on average lower growth rate (red dashed line) compared with fetuses with average EFW at time of first measurement, observation that reflects bias secondary to this statistical phenomenon.

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normal outcomes (24.2 g/d,  $P < .05$ ). Similarly, in a prospective longitudinal study of 211 women with risk factors for FGR or with SGA fetus, Karlsen et al<sup>41</sup> found that conditional percentiles improved the prediction of adverse perinatal outcomes beyond that

FIGURE 5

### Choice of outcome measures in studies assessing predictive accuracy of growth velocity and conditional percentiles



**A**, Finding of abnormally low growth velocity may improve detection of fetal growth restriction (FGR) despite normal size percentiles before and after birth (34th percentile at 36 weeks and 28th percentile at birth in current example). **B**, Similarly, finding of normal growth velocity may decrease false-positive diagnosis of FGR in cases of constitutionally small fetuses with low size percentiles before and after birth (7th percentile at 36 weeks and 9th percentile at birth in current example). However, it is clear from figure that if outcome measure used to validate antenatal diagnosis of FGR was measure of size at birth (eg, birthweight <10th percentile), then fetal size percentile at time of last ultrasound (which is measure of size as well and is therefore highly correlated with birthweight percentile, red arrows) will perform better than fetal growth velocity, leading to potentially wrong conclusion that fetal size percentiles at the time of the most recent ultrasound exam are more accurate in diagnosing FGR than fetal growth velocity. Instead, antenatal diagnosis of FGR should be validated against more reliable postnatal features of FGR such as adverse neonatal outcomes or anthropometric features characteristics of FGR.

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achieved with conventional size percentiles alone. Finally, Sovio et al,<sup>65</sup> in one of the very few prospective studies where ultrasound findings remained blinded, compared a policy of routine third-trimester ultrasound (at 28 and 36 weeks) vs selective (clinically indicated) third-trimester ultrasound for the prediction of SGA at birth (defined as birthweight <10th percentile) and neonatal morbidity in 3977 unselected nulliparous women with singleton pregnancy. They found that EFW <10th percentile was associated with neonatal morbidity only if the fetal AC growth velocity was in the lowest decile (relative risk [RR], 3.9 [95% CI, 1.9–8.1] for any neonatal morbidity; RR, 17.6 [95% CI, 9.2–34.0] for SGA at birth plus any neonatal morbidity). These findings provide support to the hypothesis that measures of fetal growth can improve the predictive accuracy for the diagnosis of FGR and adverse perinatal outcomes beyond that achieved with conventional size percentiles.

### Fetal body proportions

#### Rationale for the use of fetal body proportions

Fetuses suspected to be growth restricted have been traditionally classified as having an either symmetric or asymmetric pattern based on the ratio between AC and another reference biometric index. The rationale underlying this classification is the hypothesis that this pattern may provide information on the etiology of FGR (ie, constitutional, placental, or intrinsic fetal abnormalities), timing of onset of FGR (early vs late), duration of FGR, and risk of adverse outcome.<sup>67-71</sup>

The brain-sparing phenomenon suggests that fetal AC will be the first biometric index to be affected in cases of placental insufficiency, leading to the assumption that FGR with an asymmetric pattern (ie, small AC in relation to another reference biometric index that is unaffected by fetal malnutrition) is more likely to be the result of placental insufficiency and is at higher risk of

adverse perinatal outcomes.<sup>13</sup> This assumption is in line with the postnatal observation that a low ponderal index in the neonate is suggestive of malnutrition and is associated with adverse outcome.<sup>72</sup>

The rationale for a correlation between FGR pattern and timing of insult leading to FGR is based on the understanding of the mechanisms responsible for fetal growth in different phases of development, where early fetal growth is the result of hyperplasia while growth in late pregnancy (>32 weeks) is mainly the result of hypertrophy. Based on that, it is assumed that insults that take place in late pregnancy, when most fetal fat and glycogen deposition occurs, will result in an asymmetric pattern with small AC and smaller amount of fat.<sup>71</sup>

However, data regarding the predictive value of the pattern of fetal growth for the etiology of FGR, timing of FGR, and risk of adverse outcomes are conflicting.

#### Common fetal body proportions used to assess fetal asymmetry

Fetal body proportions used to assess fetal asymmetry are based on a ratio between AC and a reference biometric index assumed to be less sensitive to placental insufficiency. The most commonly used ratios are the HC/AC ratio, transverse cerebellar diameter (TCD)/AC ratio, and FL/AC ratio.

**HC/AC ratio.** Fetal HC is thought by many to be the ideal reference biometric index given that it is only minimally affected by placental insufficiency or by external pressure. Several nomograms for the HC/AC ratio have been published.<sup>67,73,74</sup> The median HC/AC ratio in early pregnancy is about 1.2 and decreases in linear fashion along gestation, reaching a value of about 1.0 at term (Figure 6).

Dashe et al,<sup>74</sup> in a cohort of 1364 SGA fetuses, reported an association between an asymmetric pattern as defined by HC/AC ratio >95th percentile and adverse pregnancy outcomes (including preterm birth, lower birthweight, hypertensive complications, operative delivery for

fetal distress, and neonatal morbidity), while the outcome of symmetric SGA fetuses was not different than that of normally grown fetuses. In contrast, others found the predictive value of HC/AC ratio for adverse pregnancy outcomes is low and therefore of limited clinical usefulness.<sup>70,75</sup> Moreover, David et al<sup>70</sup> reported that when adjustment was made for other sonographic factors such as umbilical artery Doppler (which was the strongest predictor of adverse outcome in their cohort of SGA fetuses), HC/AC ratio was no longer predictive of adverse outcomes. Finally, Colley et al,<sup>72</sup> in a study of 999 infants who underwent anthropometric assessment after delivery, found that the HC/AC ratio was poorly correlated with the ponderal index (an established measure of neonatal wasting), and therefore concluded that the use of HC/AC ratio as a measure of asymmetric growth pattern secondary to intrauterine malnutrition should be abandoned.

**TCD/AC ratio.** “Transverse cerebellar diameter” refers to the maximum transverse diameter of the fetal cerebellum. Since the fetal cerebellar hemispheres are located in the posterior cranial fossa, which is resistant to external pressure and growth deviations, it is considered to be an accurate indicator of gestational age with minimal variability even in cases of fetal growth impairment.<sup>76-78</sup> Several nomograms for the TCD/AC ratio are available,<sup>73,79-81</sup> all consistently indicating that from around 21-22 weeks the fetal TCD/AC ratio is gestational-age independent, remaining constant throughout the remainder of pregnancy (median value 0.13) (Figure 6).

Several studies reported that an asymmetric pattern defined as TCD/AC ratio >95th percentile is predictive of birthweight <10th percentile for gestational age.<sup>78,81-85</sup> Meyer et al,<sup>84</sup> in a prospective study of 825 low-risk pregnancies and 158 pregnancies at risk of FGR, found the TCD/AC ratio to have high sensitivity (98%) for asymmetric SGA neonate (defined as birthweight <10th percentile and high neonatal HC/AC ratio) and concluded that the

TCD/AC ratio is an accurate, gestational-age-independent method of identifying SGA infants and may be especially useful in the diagnosis of SGA in pregnancies with uncertain gestational age. However, Snijders et al,<sup>86</sup> in a study of 103 fetuses with FGR, found that in contrast to previous reports, the growth of the TCD was actually affected in cases of severe FGR (although to a lesser degree than other biometric indices such as HC, AC, and FL), and therefore concluded that TCD may not be a reliable estimate of gestational age in pregnancies complicated by FGR, and that while the TCD/AC ratio may be of value in cases of mild-moderate FGR, it is not a reliable predictor of severe FGR. This reservation has been confirmed by others.<sup>83</sup>

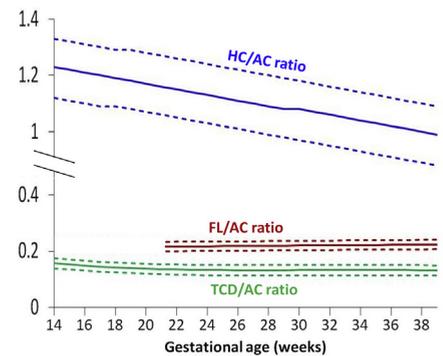
**FL/AC ratio.** Another body proportion proposed to be useful in the detection of FGR is the FL/AC ratio. Hadlock et al<sup>87</sup> noticed that in normal pregnancies, the FL/AC ratio is relatively constant >21 weeks of gestation (mean  $\pm$  SD 0.22  $\pm$  0.02) (Figure 6). Although a high FL/AC ratio (>90th percentile) was found to be associated with birthweight <10th percentile for gestational age, the association was reported to be weak and lower than that observed for AC <10th percentile or EFW <10th percentile, leading to the conclusion that the FL/AC ratio is of no clinical use.<sup>87,88</sup> Of note, isolated fetal short femur in the second trimester has been found to be associated with FGR,<sup>89-92</sup> which can further explain the limited predictive value of the FL/AC ratio.

#### Fetal asymmetry and etiology for FGR

As described above, it has been traditionally assumed that assessment of fetal body proportions may provide information on the underlying etiology of FGR, so that intrinsic fetal causes of FGR such as chromosomal abnormalities were thought to be associated with early-onset symmetric pattern while placental insufficiency was considered to be associated with late-onset asymmetric pattern.<sup>68,69,71,93</sup>

However, larger studies have challenged this paradigm. Snijders et al<sup>94</sup>

**FIGURE 6**  
Commonly used fetal body proportions



Data represent normal values along gestation for head circumference (HC) to abdominal circumference (AC) ratio (blue lines),<sup>73</sup> transverse cerebellar diameter (TCD)/AC ratio (green lines),<sup>73</sup> and femur length (FL)/AC ratio (red lines).<sup>87</sup> Values are presented as median (solid lines) and 5th and 95th percentiles (dashed lines). Median HC/AC ratio in early pregnancy is about 1.2 and decreases in linear fashion along gestation, reaching value of about 1.0 at term. TCD/AC ratio is gestational-age independent >21 weeks and remains constant throughout gestation (median 0.13). FL/AC ratio is relatively constant >21 weeks of gestation (mean  $\pm$  SD 0.22  $\pm$  0.02).

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reported on the outcomes of 458 FGR fetuses referred at 17-39 weeks' gestation tested for karyotype. Fetal karyotype was abnormal is 19% (38/458) of cases, with the most common findings being triploidy and trisomy 18 in those referred <26 and >26 weeks of gestation, respectively. In contrast to the assumption described above, fetuses with abnormal karyotype had an asymmetric pattern (high HC/AC ratio) compared with growth-restricted fetuses with normal chromosomes. This was mainly attributed to an asymmetric pattern among fetuses with nonmolar triploidy, as well as fetuses with trisomy 18 at >30 weeks of gestation. It should be noted that fetuses with nonmolar triploidy displayed an unusually high HC/AC ratio (>1.4), which is an uncommon finding among fetuses with asymmetric FGR and normal karyotype. The authors

hypothesized that the asymmetric pattern of FGR fetuses with abnormal karyotype may be due to concomitant placental insufficiency secondary to the abnormal placental karyotype, which is supported by reports of high rate of abnormal umbilical artery Doppler in fetuses with abnormal karyotype.<sup>94-97</sup> It should be emphasized, however, that unlike umbilical artery Doppler, the uterine artery Doppler is likely to be normal among fetuses with FGR and abnormal karyotype.<sup>94,98</sup> Thus, in fetuses with early-onset severe FGR (with or without abnormal umbilical artery Doppler), the presence of an unusually high HC/AC ratio (>1.4) and normal uterine artery Doppler is associated with increased risk of abnormal karyotype, especially triploidy.

Additional evidence that questions the relationship between asymmetric pattern and placental insufficiency comes from a retrospective study of 107 pregnancies complicated by severe early-onset placenta-related FGR (64% had absent diastolic flow and 36% had reverse diastolic flow in the umbilical artery).<sup>99</sup> The authors found that only 58% (62/107) of these euploid fetuses with obvious placental insufficiency had an asymmetric pattern (HC/AC ratio >95th percentile). Instead, it seems that the timing of insult is more important than the etiology of FGR in determining fetal growth pattern, with early insults (placental or fetal) resulting in symmetric pattern while insults taking place later in pregnancy resulted in an asymmetric pattern.<sup>71,75</sup>

### Implications of fetal body proportion for EFW

Sonographic models for EFW are based on equations that incorporate  $\geq 1$  fetal body parts including BPD, HC, AC, and FL. Given that most of these models were generated from normal or unselected fetuses, it is reasonable to assume that these models would be less accurate in fetuses with asymmetric SGA since the coefficients of the various biometric indices in these models do not account for the different relative body proportions in these fetuses with asymmetric SGA.<sup>26</sup> Indeed, in a study of 43

fetuses with severe FGR, Proctor et al<sup>100</sup> found that while the standard Hadlock equations that include 3 or 4 indices performed best in fetuses with symmetric FGR, models that excluded FL (eg, Hadlock 3 equation based on BPD and AC) performed best in cases of asymmetric FGR. The use of models that include FL in fetuses with asymmetric FGR resulted in underestimation of birthweight by 11-13%.

### Summary

In the current article we reviewed 2 strategies that may improve the diagnostic accuracy of sonographic fetal biometry for FGR.

Serial ultrasound evaluations can be interpreted as fetal growth velocity, conditional percentiles, projection-based methods, or IGA and appear promising in high-risk pregnancies where they seem to improve the detection of growth-restricted fetuses at increased risk of adverse perinatal outcomes and, at the same time, decrease the risk of falsely diagnosing healthy constitutionally SGA fetuses as growth restricted. The utility of this approach in low-risk pregnancies remains unclear and is not currently justified. We recognize that the use of this strategy is potentially complicated and time-consuming, and believe that the development of online calculators can simplify the use of these tools and make this approach more accessible to clinical care providers beyond the research domain. Further studies are needed to quantify the predictive accuracy of these tools, to determine the optimal timing of the conditioning ultrasound, the optimal interval between exams, and the overall cost-effectiveness of the screening program. It should be noted that the outcome measures used to validate the performance of these approaches should be based on adverse perinatal outcomes or neonatal anthropometric features of FGR rather than on the diagnosis of SGA at birth, to address the reality that failure to achieve a pre-determined growth potential results in delivery across a wider range of birthweight centiles than the traditional 10th centile cut-off.

The second strategy of analysis of fetal body proportions to classify fetuses as symmetric or asymmetric based on several ratios has the inherent advantage of being simple and cost-effective. However, although abnormal ratios are associated with SGA at birth and with adverse perinatal outcomes, their predictive accuracy is too low for clinical purposes. Furthermore, these associations are obviated by other more specific measures of placental function, such as Doppler studies.

Still, these ratios may be beneficial in specific circumstances such as the finding of an unusually high HC/AC ratio (>1.4) in fetuses with early-onset severe FGR, which may increase the risk of nonmolar triploidy. In addition, despite their limited predictive accuracy, these ratios may become abnormal early in the course of FGR and may therefore identify pregnancies that may benefit from closer monitoring of fetal growth.

Further studies are needed to determine whether, when combined with other predictive tools such as umbilical artery or middle cerebral artery Doppler, these ratios can contribute to the diagnosis of FGR, especially in late FGR where umbilical artery Doppler is typically normal. Finally, future studies should determine whether combining the 2 approaches discussed in the current article by using serial assessment of fetal body proportions (eg, serial assessments of the HC/AC ratio) can further improve the diagnosis of FGR and adverse perinatal outcome. ■

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**Appendix****Example for interpretation of fetal growth velocity**

In the case described in [Figure 1, A](#), estimated fetal weight was 1692 g at 30 weeks and 2074 g at 34 weeks, translating into a fetal growth velocity of 95 g/wk. Based on

the growth velocity standard of Owen et al,<sup>29</sup> the mean  $\pm$  SD growth velocity during the 30- to 34-week interval is 26.3  $\pm$  4.3 g/d. Assuming that the growth velocity within this time interval follows a normal distribution, the third percentile (equivalent to a z-score of  $-1.88$ )

for growth velocity within this time interval would be: mean  $- 1.88 \times$  SD =  $26.3 - 1.88 \times 4.3 = 18.2$  g/d or 127 g/wk. The fact that the observed growth velocity (95 g/wk) is less than third percentile of the expected growth velocity raises concern regarding fetal growth restriction.

## OBSTETRICS

# What birthweight percentile is associated with optimal perinatal mortality and childhood education outcomes?



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**BACKGROUND:** Small for gestational age, defined as birthweight <10th percentile for gestational age, is known to be associated with clinically meaningful impairments in health and development. The effects of variation within the normal range of birthweight percentile on perinatal mortality and childhood education remain less well defined.

**OBJECTIVE:** We sought to quantify the association among birthweight percentile, perinatal mortality, and educational outcomes and to determine the optimal birthweight percentile for those outcomes in Aboriginal and non-Aboriginal Australian children.

**STUDY DESIGN:** This was a retrospective cohort study. Perinatal data for all children born in the Northern Territory, Australia, from 1999 through 2008 were linked to measures of educational attainment at age 8–9 years. Multivariable analysis was used to determine the optimal birthweight percentile for low perinatal mortality and high reading and numeracy scores.

**RESULTS:** The birth cohort contained 35,239 births (42% Aboriginal), of which 11,214 had linked and valid education records. Median birthweight percentile was 29.2 in Aboriginal infants and 44.0 in non-Aboriginal infants. The odds of perinatal mortality decreased by 4% with each 1-percentile increase birthweight percentile overall (adjusted odds ratio, 0.96;  $P = .000$ ) and lowest mortality rates were at the 61st and 78th

percentile in Aboriginal and non-Aboriginal infants, respectively. Although birthweights <10th percentile were associated with greatly increased odds of perinatal mortality, the increased risk extended well beyond this cut-off. Birthweight percentile was also positively correlated with scores in reading ( $P = .000$ ) and numeracy ( $P = .000$ ). In non-Aboriginal children, reading and numeracy scores peaked at the 66th percentile, but for Aboriginal children there was continuous benefit with increasing birthweight percentile. Birthweight percentile explained 1% of the variation in education outcomes, with much greater variation explained by other perinatal and sociodemographic factors.

**CONCLUSION:** Birthweights between the 50th–93rd percentiles were most consistently associated with both low perinatal mortality and high reading and numeracy scores, suggesting that small for gestational age does not sufficiently capture the risks associated with variation in fetal growth. Our data indicate that the effect of birthweight percentile accounts for 1% of variation in perinatal and education outcomes.

**Key words:** Aboriginal, Australia, birthweight, birthweight percentile, data linkage, education, fetal growth, indigenous, National Assessment Program—Literacy and Numeracy, Northern Territory, numeracy, perinatal mortality, pregnancy, reading, school, small for gestational age

## Introduction

Small for gestational age (SGA) (<10th percentile) is the outcome of a spectrum of influences on fetal growth and well-being that includes, but is not limited to, maternal malnutrition, placental pathology, and maternal exposure to stress, smoking, and alcohol consumption during pregnancy.<sup>1</sup> The short- and long-term outcomes for infants born SGA has been documented since 1967,<sup>2</sup> and range from perinatal morbidity and mortality to developmental delays, poor academic achievement, mental illness, and non-communicable diseases.<sup>3–6</sup> The outcomes associated with variation of fetal growth within the normal range (>10th percentile) is less clear. Although it has long been recognized that fetal growth is a continuum with no precise at-risk cut-off,

clinicians and researchers continue to dichotomize fetal growth. Recent studies have shown unambiguous variation in perinatal mortality rates across the entire spectrum of fetal growth, suggesting the existence of an optimal birthweight for gestational age and challenging the dichotomization paradigm.<sup>3,4</sup> Whether or not an optimal birthweight could be applied across different populations is heavily debated,<sup>7,8</sup> but results of the INTERGROWTH-21st project suggest that fetal growth patterns are highly comparable between different populations when maternal conditions are optimal.<sup>9</sup>

In common with many indigenous and disadvantaged peoples worldwide, in Australia, Aboriginal and Torres Strait Islander people (hereafter referred to respectfully as Aboriginal Australians) experience higher rates of health and socioeconomic disadvantage compared to the wider population.<sup>10,11</sup> The negative impacts of colonization, structural violence, and the historical removal of

children of mixed ethnicity on current Aboriginal health and well-being are now widely acknowledged.<sup>10</sup> Australian governments, at both national and state levels, have identified focus areas to improve Aboriginal outcomes, including infant mortality, early childhood development, and education.<sup>12</sup> Studies have identified the critical importance of early childhood development on long-term outcomes and economic burden,<sup>13</sup> but one area that remains less explored is the possible role of fetal growth and development in the perpetuation and intergenerational transmission of disadvantage through poor health and education.

The aim of this study was to examine the association between birthweight percentile and: (1) perinatal mortality and (2) education in Aboriginal and non-Aboriginal Australian children, with the hypothesis that optimal outcomes would occur in infants born between the 50th–97th percentiles and that

lower birthweight percentiles in Aboriginal infants would contribute to the disparity in outcomes.

## Materials and Methods

This was a retrospective, whole-of-population, data linkage study spanning pregnancy and childhood up to 8-9 years of age. The study used existing data from 3 administrative data sets: the Northern Territory perinatal data register, Northern Territory government school student information, and the Australian National Assessment Program—Literacy and Numeracy (NAPLAN) database. Probabilistic record linkage was undertaken by a data linkage facility (SA-NT DataLink, Adelaide, Australia), and involved calculating the probability that records in different data sets belong to the same person, based on concordance of pre-determined identifiers (eg, name, date of birth, gender, address). Records were assigned a unique linkage key for each individual, and then returned to the respective data custodian, who then compiled a deidentified research data set.

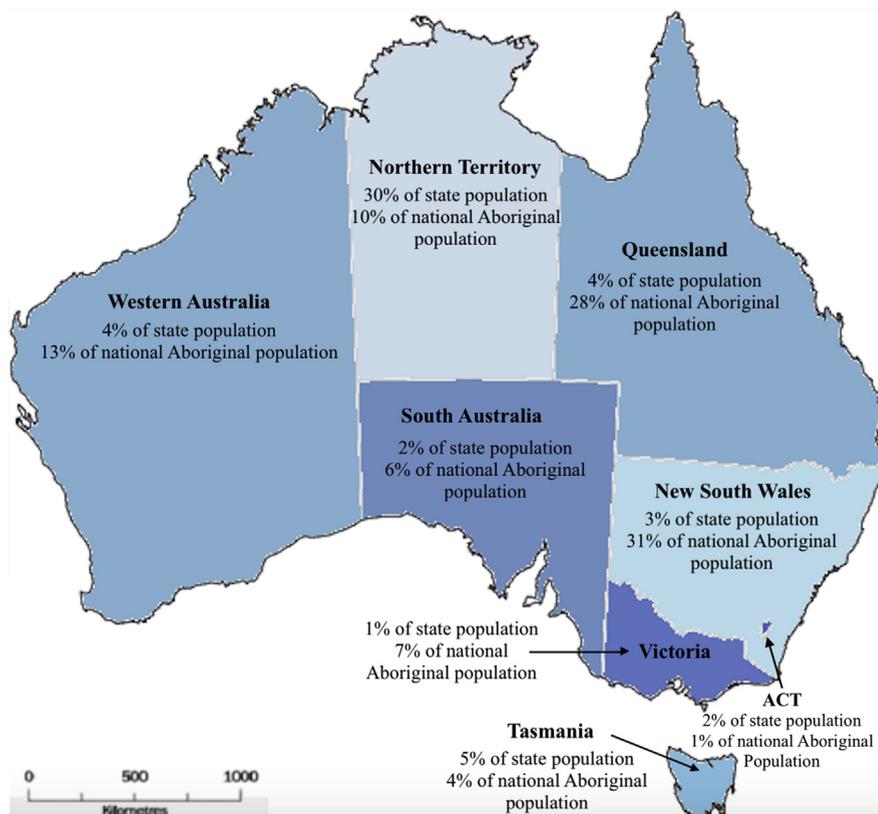
## Subjects

The birth cohort included 35,239 births occurring in the Northern Territory (Figure 1) to Northern Territory resident mothers, from Jan. 1, 1999, through Dec. 31, 2008, after the exclusion of plural births, births occurring <20 weeks or >42 weeks completed gestation, and neonates with unknown Aboriginal status. Of this cohort, 11,214 were linked to both student information and year-3 reading and numeracy results (Figure 2).

## Data sources

The Northern Territory perinatal data set is a statutory collection that contains antenatal and labor information for all births in the Northern Territory, collected by the birth attendant. Death registration data were added to the data set. The student information data set contains demographic information of children and their primary caregivers, provided at the time of school enrollment. NAPLAN is an Australia-wide, standardized, academic test. Results from this test were available from 2008

**FIGURE 1**  
Percentage of Aboriginal Australians by state and territory



Percentages are expressed as proportion of total state population and as proportion of national Aboriginal and Torres Strait Islander population. Total Australian population was 22,620,600 in 2011. Of population, 1% resided in Northern Territory, 32% in New South Wales, 25% in Victoria, 20% in Queensland, 11% in Western Australia, 7% in South Australia, 2% in Tasmania, 2% in Australian Capital Territory. Generated using data from Australian Bureau of Statistics Census of Population and Housing, 2011.

ACT, Australian Capital Territory.

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through 2014, for students enrolled in a government school.

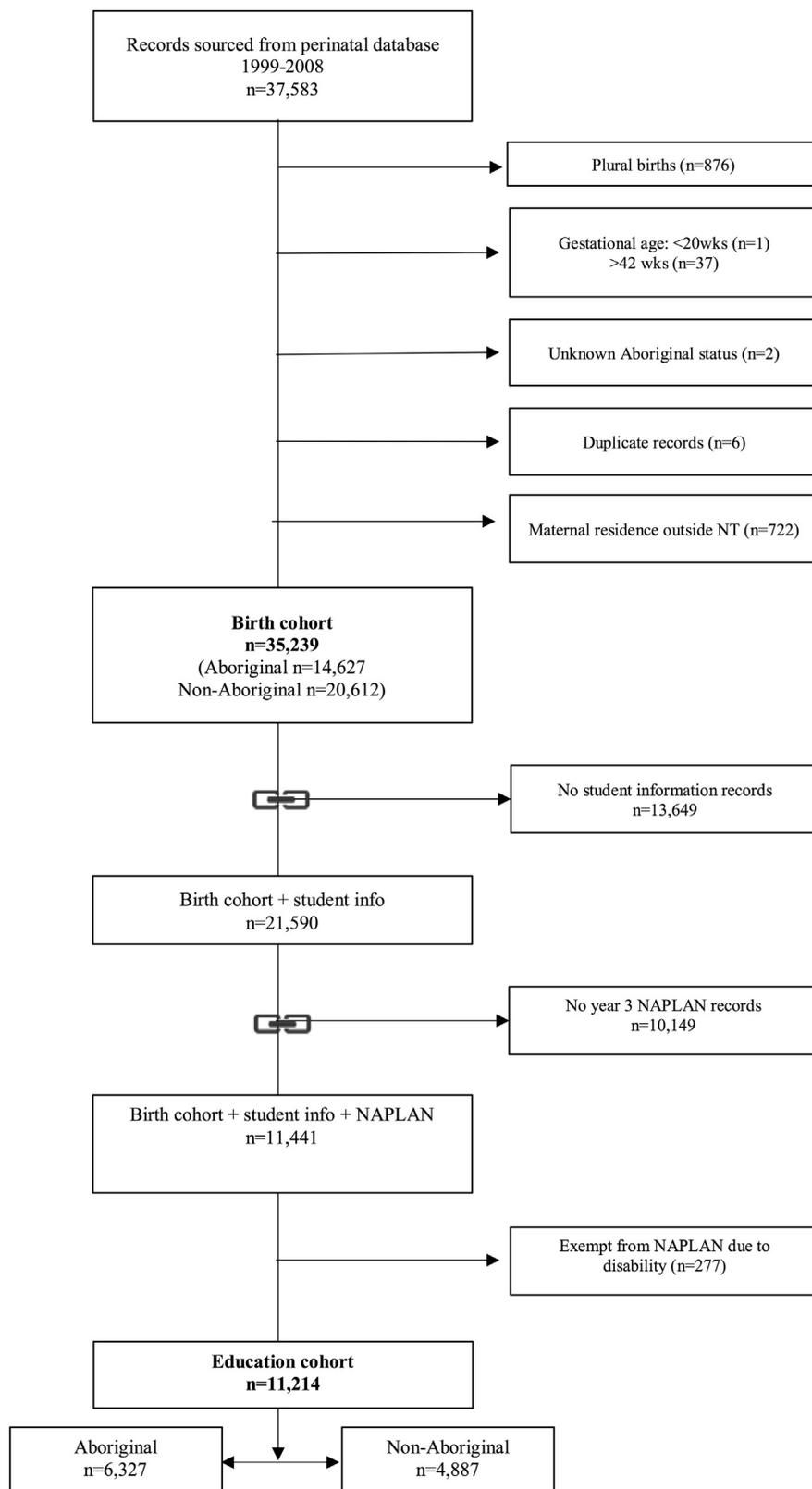
## Outcome measure

The first outcome measured was perinatal death, defined as a fetal death (of at least 20 weeks completed gestation) or neonatal death (within 28 days of birth).<sup>11</sup> The second outcome examined was year-3 school test results, as measured by NAPLAN (median age 8.4 years). Scores in reading and numeracy were chosen due to their reported consistency and previous utility and because they allow for direct comparison of performance across all years and year levels.<sup>14,15</sup>

Birthweight percentiles were used as the primary explanatory variable, due to

their previously reported utility and standardization for gestational age. Birthweight percentiles were calculated for each record using birthweight, gestational age, and gender. An Australian-European standard developed by Gardosi et al<sup>16</sup> and incorporating Hadlock intrauterine estimated fetal weight standard was used for all infants. This prevented the normalizing of lower birthweights in Aboriginal fetuses and neonates. In addition to maintaining the continuous birthweight percentile variable a categorical variable, with cut-offs at the 2.3rd, 7th, 16th, 31st, 50th, 69th, 84th, 93rd, and 97.7th percentiles, was generated (ie, 0.5 SD widths).

**FIGURE 2**  
Formation of the birth and education cohort using data linkage



Aboriginal status was based on records in multiple data sets based on a hierarchy of quality, commencing with health data. Aboriginal status in health records has been estimated to have 98% consistency between electronic patient records and self-report at interview.<sup>17</sup> Other explanatory variables were selected a priori based on existing literature and included gender, gestational age (based on first day of last menstrual period or early pregnancy ultrasound), parity, maternal age, smoking and alcohol consumption during pregnancy, maternal comorbidities, age at school testing, primary caregiver education, English as a second language, geographical remoteness, and socioeconomic status (SES).<sup>5,14,18-21</sup>

Remoteness was assigned using the 2011 Accessibility/Remoteness Index of Australia (ARIA+) and SES was assigned using the Socioeconomic Indexes for Areas (SEIFA): Index of Relative Advantage and Disadvantage.<sup>22,23</sup> Both remoteness and SES were assigned at the community level, based on the school that each child attended.

### Statistical analysis

Perinatal mortality rates were calculated for each birthweight percentile category using the number of deaths as the numerator, and total births as the denominator. Multivariable logistic regression was used to examine the association between birthweight percentile (continuous) and perinatal mortality and to assess the odds ratio (OR) of perinatal mortality in each birthweight percentile category. Models were built using a stepwise approach ( $P$ -to-add  $< .2$ ). Variables that altered the association between birthweight percentile and the outcome were retained regardless of  $P$  value.

Progressive linkage and exclusion criteria for formation of birth cohort and education cohort. Chain symbol indicates linkage of records in student information data set and National Assessment Program—Literacy and Numeracy (NAPLAN) data set with records in birth cohort.

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TABLE 1

**Summary and comparison of perinatal and sociodemographic risk factors in birth cohort and linked education cohort by Aboriginal status**

	Birth cohort: 35,239		Education cohort: 11,214	
	Aboriginal	Non-Aboriginal	Aboriginal	Non-Aboriginal
Total	14,627 (41.5)	20,612 (58.5)	6327 (56.4)	4887 (43.6)
Sex				
Male	7600 (51.96)	10,507 (51.0)	3253 (51.4)	2425 (49.6)
Female	7022 (48.01)	10,091 (48.9)	3074 (48.6)	2462 (50.4)
Missing	5 (0.03)	14 (0.1)	0	0
Parity				
0	4658 (31.9)	9107 (44.2)	2056 (32.5)	1938 (39.7)
1	3683 (25.2)	6662 (32.3)	1550 (24.5)	1615 (33.0)
>1	6281 (42.9)	4832 (23.4)	2717 (42.9)	1330 (27.2)
Missing	5 (0.0)	11 (0.1)	4 (0.1)	4 (0.1)
Alcohol during pregnancy				
Yes	1527 (10.5)	1547 (7.5)	666 (10.5)	430 (8.8)
No	10,260 (70.1)	17,199 (83.4)	4489 (70.9)	4034 (82.5)
Missing	2840 (19.4)	1866 (9.1)	1172 (18.6)	423 (8.7)
Smoking during pregnancy				
Yes	5982 (40.9)	3715 (18.0)	2618 (41.4)	1084 (22.2)
No	6234 (42.6)	15,436 (74.9)	2771 (43.8)	3520 (72.0)
Missing	2411 (16.5)	1461 (7.1)	938 (14.8)	283 (5.8)
Maternal age, y				
Mean (SD)	24.0 (6.1)	29.4 (5.6)	23.7 (6.0)	29.1 (5.8)
<18	2027 (13.9)	228 (1.1)	980 (15.5)	81 (1.7)
18–19	1929 (13.2)	620 (3.0)	880 (13.9)	164 (3.4)
20–24	4551 (31.1)	3376 (16.4)	1916 (30.3)	867 (17.7)
25–29	3287 (22.5)	6142 (29.8)	1413 (22.3)	1416 (29.0)
30–34	1894 (12.9)	6385 (31.0)	794 (12.6)	1470 (30.0)
≥35	939 (6.4)	3860 (18.7)	344 (5.4)	888 (18.2)
Missing	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)
Birthweight, g				
Mean (SD)	3125.2 (677.9)	3386.9 (578.1)	3161.8 (600.1)	3364.9 (550.5)
Missing	2 (0.0)	6 (0.0)	0 (0.0)	1 (0.0)
Gestational age, completed wk				
Mean (SD)	38.3 (2.8)	39.0 (2.1)	38.6 (2.1)	39.0 (1.7)
Median (IQR)	39 (38–40)	39 (38–40)	39 (38–40)	39 (38–40)
Birthweight percentile				
Median (IQR)	29.2 (10.1–60.1)	43.9 (19.3–71.9)	28.3 (9.9–58.8)	41.4 (17.3–69.6)
<2.3	1252 (8.6)	805 (3.9)	527 (8.3)	214 (4.4)
2.3–<7	1566 (10.7)	1280 (6.2)	701 (11.1)	338 (6.9)
7–<16	2160 (14.8)	2293 (11.1)	960 (15.2)	596 (12.2)

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(continued)

TABLE 1

**Summary and comparison of perinatal and sociodemographic risk factors in birth cohort and linked education cohort by Aboriginal status** (continued)

	Birth cohort: 35,239		Education cohort: 11,214	
	Aboriginal	Non-Aboriginal	Aboriginal	Non-Aboriginal
16—<31	2574 (17.6)	3331 (16.2)	1133 (17.9)	805 (16.5)
31—<50	2430 (16.6)	3761 (18.3)	1058 (16.7)	901 (18.4)
50—<69	1790 (12.2)	3483 (16.9)	764 (12.1)	783 (16.0)
69—<84	1197 (8.2)	2485 (12.1)	506 (8.0)	548 (11.2)
84—<93	678 (4.6)	1511 (7.3)	268 (4.3)	341 (7.0)
93—<97.7	445 (3.0)	869 (4.2)	199 (3.2)	185 (3.8)
>97.7	524 (3.6)	783 (3.8)	210 (3.2)	175 (3.6)
Missing	11 (0.1)	12 (0.1)	1 (0.0)	1 (0.0)

Categorical data presented as number (percentage) for each group and continuous data presented as mean (SD) or median (IQR).

Compared to non-Aboriginal children without National Assessment Program—Literacy and Numeracy (NAPLAN) records, those in education cohort had lower birthweight percentiles ( $P = .0000$ ) and were born to younger mothers ( $P = .0017$ ) with higher parity ( $P = .000$ ), who were more likely to smoke ( $P = .000$ ) or drink ( $P = .000$ ) during pregnancy. Aboriginal children with NAPLAN records were also born to younger mothers ( $P = .0000$ ), but were not different in terms of birthweight percentile ( $P = .0615$ ), parity ( $P = .171$ ), maternal smoking ( $P = .197$ ), or alcohol consumption ( $P = .591$ ) compared to those without NAPLAN records.  $P$  values obtained from  $\chi^2$  test of proportion, independent  $t$  test and Wilcoxon rank sum test.

IQR, interquartile range.

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For the education cohort, mean reading and numeracy scores were calculated in each birthweight percentile category. Multivariable linear regression was used to assess the association between birthweight percentile and reading and numeracy scores and to determine the birthweight percentile category with the highest scores, after controlling for perinatal confounders, maternal education, geographic remoteness, and SES. Interaction terms were used to test for gender-specific effects.

Most explanatory variables in the education analysis had <2% missing values with the exception of maternal smoking (Aboriginal: 19.5%, non-Aboriginal: 12.6% missing) and alcohol consumption during pregnancy (25.3%, 16.0%), parent-1 education (27.6%, 6.2%), reading score (19.7%, 3.8%), and numeracy score (20.2%, 4.0%). To avoid sampling bias, missing data were imputed using chained equations under the assumption of missing at random using a set of 20 imputation data sets. The results were compared for consistency with complete case analysis. All analysis was conducted separately for Aboriginal and non-Aboriginal infants. Statistical analyses were conducted with

software (Stata, Version 14; Stata Corp, College Station, TX).

### Approval for the study by the local human investigations committee

The study protocol was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HR-10-1458), Central Australian Human Research Ethics Committee (2010-09-06), and University of Newcastle Human Research Ethics committee (H-2016-0059).

### Glossary

- ARIA+ is a measure of geographical remoteness, determined by the average distance by road to service centers. ARIA+ is an updated version of the original measure. ARIA+ scores are grouped into 5 areas: major cities, inner regional, outer regional, remote, or very remote. In the Northern Territory there are no major cities or inner regional areas.<sup>22</sup>
- SEIFA is a measure of the relative socioeconomic advantage or disadvantage of a community based on employment, education, housing, and other factors.<sup>23</sup>

- NAPLAN is an Australia-wide, standardized, academic test conducted at ages 8, 10, 12, and 14 years to assess performance in reading, spelling, language conventions, and numeracy.<sup>15</sup>

### Results

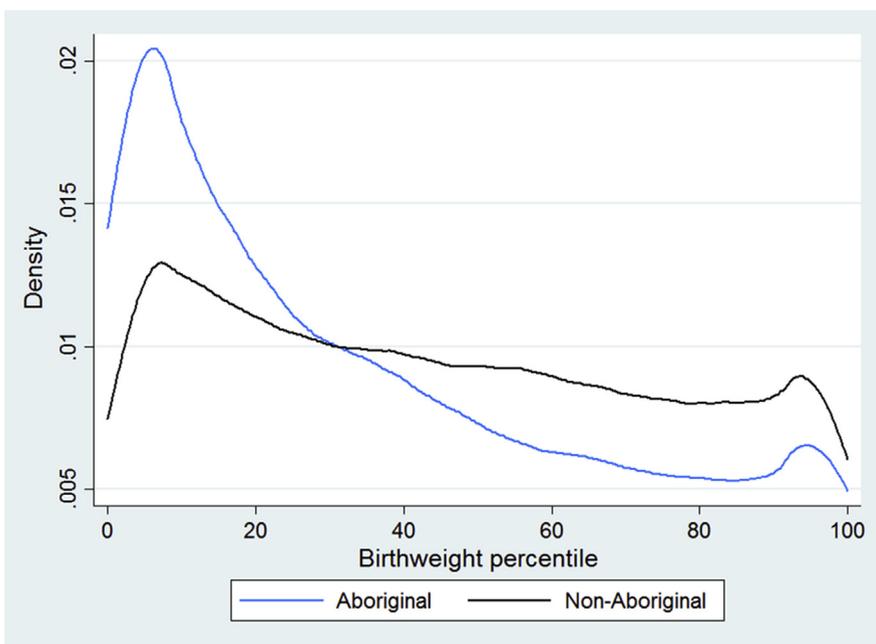
A summary of perinatal and socio-demographic risk factors for the birth cohort and the cohort with reading and numeracy results are presented by Aboriginal status in Table 1. There was a higher proportion of Aboriginal children in the education cohort.

In the birth cohort, the median birthweight percentile was 29.2 (interquartile range, 10.1-60.1) in Aboriginal neonates and 44.0 (interquartile range, 19.3-71.9) in non-Aboriginal neonates (Wilcoxon rank sum:  $P < .0005$ ). Relative to non-Aboriginal infants, there was a profound downward shift in the entire distribution of birthweight percentiles in Aboriginal infants and a lower density of birthweight percentiles between the 50th-90th percentiles, which was the hypothesized optimal range (Figure 3). Similar patterns were evident when restricted to term births (not shown).

### Optimal birthweight percentile for perinatal survival

There were 294 Aboriginal perinatal deaths and 185 non-Aboriginal perinatal deaths recorded in the data set, of which the majority were fetal deaths for both groups. Perinatal mortality rates were 20.1 per 1000 Aboriginal births and 9.0 per 1000 non-Aboriginal births ( $\chi^2$ :  $P < .0005$ ). Examination of birthweight percentile as a continuous variable (Table 2) revealed that the OR of perinatal mortality decreased by 4% with each 1-percentile increase in birthweight percentile in both Aboriginal (adjusted OR, 0.96; 95% confidence interval [CI], 0.94–0.98;  $P < .001$ ) and non-Aboriginal (adjusted OR, 0.96; 95% CI, 0.93–0.98;  $P < .001$ ) infants. The association remained significant when the analysis was limited to infants born between the 10th–90th percentiles ( $P = .029$  and  $P = .004$  in Aboriginal and non-Aboriginal infants, respectively). The addition of a squared term for birthweight percentile significantly improved the models (likelihood ratio test:  $P < .05$ ), indicating that the association between birthweight percentile and perinatal death was quadratic, with the lowest mortality at the 61st percentile in Aboriginal infants and the 78th percentile in non-Aboriginal infants. The nature of this quadratic relationship is illustrated in Figure 4, which clearly demonstrates a stepwise decrease in the odds of perinatal mortality as birthweight percentile increases: there is a nadir between the 84th–93rd percentiles, at which point the odds of perinatal mortality increased again. For both Aboriginal and non-Aboriginal populations, the infants with birthweights <31st percentile had significantly higher perinatal mortality than those born between the 84th–93rd percentiles (except Aboriginal infants between the 7th–16th percentiles, which was not significant) (Table 3). Aboriginal infants with birthweights >93rd percentile had significantly higher perinatal mortality than those between the 84th–93rd percentiles (Table 3). In all models, birthweight percentile explained 1% of

**FIGURE 3**  
Distribution of birthweight percentiles in Aboriginal and non-Aboriginal fetuses and neonates



In contrast to distribution of birthweight percentiles in non-Aboriginal children, there is high density of Aboriginal birthweight percentiles <20th percentile and comparatively fewer birthweight percentiles between 60th–90th percentiles. Peak around 90th–100th percentiles in both groups is attributable to maternal diabetes. Same patterns were evident when restricted to term births.

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variation in perinatal mortality. Gestational age explained much of the remaining variance accounted for by the models.

### Optimal birthweight percentile for reading and numeracy

Our education cohort represented 64% of all Northern Territory children who

**TABLE 2**  
Logistic regression models with birthweight percentile as continuous predictor of perinatal mortality in Aboriginal and non-Aboriginal pregnancies 1999 through 2008

Birthweight percentile	Aboriginal: n = 14,616		Non-Aboriginal: n = 20,600	
	Crude OR (95% CI)	aOR <sup>a</sup> (95% CI)	Crude OR (95% CI)	aOR <sup>a</sup> (95% CI)
Linear term	0.96 (0.95–0.98) <sup>b</sup>	0.96 (0.94–0.98) <sup>b</sup>	0.94 (0.92–0.96) <sup>b</sup>	0.96 (0.93–0.98) <sup>b</sup>
Squared term	1.0004 (1.0003–1.0006) <sup>b</sup>	1.0003 (1.0001–1.0005) <sup>b</sup>	1.0005 (1.0003–1.0007) <sup>b</sup>	1.0003 (1.0001–1.0005) <sup>c</sup>
R <sup>2</sup>	0.01	0.46	0.03	0.50

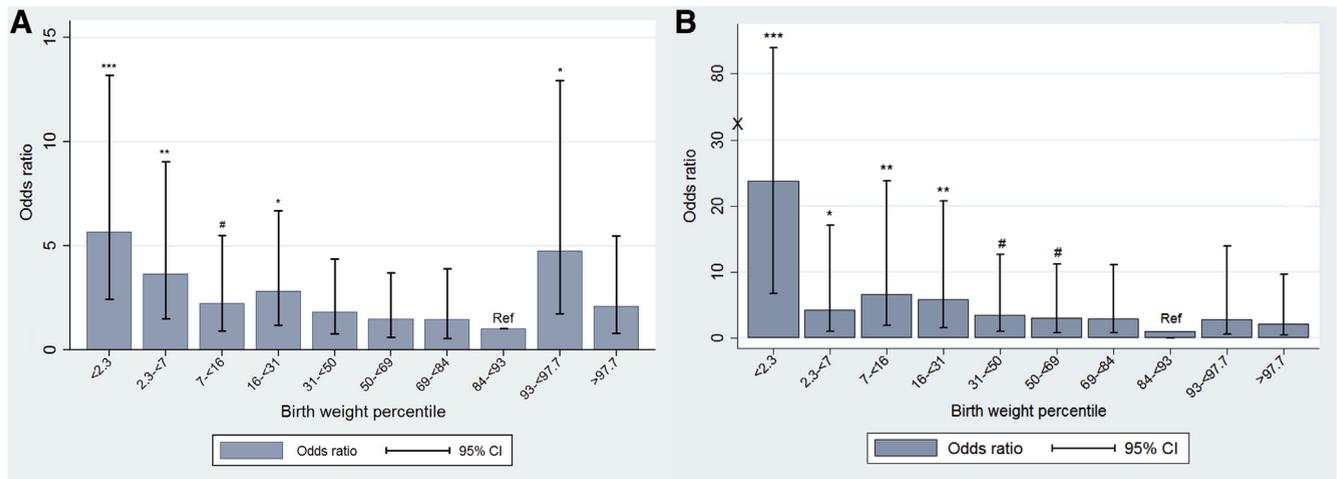
Crude OR obtained from univariate logistic analysis and aOR obtained from multivariable logistic analysis.

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

<sup>a</sup> Model adjusted for gestational age, preeclampsia, and maternal diabetes; <sup>b</sup>  $P = .000$ ; <sup>c</sup>  $P = .022$ .

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**FIGURE 4**  
Odds of perinatal death in each category of birthweight percentile



Adjusted odds ratios and 95% confidence intervals (CI) for association between birthweight percentile and perinatal mortality in **A**, Aboriginal and **B**, non-Aboriginal fetuses and neonates. Logistic regression models were adjusted for gestational age, preeclampsia, and maternal diabetes. There was evidence of stepwise increase in perinatal mortality as birthweight percentile decreases <84th–93rd percentiles in both Aboriginal and non-Aboriginal fetuses and neonates. \*\*\* $P < .001$ , \*\* $P < .01$ , \* $P < .05$ , # $P < .1$ .

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participated in the year-3 NAPLAN test from 2008 through 2014 at a government school, or 40% of the eligible birth cohort (excludes children born in 2007

through 2008 as they were too young to sit the test). A summary of socioeconomic factors in Aboriginal and non-Aboriginal children and their univariate

association with reading and numeracy scores are presented in [Table 4](#).

In adjusted models, reading and numeracy scores were significantly

**TABLE 3**  
Logistic regression models with birthweight percentile (categorical) as predictor of perinatal mortality in Aboriginal and non-Aboriginal pregnancies 1999 through 2008

Birthweight percentile	Aboriginal: n = 14,616			Non-Aboriginal: n = 20,600		
	No. (rate)	Crude OR (95% CI)	aOR <sup>a</sup> (95% CI)	No. (rate)	Crude OR (95% CI)	aOR <sup>a</sup> (95% CI)
<2.3	52 (41.53)	2.89 (1.46–5.73) <sup>b</sup>	5.64 (2.42–13.18) <sup>c</sup>	47 (58.39)	18.68 (7.40–47.15) <sup>c</sup>	23.82 (6.76–84.02) <sup>c</sup>
2.3–<7	25 (15.96)	1.08 (0.52–2.27)	3.65 (1.48–9.02) <sup>b</sup>	10 (7.81)	2.37 (0.81–6.96)	4.23 (1.05–17.04) <sup>d</sup>
7–<16	27 (12.50)	0.85 (0.41–1.76)	2.24 (0.91–5.49) <sup>e</sup>	25 (10.90)	3.32 (1.27–8.69) <sup>d</sup>	6.63 (1.85–23.82) <sup>b</sup>
16–<31	43 (16.71)	1.13 (0.57–2.27)	2.82 (1.19–6.67) <sup>d</sup>	23 (6.90)	2.09 (0.79–5.52)	5.81 (1.63–20.79) <sup>b</sup>
31–<50	37 (15.23)	1.03 (0.51–2.09)	1.81 (0.75–4.35)	27 (7.18)	2.18 (0.84–5.67)	3.51 (0.97–12.69) <sup>e</sup>
50–<69	28 (15.64)	1.06 (0.51–2.20)	1.49 (0.60–3.70)	17 (4.88)	1.48 (0.54–4.01)	3.02 (0.81–11.24) <sup>e</sup>
69–<84	20 (16.71)	1.14 (0.53–2.44)	1.47 (0.56–3.88)	17 (6.84)	2.07 (0.76–5.64)	2.89 (0.75–11.14)
84–<93	10 (14.75)	Reference		5 (3.31)	Reference	
93–<97.7	20 (44.94)	3.14 (1.46–6.78) <sup>b</sup>	4.73 (1.73–12.93) <sup>d</sup>	4 (4.60)	1.39 (0.37–5.20)	2.78 (0.55–13.91)
>97.7	25 (47.71)	3.35 (1.59–7.03) <sup>c</sup>	2.09 (0.80–5.46)	6 (7.67)	2.33 (0.71–7.65)	2.14 (0.47–9.69)
R <sup>2</sup>		0.02	0.48		0.06	0.51

Data presented compared to reference category.

Crude OR obtained from univariate logistic analysis and aOR obtained from multivariable logistic analysis.

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

<sup>a</sup> Model adjusted for gestational age, preeclampsia, and maternal diabetes; <sup>b</sup>  $P < .01$ ; <sup>c</sup>  $P < .001$ ; <sup>d</sup>  $P < .05$ ; <sup>e</sup>  $P < .1$ .

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TABLE 4

**Descriptive data for education cohort on socioeconomic variables used in multivariable analysis and univariate associations between socioeconomic variables and reading and numeracy scores**

	Aboriginal: n = 6326			Non-Aboriginal: n = 4886		
	Percentage	Mean reading score	Mean numeracy score	Percentage	Mean reading score	Mean numeracy score
Total	6327	239.0	265.5	4887	381.9	374.0
Sex						
Male	51.4	227.7 <sup>a</sup>	260.1 <sup>a</sup>	49.6	374.6 <sup>a</sup>	377.0 <sup>a</sup>
Female	48.6	250.5	270.9	50.4	389.0	371.0
English as second language						
No	20.7	315.9 <sup>a</sup>	321.9 <sup>a</sup>	69.4	385.5 <sup>a</sup>	377.8 <sup>a</sup>
Yes	79.3	215.0	248.0	30.6	373.7	365.3
Remoteness						
Outer regional	18.2	317.0 <sup>a</sup>	321.5 <sup>a</sup>	76.3	381.9	374.0
Remote	17.5	279.5	292.8	16.7	384.1	371.2
Very remote	63.6	198.5	237.1	5.9	367.9	374.1
Missing	0.7	235.5	253.9	1.1	424.8	416.8
Socioeconomic status						
Low	73.3	210.4 <sup>a</sup>	244.3 <sup>a</sup>	13.3	346.5 <sup>a</sup>	350.0 <sup>a</sup>
Medium	21.2	303.2	313.1	51.0	375.9	369.3
High	4.9	334.1	338.9	34.6	402.8	388.7
Missing	0.6	235.5	253.9	1.1	424.8	416.8
Parent education <sup>b</sup>						
9	29.6	224.0 <sup>a</sup>	250.9 <sup>a</sup>	5.0	345.8 <sup>a</sup>	341.2 <sup>a</sup>
10	20.0	256.4	277.9	18.0	356.7	357.5
11	11.8	284.2	297.2	16.5	367.9	366.6
12	11.0	303.6	312.5	54.3	399.0	385.1
Missing	27.6	185.7	231.6	6.2	370.0	368.9

Data presented as percentage of total Aboriginal and non-Aboriginal education cohort and as mean reading and numeracy scores attained according to each variable. Differences between Aboriginal and non-Aboriginal children were significant for all variables ( $P = .000$ ) except gender. Range of reading and numeracy scores were  $-20$  to  $574$  and  $-10$  to  $625$  in Aboriginal children, respectively. Range of reading and numeracy scores were  $3-771$  and  $0-672$  in non-Aboriginal children, respectively.

<sup>a</sup>  $P < .05$  from independent  $t$  test (sex, English as second language) and Cuzick test for trend across ordered groups (remoteness, socioeconomic status, and parent education) indicates significant association between reading or numeracy and respective explanatory variable; <sup>b</sup> Primary caregiver school education attainment.

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correlated with birthweight percentile in Aboriginal and non-Aboriginal children. Results from linear regression analysis on the imputed data set are shown in Table 5. In Aboriginal children, increasing birthweight percentile was associated with a linear increase in reading ( $\beta = 0.12$ ; 95% CI, 0.02–0.21;  $P < .05$ ) and numeracy ( $\beta = 0.17$ ; 95% CI, 0.09–0.24;  $P < .001$ ) performance. In non-Aboriginal children, increasing birthweight percentile was also associated with higher reading ( $\beta = 0.51$ ; 95%

CI, 0.18–0.83;  $P < .01$ ) and numeracy ( $\beta = 0.53$ ; 95% CI, 0.28–0.77;  $P < .001$ ) scores. The addition of a squared term improved the fit of the model in non-Aboriginal children, indicating a quadratic association between birthweight percentile and reading and numeracy scores (turning point = 66th percentile), which contrasted against the linear association observed in Aboriginal children (Figure 5). Aboriginal infants with birthweights  $<50$ th percentile had significantly lower

numeracy scores than those in the 93rd–97.7th birthweight percentile range. Non-Aboriginal infants with birthweights  $<31$ st percentile had significantly lower reading and numeracy scores than those between the 69th–84th birthweight percentile (Table 6). Birthweight percentile explained 1% of variation in reading and numeracy scores, which was relatively small compared to other variables in the model such as parental education. When the cohort was

**TABLE 5**  
**Summary of linear regression coefficients (95% confidence interval) for reading and numeracy scores**

Birthweight percentile	Aboriginal: n = 6326 <sup>a</sup>				Non-Aboriginal: n = 4886 <sup>a</sup>			
	Reading		Numeracy		Reading		Numeracy	
	Crude	Adjusted <sup>b</sup>	Crude	Adjusted <sup>b</sup>	Crude	Adjusted <sup>b</sup>	Crude	Adjusted <sup>b</sup>
Linear term <sup>c</sup>	0.33 (0.23–0.44) <sup>d</sup>	0.15 (0.05–0.25) <sup>e</sup>	0.33 (0.24–0.41) <sup>d</sup>	0.21 (0.13–0.28) <sup>d</sup>	0.61 (0.26–0.95) <sup>d</sup>	0.49 (0.17–0.81) <sup>f</sup>	0.58 (0.32–0.84) <sup>d</sup>	0.51 (0.27–0.76) <sup>d</sup>
Squared term	n/a	n/a	n/a	n/a	–0.004 (–0.008 to –0.001) <sup>e</sup>	–0.003 (–0.007 to –0.0001) <sup>e</sup>	–0.004 (–0.007 to –0.002) <sup>f</sup>	–0.004 (–0.006 to –0.001) <sup>f</sup>
Adjusted R <sup>2c</sup>	0.01	0.25	0.01	0.25	0.004	0.14	0.01	0.12

Numbers presented are nonstandardized regression coefficients  $\beta$  (95% confidence interval).

Crude regression coefficients obtained from univariate linear analysis and adjusted regression coefficients obtained from multivariable linear analysis.

n/a, not applicable.

<sup>a</sup> Number of observations in imputed data set; <sup>b</sup> Model adjusted for gender, age at test, English as second language, parity, maternal age at birth, maternal alcohol consumption during pregnancy, gestational age, primary caregiver education, socioeconomic status, and geolocation; <sup>c</sup> Obtained from complete case analysis—N for complete case analysis varied with missing data—Aboriginal: reading crude n = 5079, adjusted n = 3155—numeracy crude n = 5048, adjusted n = 3139—coefficients from complete case analysis were 0.15 (reading, adjusted), 0.21 (numeracy, adjusted)—non-Aboriginal: reading crude n = 4701, adjusted n = 3994—numeracy crude n = 4692, adjusted n = 3990—coefficients from complete case analysis were 0.54 (reading, adjusted), 0.55 (numeracy, adjusted); <sup>d</sup>  $P < .001$ ; <sup>e</sup>  $P < .05$ ; <sup>f</sup>  $P < .01$ .

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restricted to term births, analysis yielded similar results. There were no significant gender-birthweight percentile interactions.

## Comment

This study, to our knowledge, is the first to identify the optimal birthweight percentile for perinatal survival and childhood education outcomes separately for the Aboriginal and non-Aboriginal populations. In both groups, the lowest rates of perinatal mortality were observed in infants born >50th percentile of birthweight, and similarly the highest reading and numeracy scores were also seen in children with birthweights >50th percentile. Aboriginal infants born in the Northern Territory from 1999 through 2008 were significantly smaller for their gestational age than non-Aboriginal infants, and this was associated with higher perinatal mortality rates and lower academic scores. Similar to previous studies, birthweight percentile contributed to approximately 1% of the variation in education outcomes.<sup>24</sup>

Strengths of this study include the large sample and the high proportion of Aboriginal participants, with close to 98% coverage of all Northern Territory births.<sup>11</sup> Our unique data set allowed

follow-up of the individuals from birth to 8–9 years of age, providing a clearer picture of how fetal growth affects the life-course trajectory. However, the accuracy of data collected for nonresearch purposes is often difficult to determine. Residual confounding cannot be excluded and due to the observational nature of this research, it is difficult to comment on how the complex nexus among physical, social, and cultural health and well-being contributed to the association observed among birthweight percentile, perinatal mortality, and particularly school performance. SES and remoteness were recorded at the community level according to the child's school, and therefore may not have accurately reflected the individual's SES or home locality.

Reading and numeracy results were available for 40% of the eligible birth cohort. There are several reasons for nonlinkage in the Northern Territory, such as high rates of interstate migration, particularly among non-Aboriginal families.<sup>14</sup> Secondly, student information and test scores were not available for the 21% of Northern Territory children enrolled in a nongovernment school during the study period. The degree of attrition was assessed and demographic

differences between the birth and education cohorts were consistent with an overrepresentation of more disadvantaged children in the education cohort. These differences were small and deemed unlikely to affect the external validity of the study.

Argument surrounds the use of birthweight percentile to define perinatal and long-term outcomes in infants. Not all SGA infants are pathologically so: there is a proportion, perhaps at least 20%, that are considered to be constitutionally small and experience better short-term outcomes.<sup>25</sup> However, SGA infants with normal Doppler parameters experience perinatal and neurocognitive outcomes that are significantly worse than non-SGA infants.<sup>26</sup> In addition, constitutional smallness is often defined using maternal characteristics and does not account for the transgenerational nature of malnutrition and disadvantage.

Consistent with population studies from other high-income countries we have demonstrated that although infants born <10th percentile of birthweight for gestational age are at greatly increased risk of perinatal mortality, the risk extends well beyond this cut-off.<sup>3,4,27</sup> Both Francis et al<sup>4</sup> and Vasak et al<sup>3</sup> found that rates of perinatal mortality were lowest between the 50th–97th birthweight

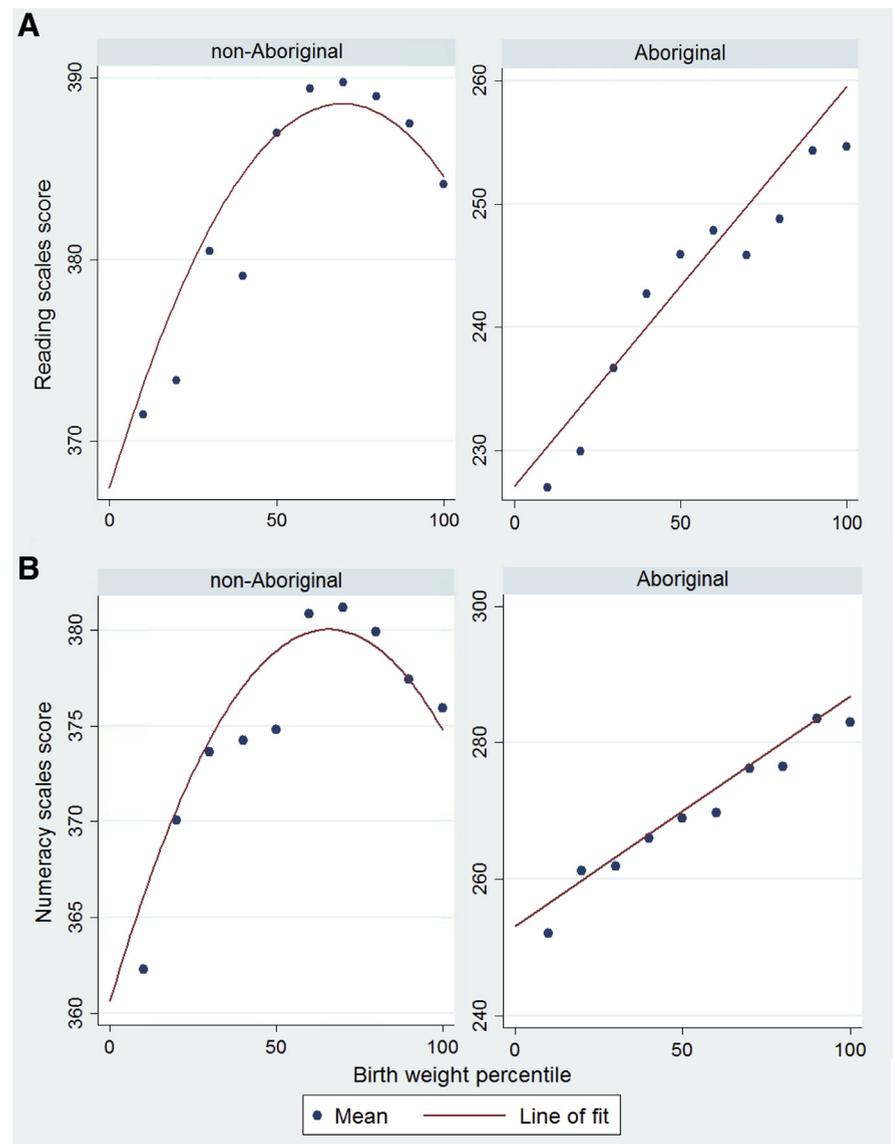
percentiles. Increasing birthweight percentiles, up to the 90th percentile, have been shown to be associated with improved placental blood flow and reduced incidence of fetal hypoxia, which may explain improved perinatal survival at higher birthweight percentiles.<sup>28</sup>

The pattern of mortality in Aboriginal infants was different to that observed in non-Aboriginal infants in both the current and previous studies.<sup>3,4</sup> Although perinatal mortality rates were shown to decrease with increasing birthweight percentile overall, there was a significant rise in mortality among the largest Aboriginal infants in our cohort. Higher rates of maternal diabetes and obesity, birth asphyxia, birth trauma, cesarean delivery, and meconium aspiration have been suggested as probable causes of high mortality in large infants.<sup>29</sup> Further research is needed to explain this association in our cohort.

The quadratic association between birthweight percentile and education in non-Aboriginal children is robust, concurring with 2 large studies by Malacova et al<sup>18,21</sup> from Western Australia and a comprehensive review by Shenkin et al.<sup>24</sup> The nature of this quadratic association suggests that the benefit of increasing birthweight plateaus above the optimal birthweight percentile, which is likely between the 69th-84th percentiles. Biologically plausible mechanisms by which lower birthweights predisposes to neurocognitive deficits have been described, however, not all studies are in agreement.<sup>30,31</sup> Guthridge et al<sup>14</sup> found no association between low birthweight and the odds of scoring below the national minimum standard in reading or numeracy in Northern Territory children, with the exception of numeracy in Aboriginal children. The use of dichotomous variables, differences in controlling for sociodemographic risk factors, and smaller cohort size may explain these differences.

Interestingly, in Aboriginal children, the association between birthweight percentile and reading and numeracy is linear. There are no previous data for Aboriginal children from which to draw comparisons and we can only speculate as to the reason for this difference.

**FIGURE 5**  
Association between birthweight percentile and reading and numeracy scores



Mean domain scores were calculated at 10-percentile intervals and overlaid on line of fit graph for association between birthweight percentile and **A**, reading and **B**, numeracy in Aboriginal and non-Aboriginal children. Association in non-Aboriginal children fits quadratic model and in Aboriginal children linear model.

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Possibly, it could be an indication that many Aboriginal fetuses in our cohort grew in a compromised intrauterine environment, and that this had negative implications for brain development with only the larger Aboriginal infants being free from this constraint. This is not to say that macrosomic babies born to diabetic mothers are healthy, and indeed

their perinatal mortality rates are high. In comparison, most non-Aboriginal fetuses likely grew in a more conducive environment such that the prevalence of asphyxia, birth trauma, and unmeasured family-level factors in the largest infants may have mitigated the neurocognitive benefit of increasing birthweight percentile.<sup>32</sup> Furthermore, our findings

TABLE 6

Summary of linear regression coefficients (95% confidence interval) for reading and numeracy scores using birthweight percentile as categorical explanatory variable for Aboriginal (n = 6326<sup>a</sup>) and non-Aboriginal (n = 4886<sup>a</sup>) children

Birthweight percentile	Reading		Numeracy	
	Crude	Adjusted <sup>b</sup>	Crude	Adjusted <sup>b</sup>
<b>Aboriginal</b>				
<2.3	-39.92 (-60.83 to -19.01) <sup>c</sup>	-18.86 (-37.63 to -0.10) <sup>d</sup>	-30.98 (-45.52 to -16.44) <sup>e</sup>	-18.22 (-31.01 to -5.42) <sup>c</sup>
2.3-<7	-25.02 (-45.47 to -4.57) <sup>d</sup>	-9.58 (-28.07 to 8.91)	-25.77 (-40.14 to -11.40) <sup>c</sup>	-16.87 (-29.53 to -4.21) <sup>e</sup>
7-<16	-34.18 (-54.55 to -13.80) <sup>c</sup>	-18.38 (-36.65 to -0.12) <sup>d</sup>	-25.8 (-39.40 to -12.20) <sup>c</sup>	-16.82 (-28.62 to -5.01) <sup>c</sup>
16-<31	-20.74 (-39.80 to -13.80) <sup>d</sup>	-10.58 (-27.20 to 6.04)	-15.83 (-29.24 to -2.41) <sup>e</sup>	-10.82 (-22.27 to 0.62) <sup>d</sup>
31-<50	-16.66 (-36.04 to 2.72) <sup>f</sup>	-5.76 (22.90 to 11.38)	-14.5 (-28.12 to -0.85) <sup>d</sup>	-9.45 (-21.27 to 2.38) <sup>d</sup>
50-<69	-14.34 (-34.76 to 6.09)	-9.63 (-27.55 to 8.28)	-9.37 (-23.40 to 4.65)	-7.76 (-19.72 to 4.21)
69-<84	-6.81 (-27.80 to 14.18)	-3.91 (-22.88 to 14.31)	-2.94 (-17.38 to 11.49)	-2.76 (-15.12 to 9.60)
84-<93	-7.36 (-30.49 to 15.78)	-5.79 (25.88 to 14.31)	-1.25 (-17.46 to 14.97)	-1.72 (-15.95 to 12.50)
93-<97.7	Reference		Reference	
>97.7	-17.29 (-44.03 to 9.45)	-14.31 (-37.68 to 9.05)	-9.62 (-28.59 to 9.34)	-8.48 (-24.93 to 8.01)
Adjusted R <sup>2g</sup>	0.01	0.26	0.004	0.26
<b>non-Aboriginal</b>				
<2.3	-22.32 (-37.92 to -6.71) <sup>e</sup>	-16.06 (-30.37 to -1.76) <sup>d</sup>	-23.21 (-35.09 to -11.32) <sup>c</sup>	-19.12 (-30.40 to -7.84) <sup>c</sup>
2.3-<7	-14.17 (-26.93 to -1.42) <sup>d</sup>	-11.93 (-24.11 to 0.24) <sup>f</sup>	-15.9 (-25.42 to -6.38) <sup>c</sup>	-12.32 (-21.55 to -3.08) <sup>e</sup>
7-<16	-20.92 (-31.88 to -9.95) <sup>c</sup>	-16.59 (-26.83 to -6.35) <sup>e</sup>	-14.47 (-22.78 to -6.17) <sup>c</sup>	-11.13 (19.01 to 3.24) <sup>e</sup>
16-<31	-11.36 (-21.61 to 1.10) <sup>d</sup>	-11.8 (-21.29 to -2.31) <sup>d</sup>	-7.63 (-15.25 to -0.01) <sup>d</sup>	-7.46 (-14.63 to -0.30) <sup>d</sup>
31-<50	-6.02 (-16.01 to 3.96)	-3.76 (-12.91 to 5.38)	-5.69 (-13.41 to 2.02)	-3.74 (-10.97 to 3.48)
50-<69	-2.37 (-12.71 to 7.97)	-1.1 (-10.76 to 8.57)	-1.61 (-9.34 to 6.11)	-0.14 (-7.49 to 7.21)
69-<84	Reference		Reference	
84-<93	-9.63 (-22.56 to 3.31)	-9.09 (-21.13 to 2.95)	-7.32 (-17.03 to 2.40)	-8.38 (-17.52 to 0.76) <sup>f</sup>
93-<97.7	-9.6 (-26.87 to 7.68)	-6.1 (-21.87 to 9.66)	-1.59 (-14.18 to 11.01)	-0.05 (-11.59 to 11.49)
>97.7	0.8 (-16.20 to 17.79)	2.46 (-13.71 to 18.62)	-6.58 (-20.09 to 6.92)	-5.77 (-18.68 to 7.14)
Adjusted R <sup>2g</sup>	0.01	0.14	0.01	0.12

Numbers presented are nonstandardized regression coefficients  $\beta$  (95% confidence intervals). Regression coefficients represent mean change in reading or numeracy score associated with each category of birthweight percentile compared to reference category.

Crude regression coefficients obtained from univariate linear analysis and adjusted regression coefficients obtained from multivariable linear analysis.

<sup>a</sup> Number of observations in imputed data set; <sup>b</sup> Model adjusted for gender, test age, English as second language, parity, maternal age at birth, maternal alcohol consumption during pregnancy, gestational age, primary caregiver education, socioeconomic status, and geolocation; <sup>c</sup>  $P < .001$ ; <sup>d</sup>  $P < .05$ ; <sup>e</sup>  $P < .01$ ; <sup>f</sup>  $P < .1$ ; <sup>g</sup> Obtained from complete case analysis—N for complete case analysis varied with missing data—Aboriginal: reading crude n = 5079, adjusted n = 3155—numeracy crude n = 5048, adjusted n = 3139—non-Aboriginal: reading crude n = 4701, adjusted n = 3994—numeracy crude n = 4692, adjusted n = 3990—reference categories were chosen as those with highest mean reading and numeracy scores in univariate analysis.

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provide some evidence that the range of birthweight percentile that is optimal for short-term survival is different to that which is optimal for academic outcomes, particularly in Aboriginal infants.

Our results provide further evidence that the trajectory for long-term disadvantage begins in utero; this has important implications for clinical practice in

obstetrics. Although birthweight percentile contributes to only 1% of variation in outcomes overall, the widespread implementation of strategies to reduce the rates of birthweights <50th percentile could have meaningful implications on the population level. Strategies with proven success at reducing the incidence of SGA and low

birthweight include nutritional education, supplementation with vitamin A, low-dose calcium, zinc, and multiple micronutrients.<sup>33</sup> Balanced protein/energy supplementation reduced rates of SGA by 21% and stillbirth by 40%.<sup>34</sup> These recommendations should be made to women both before and during pregnancy and their benefit would be

expected to be greatest in populations with lower birthweight percentiles and less nutritional security, such as Aboriginal Australians and African Americans. Whether strategies to increase birthweight percentile will translate directly to reduced mortality remains unknown.

Although Aboriginal Australians are subject to a number of social, political, and economic adversities that contribute to poor health and well-being across the life course, improvements in fetal growth may help to reduce some of the burden suffered by new generations of Aboriginal children, and similar conclusions likely apply to other disadvantaged communities. Interventions to increase fetal growth must be nested within holistic policies that aim to tackle multi-generational disadvantage and poverty. The high rates of smoking during pregnancy among Aboriginal women, which were 48.1% in 2012,<sup>11</sup> also need to be addressed.<sup>35</sup>

Further research is warranted: reasons for high rates of perinatal mortality in large Aboriginal infants need exploration and the effect of nutritional interventions during pregnancy on long-term cognitive outcomes in the offspring lacks high-quality evidence.

## Conclusion

This study has demonstrated that the odds of perinatal mortality decrease with increasing birthweight percentile, and that the benefit of increasing birthweight percentile extends to reading and numeracy performance during childhood. Birthweights between the 50th-93rd percentiles were most consistently associated with both a low perinatal mortality and high reading and numeracy scores in Aboriginal and non-Aboriginal children. This suggests that health and academic trajectories begin in utero, and that SGA does not sufficiently acknowledge the lasting effects of normal variations in fetal growth. We estimate that the effect of birthweight percentile accounts for approximately 1% of variation in perinatal and education outcomes, with greater variance due to factors such as gestational age and parental education. ■

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# Screening for fetal growth restriction using fetal biometry combined with maternal biomarkers



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## “Fetal growth restriction” and “small for gestational age”: differences between 2 commonly used terms and clinical implications

“Fetal growth restriction” (FGR) is defined as the failure of the fetus to reach its genetically determined growth potential. FGR is a major determinant of perinatal and childhood morbidity and mortality, and is associated with the risk of chronic diseases in later life.<sup>1-3</sup> An obstacle to the study of FGR is that there are no gold standard definition and diagnostic criteria for this condition. The size of the fetus or newborn is quantified with reference to the normal range for gestational age (GA) and those with birthweight (BW) <10th percentile are called “small for gestational age” (SGA). Inaccurately, the small size of the baby often becomes synonymous with FGR, and different thresholds for these measurements are used to define a FGR infant (eg, <2500 g, <10th percentile, or <3rd percentile).

Although SGA and FGR are sometimes used interchangeably, the 2 terms

Fetal growth restriction is a major determinant of perinatal morbidity and mortality. Screening for fetal growth restriction is a key element of prenatal care but it is recognized to be problematic. Screening using clinical risk assessment and targeting ultrasound to high-risk women is the standard of care in the United States and United Kingdom, but the approach is known to have low sensitivity. Systematic reviews of randomized controlled trials do not demonstrate any benefit from universal ultrasound screening for fetal growth restriction in the third trimester, but the evidence base is not strong. Implementation of universal ultrasound screening in low-risk women in France failed to reduce the risk of complications among small-for-gestational-age infants but did appear to cause iatrogenic harm to false positives. One strategy to making progress is to improve screening by developing more sensitive and specific tests with the key goal of differentiating between healthy small fetuses and those that are small through fetal growth restriction. As abnormal placentation is thought to be the major cause of fetal growth restriction, one approach is to combine fetal biometry with an indicator of placental dysfunction. In the past, these indicators were generally ultrasonic measurements, such as Doppler flow velocimetry of the uteroplacental circulation. However, another promising approach is to combine ultrasonic suspicion of small-for-gestational-age infant with a blood test indicating placental dysfunction. Thus far, much of the research on maternal serum biomarkers for fetal growth restriction has involved the secondary analysis of tests performed for other indications, such as fetal aneuploidies. An exemplar of this is pregnancy-associated plasma protein A. This blood test is performed primarily to assess the risk of Down syndrome, but women with low first-trimester levels are now serially scanned in later pregnancy due to associations with placental causes of stillbirth, including fetal growth restriction. The development of “omic” technologies presents a huge opportunity to identify novel biomarkers for fetal growth restriction. The hope is that when such markers are measured alongside ultrasonic fetal biometry, the combination would have strong predictive power for fetal growth restriction and its related complications. However, a series of important methodological considerations in assessing the diagnostic effectiveness of new tests will have to be addressed. The challenge thereafter will be to identify novel disease-modifying interventions, which are the essential partner to an effective screening test to achieve clinically effective population-based screening.

**Key words:** A-disintegrin and metalloprotease 12, alpha fetoprotein, biomarker, fetal biometry, fetal death, human chorionic gonadotropin, human placental lactogen, inhibin, models, placenta, placental growth factor, placental protein 13, prediction, pregnancy-associated plasma protein-A, randomized controlled trial, review, screening, small for gestational age, soluble endoglin, soluble fms-like tyrosine kinase-1, stillbirth, study design, ultrasound

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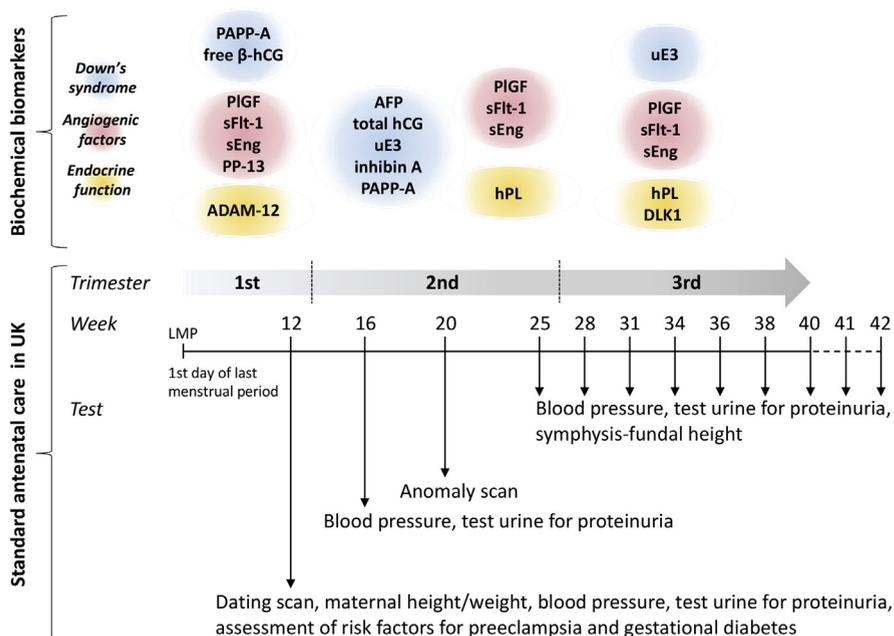
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are distinct, as many SGA infants are constitutionally small and healthy. Hence, clinical research on screening for FGR has to address 2 main issues: (1) the sensitive and specific detection of SGA fetuses, and (2) the ability to discriminate between FGR and healthy SGA. The

causes of FGR can be broadly categorized into maternal (eg, pregnancy-associated hypertensive diseases, autoimmune disease, poor nutrition, substance abuse, and teratogen exposure),<sup>4-6</sup> fetal (eg, multiple gestations, infections, genetic and structural disorders),<sup>7,8</sup> or placental.

**FIGURE 1**  
**Standard antenatal care in United Kingdom (UK) and biochemical markers measured throughout pregnancy**



Measurement of pregnancy biomarkers in relation to UK antenatal care schedule. Biomarkers measured in clinical and research settings during pregnancy are plotted on a time scale representing standard antenatal care for nulliparous women in UK, which includes 10 routine midwife visits and additional visits for women delivering >40 weeks of gestation.

*ADAM12*, A-disintegrin and metalloprotease 12; *AFP*, alpha fetoprotein; *DLK1*, delta-like 1 homolog; *hCG*, human chorionic gonadotropin; *hPL*, human placental lactogen; *PAPP-A*, pregnancy-associated plasma protein A; *PIGF*, placental growth factor; *PP*, placental protein; *sENG*, soluble endoglin; *sFLT1*, soluble fms-like tyrosine kinase-1; *uE3*, unconjugated estriol

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It is thought that placental dysfunction accounts for the majority of FGR cases.<sup>9</sup> Hence, one of the most promising approaches to screening for FGR is to combine ultrasonic fetal biometry with measurement of biomarkers of abnormal placentation in the mother's blood.

### Current status of screening with fetal biometry

In many countries, including the United Kingdom and United States, ultrasound scanning after the 20-week anomaly scan is only performed on the basis of clinical indications as universal ultrasound is not supported by the most recent Cochrane review.<sup>10</sup> It is worth noting that the evidence base can be described as an absence of evidence rather than compelling high-quality evidence of the absence of clinical effectiveness of screening. This is due to a number of

problems with the 13 studies analyzed in the systematic review, including limited statistical power and lack of an effective interventional strategy.<sup>11</sup> Nevertheless, the current approach to screening for FGR is to assess the women for preexisting risk factors, acquired complications of pregnancy, and clinical examination (eg, symphysis-fundal height measurements) (Figure 1). Women identified as high risk using these methods are then selected for ultrasonographic assessment. Screening for FGR is just one element of the universal ultrasound.<sup>12</sup> Other elements include macrosomia, late presentation of fetal anomalies, abnormalities of amniotic fluid volume, and diagnosis of undetected malpresentation.

### Ultrasonic markers of FGR

Fetal biometry and Doppler flow velocimetry are the primary methods used

currently to diagnose FGR. The use of ultrasound markers of FGR is discussed in detail elsewhere in this issue, and will be only briefly summarized here. An estimated fetal weight (EFW) is derived from ultrasonic measurements of head size, abdominal circumference, and femur length, and an EFW centile is calculated using a reference standard.<sup>13,14</sup> While a single measurement of fetal size and the EFW <10th centile cut-off appears to be insufficient to discriminate growth-restricted and healthy small fetuses, serial fetal biometry reveals the growth trajectory of the fetus, and this helps differentiate between healthy SGA and FGR.<sup>15,16</sup> Doppler flow velocimetry provides information on the resistance to blood flow in the fetoplacental unit and it features in several proposed FGR definitions.<sup>17</sup> High-resistance patterns of flow in the uterine and umbilical arteries in early and mid pregnancy have been associated with an increased risk of preeclampsia, FGR, and stillbirth.<sup>18-22</sup> Other measurements associated with adverse pregnancy outcomes are middle cerebral artery and ductus venosus flow resistance, and cerebroplacental ratio (reviewed elsewhere).<sup>17,18,23</sup>

### Biochemical biomarkers for FGR

Abnormal placentation leads to inadequate remodeling of maternal spiral arteries, altered uteroplacental blood perfusion, and impaired materno-fetal exchange of nutrients, gases, and waste products. These defects, collectively referred to as placental insufficiency, are thought to be underlying mechanisms of placently-related complications including FGR, preeclampsia, and stillbirth. Hence, biochemical markers reflective of placental insufficiency become attractive tools to identify women at risk of these adverse pregnancy outcomes (Figure 1 and Table 1).

### First-trimester screening

It is increasingly recognized that placental dysfunction leading to disease in the second half of pregnancy has its origins in the first trimester of pregnancy.<sup>24</sup> Studies of associations have been facilitated by the secondary analysis

**TABLE 1**  
**Maternal circulating biochemical markers for predicting fetal growth restriction**

Biomarker	Main function	Changes in maternal circulating levels frequently associated with FGR		
		1st Trimester	2nd Trimester	3rd Trimester
<b>Down syndrome biomarkers</b>				
PAPP-A	<ul style="list-style-type: none"> <li>Protease activity toward IGFs</li> <li>Decrease of IGF bioavailability and signaling</li> </ul>	↓	↓	
hCG	<ul style="list-style-type: none"> <li>Maintenance of progesterone secretion from corpus luteum</li> </ul>	↓	↑	
AFP	<ul style="list-style-type: none"> <li>Protein of fetal origin with similar function to albumin in adult</li> <li>Carrier-molecule for several ligands (bilirubin, steroids, and fatty acids)</li> </ul>		↑	
uE3	<ul style="list-style-type: none"> <li>Estrogen agonist</li> </ul>		↓	↓
inhibin A	<ul style="list-style-type: none"> <li>Negative feedback on pituitary follicle-stimulating hormone secretion</li> <li>Preventing ovulation during pregnancy</li> </ul>		↑	
<b>Angiogenic factors</b>				
PlGF	<ul style="list-style-type: none"> <li>Member of VEGF family</li> <li>Proangiogenic factor</li> </ul>	↓	↓	↓
sFLT1	<ul style="list-style-type: none"> <li>Decrease of PlGF and VEGF bioavailability and signaling</li> </ul>	↑, ↓	↓, =	↑
sFLT1:PlGF ratio		↑	↑	↑
sENG	<ul style="list-style-type: none"> <li>Decrease of TGF-<math>\beta</math>1 and TGF-<math>\beta</math>3 bioavailability and signaling</li> </ul>	↑	↑	↑
PP-13	<ul style="list-style-type: none"> <li>Promoting trophoblast invasion and spiral artery remodeling</li> </ul>	↓, =		
<b>Hormonal factors</b>				
ADAM12	<ul style="list-style-type: none"> <li>Protease activity toward IGFs</li> <li>Decrease of IGF bioavailability and signaling</li> </ul>	↓		
hPL	<ul style="list-style-type: none"> <li>Induction of maternal insulin resistance and lipolysis</li> <li>Induction of mammary glands development and milk production</li> </ul>		↓	↓
DLK1	<ul style="list-style-type: none"> <li>Adipose tissue homeostasis</li> <li>Maternal metabolic adaptation to pregnancy</li> </ul>			↓

ADAM12, A-disintegrin and metalloprotease 12; AFP, alpha fetoprotein; DLK1, delta-like 1 homolog; FGR, fetal growth restriction; hCG, human chorionic gonadotropin; hPL, human placental lactogen; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; PAPP-A, pregnancy-associated plasma protein A; PlGF, placental growth factor; PP, placental protein; sENG, soluble endoglin; sFLT1, soluble fms-like tyrosine kinase-1; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; uE3, unconjugated estriol.

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of first-trimester biomarkers derived from the placenta, which were evaluated in screening studies for aneuploidies.

**Down syndrome markers: PAPP-A and  $\beta$ -hCG.** Low maternal circulating levels of pregnancy-associated plasma protein A (PAPP-A) and high concentrations of the free beta subunit of human chorionic gonadotropin ( $\beta$ -hCG) are

both associated with the risk of Down syndrome.<sup>25</sup> PAPP-A determines the availability of the insulin-like growth factors, key pregnancy growth hormones, as it is a protease that acts on insulin-like growth factor binding proteins. A causal role for PAPP-A in controlling fetal growth has been established in the PAPP-A knockout mouse.<sup>26</sup> In women, low serum

concentrations of PAPP-A in the first trimester are associated with an increased risk of FGR, preterm delivery, preeclampsia, and stillbirth.<sup>27-33</sup> The last of these associations is particularly strong for stillbirth associated with placental dysfunction (preeclampsia, FGR, and abruption).<sup>34</sup> In the United Kingdom, and many other countries, low first-trimester PAPP-A levels are an

indication for late pregnancy ultrasonic assessment of fetal growth.<sup>35,36</sup> Human chorionic gonadotrophin (hCG) is predominantly produced by the placental syncytiotrophoblast cells.<sup>37</sup> hCG is a glycoprotein composed of an  $\alpha$ -subunit (common to luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone) and a  $\beta$ -subunit (unique to hCG). In first-trimester Down syndrome screening the  $f\beta$ -hCG is measured.<sup>25</sup> In general, extremes of  $f\beta$ -hCG in the first trimester are less strongly associated with adverse outcome than low PAPP-A.<sup>27,30-33</sup>

*Other placental markers: PIGF, sFLT1, sENG, PP-13 and ADAM-12.* While many of the largest studies of first-trimester markers have focused on secondary analysis of Down syndrome screening research, other investigators focused on measuring proteins on the basis of a known role in placentation. Angiogenic factors play a key role in the extensive vasculature remodeling of the uterus during pregnancy. The placenta itself produces several factors with proangiogenic or antiangiogenic activity and regulation of their expression and secretion is necessary for optimal placentation, maternal adaptation to pregnancy and, consequently, fetal development and growth. Preeclampsia-like changes were induced in pregnant rats by adenoviral-mediated expression of soluble fms-like tyrosine kinase-1 (sFLT1)<sup>38</sup> or soluble endoglin (sENG) alone or in combination with sFLT1.<sup>39</sup> Placental growth factor (PIGF) is a proangiogenic factor highly expressed in placenta throughout all stages of pregnancy. It is readily detectable in maternal circulation where it may have direct effects on endothelial maintenance and well-being. Consistent with this role, low first-trimester levels of this factor have been shown to be associated with an increased risk of later adverse perinatal outcome, including preeclampsia and SGA.<sup>31,40,41</sup> The results are variable for antiangiogenic factors. High maternal levels of sENG in the first trimester were associated with preeclampsia and SGA.<sup>41</sup> However, results are less consistent for

sFLT1.<sup>40,42,43</sup> A large-scale study employing correction of analyte levels using multiples of the median (MoMs) actually demonstrated that low sFLT1 levels were associated with an increased risk of SGA, preterm birth, and stillbirth,<sup>40</sup> whereas data in later pregnancy indicate the opposite association (see below). These findings indicate that the commonly used sFLT1:PIGF ratio should be interpreted cautiously in the first trimester. Finally, increased attention has been paid to longitudinal changes of these factors during pregnancy, but the results are inconclusive.<sup>41,44,45</sup>

Data exist from a number of other proteins. Low maternal first-trimester levels of placental protein-13 (PP-13), another protein regulating placental vascular development, have been reported in pregnancies complicated by SGA,<sup>31,46</sup> but results are, again, inconsistent.<sup>47,48</sup> Similarly, A-disintegrin and metalloprotease 12 (ADAM12), a protease with similar function to PAPP-A, was reduced between 11-14 weeks in mothers who subsequently delivered small infants (BW <5th or <10th centile).<sup>31,49,50</sup>

### Second and third trimester

The screening efficacy of tests performed in the second and third trimester was assessed for 2 main reasons: (1) the availability of data collected during screening studies for the identification of aneuploidies and birth defects during the second trimester; and (2) the idea that measurements performed in the third trimester may have better predictive ability due to being temporally closer to the onset of disease.<sup>51</sup>

*Down syndrome and anomaly screening: AFP, total hCG, uE3 and inhibin A.* The second-trimester quadruple screening is performed at 15-22 weeks of gestation and includes measurements of alpha fetoprotein (AFP), hCG (intact and/or its  $\beta$ -subunit), unconjugated estriol (uE3), and inhibin A.<sup>52</sup> These factors may also provide information on placental permeability (AFP) and endocrine activity (hCG, uE3, and inhibin A). Hence, many studies have addressed their ability

to predict placentally-related pregnancy complications.

Elevated maternal serum levels of AFP are associated with SGA (BW <5th centile) with or without preterm delivery<sup>53,54</sup> and stillbirth due to reduced BW (<5th centile).<sup>55</sup> The combination of low PAPP-A in the first trimester and high AFP in the second trimester is particularly strongly predictive of severe FGR.<sup>56,57</sup> In the FASTER trial,  $f\beta$ -hCG alone ( $\geq 2.0$  MoM) was not associated with any adverse outcome studied. In contrast, maternal circulating AFP ( $\geq 2.0$  MoM), inhibin A ( $\geq 2.0$  MoM), and uE3 ( $\leq 0.5$  MoM) were significantly associated with an increased risk of delivering SGA infant.<sup>58</sup> The risk was particularly high when measurements were combined. In other studies, women with an elevation of hCG alone (threshold starting at >2.5 MoM) or in combination with high AFP had an increased risk of SGA.<sup>54,59</sup> Low levels of uE3 alone or in combination with AFP and/or hCG were associated with SGA (BW <5th percentile).<sup>54,60</sup>

*Other placental markers: sFLT1, PIGF, sENG, hPL, uE3.* A number of large-scale studies have analyzed biomarkers in the second and third trimester with the aim of identifying useful candidates for FGR screening. The SCOPE study recruited >5000 low-risk women and reported that maternal levels of sFLT1 and PAPP-A were decreased in pregnancies with SGA without maternal hypertension, whereas PAPP-A and PIGF were decreased in pregnancies with SGA and maternal hypertension.<sup>61</sup> Multi-center studies conducted by Prof Kypros Nicolaides have assessed the predictive associations of a number of circulating biomarkers at different stages in the second and third trimesters. At 19-24 weeks of gestation, maternal PIGF was lower and AFP was higher in women who subsequently delivered a SGA infant preterm. Term SGA was associated with lower maternal levels of PIGF, sFLT1, and PAPP-A.<sup>53</sup> When measured at 30-34 weeks, low PIGF and high sFLT1 were associated with delivery of a SGA infant<sup>62</sup> and the associations were stronger for preterm SGA. At 35-37 weeks PIGF and

sFLT1 concentrations in the lowest and highest 5th centile, respectively, were associated with SGA.<sup>63</sup> Moreover, extremes of the ratio have also been associated with the subsequent risk of intrauterine fetal death.<sup>64</sup>

Mothers with a reduced rate of decrease of the antiangiogenic factor sENG between the first and second trimesters had a higher risk of adverse pregnancy outcome, including SGA (BW <10th centile).<sup>65</sup> Moreover, as mentioned above, maternal plasma sENG concentrations remained elevated throughout the second and third trimester in patients destined to deliver a SGA neonate.<sup>41</sup> Maternal serum levels of the hormones human placental lactogen and uE3 were shown to be reduced in pregnancies with SGA fetuses in the second and third trimesters.<sup>66,67</sup>

**Strength of prediction.** A systematic review evaluated the strength of association between a wide range of biomarkers and uteroplacental Doppler and different causes of stillbirth. The review concluded that only high-resistance patterns of uterine Doppler in the second trimester and low PAPP-A in the first trimester had associations in the clinically useful range, with positive likelihood ratios of 5-15.<sup>68</sup> Moreover, these strong associations were only observed for the subtypes of stillbirth attributed to placental dysfunction. However, the review did not report the combination of ultrasound and biomarkers. The same authors also evaluated 53 studies and 37 potential biomarkers for FGR screening, and suggested that none of the proposed maternal circulating factors had a high predictive accuracy.<sup>69</sup> Their conclusion was that combining biomarkers with biophysical measurements and maternal characteristics could be a more effective strategy. Table 2 summarizes the strongest associations identified in the 2 meta-analyses.

**Combined assessment using ultrasonic biometry and biomarkers.** An international, prospective, multicenter observational study determined the prediction of SGA achieved by the combination of

ultrasonic fetal biometry and maternal serum PIGF in women who were identified as clinically small for dates between 24-37 weeks of gestation. While the study demonstrated that median PIGF concentrations were lower in SGA pregnancies,<sup>70</sup> these authors reported that the combination of EFW and of PIGF had only modest test performance. However, it should be borne in mind that many SGA infants are healthy, ie, they are constitutionally small. It would not be expected that PIGF, a test for pathology, would be strongly associated with the delivery of a healthy small infant. A study by Valino et al<sup>63</sup> reported that placental biomarkers measured at 35-37 weeks performed poorly as a screening test for perinatal morbidity. An important feature of that study was that the results of ultrasound scans, performed at the same time as the biomarker, were reported and would have influenced clinical care. Both of these studies raise important questions about the methodological approach to future studies attempting to develop novel screening tests for FGR, and these are discussed below.

We performed a prospective study of unselected nulliparous women, the Pregnancy Outcome Prediction (POP) study, which combined the use of ultrasound and biochemical markers, where the results of both were blinded.<sup>71,72</sup> The analysis of this study is ongoing. However, we have published a preliminary report that the combination of ultrasonic EFW <10th percentile and an elevated sFLT1:PIGF ratio at 36 weeks of gestation was strongly predictive for late FGR (BW <10th centile plus perinatal morbidity and/or preeclampsia), with a positive likelihood ratio of 17.5 and a sensitivity and specificity of 38% and 98%, respectively.<sup>73</sup>

### Future directions

Despite years of research, screening for FGR remains clinical. Implementation of ad hoc screening using ultrasound appears to cause more harm than good.<sup>11</sup> This probably reflects the fact that, currently, the primary intervention to manage FGR is delivery of the infant. In the event of a false-positive diagnosis

in the preterm or early term weeks of gestational age, the effect will be to cause harm through the associations between earlier delivery and neonatal morbidity. The lack of progress could lead to the perception that the task being attempted is futile. However, there are a number of issues about the approach to this problem that have been relatively neglected. We believe that addressing some of the issues outlined below may help accelerate research into clinically useful tools for screening and intervention (Figure 2).

**Identifying populations to screen.** One of the most important screening parameters is the positive predictive value (PPV) of the test. For the individual woman, this might, indeed, be her primary interest: how likely is it that she will experience an adverse event? The PPV is determined by 2 factors: the prior odds of disease and the positive likelihood ratio of the test. Much of the research on screening has focused on the latter. However, if a woman has a very low prior risk of an outcome, even a highly predictive test may result in a low absolute risk that she experiences disease. This issue suggests that screening efforts might initially focus on high-risk and nulliparous women. In the latter group the key marker of risk in pregnancy, ie previous pregnancy outcome, is necessarily absent. Screening studies that include a high proportion of parous women with previous normal pregnancies will tend to yield results with low PPVs.

**High-quality studies of diagnostic effectiveness.** With the increasing awareness of the importance of evidence-based medicine, it is universally recognized that new interventions, such as novel drugs, must be evaluated, wherever possible, by a double-blind, randomized controlled trial (RCT). This is due to the biases that result from patients and their caregivers being aware of allocation to the novel treatment. The equivalent approach in studies of diagnostic effectiveness is to blind the results of the new test. If a research study of screening reveals the test result, it ceases to be purely a

**TABLE 2**  
**Predictive accuracy of maternal circulating biomarkers for stillbirth and fetal growth restriction**

Biomarker	Outcome	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Population, n
<b>Down syndrome biomarkers</b>						
PAPP-A	Stillbirth	3.3 (1.8–6.0)	0.9 (0.8–1.0)	15 (8–26)	95 (95–96)	21,158 <sup>97,98</sup>
	Placental abruption and/or SGA-related stillbirth	14.1 (9.3–21.4)	0.3 (0.1–0.8)	70 (40–89)	95 (95–96)	7919 <sup>34</sup>
hCG	Stillbirth	2.8 (1.9–4.3)	0.4 (0.2–1.0)	70 (40–89)	75 (73–77)	2406 <sup>99</sup>
AFP	Stillbirth	4.0 (3.4–4.7)	0.9 (0.9–0.9)	9 (8–11)	98 (98–98)	186,802 <sup>60,100–106</sup>
uE3	Stillbirth	4.0 (3.0–5.3)	0.9 (0.8–0.9)	15 (11–20)	96 (96–96)	58,417 <sup>58,60,107</sup>
Inhibin A	Stillbirth	6.1 (4.0–9.3)	0.8 (0.8–0.9)	19 (12–27)	97 (97–97)	33,145 <sup>58</sup>
PAPP-A + maternal characteristics	Stillbirth	3.5 (2.8–4.4)	0.7 (0.6–0.8)	35 (28–43)	90 (90–90)	33,452 <sup>108</sup>
+ US markers	SGA-related stillbirth	4.4 (3.2–5.9)	0.6 (0.5–0.8)	44 (31–57)	90 (90–90)	33,365 <sup>108</sup>
Inhibin A + maternal characteristics	Stillbirth	4.1 (2.8–6.0)	0.8 (0.8–0.9)	20 (14–29)	95 (95–95)	35,253 <sup>109</sup>
<b>Angiogenic factors</b>						
PIGF	FGR	1.3 (1.2–1.5)	0.9 (0.8–0.9)	38 (35–42)	71 (70–72)	5709 <sup>45,110–118</sup>
	FGR with BW <5th centile and abnormal UT-Doppler	2.0 (1.3–3.0)	0.5 (0.3–1.0)	65 (43–82)	67 (58–76)	124 <sup>119,120</sup>
	FGR with placental pathology	19.8 (7.6–51.3)	0.0 (0.0–0.3)	100 (70–100)	95 (88–98)	88 <sup>117</sup>
sFLT1	FGR with BW <5th centile and abnormal UT-Doppler	1.9 (1.3–2.6)	0.4 (0.2–0.9)	75 (53–89)	60 (50–69)	124 <sup>119,120</sup>
sFLT1:PIGF ratio	FGR with BW <5th centile and abnormal UT-Doppler	1.7 (1.2–2.4)	0.4 (0.2–1.0)	75 (53–89)	57 (47–66)	124 <sup>119,120</sup>
sENG	FGR with BW <5th centile	1.8 (1.4–2.3)	0.6 (0.5–0.7)	61 (52–69)	67 (60–7)	355 <sup>45</sup>
sENG slope	FGR with BW <10th centile	2.4 (1.4–4.3)	0.9 (0.8–1.0)	19 (14–27)	92 (88–95)	346 <sup>65</sup>
VEGF	FGR with BW ≤2SD	4.4 (1.6–12.2)	0.5 (0.2–1.1)	56 (27–81)	88 (74–95)	49 <sup>121</sup>
Angiopoietin	FGR with BW <10th centile and UA-Doppler	4.3 (1.9–9.4)	0.1 (0.0–0.7)	92 (67–99)	78 (58–90)	36 <sup>122</sup>
<b>Hormonal factors, endothelial stress markers, and cytokines</b>						
ADAM12	FGR with BW <5th centile	2.2 (1.6–3.1)	0.9 (0.9–1.0)	12 (10–14)	95 (93–96)	1947 <sup>50,123,124</sup>
IGFBP-1	FGR with BW <10th centile	2.7 (1.1–6.5)	0.8 (0.7–1.0)	24 (12–43)	91 (85–95)	172 <sup>125</sup>
PP-13	FGR with BW <5th centile	3.6 (2.8–4.7)	0.7 (0.6–0.8)	34 (27–42)	91 (90–92)	3854 <sup>46,126,127</sup>
Leptin	FGR with BW <10th centile	2.2 (1.4–3.5)	0.5 (0.3–0.9)	63 (41–81)	72 (63–79)	139 <sup>128</sup>
Fibronectin	FGR with BW <10th centile	13.3 (5.0–35.0)	0.5 (0.2–0.8)	57 (33–79)	96 (90–98)	130 <sup>129</sup>
Homocysteine	FGR with BW <10th centile	2.3 (1.7–3.1)	0.8 (0.8–0.9)	26 (19–33)	89 (87–90)	2088 <sup>130,131</sup>
sVCAM-1	FGR with BW <10th centile	9.0 (3.9–20.7)	0.9 (0.7–1.0)	16 (7–30)	98 (97–99)	1404 <sup>132</sup>
sICAM-1	FGR with BW <10th centile	19.2 (11.5–32.1)	0.6 (0.5–0.8)	42 (28–58)	98 (97–99)	1404 <sup>132</sup>
IFN-γ	FGR with BW <10th centile	2.8 (1.4–5.6)	0.7 (0.6–0.9)	35 (24–48)	87 (78–93)	128 <sup>133</sup>
IL-1Ra	FGR with BW <10th centile	3.0 (1.7–5.1)	0.6 (0.4–0.8)	54 (42–67)	82 (71–89)	128 <sup>133</sup>

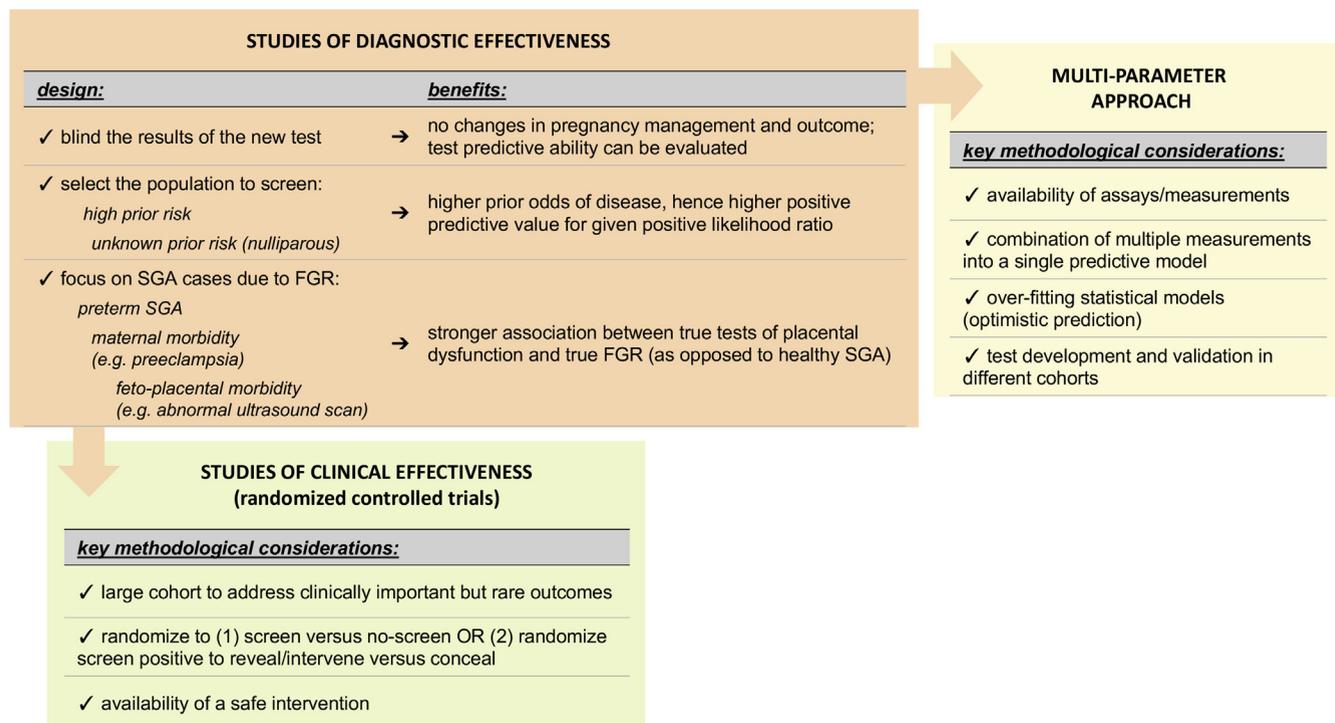
Based on Conde-Agudelo et al.<sup>68,69</sup>

ADAM12, A-disintegrin and metalloprotease 12; AFP, alpha fetoprotein; BW, birthweight; CI, confidence interval; FGR, fetal growth restriction; hCG, human chorionic gonadotropin; IFN, interferon; IGFBP, insulin-like growth factor binding protein; IL-1Ra, interleukin-1 receptor antagonist; LR, likelihood ratio; PAPP-A, pregnancy-associated plasma protein A; PIGF, placental growth factor; PP, placental protein; sENG, soluble endoglin; sFLT1, soluble fms-like tyrosine kinase-1; sICAM, soluble intercellular adhesion molecule; sVCAM, soluble vascular cell adhesion molecule; UA, umbilical artery; uE3, unconjugated estriol; US, ultrasound; UT, uterine artery; VEGF, vascular endothelial growth factor.

Gaccioli. Screening for fetal growth disorders. *Am J Obstet Gynecol* 2018.

FIGURE 2

## Summary of key points to improve fetal growth restriction screening



FGR, fetal growth restriction; SGA, small for gestational age.

Gaccioli. Screening for fetal growth disorders. *Am J Obstet Gynecol* 2018.

research study and becomes an ad hoc screening program. Such an approach may arise from a perception that it would be unethical to conceal the result of a screening test and is based on the assumption that revealing the result of the test would produce a net benefit. This is true for some situations, such as diagnosis of major placenta previa by ultrasound scan. However, given that screening for SGA in France actually seemed to result in net harm<sup>11</sup> and given that routine ultrasound screening has not been shown to be safe and effective,<sup>10</sup> it could equally be argued that revealing the result of an unproven screening test and intervening on the basis of the result is unethical. Similarly, there are several studies evaluating the combination of ultrasound and biomarkers where the ultrasound scan result is revealed but the biochemical tests are not. In these cases, the ability of the biochemical test to predict the adverse outcome may be underestimated due to interventions

initiated by an abnormal ultrasound result. These issues underline the value of studies where all new elements of the approach to screening are conducted blind, wherever possible. These examples indicate that blinding of test results in studies of diagnostic effectiveness is justified. Otherwise, it is very hard to see how progress on screening using new diagnostic tests in pregnancy can be achieved.

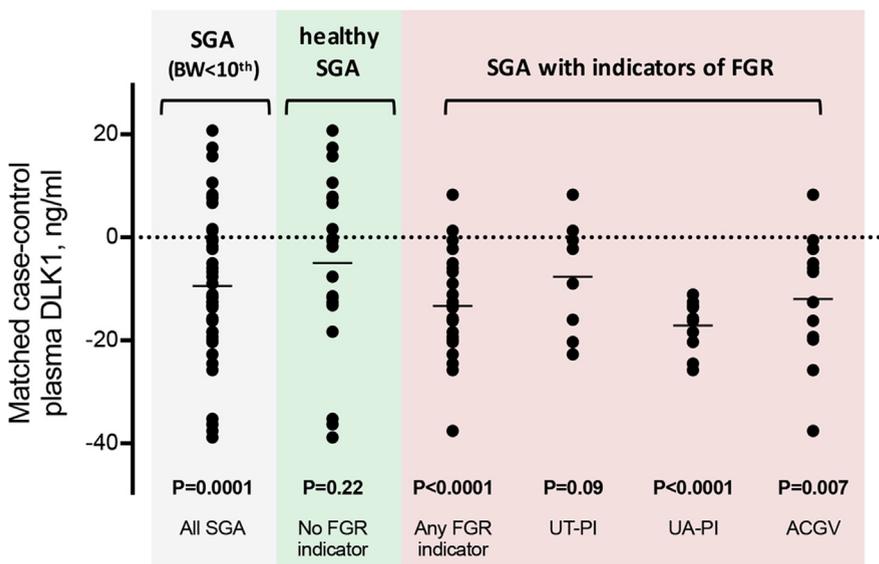
**Classification of SGA.** SGA is defined on the basis of an arbitrary threshold of BW percentile. It follows that many infants born SGA were healthy. Using unqualified SGA as an outcome may, therefore, lead to weaker associations with an effective screening test than would have been obtained if the analysis was focused on cases of SGA where the baby was small due to FGR. A number of studies of candidate biomarkers have shown stronger associations with preterm compared to term SGA. These results

might indicate that FGR is more common at preterm gestational ages. However, another interpretation is that the population of SGA infants delivered preterm is enriched with cases of true FGR compared to SGA births at term. Similarly, the association between a true test of placental dysfunction and SGA is likely to be stronger when the outcome of SGA is combined with an indicator of maternal or perinatal morbidity, such as preeclampsia or asphyxia, respectively. Therefore, studies that simply report the screening statistics for all SGA without reference to whether there was evidence supporting a pathological cause may underestimate the screening performance of an informative test.

Assessment of new biomarkers may also be facilitated by phenotyping SGA using prenatal ultrasound. We have recently shown an association between SGA and low maternal plasma levels of the noncanonical NOTCH1 ligand delta-like 1 homolog (DLK1).<sup>74</sup> Using

FIGURE 3

**Low maternal delta-like 1 homolog (DLK1) levels are associated with fetal growth restriction (FGR)**



Maternal circulating DLK1 and fetal growth. Scatterplot of differences in maternal plasma concentrations of DLK1. DLK1 concentration was measured in maternal plasma from pregnancies with small for gestational age (SGA) (birthweight [BW] <10th centile) and normally grown infants ( $n = 43$  matched pairs; matching was based on maternal age, body mass index, smoking status, fetal sex, and mode of delivery). FGR indicators are: uterine artery (UT)-pulsatility index (PI) in 10th decile at 20 weeks of gestational age ( $n = 8$  pairs); umbilical artery (UA)-PI in 10th decile at 36 weeks ( $n = 10$  pairs); abdominal circumference growth velocity (ACGV) in 1st decile at 20-36 weeks ( $n = 12$  pairs). Horizontal bars represent means of differences. Modified from Cleaton et al.<sup>74</sup>

Gaccioli. Screening for fetal growth disorders. *Am J Obstet Gynecol* 2018.

genetically modified mice, it was demonstrated that during pregnancy maternal circulating DLK1 is mostly of fetal origin. This protein appears to provide a link between fetal demand and maternal metabolic adaptation to pregnancy. Altered maternal levels of DLK1 were recently measured in pregnancies complicated with preeclampsia.<sup>75</sup> In our cohort, low DLK1 levels were associated with SGA only in presence of  $\geq 1$  ultrasonic indicators of FGR, and levels were not different in SGA without such markers (Figure 3). Interestingly, in every case of SGA with a high-resistance pattern of umbilical artery Doppler, maternal serum DLK1 was lower than in the matched control. This also suggests that biomarkers might help define subgroups of causes of FGR. Recent studies in human placenta have

demonstrated a correlation between methylation in the DLK1 domain and BW.<sup>76</sup>

*Developing multiparameter models.* It is possible in the future that a single highly informative marker for FGR, or a subtype of FGR, might be identified on the basis of mechanistic understanding of the cause of the disease. However, in the meantime, it is more likely that screening tests for FGR will include multiple measurements, which are derived from both imaging procedures and measurement of biomarkers. Several studies adopting this approach have been described above.<sup>61-63,73</sup> Development of screening models based on a multiparameter assessment raises several challenges. These include measuring and scaling the given parameter to generate

consistent associations in different centers, combining multiple measures into a single predictive model, and accounting for interactions between parameters. Approaching this task has a number of common pitfalls, such as overfitting statistical models leading to overly optimistic prediction. These issues necessitate the use of statistical methods that account for optimism<sup>77</sup> and underline the value of studies that assess the development and validation of the novel test in separate groups of patients.<sup>78,79</sup>

These issues are particularly important when using “omic” methods that might yield hundreds or thousands of data points per patient. These methods carry a high risk of generating overly optimistic prediction and they require a rigorous methodological approach. Nevertheless, next-generation sequencing allows for unbiased interrogation of genomes or transcriptomes in clinical specimens, providing unprecedented opportunities to accelerate the discovery of novel biomarkers in FGR screening. A successful application of the next-generation sequencing techniques to the biomarkers discovery field has been maternal circulating cell-free fetal DNA measurement for Down syndrome and trisomy 18 screening.<sup>80,81</sup> Elevated maternal cell-free fetal DNA levels have also been measured in pregnancies complicated by FGR compared to normal pregnancies,<sup>82</sup> but more recent data were not always consistent with these initial findings.<sup>83,84</sup>

Given the key role of the placenta in the etiology of FGR, an alternative approach is to study the differences in the placental transcriptome comparing cases of FGR and controls. This may allow identification of placental pathways altered in FGR and potential biomarkers for the condition; although, so far, this approach has been extensively utilized in relation to preeclampsia.<sup>85-87</sup> Development of biomarkers would follow either by measurement of differentially expressed RNA molecules (messenger RNAs [mRNAs], microRNAs [miRNAs], and long non-coding RNAs [lncRNAs]) or by measurement of the proteins encoded by the differentially expressed

genes. The exemplar of this approach is the identification of the role of sFLT1 in preeclampsia: microarray studies identified up-regulation of *FLT1* as one of the key changes in the preeclamptic placenta and this was paralleled by elevated levels of sFLT1 protein in the maternal circulation.<sup>38</sup> Prof Stephen Tong's group has used the alternative approach of measuring mRNAs in the mother's plasma and they have identified a number of placental transcripts measured in maternal blood at 26-30 weeks of gestation, which were associated with the subsequent risk of term FGR.<sup>88,89</sup> Proteomic and metabolomic technologies offer theoretical advantages, because proteins and metabolites are potentially more closely linked to the phenotype under investigation than mRNA. One example of a validated proteomics study of FGR identified apolipoproteins CII and CIII in maternal serum of mothers with FGR compared to gestational age matched controls.<sup>90</sup> Despite the vast opportunities of omic research, there are still many challenges, including the difficulty related to handling large and highly complex data sets. To date, most omic studies assessing pregnancy disorders display several limitations: small sample sizes, lack of predictive ability, and the absence of validation experiments. A set of guidelines published by the Institute of Medicine<sup>91</sup> may help standardization of future omic research.

*Identifying novel biomarkers.* It is apparent from the summary above that many biomarkers identified for FGR were originally developed as predictive tests for other conditions, such as Down syndrome and preeclampsia. A PubMed search yields approximately 3 times the number of citations for genetic array studies of the placenta in preeclampsia compared with FGR. Moreover, given the issues of phenotyping discussed above, application of omic methods to the placenta in cases of SGA will require detailed phenotyping of the patient. Hence, a further approach to improving screening for FGR would be to increase the efforts to identify the biological pathways underlying placental

dysfunction in optimally phenotyped cases of FGR.

*Meaningful clinical outcomes.* An extension of the issues relating to phenotyping is the identification of clinically important outcomes when studying FGR. Studies that focus on SGA have a limited potential as this would not be a likely primary outcome in trials of screening and intervention until disease-modifying therapies are available. The most serious adverse outcome of FGR is intrauterine fetal death. However, this outcome affects about 4 per 1000 pregnancies. Even the highest estimates indicate that 50% of stillbirths might be due to FGR.<sup>92</sup> Other studies suggest that the proportion may be lower.<sup>93</sup> To be powered to study stillbirth related to FGR, tens of thousands of women or, in the case of a very strongly predictive test, many thousands of women would need to be recruited. Given the expense involved, many studies use nonlethal proxies of stillbirth due to FGR. While it is likely that true FGR has common features whether the baby survives or dies, the use of weak proxies will tend to obscure associations. One commonly used proxy is cesarean delivery for fetal distress, which is particularly problematic when it is employed in situations where the novel test result has been revealed. If the attending clinician is aware that a scan has identified a baby as suspected FGR, this could lead to an association with antepartum or intrapartum cesarean delivery for fetal distress even where the new test is not informative. There are a number of possible approaches to developing meaningful clinical outcomes. One might be to combine an assessment of the infant's BW with anthropometric measures that support a diagnosis of FGR. This would allow some degree of separation between healthy SGA and FGR. However, this assumes that such measures are reproducible and will correlate with clinically meaningful outcomes. One approach we have used is to combine SGA birth weight with clinical complications consistent with FGR. These include signs of fetal asphyxia or compromise, such as depressed

5-minute Apgar score, the presence of metabolic acidosis in cord blood gases obtained at delivery, and admission to the neonatal intensive care unit.<sup>16</sup> The last of these could reflect asphyxia or it could reflect other complications of FGR, such as hypoglycemia. Finally, the coexistence of SGA and maternal preeclampsia is suggestive that the baby's small size is more likely to be due to placental dysfunction and this could also have utility in differentiating between healthy and pathological SGA infants.

*The future for RCTs of screening and intervention.* Given the capacity for screening to cause harm, any future program of screening and intervention will need to be evaluated by an RCT. We have previously discussed some of the issues around the design of such studies (Figure 3).<sup>51,94</sup> If the primary outcome is clinically important it is likely that any trial will have to be very large (>10,000 women). Sample size can be reduced by randomizing screen-positive women to revealing the result plus intervention vs concealing the result. It should also be self-evident that a trial of screening will only improve outcomes if the screening test is coupled to an effective intervention. At present, the primary disease-modifying intervention is to deliver the baby. Given the strong associations between preterm birth and perinatal morbidity and mortality, we have suggested that this provides a rationale for focusing initial efforts on screening for FGR at term. However, mechanistic understanding of the causes of FGR could lead to the development of novel therapeutic approaches, such as repurposing of existing drugs<sup>95</sup> and gene therapy.<sup>96</sup> ■

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## OBSTETRICS

# The effect of customization and use of a fetal growth standard on the association between birthweight percentile and adverse perinatal outcome



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**BACKGROUND:** It has been proposed that correction of offspring weight percentiles (customization) might improve the prediction of adverse pregnancy outcome; however, the approach is not accepted universally. A complication in the interpretation of the data is that the main method for calculation of customized percentiles uses a fetal growth standard, and multiple analyses have compared the results with birthweight-based standards.

**OBJECTIVES:** First, we aimed to determine whether women who deliver small-for-gestational-age infants using a customized standard differed from other women. Second, we aimed to compare the association between birthweight percentile and adverse outcome using 3 different methods for percentile calculation: (1) a noncustomized actual birthweight standard, (2) a noncustomized fetal growth standard, and (3) a fully customized fetal growth standard.

**STUDY DESIGN:** We analyzed data from the Pregnancy Outcome Prediction study, a prospective cohort study of nulliparous women who delivered in Cambridge, UK, between 2008 and 2013. We used a composite adverse outcome, namely, perinatal morbidity or preeclampsia. Receiver operating characteristic curve analysis was used to compare the 3 methods of calculating birthweight percentiles in relation to the composite adverse outcome.

**RESULTS:** We confirmed previous observations that delivering an infant who was small for gestational age (<10th percentile) with the use of a fully customized fetal growth standard but who was appropriate for gestational age with the use of a noncustomized actual birthweight standard was associated with higher rates of adverse outcomes.

However, we also observed that the mothers of these infants were 3–4 times more likely to be obese and to deliver preterm. When we compared the risk of adverse outcome from logistic regression models that were fitted to the birthweight percentiles that were derived by each of the 3 predefined methods, the areas under the receiver operating characteristic curves were similar for all 3 methods: 0.56 (95% confidence interval, 0.54–0.59) fully customized, 0.56 (95% confidence interval, 0.53–0.59) noncustomized fetal weight standard, and 0.55 (95% confidence interval, 0.53–0.58) noncustomized actual birthweight standard. When we classified the top 5% of predicted risk as high risk, the methods that used a fetal growth standard showed attenuation after adjustment for gestational age, whereas the birthweight standard did not. Further adjustment for the maternal characteristics, which included weight, attenuated the association with the customized standard, but not the other 2 methods. The associations after full adjustment were similar when we compared the 3 approaches.

**CONCLUSION:** The independent association between birthweight percentile and adverse outcome was similar when we compared actual birthweight standards and fetal growth standards and compared customized and noncustomized standards. Use of fetal weight standards and customized percentiles for maternal characteristics could lead to stronger associations with adverse outcome through confounding by preterm birth and maternal obesity.

**Key words:** adverse perinatal outcome, birthweight, customization, fetal growth, small for gestational age

Abnormal birthweight is one of the major associations with adverse pregnancy outcome. Small-for-gestational-age (SGA) birthweight is sometimes caused by fetal growth restriction that is associated with an increased risk of preeclampsia and perinatal morbidity and death.<sup>1</sup> Large-for-gestational-age (LGA) birthweight is sometimes caused by excessive fetal growth that is associated with maternal obesity and/or diabetes mellitus and can also result in perinatal morbidity and death.<sup>2</sup> Understanding the causes, nature,

and strength of these associations is important because assessment of abnormal fetal growth with the use of ultrasound scanning is one of the key methods for the identification of pregnancies that are at increased risk of complications. Multiple other factors determine the size of the fetus, most obviously the gestational age and fetal sex. However, there is still a great deal of variability in fetal size, which is not explained by these factors. Hence, the populations of SGA and LGA fetuses and infants contain large numbers of healthy pregnancies; a key challenge in assessment of these associations and exploiting them for clinical risk assessment is differentiation between healthy and pathologic pregnancies

in which the fetus is either SGA or LGA.

One approach to this task is to adjust the estimate of the birthweight percentile for the maternal characteristics that are associated with birthweight, such as parity, ethnicity, bodyweight, and height.<sup>3</sup> The appropriateness of this is debated because it is unclear whether some of these features are truly physiologic determinants of growth or whether growth lies on the causal pathway between the maternal characteristic and adverse outcome.<sup>4</sup> For example, nulliparity is associated with reduced fetal growth and is also associated with an increased risk of stillbirth and preeclampsia.<sup>5</sup> Adjustment of birthweight

percentile for nulliparity potentially could make birthweight percentile a poorer predictor of adverse outcome if fetal growth lies on the causal pathway. A further complexity is how to assess the size of the fetus at preterm gestational ages. Studies have shown that slowing of fetal growth in the second trimester is a risk factor for spontaneous preterm birth.<sup>6,7</sup> It follows that the distribution of actual birthweights at a given week of gestational age preterm may be shifted towards lower values when compared with on-going pregnancies. A study of fetal weight and birthweight percentiles from the InterGrowth21 study demonstrated that, at 28 weeks gestation, the 50th percentile of birthweight was actually <3rd percentile of estimated fetal weight.<sup>8</sup> These observations suggest that assessment of birthweight at preterm gestational ages should be performed with the use of a fetal growth standard. However, a consequence of this will be that a much larger proportion of preterm infants will be classified as SGA. This will complicate comparisons of birthweight standards because, by far, the strongest risk factor for perinatal morbidity and death is preterm birth.

The aim of the present study was to compare the associations between birthweight percentile calculated with the use of a noncustomized standard based on observed birthweights at a given week of gestation with percentiles that are calculated with the use of a fetal growth standard, with and without customization for maternal characteristics.

## Methods

### Study design and data collection

The Pregnancy Outcome Prediction study was a prospective cohort study that has been described previously in detail.<sup>9</sup> In brief, nulliparous women who attended the Rosie Hospital for their dating ultrasound scan between January 14, 2008, and July 31, 2012, with viable singleton pregnancy were eligible for the study. The study involved a booking visit at approximately 12 weeks gestation and 3 subsequent visits at approximately 20,

28, and 36 weeks gestation. The 20-week visit included a questionnaire that was completed by interview to retrieve demographic data and medical history. Outcome data were ascertained by review of case records by research midwives. Record linkage to clinical electronic databases of delivery (Protos) and a neonatal intensive care database (Badgernet) was performed. Ethical approval for the study was given by the Cambridgeshire 2 Research Ethics Committee (reference number, 07/H0308/163); all participants provided written informed consent.

### Exclusions

Records with missing data on birthweight, gestational age, fetal sex, or birth outcome and all records in which data on any of the variables that were used for customization (maternal weight, height or ethnicity) were missing were excluded. Miscarriages, terminations of pregnancy, and antepartum stillbirths were also excluded because of the complexities in categorization of birthweight because of maceration after intrauterine fetal death.

### Exposures and outcomes

Customized birthweight percentiles (corrected for parity, height, weight, ethnicity, gestational age at birth, and fetal sex) were obtained from the latest model of Gestation-Related Optimal Weight (GROW; version 6.7.8.1; Perinatal Institute, Birmingham, UK) with the use of a bulk percentile calculator (Perinatal Institute).<sup>10</sup> Partial customization was performed with the same fetal weight standard<sup>11</sup> and centile calculator but correcting only for gestational age at birth and fetal sex (we call these population percentiles using fetal weight standard). Population-based birthweight percentiles were calculated from a UK 1990 reference with the use of the zanthro package (Stata Corporation, College Station, TX) and correction for gestational age at birth and fetal sex; the actual birthweight standard was used in these calculations.<sup>12</sup>

### Exposures

SGA was defined as birthweight <10th percentile. To understand how maternal

and obstetric characteristics might have varied in previous analyses, we described the cohort using 4 groups: (1) not SGA, (2) SGA with the use of customized but not population percentile, (3) SGA with the use of population but not customized percentile, and (4) SGA with the use of both customized and population percentile. Any differences in the analyses may be attributed to either customization or different reference standard. To compare the different methods, 3 different percentiles were compared: (1) a birthweight standard,<sup>12</sup> (2) a sex and gestational age corrected fetal weight standard,<sup>11</sup> and (3) a fully customized standard.

### Outcome

Maternal preeclampsia (defined on the basis of the 2013 American College of Obstetricians and Gynecologists criteria, as described previously<sup>13</sup>), perinatal death or morbidity (5-minute Apgar score <7, metabolic acidosis [defined as a cord blood pH <7.1 and base deficit >10 mmol/L], or admission to the neonatal unit at term for  $\geq 48$  hours within  $\leq 48$  hours of birth, defined in Sovio et al<sup>1</sup>) was used as a composite outcome. The present analysis excluded antepartum stillbirths but included other nonanomalous perinatal deaths (intrapartum stillbirths and neonatal deaths).

### Statistical analysis

Maternal characteristics and birth outcomes were compared among the 4 groups with the use of a Kruskal-Wallis test for continuous characteristics and Pearson Chi-square test for categorical characteristics. When the global probability value indicated highly statistically significant differences ( $P < .001$ ), selected pairwise comparisons among subgroups were performed with the use of Wilcoxon rank-sum (Mann-Whitney) test for continuous characteristics and either Pearson Chi-square test or Fisher's exact test for categorical characteristics, as appropriate. The linearity of association between gestational age and the outcome and between birthweight percentile and the outcome was tested with the use of fractional polynomial logistic regression analysis. Because the association

**TABLE 1**  
**Characteristics of the study sample by small-for-gestational-age group (total n = 4095)**

Characteristic	Not small for gestational age (n=3631)	Small for gestational age			P value
		Customized fetal weight standard (n=102)	Population birthweight standard (n=59)	Both standards (n=303)	
Age, y <sup>a</sup>	30 (27–33)	31 (25–34)	30 (27–34)	30 (27–34)	.90
Age at which patient stopped full-time education <sup>a</sup>	21 (18–23)	19 (16–22)	21.5 (18–24)	21 (18–23)	<.001
Missing data, n (%)	111 (3.1)	0	1 (1.7)	9 (3.0)	
Deprivation quartile, n (%)					.21
1 (Lowest)	880 (24)	24 (24)	16 (27)	71 (23)	
2	879 (24)	25 (25)	14 (24)	59 (19)	
3	878 (24)	19 (19)	10 (17)	79 (26)	
4 (Highest)	846 (23)	28 (27)	18 (31)	81 (27)	
Missing data	148 (4.1)	6 (5.9)	1 (1.7)	13 (4.3)	
Married, n (%)	2495 (69)	56 (55)	45 (76)	183 (60)	<.001
Smoker, n (%)	158 (4.4)	9 (8.8)	3 (5.1)	37 (12)	<.001
Any alcohol consumption, n (%)	162 (4.5)	6 (5.9)	5 (8.5)	12 (4.0)	.42
Missing data	2 (0.1)	0	0	0	
Ethnicity, n (%)					<.001
Non-white	203 (5.6)	2 (2.0)	15 (25)	14 (4.6)	
White	3428 (94)	100 (98)	44 (75)	289 (95)	
Weight, kg <sup>a</sup>	66 (59–75)	75 (65–90)	56 (51–58)	66 (58–74)	<.001
Height, cm <sup>a</sup>	165 (161–170)	167 (164–172)	158 (156–162)	164 (160–168)	<.001
Body mass index, kg/m <sup>2a</sup>	24 (22–27)	27 (23–32)	22 (20–23)	24 (22–27)	<.001
Body mass index category, n (%)					<.001
Normal weight (<25 kg/m <sup>2</sup> )	2108 (58)	40 (39)	53 (90)	180 (59)	
Overweight (25 to <30 kg/m <sup>2</sup> )	1037 (29)	27 (26)	5 (8.5)	82 (27)	
Obese (≥30 kg/m <sup>2</sup> )	486 (13)	35 (34)	1 (1.7)	41 (14)	
Perinatal outcome, n (%)	229 (6.3)	11 (11)	4 (6.8)	45 (15)	<.001
Preeclampsia, n (%)	221 (6.1)	18 (18)	3 (5.1)	29 (10)	<.001
Composite outcome, n (%)	425 (12)	27 (26)	7 (12)	64 (21)	<.001
Birthweight, kg <sup>a</sup>	3490 (3210–3780)	2900 (2545–3035)	3030 (2850–3170)	2780 (2540–2930)	<.001
Gestational age, wk <sup>a</sup>	40.3 (39.1–41.1)	39.6 (37.9–40.4)	41.3 (40.3–41.7)	40.6 (39.6–41.3)	<.001
Preterm birth, n (%)					<.001
Preterm: 24–32 wk	26 (0.7)	3 (2.9)	0	7 (2.3)	
Preterm: 33–36 wk	117 (3.2)	13 (13)	2 (3.4)	0 (3.0)	
Term: ≥ 37 wk	3488 (96)	86 (84)	57 (97)	287 (95)	
Induction of labor, n (%)	1150 (32)	39 (38)	23 (39)	96 (32)	.34

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(continued)

TABLE 1

Characteristics of the study sample by small-for-gestational-age group (total n = 4095) (continued)

Characteristic	Not small for gestational age (n=3631)	Small for gestational age			P value
		Customized fetal weight standard (n=102)	Population birthweight standard (n=59)	Both standards (n=303)	
Mode of delivery, n (%)					<.001
Spontaneous vaginal	1752 (48)	47 (46)	25 (42)	158 (52)	
Assisted vaginal	866 (24)	22 (22)	22 (37)	64 (21)	
Intrapartum cesarean	656 (18)	9 (8.8)	9 (15)	42 (14)	
Prelabor cesarean	349 (10)	24 (24)	3 (5.1)	39 (13)	
Missing data	7 (0.2)	0	0	0	

<sup>a</sup> Data are given as median (interquartile range) as appropriate. Comparisons among the 4 groups were done with the use of a Kruskal-Wallis test for continuous characteristics and Pearson Chi-square test for categorical characteristics. For fields in which there is no category labelled missing, data were 100% complete. Maternal age was defined as age at recruitment; maternal weight was measured at the time of the dating scan, and maternal height was measured at the time of the 20-week scan. All other maternal characteristics were defined by self-report at the 20-week interview, from examination of the clinical case record, or linkage to the hospital's electronic databases. <sup>1</sup> Deprivation was quantified with the use of the Index of Multiple Deprivation 2007,<sup>15</sup> which is based on census data from the area of the mother's postcode.

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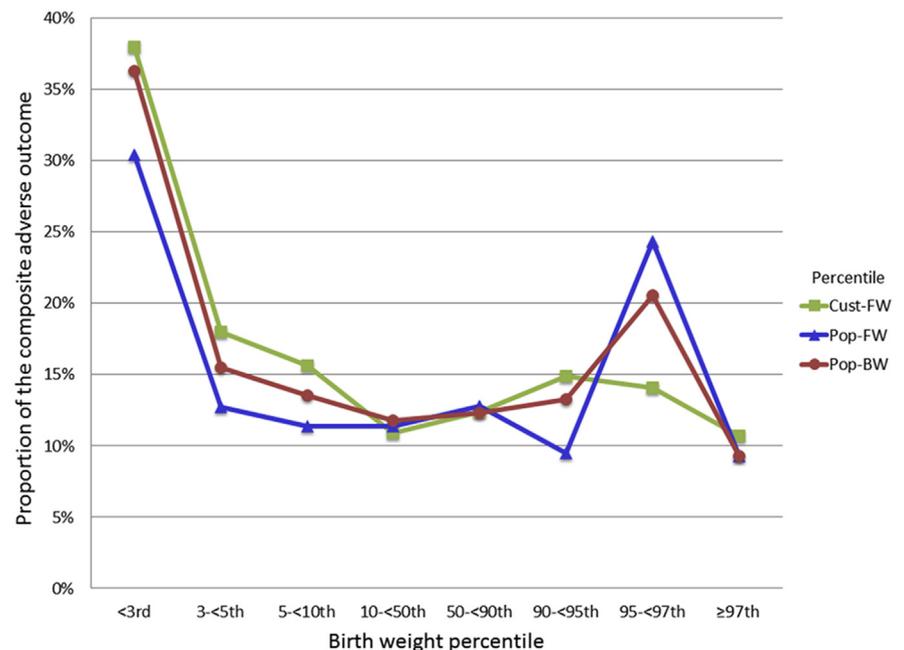
between birthweight percentile and the outcome was nonlinear, the best-fitting degree-2 fractional polynomial model was chosen to represent this association. Fractional powers were chosen from the set (-2, -1, -0.5, 0, 0.5, 1, 2, 3). This was repeated for all 3 birthweight percentiles. The predicted risk of outcome was calculated from the fractional polynomial model with the use of Stata postestimation command `—predict—` with option `pr`, and the `—centile—` command with option `c(90,95)` were used to obtain the top 10% and top 5% risk cut-offs, respectively. The predicted risk was analyzed as a continuous variable, receiver operating characteristic (ROC) curves were estimated, and the areas under the ROC curves were compared. Logistic regression models were then fitted between high predicted risk (top 5% or top 10%) and the composite adverse outcome with and without adjustment for gestational age and other characteristics used in customization. Odds ratios (OR) and 95% confidence intervals (CI) were estimated. The association between maternal characteristics and fetal weight at 36 weeks and birthweight was modeled with the use of linear regression; adjusted  $r^2$  was calculated to estimate the variance in weight explained by the maternal characteristics.

## Results

In total, 4095 women were included in the analysis. In Table 1, we present the characteristics of the cohort in relation

to the SGA classifications frequently used in previous studies, namely into each of the 4 groups: (1) not SGA using both methods (n=3631), (2) SGA

FIGURE 1  
Proportion of the composite adverse outcome



Proportion (%) of the composite adverse outcome in relation to birthweight percentile category.

Cust-FW, customized fetal weight standard; Pop-BW, population birthweight standard (adjusted only for sex and gestational age); Pop-FW, population fetal weight standard (adjusted only for sex and gestational age).

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using the customized method only (SGA-cust;  $n=102$ ), (3) SGA using the population birthweight-based standard only (SGA-pop;  $n=59$ ), and (4) SGA by both methods (SGA-both;  $n=303$ ). This analysis recapitulated the same observation described by many previous studies of increased proportions of pregnancies that are associated with perinatal morbidity and preeclampsia where the infant was SGA-cust (composite outcome 26% vs 12% in the SGA-pop group;  $P=.03$ ). However, the SGA-cust group also had much higher rates of preterm birth (16% vs 3%;  $P=.02$ ) and maternal obesity (34% vs 2%;  $P<.001$ ) than the SGA-pop group. Pregnancies classified as SGA-pop were more often nonwhite (25% vs 2%;  $P<.001$ ), weighed less (56 vs 75 kg;  $P<.001$ ), were shorter (158 vs 167 cm;  $P<.001$ ), had a lower body mass index (22 vs 27 kg/m<sup>2</sup>;  $P<.001$ ), delivered later (41.3 vs 39.6 wk,  $P<.001$ ), and had greater proportions of assisted vaginal deliveries (37% vs 22%;  $P=.03$ ) than the SGA-cust group. Pregnancies that were classified as SGA-both had a higher smoking prevalence than the other groups combined (12% vs 4%;  $P<.001$ ), had the lowest birthweight of all the 4 groups (2780 vs 3465 g;  $P<.001$ ), and were the most likely to have an adverse perinatal outcome (15% vs 6%;  $P<.001$ ).

We then sought to perform a standardized comparison of the 3 main methods for classifying birthweight percentile as SGA: (1) using a noncustomized birthweight standard (adjusted only for sex and gestational age), (2) using a noncustomized fetal weight standard (adjusted only for sex and gestational age), and (3) using a customized fetal weight standard (adjusted for parity, height, weight, ethnicity, sex, and gestational age). We studied each of these methods in relation to a composite adverse pregnancy outcome: perinatal morbidity and/or maternal preeclampsia. First, we plotted the raw data on the composite adverse outcome in relation to birthweight percentile categories (Figure 1). The patterns were broadly similar across the 3 forms of classification.

However, at the lower end of the birthweight percentile range, the customized group had the highest proportion of adverse outcomes; at the upper end of the range, there were greater proportions with adverse outcomes in the other 2 groups.

Given the nonlinear associations between birthweight percentile and the composite adverse outcome, we calculated the predicted risk of the outcome for each woman from a fractional polynomial logistic regression model and analyzed this as a continuous variable using ROC curve analysis (Figure 2). There were highly statistically significant associations ( $P<.0001$ ) between all 3 estimates of birthweight percentile and the composite outcome. However, the area under the ROC curve was virtually identical with all 3 methods, and we observed no statistically significant difference ( $P=.07$ ). None of the methods was associated strongly with the composite outcome (the area under the ROC curve was  $<0.6$  for all methods).

We then sought to determine the independent predictive association for each of the approaches in which we could compare like with like and adjust for any associated maternal characteristics. We identified the women in the top 5% and 10% of predicted risk of the composite adverse outcome using the 3 methods (this approach ensured that the same number of women were treated as high risk using the 3 methods). We then performed univariable and multivariable analysis of the associations with the composite adverse outcome (Table 2). All 3 methods demonstrated stronger associations with the top 5% of predicted risk than the top 10%, as expected. For classification of the top 5% of predicted risk as high risk, the methods that used a fetal growth standard showed attenuation after adjustment for gestational age, whereas the birthweight standard did not. Further adjustment for the maternal characteristics, which included body mass index, attenuated the association with the customized standard, but not the other 2 methods. The associations after full adjustment were similar comparing the 3

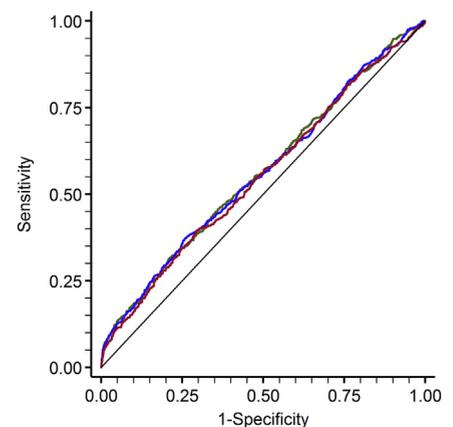
approaches (each of the odds ratios were within the 95% confidence interval of the other 2 odds ratios).

Finally, we performed linear regression analysis to determine what proportion of the variation in weight could be attributed to maternal characteristics (Table 3). When the outcome was the estimated fetal weight at 36 weeks gestation,  $r^2$  was 5.5%; when the outcome was birthweight,  $r^2$  was 4.4%.

## Comment

We confirmed many previous observations that pregnancies identified as SGA only by a customized growth standard had higher rates of complications than non-SGA pregnancies.<sup>14</sup> Taken at face value, this analysis might be used as further evidence for the beneficial effect of “customizing” birthweight percentile. However, this group was also far more likely to be

**FIGURE 2**  
Receiver operating characteristic curve analysis



Receiver operating characteristic curve analysis between the predicted risk and the composite adverse outcome with the use of the customized fetal weight standard (green), the population fetal weight standard (blue), and the population birthweight standard (red). The areas under the receiver operating characteristic curves were 0.56 (95% confidence interval, 0.54–0.59), 0.56 (95% confidence interval, 0.53–0.59) and 0.55 (95% confidence interval, 0.53–0.58), respectively.

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TABLE 2

**The risk of composite adverse outcome by screen positive status (predicted risk within top 5% or 10%) at birth (n = 4095)**

Screen positive	n/N (%)	Odds ratio (95% confidence interval)		
		Unadjusted	Adjusted for gestational age	Fully adjusted
Within top 5%				
Customized fetal weight standard	61/204 (29.90)	3.17 (2.31–4.34)	2.90 (2.10–3.99)	2.73 (1.96–3.79)
Population fetal weight standard	59/204 (28.92)	3.01 (2.19–4.13)	2.75 (1.99–3.80)	2.80 (2.01–3.90)
Population birthweight standard	54/204 (26.47)	2.63 (1.90–3.64)	2.62 (1.89–3.65)	2.66 (1.90–3.73)
Within top 10%				
Customized fetal weight standard	90/409 (22.00)	2.12 (1.64–2.73)	2.00 (1.54–2.59)	1.86 (1.43–2.43)
Population fetal weight standard	86/409 (21.03)	1.98 (1.53–2.56)	1.86 (1.43–2.42)	1.75 (1.34–2.29)
Population birthweight standard	79/409 (19.32)	1.75 (1.34–2.28)	1.71 (1.31–2.23)	1.58 (1.20–2.08)

Odds ratios are referent to infants who were in the bottom 95% or 90% of predicted risk, respectively. Fully adjusted model included the variables used in customization (gestational age at birth, fetal sex, maternal height, weight at booking, and ethnic group) as covariates. Because of small numbers in some ethnic groups, all non-white ethnicities were grouped together for the adjustment. No adjustment was made for parity because all women were nulliparous.

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born preterm and the mothers of these infants to have a higher body mass index. The proportion of preterm birth in this group was almost 4-fold greater than in the non-SGA group, and the proportion of mothers who were obese was almost 3-fold greater. The former observation likely relates to the use of a fetal growth standard because far more preterm infants are classified as SGA when a fetal growth standard is used compared with a birthweight standard. The latter observation is likely explained by the correction of birthweight percentile for the mother's weight. However, it is arguable whether obesity should be regarded, from an evolutionary perspective, as a physiologic determinant of normal fetal growth. Previous studies have shown that classification of infants as SGA on the basis of a customized birthweight percentile is a better predictor of adverse perinatal outcome than a noncustomized birthweight standard. However, the data in Table 1 indicated that these observations should be treated cautiously because they could be due to confounding by preterm birth and obesity.

We then set out to establish whether customization of birthweight percentile resulted in a stronger association with a composite outcome of either

preeclampsia or perinatal morbidity, independently of these confounders. First, we observed that all 3 methods of calculating birthweight percentile were associated with an increased risk of adverse outcome. To allow a standardized comparison of the 3 methods, we treated each as a continuous variable and assessed model discrimination using the area under the ROC curve. We performed the analysis in such a way as to capture associations with both reduced and excessive growth. Overall, using this approach, we found no clear evidence that 1 method was superior to the other methods in the identification of adverse pregnancy outcomes. With the

use of the top 5% of predicted risk, both methods that used a fetal growth standard demonstrated a weaker association when adjusted for gestational age, whereas adjustment had no effect on the strength of association with the birthweight-based standard. There was a further reduction in the strength of association on adjustment for maternal characteristics with the top 5% of predicted risk based on a customized percentile, but not with the other 2 methods. These findings indicate that the use of a fetal growth standard results in a stronger association with adverse outcome, partly through a tendency to classify more preterm births as SGA. Given that

TABLE 3

**Variation in estimated fetal weight and birthweight explained by maternal characteristics**

Variable	Maternal characteristic: adjusted $r^2$ (%)			
	Height	Weight at booking	Ethnic group	Total
Estimated fetal weight at 36 weeks gestation	1.7	5.3	0.1	5.5
Birthweight	3.2	2.8	0.4	4.4

Estimated fetal weight was calculated from the measurements of fetal head, abdomen, and femur with the use of a Hadlock formula as previously described<sup>11,16</sup>; it was available for 3802 of the 4095 women who were included in the study population. Maternal weight had a nonlinear association with estimated fetal weight and birthweight, and both linear and quadratic terms were included in the regression models.

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gestational age is one of the major determinants of adverse perinatal outcome, it is self-evident that any classification that enriches for this group will be more associated strongly with morbidity.

The use of customized percentiles has the potential to create a number of problems in the interpretation of relationships between birthweight percentile and adverse outcome. First, neonatologists use birthweight-based charts. Clearly, there is potential for confusion and miscommunication if the obstetric and neonatal teams are using different methods for quantification. Second, the actual equation used in GROW is updated regularly. Hence, comparison of data from 2 different time periods with the use of 2 different iterations of the method will be difficult because it is uncertain whether “like” is being compared with “like.” Third, customization based on maternal weight involves making a decision about the threshold of weight when further adjustment is not performed. It is not clear how such a threshold is selected. Fourth, customization may “account” for apparent physiologic determinants of growth that actually lie on the causal pathway and are associated with the risk of adverse outcome. Consistent with this, a recent comparison of noncustomized vs partially customized (accounting for maternal height and parity) birthweight percentile actually showed a weaker association between birthweight percentile and the risk of perinatal death at term after partial customization.<sup>4</sup> These issues may be worth trying to overcome if it is clear that the method works. However, we found no strong evidence to support this and, indeed, identified confounders that may explain the apparent stronger associations in other studies. Finally, although it seems intuitively appealing, if not obvious, that taking maternal characteristics into account would strengthen associations, we observed that maternal characteristics accounted for a relatively modest proportion of the variability (approximately 5%) in both estimated fetal weight and

birthweight. Another approach would be to use each fetus as its own control and to determine the appropriateness of growth using the growth velocity; we have provided high-quality evidence from a prospective level 1 study of diagnostic effectiveness to demonstrate that this approach may be the optimal means for the characterization of fetal growth in both SGA and LGA infants.<sup>1,2</sup> A further approach would be to combine ultrasonic assessment of fetal growth with maternal blood biomarkers of placental dysfunction. ■

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# Pathophysiology of placental-derived fetal growth restriction



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## Introduction

The kinetics of placental and fetal growth are closely interrelated, and are important features predicting postnatal health and in particular cardiovascular adaptations in childhood.<sup>1,2</sup> Fetal growth is dependent on nutrient availability, which in turn is related to the maternal diet, uteroplacental blood supply, placental villous development, and the capacity of the villous trophoblast and fetoplacental circulation to transport these nutrients. At birth, the fetoplacental weight ratio gives a retrospective indication of the efficiency of the placenta to support growth of the fetus, and estimates the potential risks for chronic diseases in later life through developmental programming.<sup>2,3</sup>

Fetal growth restriction (FGR) is defined as the failure of the fetus to achieve its genetically determined growth potential.<sup>4</sup> FGR can have many causes, but the majority of cases that are not associated with fetal congenital malformations, fetal genetic anomalies, or infectious etiology are thought to arise from compromise of the uterine circulation to the placenta. Sufficient dilatation of the uteroplacental circulation

Placental-related fetal growth restriction arises primarily due to deficient remodeling of the uterine spiral arteries supplying the placenta during early pregnancy. The resultant malperfusion induces cell stress within the placental tissues, leading to selective suppression of protein synthesis and reduced cell proliferation. These effects are compounded in more severe cases by increased infarction and fibrin deposition. Consequently, there is a reduction in villous volume and surface area for maternal-fetal exchange. Extensive dysregulation of imprinted and nonimprinted gene expression occurs, affecting placental transport, endocrine, metabolic, and immune functions. Secondary changes involving dedifferentiation of smooth muscle cells surrounding the fetal arteries within placental stem villi correlate with absent or reversed end-diastolic umbilical artery blood flow, and with a reduction in birthweight. Many of the morphological changes, principally the intraplacental vascular lesions, can be imaged using ultrasound or magnetic resonance imaging scanning, enabling their development and progression to be followed in vivo. The changes are more severe in cases of growth restriction associated with preeclampsia compared to those with growth restriction alone, consistent with the greater degree of maternal vasculopathy reported in the former and more extensive macroscopic placental damage including infarcts, extensive fibrin deposition and microscopic villous developmental defects, atherosclerosis of the spiral arteries, and noninfectious villitis. The higher level of stress may activate proinflammatory and apoptotic pathways within the syncytiotrophoblast, releasing factors that cause the maternal endothelial cell activation that distinguishes between the 2 conditions. Congenital anomalies of the umbilical cord and placental shape are the only placental-related conditions that are not associated with maldevelopment of the uteroplacental circulation, and their impact on fetal growth is limited.

**Key words:** AKT/mTOR, apoptosis, atherosclerosis, chorion laeve, electron transport chain, extravillous trophoblast, failure of physiologic transformation, fetal growth restriction, fetoplacental weight ratio, hemochorial placentation, interstitial trophoblast, intervillous space, intraplacental oxygen concentration, mitochondria, oxidative stress, perivillous fibrin deposition, placenta, placental infarct, placental inflammation, placental location, reactive oxygen species, spiral arteries, ultrasound imaging, unfolded protein response, villi regression, villous hypoplasia

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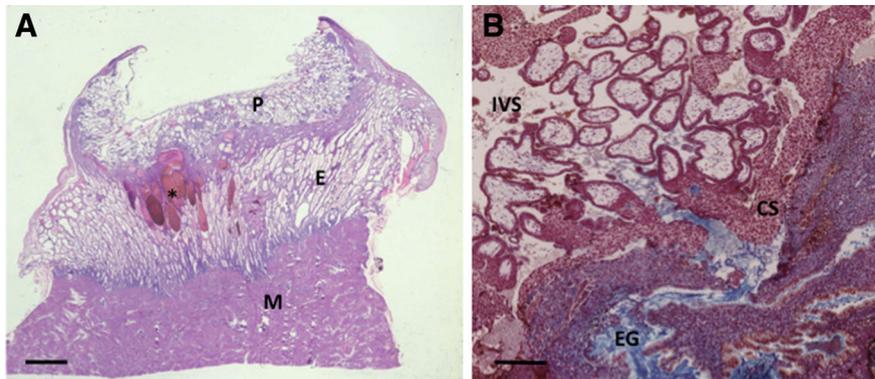
together with rapid villous angiogenesis are the key factors necessary for adequate placental development and function, and subsequent fetal growth.

The etiopathology of FGR due to abnormal development of the uteroplacental circulation and its impact on placental development and structure has been studied for >5 decades.<sup>5</sup> Ultrasound imaging, and in particular color Doppler imaging, has allowed the study of both the umbilicoplacental and uteroplacental circulations from the first trimester of gestation onward.<sup>6,7</sup> These

techniques have been used extensively in the screening of placental-related complications of pregnancy, such as preeclampsia,<sup>8,9</sup> and the management of a fetus presenting with primary or secondary FGR.<sup>10</sup> More recently, 3-dimensional Doppler imaging<sup>11,12</sup> and magnetic resonance imaging (MRI)<sup>13</sup> have been used to study the development of the placental and fetal circulations, but their use in clinical practice remains limited.

Placental-related complications of pregnancy that lead to FGR have their

**FIGURE 1**  
**Histotrophic nutrition of the placenta during the first trimester**



Photomicrographs of archival placenta (P) in situ specimen (H710) at 6 weeks' gestational age demonstrating histotrophic nutrition. **A**, Gestational sac with developing P is implanted in superficial endometrium (E), and was opened during processing to remove embryo. Glands in E beneath sac are highly active, although hemorrhage occurred in some (\*). Scale bar = 2 mm. **B**, Higher power view of interface between P and E showing opening of E gland (EG) into intervillous space (IVS) through cytotrophoblastic shell (CS) and developing basal plate. Scale bar = 250  $\mu\text{m}$ . Modified.<sup>16,177</sup>

M, myometrium.

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pathophysiological roots in the early stages of placentation and can manifest themselves from the end of the first trimester of pregnancy when the definitive placenta is forming.<sup>14,15</sup> Considerable remodeling of the placenta takes place toward the end of the first trimester/start of the second trimester, associated with onset of the maternal arterial circulation when the placenta becomes fully hemochorial. Events at this time potentially impact the final size of the placenta, and hence its functional capacity. This concept is supported by findings in utero showing that pregnancies complicated with FGR, with or without accompanying preeclampsia later in pregnancy, have a smaller placenta volume and higher uterine resistance to blood flow compared to healthy controls from the beginning of the second trimester.<sup>9</sup>

The relationships between abnormal placental development and FGR are complex. Isolating the placental causes of FGR can be difficult as many clinical studies are small, retrospective, and often multivariate with confounding factors such as maternal smoking and ethnicity. Also, many potential stressors

converge on the same intracellular pathways, and separating the influence of, for example, glucose as compared to oxygen deprivation during periods of ischemia is impossible.

To provide a coherent account of how the FGR phenotype may arise we first consider the development of the normal placenta before discussing the molecular and clinical pathologies.

### Early development of the placenta

Initial development of the placenta takes place within the superficial layer of the endometrium, and by the end of the third week postconception villi have formed over the entire chorionic sac. This precocious growth is supported and stimulated by secretions from the underlying endometrial glands (Figure 1),<sup>16,17</sup> so-called histotrophic nutrition. The carbohydrate- and lipid-rich secretions are delivered through openings in the developing basal plate into the intervillous space, from where they are taken up by the syncytiotrophoblast. As well as providing nutrients, the secretions contain numerous growth factors that stimulate placental cell proliferation

in vitro, and most likely play an important role in regulating development and differentiation in vivo.<sup>18-20</sup>

The absence of significant maternal blood flow at this stage means that initial development takes place in a low oxygen concentration, which is physiological and should not be considered hypoxic.<sup>21</sup> This environment is thought to protect the embryo from damaging reactive oxygen species (ROS) during the period of organogenesis, but may also serve to maintain stem cell potential.<sup>22</sup> Once the main organs have differentiated there is a need for a greater supply of oxygen to support faster fetal growth,<sup>23</sup> and hence there must be a switch from histotrophic nutrition to hemotrophic supply from the maternal circulation.

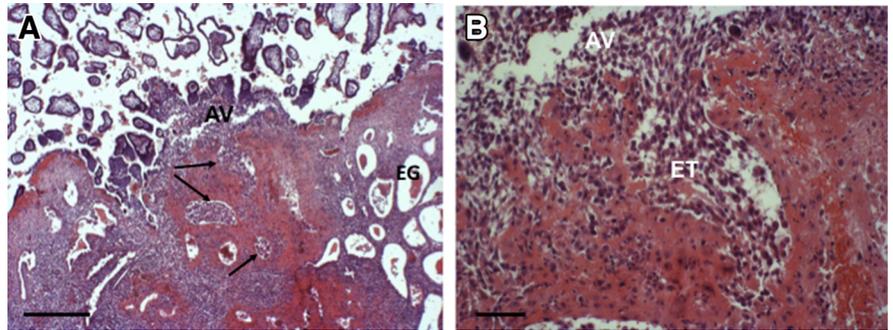
### Development of the uteroplacental circulation

The human hemochorial form of placentation poses major hemodynamic challenges. In particular, a high volume of maternal arterial blood flow has to be delivered to the placenta at a sufficiently low pressure and velocity to prevent mechanical damage to the delicate villous trees.<sup>24</sup> In normal pregnancies, the arcuate and radial arterial components of the uterine vasculature dilate under the combined effects of estrogen, progesterone, human chorionic gonadotropin, and other hormones and factors secreted by the placenta. The dilation accommodates the increased uterine flow of pregnancy, and is so marked that by around 20 weeks of gestation the diameter of the arcuate arteries is equal to that of the uterine artery.<sup>25</sup> The more distal elements of the uteroplacental vasculature undergo additional extensive remodeling under the influence of extravillous trophoblast cells that migrate out from the placenta during early pregnancy. This remodeling involves the loss of smooth muscle cells and elastin from the arterial walls, and their replacement by fibrinoid material.<sup>26</sup> As a result, these segments of the uteroplacental vasculature become inert flaccid conduits, incapable of vasoconstriction. The

extravillous trophoblast cells arise from the anchoring villi that are attached to the developing basal plate, and pass down the lumens of the spiral arteries as endovascular trophoblast, and through the decidual stroma as interstitial trophoblast. The migration of endovascular trophoblast is so extensive during the first trimester that the cells effectively plug the mouths of the spiral arteries, restricting flow to a slow seepage of plasma through a network of intercellular spaces (Figure 2).<sup>27,28</sup> The plugs begin to break down toward the end of the first trimester, and it is only after approximately 10 weeks of gestation that the maternal arterial circulation to the intervillous space is fully established, as confirmed by measurements of the rise in intraplacental oxygen concentration.<sup>29,30</sup> The interstitial trophoblast cells interact with the maternal immune system, in particular the uterine natural killer cells. Together, the extravillous trophoblast and natural killer cells are thought to release proteases and cytokines that stimulate dedifferentiation and loss of the smooth muscle cells within the arterial walls.<sup>31,32</sup> Thus, a degree of activation of the natural killer cells is necessary, and genetic studies have revealed that these immune interactions may regulate birthweight across the microsomic-macrosomic range.<sup>33</sup>

The arterial remodeling extends as far as the inner third of the myometrium, and so encompasses the hypercontractile segment of a spiral artery in the junctional zone. Consequently, there are 2 principal effects of the remodeling: firstly, dilation of the mouth of the artery reduces the velocity and pulsatility of the maternal inflow into the placental intervillous space, and secondly the loss of smooth muscle reduces the risk of spontaneous vasoconstriction.<sup>24</sup>

Remodeling of the spiral arteries extends into the second trimester, and possibly even longer. Ultrasound assessment of a cohort of 58 normotensive women revealed that blood flow from the mouths of the spiral arteries is pulsatile in all cases up to 20 weeks, and that pulsatility decreases thereafter with advancing gestational age.<sup>34</sup> By 34 weeks,

**FIGURE 2****Endovascular trophoblast plugs spiral arteries during early remodeling**

Photomicrograph of placenta in situ specimen (H673) at 8 weeks' gestational age showing endovascular trophoblast (ET) plugging of spiral artery. **A**, ET arise from anchoring villi (AV) that attach to basal plate, and can be seen virtually occluding lumen in 3 cross-sectional profiles of artery (arrows). Note deposition of fibrinoid material surrounding artery, characteristic feature of remodeling. Scale bar = 0.5 mm. **B**, Higher power view of mouth of spiral artery showing ET cells streaming into lumen from AV. Flow into intervillous space will be restricted to seepage through network of intercellular channels. Scale bar = 0.1 mm.

EG, endometrial gland.

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37% of women showed no pulsatile inflow into the placenta.

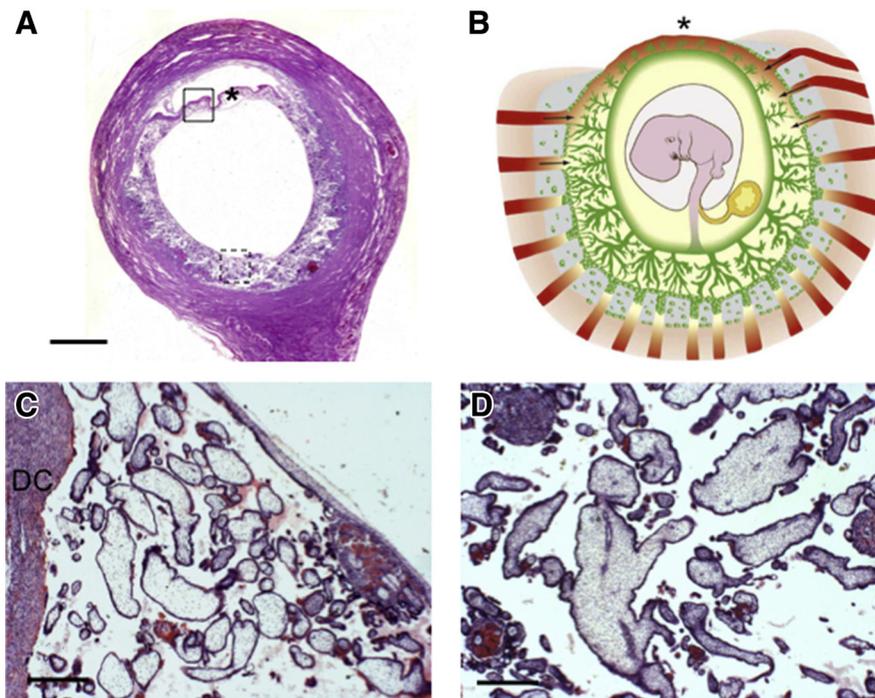
### Placental remodeling

The early or primitive placenta undergoes extensive remodeling toward the end of the first trimester. Regression of villi starts over the superficial pole of the gestational sac (Figure 3, A) and gradually extends until only those villi covering the deep pole in contact with the placental bed remain as the definitive discoid placenta. This profound remodeling raises questions regarding how and when the size and shape of the placental disc are determined, and whether further expansion and recruitment of spiral arteries can occur in later pregnancy under adverse conditions. The remodeling is associated with onset of the maternal circulation to the placenta, which starts most commonly in the peripheral regions and extends to the central zone over the next few weeks.<sup>35</sup> This pattern inversely reflects the degree of extravillous trophoblast invasion across the placental bed, which is greatest in the central region where it has been established the longest.<sup>36</sup> Hence, plugging of the arteries by endovascular

trophoblast is more extensive in the center than in the periphery. The early onset of blood flow in the periphery causes a locally high level of oxidative stress (Figure 3, B), which induces activation of the apoptotic cascade. Consequently, the villi regress, leaving only avascular, hypocellular ghosts that are incorporated into the smooth membranes (Figure 3, C and D).<sup>35</sup> At the same time, expression and activity of the principal antioxidant enzymes within the placenta increase,<sup>37</sup> and so villi in the central zone have greater defenses when the maternal blood flow reaches them.

The mature placenta is often described as discoid; however, there is considerable debate as to whether the majority are actually circular or ellipsoid. This may seem a rather academic point, but the risk of chronic disease in adult life has been associated with abnormal shape of the placenta through developmental programming of the major organ systems.<sup>38</sup> This phenomenon may reflect changes in placental function, for increased variability in shape has been linked to reduced placental efficiency as estimated by the ratio of fetal to placental

**FIGURE 3**  
**Formation of the definitive placenta and smooth membranes**



Placenta in situ specimen (H916) at 8.5 weeks' gestational age showing formation of chorion laeve. **A**, Regression of villi can be seen beginning over superficial pole of gestational sac (\*). Scale bar = 1 cm. **B**, Diagrammatic representation of how onset of maternal arterial circulation in periphery of placenta (arrows), where plugging of spiral arteries by extravillous trophoblast is least extensive, causes localized oxidative stress (\*). Stress induces apoptosis and regression of villi, giving rise to chorion laeve. **C**, Higher power view of area marked by solid-line box (**A**) over superficial pole of sac illustrating avascular villi with hypocellular stromal cores. **D**, Higher power view of area marked by dashed-line box (**A**) over central region display blood vessels, denser stromal core, and thick layer of trophoblast. **C** and **D**, Scale bars = 0.5 mm. **A**, reproduced<sup>35</sup> and **B**, modified.<sup>178</sup>

DC, decidua capsularis.

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weight.<sup>39,40</sup> Similarly, eccentricity of the point of insertion of the umbilical cord into the placenta has been linked to reduced efficiency,<sup>41</sup> acting possibly through hemodynamic effects in the fetoplacental circulation. We have speculated that excessive or asymmetrical regression of the villi due to aberrant onset of the maternal circulation may lead to abnormal placental shapes and cord insertions, and may reflect local variations in the extent of extravillous trophoblast invasion.<sup>22</sup> Support for this hypothesis comes from the strong correlation between the shape of the placenta at the end of the first trimester and at term.<sup>42</sup>

Clearly, events during the first trimester are of critical importance, and there is increasing evidence from ultrasound studies that both growth restriction and macrosomia of the placenta are initiated during this period.<sup>43</sup>

Given the regression of the peripheral villi that takes place, it is difficult to envisage how the placental footprint might extend further over the uterine surface during later pregnancy, and in so doing recruit additional spiral arteries. Rather, it seems more plausible that from 10-12 weeks onward the placenta and the uterine wall expand together.<sup>2,44</sup> It is possible that

more spiral arteries may be tapped within the placental bed during this process, and of course during normal pregnancies elaboration and remodeling of the villous trees will increase the functional capacity to meet fetal demands.<sup>45</sup>

### Deficient spiral artery remodeling

Deficiencies in extravillous trophoblast invasion and maternal arterial remodeling have been linked to the pathophysiology of the great obstetric syndromes, including growth restriction, through malperfusion of the placenta.<sup>46</sup> Studies have reported a gradient of effects, with absence of remodeling in the junctional zone and myometrial segment being associated with more severe growth restriction compounded with preeclampsia.<sup>46-50</sup> Aberrant remodeling of the more proximal radial arteries may also contribute to placental malperfusion in pathological pregnancies.<sup>51</sup> However, it must be recognized that remodeling is a continuum, and that examples of deficiently modified spiral arteries may be seen in normal pregnancies and vice versa.<sup>52</sup> In addition, histopathological reporting is generally not performed blinded to the clinical condition, knowledge of which may influence interpretation of the findings.<sup>53,54</sup>

Nonetheless, within the limitations that placental bed biopsies provide as an overview of the maternal blood supply to the placenta there is general agreement that deficient spiral artery remodeling is causal of the placental changes that predispose to FGR of maternal vascular origin.

There are many possible causes for deficient spiral artery remodeling, and the actual cause will undoubtedly differ from case to case. Inadequate histotrophic nutrition during the first few weeks of pregnancy<sup>15</sup> or excessive apoptosis within the placental bed<sup>55</sup> could lead to a reduced number of extravillous trophoblast cells. Other studies suggest interstitial trophoblast invasion is normal or even increased in cases of FGR, but that the cells fail to penetrate into the walls of the arteries.<sup>50</sup> The reason for this is not

known, but may possibly reflect abnormal interactions with the uterine natural killer cells, leading to excessive inhibition and diminished release of proteases.<sup>56</sup>

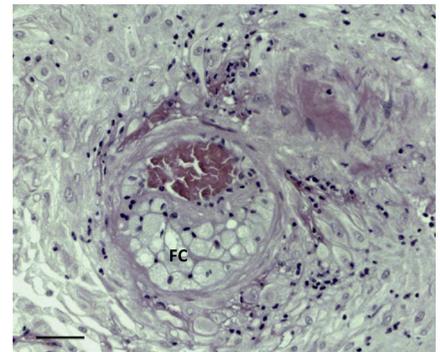
The consequences of deficient spiral arterial remodeling are multiple. Firstly, it will impact adversely on the velocity with which the maternal blood enters the placental intervillous space. Mathematical modeling has shown that the normal dilation reduces the velocity by an order of magnitude, from approximately 2-3 m/s<sup>-1</sup> to around 10 cm/s<sup>-1</sup>.<sup>24</sup> This reduction ensures even perfusion of the villous trees and adequate transit time for exchange. In pathological pregnancies inflow remains high velocity and pulsatile,<sup>34</sup> and causes mechanical damage to the placenta as will be discussed later. Secondly, retention of the vascular smooth muscle in the junctional zone is likely to cause greater intermittent perfusion of the placenta. Angiographic studies performed on the rhesus macaque, which has a similar uteroplacental circulation to the human, revealed that even in normal pregnancies blood flow from a spiral artery is intermittent.<sup>57</sup> This effect is independent of uterine contractions, and thought to be due to spontaneous vasoconstriction of the arteries involved. It might be expected, therefore, that the event will be more frequent in arteries where the junctional segment has not been remodeled, exposing the placenta to recurrent ischemia-reperfusion-type insults. Thirdly, deficient remodeling predisposes the spiral arteries to acute atherotic changes, with accumulation of foam cells and narrowing of the lumen (Figure 4). These changes are seen distal to the junctional segment, and may be induced by the high shear forces experienced or involvement in the ischemia-reperfusion insult, possibly compounded by dyslipidemia in the mother. Their effect will be to severely limit blood flow to the placenta, and so not surprisingly the lesion is associated with poor obstetric outcomes.<sup>46,58</sup>

Malperfusion of any organ is a powerful inducer of oxidative stress, and the placenta is no exception. Placental oxidative stress has been linked to

complications of pregnancy, including preeclampsia and FGR.<sup>59-61</sup> Oxidative stress is defined as a condition in which the generation of highly reactive species of oxygen overwhelms a cell's capacity to detoxify them, leading to indiscriminate damage to any biological molecules in the immediate vicinity, including proteins, lipids, and DNA. Consequently, cell function is impaired, and in the most severe cases cell death may be induced. ROS are generated physiologically as an inevitable by-product of aerobic respiration, protein folding, detoxification of drugs and xenobiotics by cytochrome P450, the response of nicotinamide adenine dinucleotide phosphate oxidase to growth factors and cytokines, and various other oxidoreductase and cyclooxygenase enzymes (Figure 5). The principal source under normal conditions is the mitochondria, for during passage of electrons along the complexes of the electron transport chain there is leakage on to molecular oxygen, particularly from complexes I and III.<sup>52</sup> The acquisition of an unpaired electron generates the superoxide free radical, and 2% of oxygen consumed during quiet respiration is converted to superoxide. This acts as a signaling intermediate, regulating the activity of redox-sensitive transcription factors to maintain metabolic homeostasis in accordance with the prevailing oxygen concentration. However, because of its potential harmful actions, excess superoxide is detoxified in the mitochondria by the enzyme superoxide dismutase through conversion to hydrogen peroxide. Being nonpolar, hydrogen peroxide can diffuse out from the mitochondria and is then further detoxified by the enzymes catalase and glutathione peroxidase within the cytoplasm (Figure 5).

Under normal conditions there is thus a homeostatic balance between generation and detoxification of ROS. However, generation of ROS is increased during hypoxia and ischemia-reperfusion, when buildup of electrons on the electron transport chain leads to a greater rate of leakage.<sup>63</sup> Thus, exposure of placental explants to cycles of hypoxia-reoxygenation is a powerful generator of oxidative stress, inducing

**FIGURE 4**  
**Atherotic changes in a spiral artery**



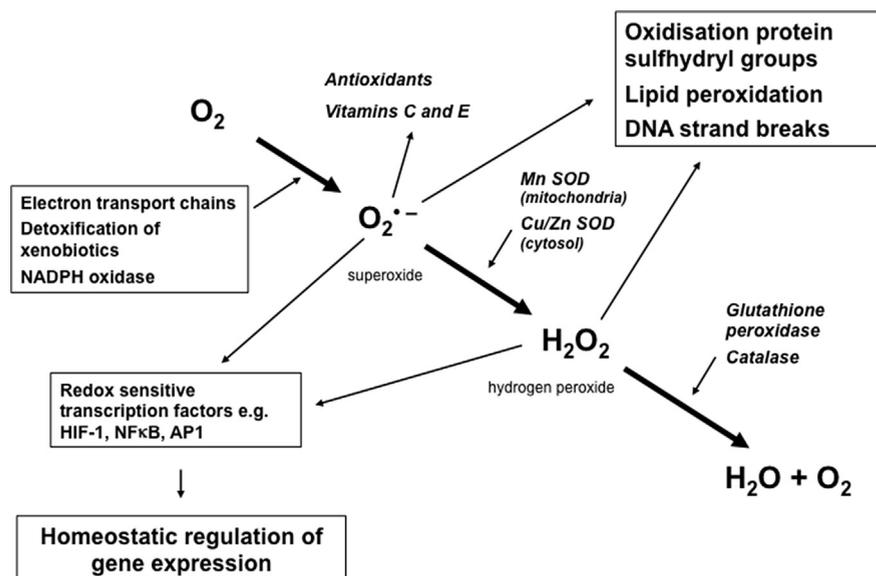
Photomicrograph of spiral artery within decidua from case of preeclampsia displaying acute atherosclerosis. Foam cells (FC) accumulate in wall of arteries, severely restricting caliber of lumen. Scale bar = 50  $\mu$ m.

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proinflammatory cytokines and even apoptosis.<sup>64-66</sup> Similar changes are seen in vivo when placentas are subjected to labor, for there is intermittent maternal perfusion of the intervillous space during uterine contractions.<sup>67</sup> The balance may also be perturbed if activity of the antioxidant enzymes is impaired. Transition metals, such as manganese, selenium, copper, and zinc, are required at the active site of these enzymes to shuttle electrons, and a dietary lack of micronutrients has been linked to complications of pregnancy.<sup>68</sup> Attempts to redress the balance by administration of antioxidant vitamins have yielded disappointing results.<sup>69</sup> One reason for this lack of success may be that oxidative stress rarely occurs in isolation, and is closely associated with other forms of cell stress, in particular endoplasmic reticulum (ER) stress. There are close physical and functional associations between mitochondria and the ER, mediated principally through calcium signaling, that integrate the 2 organelles (Figure 6).<sup>70</sup>

The ER is the organelle responsible for the synthesis, folding, and post-translational modification of all membrane-bound and secreted proteins. Because misfolded proteins are potentially toxic to cells, there is strict

**FIGURE 5**  
Intracellular generation, detoxification, and actions of reactive oxygen species



Schematic representation of cellular detoxification of reactive oxygen species (ROS). Superoxide anion ( $O_2^{\bullet-}$ ) is generated as by-product of aerobic respiration and various oxidoreductase enzymes, and acts at physiological levels as signaling intermediate to regulate transcription factors, such as hypoxia inducible factor (HIF), nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), and activator protein 1 (AP1). It can be scavenged by naturally occurring antioxidants, such as vitamins C and E, but also converted to hydrogen peroxide ( $H_2O_2$ ) by superoxide dismutase (SOD) enzymes copper/zinc (Cu/Zn) and manganese (Mn) SOD.  $H_2O_2$  is then detoxified by enzymes glutathione peroxidase and catalase. Excess levels of ROS can cause widespread damage to biomolecules, impairing cell function and leading to cell death.

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quality control within the ER comprising 3 evolutionary conserved signaling pathways collectively known as the unfolded protein response (UPR).<sup>71,72</sup> Regulation operates at various levels, but one of the most rapid and sensitive responses is to block nonessential protein synthesis to conserve resources and relieve the burden of nascent proteins on the ER folding machinery. This is achieved through phosphorylation of a key regulatory factor, the alpha subunit of eukaryotic initiation factor 2 (eIF2α), that limits assembly of ribosomal complexes on the messenger RNA (mRNA). Longer-term responses involve increasing the functional capacity of the ER by up-regulation of chaperone proteins and elaborating more cisternae to meet the synthetic and secretory demands of the cell.

Synthesis and secretion of proteins has to be closely linked to the metabolism of a cell, and regulated in relation to the supply of oxygen and nutrients. Hence, the alpha subunit of eukaryotic initiation factor 2 arm of the UPR controlling translation of mRNA can also be activated in response to hypoxia, amino acid deprivation, and other stressors.<sup>73-75</sup> In view of this wider involvement in cell homeostasis, the UPR is also referred to as the integrated stress response pathway.

### Placental molecular pathology in FGR Growth regulatory pathways

One of the principal features of the placenta in cases of FGR is the reduction in volume, surface area, and vascularization of the intermediate and terminal villi that mediate maternal-fetal

exchange.<sup>76-78</sup> This reduction appears to be due to excessive villous regression during placental remodeling, compounded by a slower rate of subsequent growth.<sup>79</sup>

In the case of the placenta, members of the insulin-like growth factor family are particularly important regulators of cell proliferation.<sup>80</sup> Their actions are integrated with oxygen and nutrient supply through the protein kinase B/mechanistic target of rapamycin (AKT/mTOR) signaling pathway, a central regulator of the translation of mRNA into protein. Activity in this pathway influences placental growth,<sup>81</sup> and is down-regulated in cases of growth restriction of maternal vascular origin (Figure 7).<sup>82,83</sup> Although this is often attributed to hypoxia secondary to deficient spiral artery conversion, no measurements have been performed in vivo to confirm placental, as opposed to fetal, hypoxia. One situation where there is no doubt the placental tissues are exposed to a low maternal arterial oxygen concentration is during pregnancy at high altitude. It is notable that a similar reduction in mTOR activity is seen in placentas from pregnancies at 3100 m, where it is accompanied by a reduction in placental villous volume and birthweight.<sup>84</sup> The changes can be mimicked by exposing placental cell lines to hypoxia in vitro, when there is a reduction in the proliferation rate commensurate with the metabolic activity of the cell type.<sup>84</sup>

The AKT/mTOR pathway also regulates expression and activity of placental transporters that are responsible for transfer of amino acids, fatty acids, and glucose. Many of these transporters are down-regulated in growth restriction,<sup>85-88</sup> which will compound the loss of functional capacity of the placenta caused by the reduction in villous surface area. Down-regulation precedes the growth restriction in response to maternal undernutrition in animal models,<sup>89</sup> suggesting that it is causal of the condition and not a response.

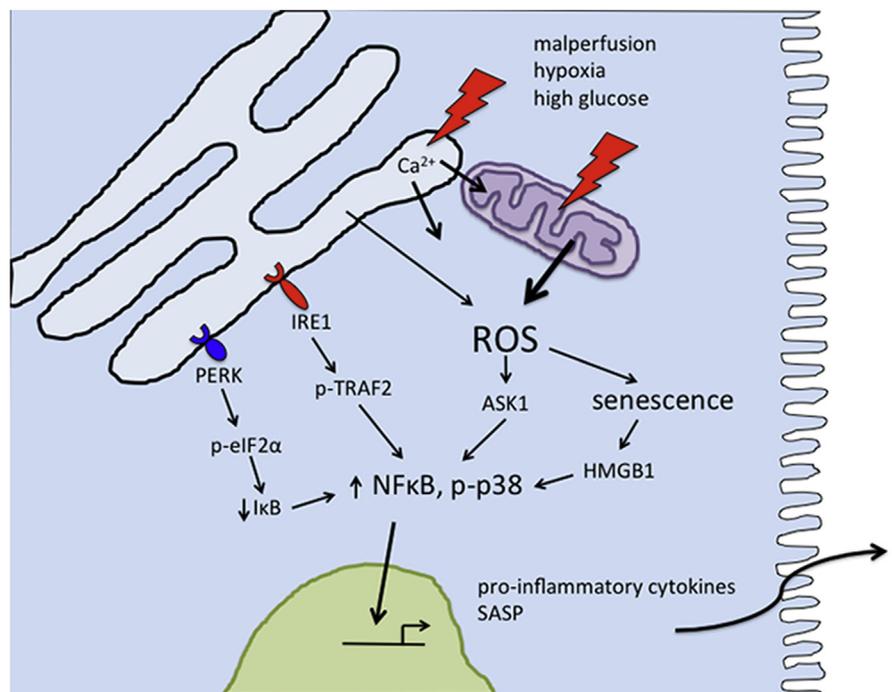
### Stress response pathways

Given the high endocrine output of the placenta, the syncytiotrophoblast contains large quantities of ER.

Activation of the UPR pathways is seen in placentas from high-altitude pregnancies, where it can be viewed as a homeostatic response to match fetoplacental growth to oxygen availability. More severe activation is seen in cases of growth restriction caused by maternal vascular compromise,<sup>83,84</sup> and the degree of activation, both in terms of individual pathways and the number of the pathways involved, is greatest in cases of growth restriction accompanied by preeclampsia. This finding is consistent with the placentas being exposed to a more severe maternal vascular insult due to the greater deficiency in spiral artery remodeling described earlier.<sup>83</sup>

The difference in the degree of activation may have pathophysiological significance, for high levels of activation of the UPR are associated with stimulation of the release of proinflammatory cytokines, cell senescence, and even apoptosis (Figure 6).<sup>90,91</sup> The nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway can be stimulated either through the inositol-requiring enzyme 1/tumor necrosis factor receptor-associated factor 2 (IRE1/TRAF2) pathway,<sup>90,92</sup> or more simply through suppression of protein synthesis. The half-life of the inhibitor of kappa B (IκB) subunit is shorter than that of NFκB, and so prolonged translational arrest will inevitably lead to an inflammatory response.<sup>93</sup> Proinflammatory cytokines and apoptotic debris have all been implicated in causing the maternal endothelial cell activation that characterizes preeclampsia, and hence, the higher level of activation of the UPR may explain the distinction between FGR alone and FGR associated with preeclampsia (Figure 7). For example, shedding of proinflammatory microparticles from the syncytiotrophoblast is seen in preeclampsia but not in FGR alone.<sup>94</sup> Exactly when the stress begins during pregnancy is difficult to determine, but we speculate that it originates around the time of onset of the maternal circulation to the placenta toward the end of the first trimester.<sup>15</sup> Perturbation of ER function could also account for the change in glycosylation seen in the

**FIGURE 6**  
Interactions between mitochondria and the ER mediated by calcium signaling



Interactions between mitochondria and endoplasmic reticulum (ER). Mitochondrial and ER membranes are closely approximated at punctate sites rich in calcium transporters and ion channels. Calcium signaling integrates functional activity of these 2 organelles, so that both contribute to increased production of reactive oxygen species (ROS) during malperfusion. ROS can stimulate secretion of pro-inflammatory cytokines and adoption of senescent-associated secretory phenotype (SASP) through activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and p38 mitogen-activated protein kinases (p-p38), via apoptosis signal-regulating kinase 1 (ASK1) and high mobility group box 1 (HMGB1) protein. High levels of activation of UPR pathways inositol-requiring enzyme 1 (IRE1) and protein kinase RNA-like endoplasmic reticulum kinase (PERK) also activate NFκB and p38 through the TNF Receptor Associated Factor 2 (TRAF2) and eukaryotic initiation factor 2 (eIF2α) respectively. Suppression of protein translation by activation of eIF2α leads to reduction of the inhibitory sub-unit of kappa B (IκB) due to its short half-life. Reproduced with permission from<sup>179</sup>.

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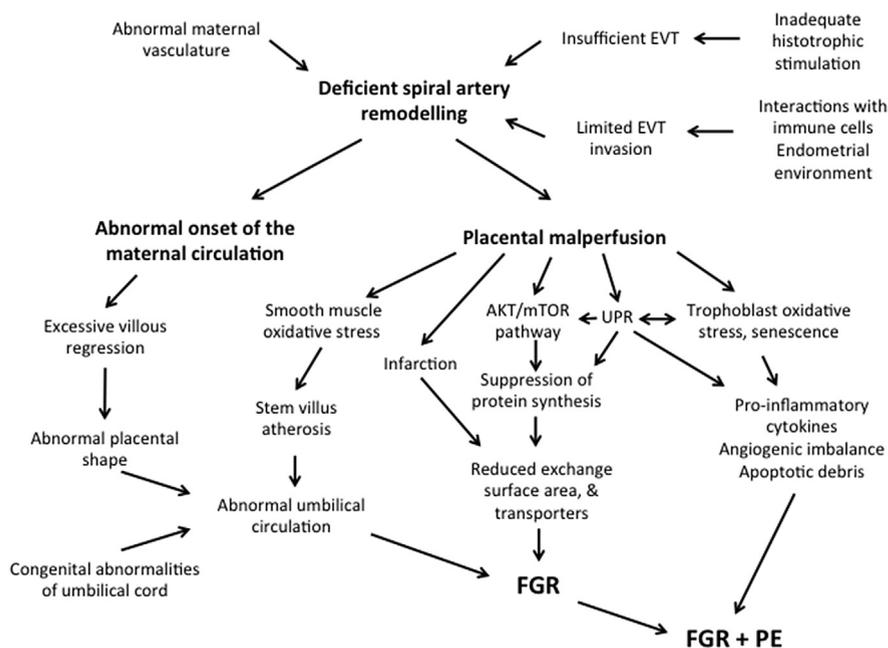
syncytiotrophoblast of the FGR placenta.<sup>95</sup>

### Transcriptomic changes

Changes in gene expression have been reported for the growth-restricted placenta employing microarray technology,<sup>96,97</sup> but in general it has yet to be determined whether the changes are responsive to, or causal of, the growth disorder. Imprinted genes that are expressed in a parent-of-origin fashion play a key role in the regulation of placental growth, and so have been the

subject of particular attention. It is notable that pleckstrin homology like domain family A member 2 (*PHLDA2*) that inhibits growth, and mesoderm specific transcript (*MEST*) that promotes growth, are up-regulated and down-regulated, respectively, in FGR.<sup>98,99</sup> However, no correlation was found between the level of gene expression and loss of imprinting, suggesting that disorders of imprinting per se are not causal of the condition. Indeed, these studies also found widespread changes in nonimprinted genes

**FIGURE 7**  
**Pathways that may lead to placental-related FGR, and FGR with preeclampsia**



Schematic representation of possible pathways leading to placental-related fetal growth restriction (FGR) alone or FGR complicated by preeclampsia (PE). See text for details.

EVT, extravillous trophoblast; UPR, unfolded protein response.

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involved in endocrine signaling, tissue growth, immune modulation, oxidative metabolism, vascular function, and metabolite transport.<sup>98</sup> A more recent comprehensive transcriptome-wide profiling of normal and growth-restricted placentas using next-generation sequencing revealed 5 network modules enriched for similar processes, including cellular respiration, amino acid transport, hormone signaling, histone modifications, and gene expression, that were associated with birthweight.<sup>100</sup> Furthermore, the hub genes for each module were significantly associated with growth restriction, and so these networks may play an important role in regulating placental function in these pathological cases.

These changes may reflect differences in gene transcription, but could also potentially arise through epigenetic changes involving microRNAs (miRs). Noncoding RNAs can bind to mRNA, regulating its stability and hence the

transcript level. They can also influence translation of the mRNA and so the level of the encoded protein. It has been reported that 97 miRs are up-regulated and 44 down-regulated in small-for-gestational-age (SGA) as compared to appropriate-for-gestational-age placentas.<sup>101</sup> Functional studies of *miR-10b*, *-363*, and *-149*, which were either significantly increased or tended to increase in the growth-restricted placentas, in a trophoblast-like cell line showed that these have a negative impact on their target genes that encode angiogenic factors and amino acid transporters. When trophoblast-like cells were exposed to nutrient restriction, *miRs-10b* and *-149* increased whereas *miR-363* decreased, suggesting that they respond to multiple cues or that different cell types within the placenta respond in different ways during growth restriction.

Placental-specific mRNAs and miRs thought to be derived from the

syncytiotrophoblast can be detected in the peripheral maternal blood, opening the possibility of their use as diagnostic biomarkers of placental dysfunction.<sup>97,102</sup>

### Placental metabolism

Data on placental metabolism in cases of growth restriction are conflicting. Placental mitochondrial content has been reported to be both increased<sup>103</sup> and decreased<sup>104</sup> based on assays of mitochondrial DNA content.<sup>105</sup> These findings have been correlated with the oxygen content in the umbilical vein. By contrast, we observed no difference in mitochondrial content in the high-altitude placenta as determined by the level of citrate synthase.<sup>106</sup> There was, however, a significant reduction in the protein, but not mRNA level, of the complexes of the electron transport chain, suggesting again a block to protein translation and a reduction in mitochondrial activity. It might be expected, therefore, that placental metabolism becomes more dependent on glycolysis, but there appears to be no change in glycogen content in the growth-restricted placenta.<sup>107</sup>

Autophagy-related proteins are regulated by UPR pathways,<sup>108</sup> and have been reported to be increased in FGR placentas where they may reflect excessive levels of organelle stress and recycling, or severe nutrient depletion.<sup>109</sup> Increased autophagy has also been observed in the placental territory of monozygotic twins with selective FGR, where it was inversely proportional to the umbilical blood flow.<sup>110</sup>

### The fetoplacental circulation

Reduced placental surface area and transport are important contributors to placental function and hence FGR, but another important factor is the resistance within the umbilical circulation. The absence or even reversal of end-diastolic flow in cases of severe growth restriction as assessed by Doppler ultrasonography will greatly impair the transport of nutrients to the fetus. These findings are not surprisingly associated with fetal hypoxia. Pathological changes have been reported in the resistance arteries within the stem villi

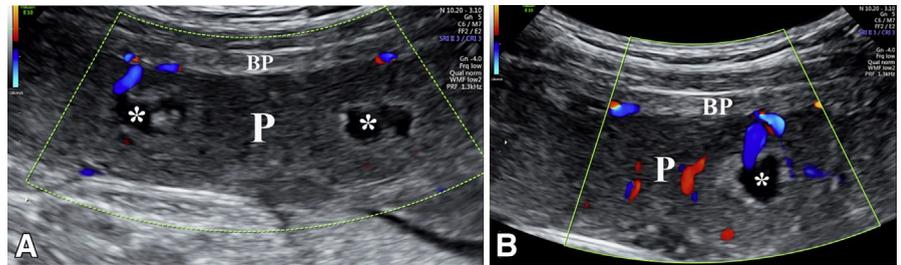
of growth-restricted placentas,<sup>111-113</sup> but the molecular mechanism underlying them has only recently been elucidated. The smooth muscle cells surrounding these arteries express the enzyme cystathionine- $\gamma$ -lyase that synthesizes hydrogen sulfide, a powerful vasodilator of the fetal placental vasculature that maintains vascular smooth muscle cells in their differentiated state.<sup>114</sup> This enzyme is reduced at the mRNA and protein levels in placentas associated with absent or reversed end-diastolic flow, and this finding is associated with dedifferentiation of the smooth muscle cells, the adoption of a synthetic phenotype, and a reduction in the lumen-to-wall ratio.<sup>115</sup> These changes can be induced by exposing explants of stem villous arteries to hypoxia-reoxygenation, indicating that the in vivo findings are likely secondary to the oxidative stress caused by the placental malperfusion. The severity of the changes correlates with the birth-weight, indicating that they may act as an important component of the placental dysfunction in growth restriction (Figure 7).

### Clinical placentology in FGR

Many, if not all, placental abnormalities have been found in association with FGR, but the results of most histopathological studies are hampered by a number of methodological factors. Most studies are retrospective based on case-series rather than case-control data and many have used different clinical definitions of FGR, mixing cases of fetuses constitutionally small (SGA) and/or born prematurely following inaccurate gestational dating or unknown gestational age (low birth-weight). Specific placental lesions have rarely formed the primary topic of investigation, more often being considered as a coincidental finding or one of several potential causes of FGR. In addition to these selection biases, confounding factors such as maternal smoking and methodologic disparities, such as the location and number of samples taken for histopathologic examination, make it difficult to evaluate the data from many studies, in particular from those early histopathologic studies performed before

**FIGURE 8**

### Ultrasound visualisation of placental lesions in FGR



Transabdominal color Doppler mapping of placenta (P) in pregnancy at 36 weeks complicated by fetal growth restriction and presenting with multiple cystic lesions (\*) corresponding to intervillous thrombosis on histopathology. **A**, Increased echogenicity in periphery of lesions due to degenerative villous tissue embedded in fibrin deposits. **B**, Uteroplacental blood arterial supply to lesion from basal plate (BP). Video clips of same lesions showing pulsatile flow from uteroplacental artery.

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routine ultrasound became available and at a time when laboratory investigations were limited.

Overall, placental lesions associated with FGR have been divided by pathologists into different categories: vascular and nonvascular, macroscopic and microscopic, congenital and acquired or secondary abnormalities.<sup>116-118</sup> The classification below is based on pathologist standardized diagnostic criteria for each individual lesion and highlights those lesions that can be diagnosed prenatally with ultrasound imaging.

### Abnormalities of placentation

Abnormal placental shapes, in particular those with irregular outlines (extrachorionic and bilobate placenta) have been associated with poor obstetric outcome, in particular poor fetal growth.<sup>119,120</sup> These anomalies are difficult to diagnose in utero by ultrasound scanning and are not routinely investigated in pregnancies complicated by FGR.

Placental location is an important factor; for example, cases of lateral placentation are more likely to be associated with FGR. A case-control study of precisely dated singleton pregnancies found that those complicated by FGR are nearly 4-fold more likely to have had a lateral placentation (odds ratio [OR], 3.8; 95% confidence interval [CI], 1.3–11.2) at 16–20 weeks, compared with anterior or posterior

placentation.<sup>121</sup> A population-based, retrospective cohort study of 544,734 singleton live births, including 2744 placenta previa found, after controlling for maternal factors including smoking and gestational age, that previa placentation is associated with a 3.7% rate of FGR (OR, 1.24; 95% CI, 1.17–1.32) at birth, independently of the 12% rate of preterm delivery.<sup>122</sup> By contrast, a retrospective cohort study of 59,149 women with singleton pregnancies undergoing ultrasound between 15–22 weeks found no difference in the incidence of FGR after adjusting for confounding factors (adjusted OR, 1.1; 95% CI, 0.9–1.5) in the 724 women presenting with placenta previa.<sup>123</sup> The pathophysiology of FGR in cases of abnormal placentation is unknown, but one can hypothesize the underdevelopment of the uteroplacental circulation and, in particular, the recruitment of spiral arteries into the final placenta is influenced by the density of the uterine terminal vascular network where the blastocyst implants. There are no clinical data on placental weight and volume to support this hypothesis.

### Macroscopic vascular anomalies

Deficient remodeling of the spiral arteries is associated with greater pulsatility of the jets of maternal blood in SGA pregnancies, as expected.<sup>34</sup> More severe vasculopathies of the arteries are associated with a combination of secondary

**TABLE 1****Pathophysiology and prenatal diagnosis of placental macroscopic vascular anomalies found in cases of fetal growth restriction**

Type of anomaly	Pathophysiology	Prenatal ultrasound imaging
Intervillous thrombosis	Focal coagulation of maternal blood inside intervillous space	Echogenic cystic lesions or hypoechoic areas on ultrasound <sup>124,130,131</sup>
Breus' mole	Massive subchorial thrombosis involving at least 50% of chorionic plate	Large echogenic lesions under fetal placental plate <sup>124,130,131</sup>
Infarcts	Villous necrosis due to obstruction of uteroplacental artery	Complex echogenic intraplacental masses close to basal plate <sup>133-138</sup>
Maternal floor infarction in size	Lesion combining parbasal villous necrosis, fibrin deposition, thrombosis, and hematoma	Diffuse hyperechogenic lesions increasing with advancing gestation <sup>134,143,144</sup>

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placental macroscopic lesions including intervillous and parbasal thrombi, hematomas, infarcts, and extensive fibrin deposition (Figure 8).<sup>116,117</sup> Placental thromboses and infarcts are the most commonly found lesions in pregnancies complicated by FGR with or without preeclampsia and both have been reported on ultrasound examinations (Table 1).<sup>124</sup>

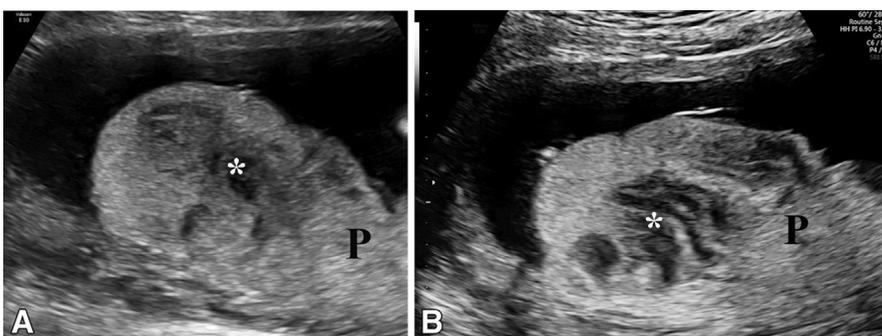
Placental thromboses are the consequence of focal coagulation of maternal

blood inside the intervillous space,<sup>124,125</sup> and are found mainly in areas of lower villous density such as under the fetal or chorionic plate, in the placental marginal areas, and in the center of cotyledons.<sup>116,117</sup> Isolated small thromboses are of no clinical significance and are commonly found in the placenta of uncomplicated pregnancies. Massive subchorial thromboses, also called “Breus’ mole,” have been reported in pregnancies complicated by FGR and

stillbirth.<sup>116,125-129</sup> A series of 14 cases found that subchorial thrombosis involving  $\geq 50\%$  of the chorionic or fetal plate is associated with a 70% incidence of FGR in those pregnancies that continue  $>24$  weeks of gestation.<sup>128</sup> The development of an intervillous thrombosis is often associated with fibrin deposition and these lesions are often described as echogenic cystic lesions or hypoechoic areas on ultrasound.<sup>124,130,131</sup> The ultrasound features, ie, echogenicity of an intervillous thrombosis will change with advancing gestation as more and more fibrin deposition will appear in its periphery and depending on when, or if, the maternal blood clots in its center (Figure 8, Videos). Large thromboses have been diagnosed prenatally on MRI.<sup>132</sup>

Placental infarcts are due to the complete obstruction of uteroplacental arteries leading to interruption of the maternal blood flow and progressive necrosis of the villous tissue, including its fetal circulation of the corresponding cotyledon(s).<sup>116,117,124</sup> Isolated small infarcts can be found in uncomplicated pregnancies but larger infarcts often associated with intervillous thromboses and extensive fibrin deposition are found in most pregnancies complicated by preeclampsia and FGR. These lesions appear as complex echogenic intraplacental masses close to the basal plate on ultrasound imaging<sup>133-138</sup> and have also been identified recently on MRI in pregnancies complicated by uteroplacental insufficiency and FGR.<sup>139,140</sup>

Maternal floor infarction is an extended lesion combining parbasal villous necrosis, fibrin deposition, thrombosis, and hematoma that is associated with a high risk of severe FGR and stillbirth.<sup>116,117,141</sup> The disorder is somewhat misnamed, because it is mainly characterized by heavy deposition of fibrin in the decidua beneath the placenta rather than by arterial occlusion and ischemic necrosis of the villi.<sup>142</sup> The fibrin deposits in floor infarcts often extend into the intervillous space, where they envelop villi, causing them to become atrophic. Similarly, massive fibrin depositions, in particular if involving  $>50\%$  of the

**FIGURE 9**  
**Ultrasound**

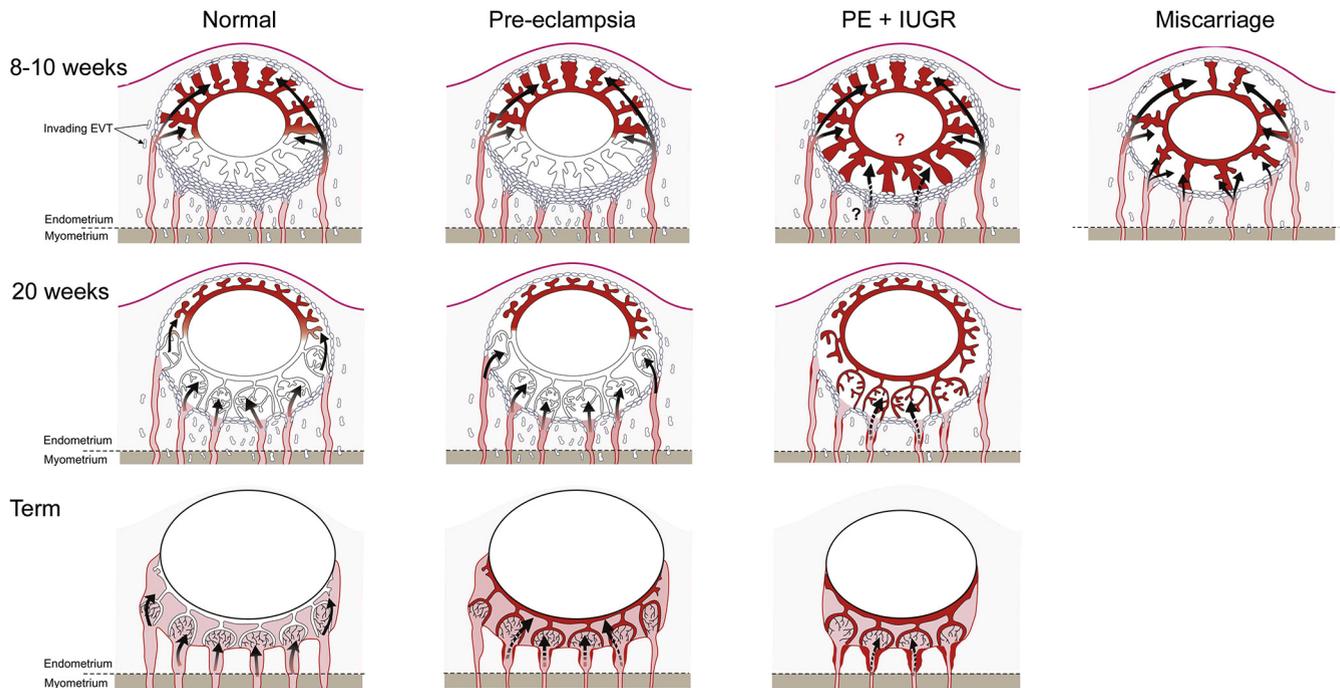
Transabdominal ultrasound longitudinal view of jellylike placenta (P) at **A**, 18 and **B**, 19 weeks in pregnancy complicated by very early-onset fetal growth restriction. P base is very narrow and most of P mass contains areas of patchy decrease in echogenicity (\*). Video clip of same P at 23 weeks showing increased thickness and patchy decrease in echogenicity secondary to fetal plate being pushed up by jetlike blood streams from spiral arteries. Massive subchorial thrombosis involving  $>70\%$  of chorionic plate, extended fibrin deposition, intervillous thrombosis, and villous infarcts were found at birth at 34 weeks.

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FIGURE 11

## Schematic of spectrum of pregnancy complications arising from deficient trophoblast invasion



Proposed relationship among degree of oxidative stress and placental development in normal pregnancies, late-onset preeclampsia (PE), early-onset PE, and miscarriage. In normal pregnancies onset of maternal circulation in periphery causes local oxidative stress, villous regression, and formation of chorion laeve. In miscarriage extravillous trophoblast (EVT) is severely deficient, leading to incomplete plugging of spiral arteries, premature and disorganized onset of blood flow, and overwhelming oxidative stress. Situation is intermediate in PE, being more severe in early-onset form of syndrome associated with fetal growth restriction (FGR). Reproduced.<sup>173</sup>

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thickening of the villous trophoblastic basal membrane.<sup>152-154</sup> This highlights the fact that the placental lesions associated with increased resistance to flow in the umbilical arterial circulation in FGR are complex and involve the entire anatomy of the villous structure, not only its terminal vasculature.

Atherosclerosis of the spiral arteries is characterized by fibrinoid necrosis of the arterial wall, subendothelial lipid-filled foam cells, and perivascular lymphocytic infiltration (Figure 4). It is histologically similar to early-stage atherosclerosis and is a common microscopic feature of preeclampsia, FGR, fetal death, and spontaneous preterm labor with intact or ruptured membranes.<sup>46,58</sup> Failure of spiral artery remodeling in the placental basal plate is associated with increased frequency of decidual artery atherosclerosis, interstitial

extravillous trophoblast, and arterial endothelial activation.<sup>46</sup> Decidual atherosclerosis is the main cause of maternal underperfusion of the intervillous space leading to fibrin deposition, thrombosis, and villous infarcts. Small lesions appear to occur at points of localized stasis at the basal plate and are probably pathological markers of more generalized disturbances in placental circulation or of hypercoagulability in the intervillous space,<sup>155</sup> leading progressively to the macroscopic vascular lesions described previously. Obstructive lesions in the myometrial segment of spiral bed arteries have been found in 70% of the FGR cases associated with preeclampsia.<sup>46</sup>

Noninfectious villitis, also called villitis of unknown etiology (VUE), has been described as a pattern of placental injury occurring predominantly in

term placentas.<sup>156</sup> High-grade lesions, affecting >10 villi per focus, have been found in fetuses presenting with FGR.<sup>156,157</sup> Their histologic characteristics are distinct from infectious villitis and thought to be caused by maternal T-lymphocytes, predominantly CD8<sup>+</sup>, that inappropriately gain access to the villous stroma.<sup>156</sup> VUE is found in 5-15% of placenta in uncomplicated pregnancies,<sup>156,157</sup> 15-100% of placenta from pregnancies complicated by FGR,<sup>158-160</sup> and 20% of placenta in pregnancies presenting with FGR and preeclampsia.<sup>161</sup> A systematic review including 12 studies focusing on placental pathologies associated with intrauterine growth restriction found significant heterogeneity in study design, which can explain the wide range in incidence of VUE in FGR placentas.<sup>157</sup> It is not known if these

lesions are the primary cause of FGR or secondary to mechanical damage to the villous surface caused by the aberrant hemodynamics (ischemia-reperfusion) of the maternal circulation in the intervillous space,<sup>24</sup> or oxidative stress and the corresponding metabolic and morphological alteration of the villous trophoblastic layer.

### Umbilical cord anomalies

FGR has been associated with abnormalities of the umbilical cord insertion, ie: eccentric, marginal, or velamentous.<sup>119,162</sup> These anomalies are rare and often associated with abnormalities of the placental shape. Thus, there are no data supporting a direct link between the location of the umbilical cord insertion and poor fetal growth.

The absence of 1 of the 2 normal umbilical arteries or single umbilical artery (SUA) cord is one of the most common congenital fetal malformations with an incidence of approximately 1% of all deliveries (Figure 10).<sup>163,164</sup> SUA occurs 3-4 times more frequently in twins, and almost invariably accompanies the acardia malformation and sirenomelia of caudal regression syndrome.<sup>163-165</sup> Most cases of SUA are part of fetal syndromes with major anatomical defects that are largely responsible for the poor perinatal outcomes. The incidence of FGR is significantly elevated among fetuses with SUA and may develop without any other congenital anomalies in around 15 of the cases.<sup>163,164,166-169</sup> A population-based, retrospective cohort study of 37,500 singleton pregnancies including 223 SUA diagnosed at birth found a higher incidence of birthweight <10th percentile (OR, 2.1; CI, 1.44–2.93) in isolated SUA.<sup>166</sup> A retrospective case-control series of 136 SUA diagnosed at second-trimester ultrasound reported isolated SUA to be an independent risk factor for FGR (adjusted OR, 11.3; 95% CI, 4.8–25.6) compared to normal 3-vessel cord.<sup>167</sup> Two recent systematic reviews reported OR ranging between 1.6 (95% CI, 0.97–2.6)<sup>170</sup> and 2.75 (95% CI, 1.97–3.83)<sup>171</sup> for SGA in isolated SUA

compared to normal cord. The use of color Doppler imaging has made the diagnosis of SUA accurate in early pregnancy,<sup>172</sup> but its detection at the first-trimester (Figure 10) or routine midpregnancy ultrasound has been mainly as part of the fetal aneuploidy screening. There is a need for a prospective case-control study on the impact on fetal growth of isolated SUA diagnosed in the first half of pregnancy.

### Conclusion

The placental changes seen in cases of FGR of noninfective and nongenetic origin form part of a spectrum of pathology associated with different degrees of deficient remodeling of the uterine spiral arteries.<sup>46,173</sup> Deficient remodeling results in maternal blood entering the placental intervillous space in jetlike streams that carve large channels and lakes within the villous trees. The high velocity, uneven and, most likely, intermittent perfusion of the placenta causes oxidative stress and activation of the UPR pathways, suppressing placental growth and compromising its endocrine and transport functions. We speculate that the pathophysiology starts toward the end of the first trimester, at the time of onset of the maternal circulation. Remodeling of the arteries and onset are linked through the endovascular trophoblast that initially plug the vessels; a deficiency in one is likely to be associated with abnormalities in the other.<sup>15</sup> When endovascular trophoblast is particularly poorly developed, onset of the maternal circulation is premature and disorganized spatially, not following the periphery to center progression seen in normal pregnancies.<sup>35,174</sup> There is overwhelming oxidative stress throughout the placental tissues, leading to widespread degeneration of the trophoblast and to miscarriage (Figure 11).<sup>175</sup> We speculate that less severe deficiencies in arterial remodeling result in ongoing pregnancies with differing degrees of compromise as discussed earlier. At one extreme will be early-onset FGR with preeclampsia where there is excessive villous regression and extensive infarction due to secondary atherotic changes, through FGR alone to

late-onset preeclampsia at the opposite extreme where there appears to be minimal placental involvement.<sup>173,176</sup>

Considering these complications of pregnancy, and others such as preterm delivery and premature rupture of the membranes,<sup>15,46</sup> as a spectrum caused by poor placentation, highlights 2 main conclusions. Firstly, there is an urgent need for more research into maternal-fetal interactions during the earliest phases of pregnancy, to understand not just the pathophysiology of FGR but this array of disorders as a whole. Secondly, clinical care should be focused just as much on the preconceptional and periconceptional periods as in later pregnancy to ensure that when the conceptus implants it does so into an endometrium that is in the healthiest state possible. ■

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# Is there a role for placental senescence in the genesis of obstetric complications and fetal growth restriction?



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The placenta ages as pregnancy advances, yet its continued function is required for a successful pregnancy outcome. Placental aging is a physiological phenomenon; however, there are some placentas that show signs of aging earlier than others. Premature placental senescence and aging are implicated in a number of adverse pregnancy outcomes, including fetal growth restriction, preeclampsia, spontaneous preterm birth, and intrauterine fetal death. Here we discuss cellular senescence, a state of terminal proliferation arrest, and how senescence is regulated. We also explore the role of physiological placental senescence and how aberrant placental senescence alters placental function, contributing to the pathophysiology of fetal growth restriction, preeclampsia, spontaneous preterm labor/birth, and unexplained fetal death.

**Key words:** aging, cellular senescence, cyclin-dependent kinase, DNA damage, fetal death, fetal growth restriction, mammalian target of rapamycin complex, membrane rupture, mitogen-activated protein kinase, oxidative stress, phosphoinositide 3-kinase, placental aging, preeclampsia, preterm birth, preterm labor, reactive oxygen species, senescence-associated heterochromatin foci, small for gestational age, stillbirth, telomere, tumor suppressor protein p53, p16, senescence-associated beta-galactosidase, senescence-associated secretory phenotype

## Cellular senescence and aging

A key feature of aging is a progressive loss of function at the cellular, tissue, and organ level, resulting in a reduced

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adaptability to stress and an increased vulnerability to disease and mortality.<sup>1</sup> In mitotic tissues, the progressive accumulation of senescent cells is thought to be one of the causal factors for aging.<sup>2</sup> Thus, the biomarkers of cellular senescence can be used as markers of tissue aging. Such biomarkers of cellular senescence have been summarized in a later section (see *Biomarkers of senescence*).

Senescent cells within tissues contribute to the aging process and disease development by altering normal cellular function, changing the behavior of neighboring cells, degrading structural components such as the extracellular matrix, and accelerating the loss of tissue regeneration capacity by reducing stem and progenitor cells.<sup>2</sup> Elimination of senescent cells can delay aging-associated disorders in mice.<sup>3</sup>

Cellular senescence is a state of irreversible, terminal arrest of cell proliferation (growth), triggered by a plethora of intrinsic and extrinsic stimuli or

stressors. These stimuli or stressors include short or dysfunctional telomeres, DNA damage (telomeric or genomic DNA), and DNA damage-response mediators, strong mitogenic signals (eg, overexpression of oncogenic renin-angiotensin system [RAS], a mutant RAS-p21 protein, renin-angiotensin system involves transmitting signals and activating signaling cascades, including mitogen-activated protein kinase [MAPK] and phosphoinositide 3-kinase/mammalian target of rapamycin complex pathways), epigenomic disruption (chromatin disruption), overexpression of certain oncogenes, deteriorating mitochondrial function, and oxidative stress created by reactive oxygen species (ROS) (reviewed in references 4-6) (Figure 1).

The stressors that trigger senescence act by 2 major pathways controlled through stabilization of the tumor suppressor protein p53 and transcriptional inactivation of the cyclin-dependent kinases (CDKs). The suppression of CDKs is produced by transcriptional activation of the CDK inhibitor p21 (also termed p21<sup>Cip1</sup>) in concert with the CDK inhibitor, p16 (also known as p16<sup>INK4a</sup>) and retinoblastoma tumor suppressor protein (pRB) (reviewed in references 7 and 8) (Figure 1).

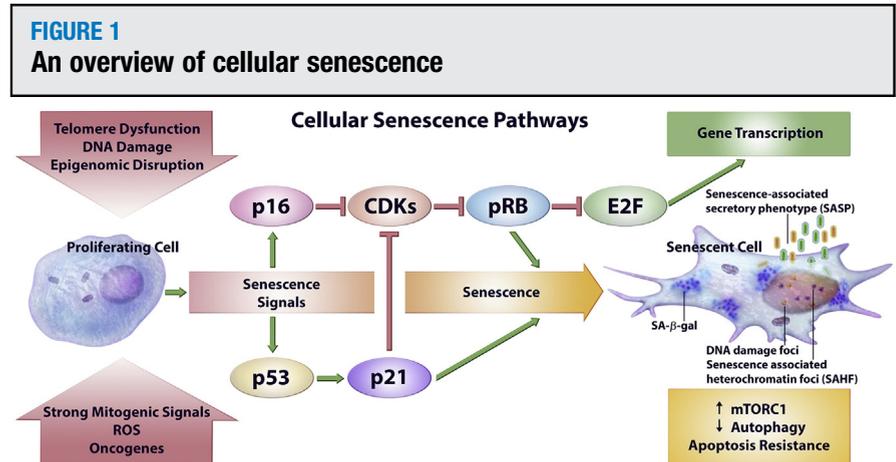
When activated, p53 inhibits cell proliferation via activation of its transcriptional target p21.<sup>8</sup> Both p21 and p16 maintain the protein pRB in its hypophosphorylated and active state.<sup>8,9</sup> Active pRB suppresses the E2F1 (a member of E2F family of transcription factors, which induce gene transcriptions that are essential for cell proliferation)-dependent expression of genes that regulate progression of the G1/S phase of the cell cycle, and thereby irreversibly blocks cell cycle entry<sup>10</sup> (see Panel 1 for cell cycle).

Silencing of E2F target genes is mediated by pRB-dependent reorganization of chromatin into distinct heterochromatin structures that accumulate in the nucleus of senescent cells termed senescence-associated heterochromatin foci (SAHF).<sup>9</sup>

Interestingly, a senescent cell can re-enter the cell cycle following inhibition of p53 if the cell senescence occurred because of activation of the p53-p21 pathway; however, cells that senesce solely via the p16-pRB pathway are unable to resume proliferation, even after the inhibition of p53, pRB, or p16.<sup>11</sup>

**Causes of cellular senescence.** A critically short telomere is thought to be one factor initiating cellular senescence. Telomeres are highly conserved repetitive DNA regions, consist of tandem arrays of the hexanucleotide sequence TTAGGG in the human, which is typically 10–15 kb long,<sup>12</sup> located at the end of linear chromosomes, and are essential for chromosomal stability and cell survival.<sup>13,14</sup>

Telomeres protect DNA ends from double-strand breaks, end-to-end fusion, and degradation by forming a protective cap with a guanine-rich single-stranded telomere overhang and telomere-binding protein complexes.<sup>15,16</sup> Because of an inability to replicate telomeric DNA at the ends of chromosomes (known as the end-replication problem of eukaryote DNA), telomeres are progressively shortened every time a cell divides.<sup>2</sup>



Telomere-dependent replicative senescence and stress-induced premature senescence act through the modulation of proteins p53 and Rb. Senescence stimuli, such as DNA damage, strong mitogenic signals, overexpression of oncogenes, epigenomic disruption, telomere dysfunction, and ROS engage in cell signaling cascades that cause activation of 1 or both of the pathways that regulate cell senescence, the p53-p21 and p16-pRB pathways. Activation of p53 induces the expression of a CDK inhibitor, p21. Senescence stimuli, which involve the p16-pRB pathway upregulate the expression of another CDK inhibitor, p16. Both p21 and p16 suppress the phosphorylation and inactivation of pRB, and hereby maintain its hypophosphorylated and active state. Active pRB halts cell cycle progression by inhibiting gene transcription via downregulating transcription factor E2F. Senescent cells remain metabolically active, despite their terminal growth arrest, and secrete proinflammatory cytokines, chemokines, growth factors, and proteases, collectively termed the senescence-associated secretory phenotype.

CDK, cyclin-dependent kinase; pRB, retinoblastoma tumor suppressor protein; Rb, retinoblastoma; ROS, reactive oxygen species.

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When telomeres reach a critical minimum length, their protective structure is distorted, resulting in the exposure of DNA ends and a DNA damage response, which lead to the activation of the cellular senescence pathway.<sup>5,14,17,18</sup> This phenomenon is commonly known as replicative senescence. Telomere

shortening is also accelerated as a consequence of environmental stressors and insults, such as hyperglycemia, hypoxia, and oxidative stress,<sup>19–22</sup> which lead to the oxidation of the guanosine residues. Telomere length is regulated by the enzyme telomerase, which is a specific reverse transcriptase capable of

### PANEL 1 CELL CYCLE

The cell cycle or cell-proliferation cycle is a series of events that take place in a mitotic cell to produce 2 daughter cells. In eukaryotic cells, the stages of the cell cycle are divided into 2 major phases: interphase and the M phase.

**Interphase:** During the interphase the cell grows in size and makes a copy of the cell's DNA (called DNA replication) to prepare for the cell division. The interphase is comprised of 3 stages: G<sub>1</sub>, S, and G<sub>2</sub>.

- **G<sub>1</sub>.** In the first gap phase, the cell increases in size, copies organelles, and makes the molecular building blocks it will need in later steps. The G<sub>1</sub> checkpoint control mechanism ensures that everything is ready for DNA synthesis.
- **S phase.** DNA synthesis occurs during this phase. It also duplicates a microtubule-organizing structure called the centrosome. The centrosomes help separate DNA during M phase.
- **G<sub>2</sub>.** The cell continues to grow in the second gap phase and synthesizes proteins and organelles. During this phase microtubules begin to reorganize to form a spindle. The G<sub>2</sub> checkpoint control mechanism ensures that everything is ready to enter the M phase and divide.

**M phase:** During the M phase, cell growth stops and cellular energy is focused on the orderly division into 2 daughter cells. At this stage the cell separates its DNA into 2 sets and divides its cytoplasm, forming 2 new cells.

G<sub>1</sub>, gap 1; G<sub>2</sub>, gap 2; M, mitotic; S, synthesis phase.

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adding telomeric repeats to the ends of the chromosome.<sup>23</sup>

Telomerase consists of a catalytic protein component, telomerase reverse transcriptase, and an RNA template component. Telomerase reverse transcriptase is considered to be the rate-limiting factor in the telomerase activity.<sup>24</sup> The absence of a functional telomerase or loss of telomerase activity leads to a progressive telomere shortening during cell division, resulting in telomere-dependent replicative senescence and an inability to further divide when a critically short telomere length is reached.<sup>18,23,25</sup>

Senescence can also be induced independently of telomere length by a process termed premature senescence. Premature senescence leads to premature aging and is linked to several disease processes.<sup>26</sup> Premature senescence occurs as a consequence of progressive DNA damage and the DNA damage response, telomere uncapping, and telomere dysfunction caused by extrinsic or intrinsic stressors including oxidative stress by ROS, resulting in end-to-end fusion and aggregation of telomeric DNA.<sup>27-29</sup> ROS stimulates senescence by inducing DNA damage and by engaging p53-p21 and p16-pRB signal transduction cascades, either directly or indirectly.<sup>5</sup> Genomic damage or epigenomic perturbation, including dysfunctional telomeres and DNA double-strand breaks, activates the DNA damage response. The resulting signal transduction pathways then lead to arrest of the cell cycle.<sup>30</sup>

### Features of cellular senescence.

Senescent cells are distinct from their proliferation-competent counterparts; the former display altered characteristics, morphologically, in gene and protein expression and in the activation of key signaling constituents.<sup>2</sup> Morphologically, senescence cells are enlarged, multinucleated, often double in volume, and adopt a flattened or more spindle-shaped morphology, depending on the type of senescence inducer.<sup>5</sup> Senescent cells are resistant to apoptosis or programmed cell death through the overexpression of the antiapoptotic Bcl-2

protein, leading to the accumulation of these cells within tissues.<sup>31</sup>

Senescent cells display significant changes in their secretory phenotype. Senescent cells remain metabolically active, despite their terminal growth arrest, and secrete proinflammatory cytokines, chemokines, growth factors, and proteases, collectively termed the senescence-associated secretory phenotype.<sup>32</sup> The expression of interleukin (IL)-1 $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, and tumor necrosis factor- $\alpha$  have been shown to increase in senescent cells.<sup>6,33</sup> Increased expression of matrix metalloproteinases (enzymes that degrade extracellular matrix proteins such as collagen and elastin) is also common.<sup>34</sup>

The senescence-associated secretory phenotype in senescent cells can induce senescence in neighboring cells,<sup>35</sup> alter the behavior of surrounding cells and tissue homeostasis by activating various cell-surface receptors and their signal transduction pathways, and induce tumorigenesis and malignant progression of nearby premalignant cells.<sup>6,8,30,36</sup> Senescence-associated  $\beta$ -galactosidase (SA- $\beta$ -gal) activity is increased in senescent cells and has been widely used as a biomarker for cellular senescence.<sup>37</sup> The SA- $\beta$ -gal most likely derives from increased lysosomal beta-galactosidase, associated with the increased lysosomal biogenesis that occurs in senescent cells.<sup>38</sup> Despite its apparent specificity for senescent cells, SA- $\beta$ -gal is not required for senescence.<sup>38</sup>

Perturbation of mitochondrial homeostasis is also an important characteristic feature of cellular senescence. Aging is generally linked to a progressive mitochondrial dysfunction.<sup>39</sup> Mitochondrial dysfunction is characterized by increased ROS generation; impaired mitochondrial dynamics (imbalance in fission and fusion; typically more fusion, resulting in the formation of abnormally enlarged mitochondria); depolarization of the inner membrane, which stalls the mitochondrial electron transport chain; reduced 5' adenosine triphosphate generation and increased 5' adenosine monophosphate-activated protein kinase activation; reduced nicotinamide adenine dinucleotide

oxidase/nicotinamide adenine dinucleotide hydroxide ratio and altered metabolism; and mitochondrial Ca<sup>2+</sup> accumulation.<sup>40</sup> These changes in mitochondrial function can induce the activation of p53-p21 and/or p16-pRB signaling pathways that eventually lead to cellular senescence<sup>40</sup> (Figure 2).

Increased mammalian target of rapamycin complex 1 (mTORC1) kinase activity is a common feature of senescent cells. mTORC1 is a conserved serine/threonine kinase, belonging to the phosphoinositide 3-kinase family that induces anabolism by regulating protein translation and nucleotide and lipid biogenesis, and inhibits the catabolic process by blocking autophagy (a process that involves fusion of acid and proteolytic enzyme containing lysosomes with autophagosomes that contain damaged organelles and misfolded proteins that is central to the cell recycling system).<sup>41</sup>

Persistent mTORC1 signaling in senescent cells may result from defects in the sensing of amino acids and growth factor starvation.<sup>42</sup> In senescent cells increased mTORC1 activity promotes protein synthesis while inhibiting cellular proliferation.<sup>36,43</sup> mTORC1 activation activates intracellular signaling cascades that regulate mitochondrial function and apoptosis<sup>44</sup> while concurrently inhibiting autophagy,<sup>45</sup> which leads to the accumulation of damaged cellular contents including misfolded proteins as well as lipid droplets that can be seen by light microscopy as granular cytoplasmic inclusions surrounding the nucleus of senescent cells.<sup>46,47</sup>

Interestingly, mTORC1 inhibition by rapamycin not only delays the progression of cellular senescence but also prevents the permanent loss of proliferative capacity and allows the arrested cells to re-enter the cell cycle.<sup>36,48-50</sup> Rapamycin can also prolong the life span of various species including yeast, flies, and mice<sup>44,51,52</sup> by blocking the effects of mTORC1.<sup>36,44</sup> In addition, metformin, a popular hypoglycaemic agent, has recently been shown to extend longevity in worms<sup>53</sup> and mice,<sup>54</sup> possibly by modulating several age-related

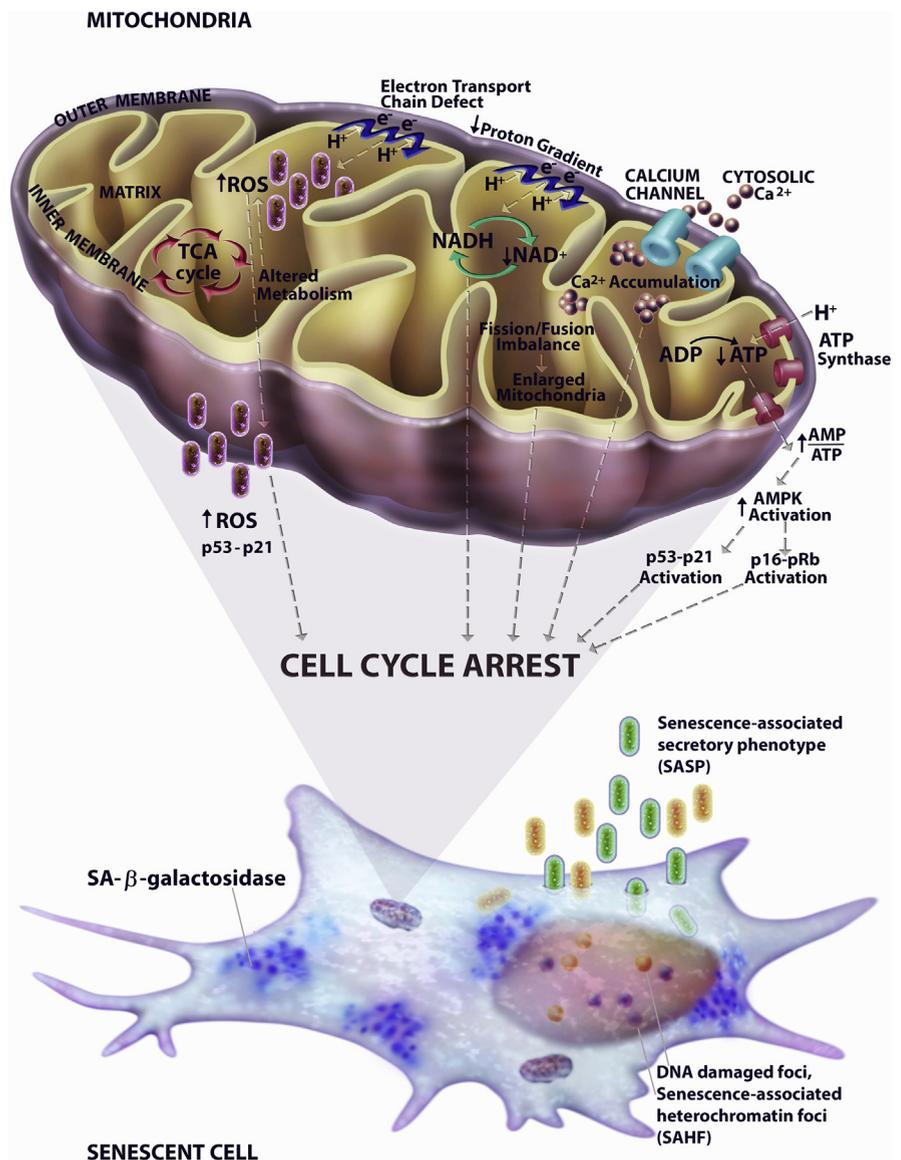
pathways, including mitochondrial function and 5' adenosine monophosphate-activated protein kinase activity and the nutrient-sensing mTORC1 pathway (reviewed in reference<sup>51</sup>).

**Biomarkers of senescence.** The importance of senescence in aging and several age-related pathological conditions has led to the identification of several senescence biomarkers (Table). The current methods to assess biomarkers of cell and tissue senescence have been reviewed by Bernardes et al.<sup>55</sup> Expression of  $\beta$ -galactosidase (SA- $\beta$ -gal) is known to be one of the well-characterized and simplified methods to detect senescence in vitro culture cells as well as for aged tissues in vivo. The assay that measures SA- $\beta$ -gal activity expressed by senescent cells can be detectable at pH 6.0 by immunohistochemistry.<sup>37</sup> SA- $\beta$ -gal is expressed in senescent cells but not in other cell types and is shown to increase in an age-dependent manner in human skin samples<sup>37</sup> and therefore is a widely used and reliable marker for the detection of senescent cells in a variety of species and pathological conditions.<sup>56-61</sup>

Another important biomarker of senescence is SAHF, both in cultured cells and in vivo. In the senescent cell nucleus, the chromatin undergoes dramatic remodeling through the formation of domains of facultative heterochromatin foci, called SAHF,<sup>62</sup> which can be visualized under microscopy as 4,6-diamidino-2-phenylindole-stained punctate areas. SAHF irreversibly silences and represses several E2F-target genes (eg, cyclin A)<sup>62</sup> and are triggered by p16 or p53 pathway activation.<sup>63</sup> Transcription starting sites are absent in SAHF regions which are enriched in transcription-silencing histone, for example, HP1, macroH2A, H3Lys9me3 (trimethylation of lysine 9 in histone 3).<sup>63</sup> Other protein complexes that have shown to be accumulated at SAHF include chromatin regulators HIRA, Asf1, and HMGA, which are considered as valuable biomarkers of senescence.<sup>55</sup>

The senescence-associated secretory phenotype, which is characterized by

**FIGURE 2**  
**Perturbation of mitochondrial homeostasis**



Changes in mitochondrial function trigger cellular senescence via activation of p53-p21 and/or p16-pRB signal transduction cascades. Figure adapted from Ziegler et al.<sup>40</sup>

pRB, retinoblastoma tumor suppressor protein.

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the secretion of inflammatory signals that resembles a local immune response, is a hallmark of senescent cells. The expression of inflammatory cytokines (IL-6) or chemokines (IL-8) has been extensively used as biomarkers for measuring senescence in cells and in tissue.<sup>64</sup> p16-pRB and p53-p21 are 2 major cellular pathways that are involved in induction of cellular

senescence as described in the previous section. Increased levels and/or activity of p16, p53, and p21 have been shown to be associated with cell senescence and are considered as important biomarkers of cell senescence and tissue aging.<sup>59,65-68</sup> Other cellular senescence markers include telomere shortening and dysfunction<sup>69,70</sup> and an activated and persistent DNA-damage response.<sup>55</sup>

**TABLE**  
**Biomarkers of senescence**

Biomarkers	Trend	References
SA- $\beta$ -gal	+	37, 56–61
SAHF		
H3Lyn9me3, H1, macroH2A	+	71–73
HMGA, HP1	+	72, 74
HIRA, Asf1	+	71
SASP		
IL-6, IL-8	+	64
Senescence inducers		
p16	+	59, 65, 66
p53/p21	+	65, 67, 68
Telomere length and DDR	–	55, 69

DDR, DNA damage response; IL, interleukin; SA- $\beta$ -gal, senescence-associated  $\beta$ -galactosidase; SAHF, senescence-heterochromatin foci; SASP, senescence-associated secretory phenotype.

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## Cellular senescence and placental aging in pathological pregnancies

**Physiological and pathological placental senescence and aging.** The placental syncytiotrophoblast is a multinucleated, single layer of terminally differentiated cells covering the chorionic villi. The layer is replenished by the fusion of cytotrophoblasts with the overlying layer of syncytiotrophoblast, resulting in a huge syncytium with multiple nuclei.

Mature (term) placental syncytiotrophoblast displays molecular markers of cellular senescence, for example, SA- $\beta$ -gal and an increased expression of the CDK inhibitors p16 and p21 and tumor suppressor p53.<sup>75</sup> Heterochromatin foci can be seen within the nuclei resulting from reorganisation of chromatin structures.<sup>47</sup> Evidence of oxidative damage and aging in the syncytiotrophoblast increases as gestation advances<sup>76</sup> and is associated with mammalian target of rapamycin complex activation and telomere shortening.

Fusion of cytotrophoblasts with the syncytiotrophoblast is a physiological process by which differentiated cytotrophoblast cells are incorporated into the syncytiotrophoblast that starts at approximately 12 weeks and continues

until term.<sup>77</sup> This process is essential to achieve the rapid and extensive expansion of the placental villi, contributing to the overall growth of the placenta and constant damage repair of the chorionic villi, which is accomplished through further fusion with underlying cytotrophoblasts.

This process requires an endogenous human defective retroviral element encoding *ERVWE1*, also known as syncytin-1 (syncytin-A in mice), which is expressed in all trophoblast cell lineages. Expression of *ERVWE1* causes cell fusion a process that induces cellular senescence in normal and cancer cells.<sup>75</sup> In syncytin-A knockout mouse embryos, failure of cytotrophoblast cell fusion results in intrauterine growth restriction (IUGR) and fetal demise in midgestation.<sup>78</sup> In humans, a reduced expression of syncytin-1 has been observed in placentas associated with IUGR and preeclampsia.<sup>79</sup>

Trophoblast senescence is a physiological phenomenon and is expected to progress gradually as pregnancy advances to term, that is with placental aging. However, premature or accelerated senescence and aging can occur as a result of placental stress that can lead to placental and clinical pathology. Premature or accelerated

senescence happens when the placenta encounters stressors including, oxidative, mitochondrial, or endoplasmic reticulum stress, which therefore contribute to the pathophysiology of pregnancy complications, such as preeclampsia and fetal growth restriction (FGR).

Low levels of stress can induce adaptive responses, including upregulation of antioxidant capacities and cell turnover by autophagy, moderate levels may interfere with stem cell behavior and reduce cell proliferation, while elevated levels of stress can cause the release of proinflammatory cytokines and antiangiogenic factors, and may contribute to the pathophysiology of preeclampsia, while chronic stress may accelerate senescence of the trophoblast.<sup>80</sup> The consequences of accelerated senescence in the cytotrophoblast/syncytiotrophoblast are potentially compromised placental nutrient transport that can cause compromised fetal growth, with or without preeclampsia.

Likewise, maternal decidual cells and fetoplacental membranes display features of senescence as pregnancy approaches term.<sup>47,81</sup> A progressive natural physiological senescence and aging of decidual cells and placental membranes may be important for modulating the cell signaling pathways that are required for the onset of labor at term. Increased expression of cellular senescence signals, including p53, p21, senescence-associated secretory phenotype (IL-6 and IL-8), and SA- $\beta$ -gal from both the maternal decidua and fetal membranes has been found to be associated with labor at term,<sup>81,82</sup> which may contribute to human parturition.

Early secretion of the senescence-associated inflammatory signals (such as IL-1 $\beta$ , IL-6, and IL-8) caused by senescence of the chorioamniotic membranes triggered by pathological processes may promote premature membrane rupture and spontaneous preterm labor.<sup>47,83</sup> It is likely that placental aging determines pregnancy duration and parturition,<sup>84</sup> and

premature aging may lead to early onset of labour.

### Placental senescence in small for gestational-age fetuses and neonates.

FGR, also called small for gestational age is defined as an estimated fetal weight below the 10th percentile for gestational age<sup>85</sup> and affects more than 15% of pregnancies worldwide.<sup>86</sup> Poor placentation and placental dysfunction are known to predispose to FGR. Placental dysfunction caused by the failure of trophoblast invasion and maternal spiral artery transformation, caused by ROS-mediated oxidative stress<sup>87-89</sup> has been reported in FGR.<sup>90</sup> ROS-induced oxidative damage affects membrane lipids, proteins, and nucleic acids (both DNA and RNA).<sup>89</sup>

In genomic and mitochondrial DNA, 8-hydroxy-2'-deoxyguanosine (8-OHdG; an oxidized derivative of deoxyguanosine) is one of the predominant forms of ROS-induced oxidative DNA lesions and has therefore been widely used as a biomarker for oxidative DNA damage. The level of 8-OHdG is reported to be significantly higher in placentas associated with FGR.<sup>91-93</sup>

Increased trophoblast senescence has been observed in FGR. FGR placentas display senescence markers, including short telomeres, telomere aggregation or dysfunction, and a reduction of telomerase activity.<sup>24,28,94-99</sup> Specifically a strong association between reduction of placental trophoblast telomere length and FGR pregnancies has been reported.<sup>24,94,98-100</sup> An absent or a decrease in telomerase activity is also observed in the placentas from FGR pregnancies.<sup>24,94-96</sup> FGR placentas display upregulation of the senescence markers p21 and p16, tumor suppressor protein p53, IL-6, and a reduced expression of antiapoptotic protein Bcl-2.<sup>27,94</sup>

There is also an elevated level of SAHF in the FGR placenta.<sup>100</sup> The presence of oxidized DNA as 8-OHdG is increased in placental trophoblast complicated by FGR.<sup>27</sup> Overall, there is a strong association between reduction of telomere length in placental trophoblast and DNA damage and FGR, suggesting that

senescence in trophoblast cells may contribute to the etiology of FGR.

### Preeclampsia and placental senescence.

Preeclampsia is a hypertensive disorder of pregnant women and often occurs in association with FGR. Preeclampsia is the leading cause of maternal and neonatal death and preterm birth, affecting 5–7% pregnancies worldwide.<sup>101-103</sup>

Preeclampsia is characterized by new-onset maternal hypertension (blood pressure  $\geq 140/90$  mm Hg), diminished uteroplacental blood flow, proteinuria ( $\geq 300$  mg per 24 hours), and edema.<sup>103</sup> An injury to the vascular endothelium is the basic pathological event in preeclampsia,<sup>89,104</sup> caused by placental oxidative and endoplasmic reticulum stress,<sup>80,105</sup> which are known to trigger cellular senescence and may therefore contribute to the clinical features of this pregnancy complication.

Increased placental or trophoblast senescence has been demonstrated in preeclampsia in terms of senescence biomarkers, including short telomeres, telomere aggregation and dysfunction and reduced telomerase activity, increased senescence-associated secretory phenotype, and increased expression of tumor suppressor p53 and CDK inhibitors p16 and p21.

In preeclamptic placentas, the formation of telomere (or nuclear) aggregate (SAHF) is increased compared with placentas from normotensive women<sup>24,28,106</sup> The expression of senescence inducers p53, p21, and p16 are higher in pregnancy complicated by preeclampsia.<sup>27,107-109</sup> Moreover, a high level of proinflammatory cytokine (IL-1 $\beta$  and IL-6) profile can be demonstrated in preeclampsia.<sup>27,110</sup> DNA oxidation as measured by the expression of 8-OHdG in preeclamptic placenta is higher than in the healthy placentas.<sup>27</sup>

### Placental senescence in spontaneous preterm labor/birth.

Preterm birth is the leading cause of neonatal death and the second leading cause of infant mortality.<sup>111</sup> Spontaneous preterm birth may occur after the spontaneous onset of labor with or without preterm premature rupture of the membrane

(pPROM). Both term and preterm labor occur through activation of a common pathway characterized by increased myometrial contractility, cervical ripening (dilatation) and decidua/chorioamniotic membrane activation, and chorioamniotic membranes rupture<sup>112,113</sup> and is likened to an inflammatory activation, particularly of cytokines and chemokines, in the gestational membranes.<sup>114</sup>

In term delivery, physiological signals activate the pathway to labor, while in preterm labor several pathological processes or conditions induce labor by activating 1 or more of the components of this pathway.<sup>112</sup> Labor promotes alterations of gene expression in placental membranes, which are compatible with the localized acute inflammatory response, without evidence of histologically observable inflammation.<sup>115</sup>

Labor is also associated with the expression of senescence-associated signals in the placental chorioamniotic membranes, for example, telomere length reduction, and increased expression of p53, p21, senescence-associated secretory phenotype (IL-6 and IL-8), and SA- $\beta$ -gal, mediated through the activation of the p38 MAPK pathway.<sup>82,116</sup>

Senescent cells may transmit inflammatory (cytokines and chemokines, the senescence-associated secretory phenotype) and senescence-promoting signals, which may cause changes in gene expression patterns in chorioamniotic membranes (overexpression of IL-8, IL-6, toll-like receptor 2 and superoxide dismutase) and in amniotic fluid (IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, IL-8) that stimulate labor.<sup>115</sup> Increased levels of antiinflammatory cytokines and chemokines, for example, tumor necrosis factor- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-8, have been found in cervicovaginal secretions in women who deliver preterm, that are associated with early-onset labor,<sup>83</sup> and early initiation of these inflammatory signals is likely to promote premature labor.

Chorioamniotic membranes from spontaneous preterm labor without acute histological chorioamnionitis (inflammation of the fetal membranes) show signs of cellular senescence, for

examples, increased levels of *CDKN1A* (the gene that encodes p21) and SA- $\beta$ -gal, and downregulated CDK and cyclins (*CCNA2*, *CCNB1*, and *CCNE1*) compared with preterm not-in-labor membranes.<sup>117</sup>

Telomeric DNA fragments released from senescent fetal cells into the amniotic fluid may induce amniotic cell senescence via the p38 MAPK activation and stimulate sterile inflammatory signals that promote parturition.<sup>118</sup> Although there is a strong association between inflammatory activation and labor (both term and preterm), whether these inflammatory signals result in the induction of labor remains unclear.

Premature senescence of the intrauterine tissues, especially the fetal membranes, triggered by senescence stimuli such as oxidative DNA damage by ROS, may contribute to spontaneous preterm labor or pPROM,<sup>119-121</sup> possibly via inflammatory signals (the senescence-associated secretory phenotype). Increased expression of the biomarkers of the senescence phenotype, for example, p53, p21 and p38 MAPK were observed in the fetal membranes in preterm births with pPROM compared with spontaneous preterm and term deliveries.<sup>121</sup>

The senescence phenotype could be induced in vitro in term fetal membranes by exposure to cigarette smoke extract. Because smoke causes oxidative stress, these data suggest that ROS-mediated damage to the fetal membranes may result in premature senescence in fetal membranes in pPROM.<sup>121</sup>

Significantly shorter telomeres are also found in fetal membranes in pPROM compared with spontaneous preterm births with intact membranes, indicating that premature senescence and aging of the placental membranes may lead to pPROM.<sup>122</sup> Studies using a mouse model suggest that in normal mouse pregnancy, progressive uterine decidual and fetal membrane senescence occur as term approaches,<sup>81</sup> while uterine p53-deficient transgenic mice show premature and accelerated decidual senescence, with increased levels of p21, IL-8, and other cytokines, and this is

associated with spontaneous preterm birth.<sup>123-125</sup>

Interestingly, an additional deletion of the p21 gene can prevent spontaneous preterm birth, indicating that p21-dependent senescence in the decidua causes preterm birth in the mouse.<sup>124</sup>

**Placental senescence and aging in late gestation and fetal death.** There is evidence of oxidative damage and aging in late gestational tissues.<sup>76</sup> It has been hypothesized that in late pregnancy, fetal needs for nutrients and oxygen rises, if the demands exceed the placenta's ability to transfer, the placenta experiences stress that stimulates ROS generation and oxidative stress, and the resulting oxidative damage leads to aging in the placental tissue.<sup>126,127</sup> The risk of fetal death increases exponentially late in pregnancy, especially after 41 weeks of gestation,<sup>128,129</sup> suggesting that placental aging plays a key role in the clinical features of this complication.

A recent study by Maiti et al<sup>76</sup> reported that placentas from unexplained intrauterine fetal death display evidence of oxidative damage and aging. Increased expression of 8-OHdG (a marker of DNA oxidation) and 4-hydroxynonenal (a marker of lipid peroxidation) have been observed in fetal death-associated placentas,<sup>76</sup> compared with term placentas; expression of both these markers has also been described to increase in aging tissues,<sup>130</sup> such as the brain in Alzheimer's disease.<sup>131,132</sup>

Also, a dysregulated lysosomal distribution and an increased autophagosome size with failure of autophagosome-lysosome fusion have also been noted in placentas associated with fetal death, suggesting an overall inhibition of autophagy. Placentas from late-term pregnancies show similar changes in oxidation of DNA and lipid, lysosomal distribution, and larger autophagosomes compared with placentas from women delivered at term.<sup>76</sup>

Increased expression of aldehyde oxidase 1 (an enzyme that is known to be involved in ROS generation<sup>133</sup>) is observed in placentas from both fetal

death and late-term pregnancies. In vitro placental explants deprived of growth factors show similar changes in oxidation of lipid, lysosomal distribution, and autophagosome size, which can be blocked by inhibitors of aldehyde oxidase 1, suggesting that this enzyme plays a key role in placental aging.<sup>76</sup>

Ferrari et al<sup>134</sup> demonstrated that unexplained fetal death-associated placentas exhibit shortened telomeres. The authors observed an overall 2-fold reduction of telomere length in placentas from fetal death (both early and late term) with or without growth restriction compared with term live-birth placentas. They also reported that the telomere length in fetal death placentas is comparable with those of pPROM, while telomeres are shorter in fetal death compared with spontaneous preterm birth.<sup>134</sup>

Taken together, reduced telomere length, increased DNA and lipid oxidation, and inhibition of autophagy, changes that are consistent with cellular senescence and aging, indicate that placental senescence and aging is an etiological factor in fetal death.

### Concluding remarks

Senescence has both beneficial and detrimental effects on gestational tissue, depending on the cell type and timing of onset. While physiological senescence in placental trophoblasts appears to be necessary for the formation of the syncytium, and growth and function of the placenta, it is likely that placental cell senescence plays a key role in pathogenesis of a number of adverse pregnancy outcomes, including FGR, preeclampsia, spontaneous preterm birth, and intrauterine fetal death. The senescence-associated secretory phenotype, especially matrix metalloproteinase that is released by the syncytiotrophoblast in early gestational tissue, may be necessary for trophoblast penetration during the lacunar stage of very early placental development.<sup>47</sup>

There is also a link between placental senescence and the onset of labor. Spontaneous preterm labor and pPROM may be promoted by premature and

accelerated senescence of placental membranes and decidua that can be induced by several endogenous and exogenous factors, such as ROS. The physiological programming of senescence may be essential in determining the timing of labor onset.

In FGR the increased expression of biomarkers of DNA damage, reduction of telomere length and telomerase activity, upregulation of senescence inducing p53 and p16, and elevated levels of senescence-associated secretory phenotype and SAHF support the concept that placental senescence and aging contribute to FGR.

There is also evidence of placental oxidative DNA damage, and premature senescence in late gestational tissues. Therefore, it would appear that aging is a key factor that may affect function in the short but important life span of the placenta. ■

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### Glossary of terms

**Telomeres:** highly conserved repetitive DNA regions and consist of tandem arrays of the hexanucleotide sequence, TTAGGG, in the human. Telomeres protect DNA ends from breaks, end-to-end fusion, and degradation by forming a protective cap with a guanine-rich single-stranded telomere overhang.

**Telomerase:** a reverse transcriptase enzyme, which regulates telomere length by adding telomeric repeats to the ends of chromosomes.

**Replicative senescence:** dependent on telomere length and occurs as a result of progressive telomere shortening during mitotic cell division. DNA polymerases are unable to replicate DNA at the ends of chromosomes (known as the end-replication problem of eukaryote DNA) leaving ~50–200 bp of unreplicated telomeric DNA in each round of DNA replication. When telomeres reach a critical minimum length, their protective structure is distorted (leads to dysfunctional telomeres), resulting in the exposure of DNA ends and a DNA damage response, which leads to the activation of the cellular senescence pathway.

**Premature senescence:** is independent of telomere length and occurs as a consequence of DNA damage and the DNA damage response caused by stress such as elevated reactive oxygen species, activation of oncogenes, telomere dysfunction, and cell-cell fusion.

**RAS:** renin-angiotensin system, a mutant renin-angiotensin system-p21 protein, renin-angiotensin system involves transmitting signals and activating signaling cascades, including mitogen-activated protein kinase and phosphoinositide 3-kinase/mammalian target of rapamycin complex pathways

**Chromatin:** Chromatin is a mass of genetic material composed of DNA and proteins, primarily histones, which condense to form chromosomes during eukaryotic cell division. Chromatin compresses the DNA into a compact unit that will be less voluminous and can fit within the nucleus. Histones help to organize DNA into structures called nucleosomes by providing a base on which the DNA can be wrapped around. Posttranslational modification to histone proteins, which includes methylation, phosphorylation, and acetylation, can cause disruption in chromatin structure.

**Heterochromatin:** a chromatin variety in which DNA, which codes inactive genes (turned off), is more condensed and associated with structural proteins. Heterochromatin protects chromosome integrity and gene regulation, while DNA, which codes genes that are actively transcribed (turned on), is more loosely packaged and associated with RNA polymerases, referred to as euchromatin.

**Cyclin-dependent kinase:** a family of multifunctional enzymes that can phosphorylate various protein substrates involved in cell cycle progression.

**Cyclin-dependent kinase inhibitors, p16 and p21:** proteins that inhibit cyclin-dependent kinase and are involved in cell cycle arrest at the G1 phase.

**p53:** a tumor suppressor gene.

**pRB:** retinoblastoma protein is a tumor suppressor, which plays a pivotal role in the negative control of the cell cycle and in tumor progression. The retinoblastoma protein represses gene transcription by directly binding to the transactivation domain of *E2F* genes and by binding to the promoter of these genes as a complex with *E2F*.

**E2F:** a group of genes that code transcription factors, such as *E2F1* and *E2F2*, in higher eukaryotes. The *E2F* family plays a crucial role in the control of cell cycle and action of tumor suppressor proteins. E2F proteins can mediate both cell proliferation and p53-dependent/independent apoptosis. The retinoblastoma protein binds to the E2 transcription factor 1 that preventing it from interacting with the cell's transcription machinery.

**Antiapoptotic Bcl-2:** a regulator protein that regulates cell death via apoptosis by inhibiting apoptosis (antiapoptotic).

**ERVWE1:** *ERVW-1 gene* (endogenous retrovirus group W envelope member 1) is a human defective retroviral fusogen found in humans and other primates that encodes the protein syncytin-1. Syncytin-1 is a cell-cell fusion protein, highly expressed in normal placental tissue whose function is most well characterized in placental development.

**p38 MAPK:** a member of mitogen-activated protein kinase, which mediates a wide variety of cellular behaviors in response to extracellular stimuli.

**mTORC1:** a conserved serine/threonine kinase that induces anabolism by regulating protein translation, nucleotide, and lipid biogenesis and inhibits the catabolic process by blocking autophagy.

**AMPK:** 5' adenosine monophosphate-activated protein kinase plays a key role as a master regulator of cellular energy homeostasis. The kinase is activated in response to stresses that deplete cellular 5' adenosine triphosphate supplies such as low glucose, hypoxia. Cellular stresses that inhibit 5' adenosine triphosphate production or increase its consumption change the 5' adenosine monophosphate/5' adenosine triphosphate ratio and activate the pathway. 5' Adenosine monophosphate-activated protein kinase activation positively regulates signaling pathways that replenish cellular 5' adenosine triphosphate supplies, including fatty acid oxidation and autophagy.

**Reactive oxygen species:** oxygen-free radicals that contain 1 or more unpaired electrons, produced as byproducts of mitochondrial respiration and metabolism, and are capable of activating and modulating various signaling pathways, including those involved in cell growth, differentiation, and metabolism. Examples include peroxides, superoxide, hydroxyl radical, and singlet oxygen.

**SA- $\beta$ -gal:** senescence-associated beta-galactosidase is a hydrolase enzyme that catalyzes the hydrolysis of  $\beta$ -galactosides into monosaccharides only in senescent cells. Therefore, expression of SA- $\beta$ -gal is considered to be a biomarker of cellular senescence.

**8-OHdG:** 8-hydroxy-2'-deoxyguanosine is an oxidized derivative of deoxyguanosine. In genomic and mitochondrial DNA, 8-hydroxy-2'-deoxyguanosine is one of the major products of free radical-induced oxidative lesions and has therefore been widely used as a biomarker for DNA damage and oxidative stress.

**Mitochondrial fusion and fission:** Mitochondria are dynamic organelles that constantly fuse (fusion) and divide (fission) and are termed mitochondrial dynamics. Mitochondria fusion and fission are important for mitochondrial inheritance and for the maintenance of mitochondrial functions. Fusion helps mitigate stress by mixing the contents of partially damaged mitochondria as a form of complementation. Fission is needed to create new mitochondria, but it also contributes to quality control by enabling the removal of damaged mitochondria and can facilitate apoptosis during high levels of cellular stress.

# Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: a systematic review and meta-analysis



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**G**rowth restriction is associated with an increased risk of adverse pregnancy outcomes, such as fetal death, perinatal morbidity, neonatal mortality, suboptimal neurodevelopment,<sup>1-4</sup> and adverse effects into adolescence and adulthood.<sup>5</sup> Suboptimal antenatal care for growth-restricted fetuses has been identified as a major cause of avoidable perinatal death,<sup>6</sup> and accordingly, growth-restricted fetuses not identified prenatally show an increased risk of fetal death,<sup>7</sup> and perinatal complications.<sup>8</sup>

In cases of early-onset growth restriction, placental insufficiency is commonly reflected in the umbilical artery waveform.<sup>9</sup> A smaller cross-section of the vasculature caused by such mechanisms as

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**OBJECTIVE:** The objective of the study was to establish the risk of fetal death in early-onset growth-restricted fetuses with absent or reversed end-diastolic velocities in the umbilical artery or ductus venosus.

**DATA SOURCES:** A systematic search was performed to identify relevant studies published in English, Spanish, French, Italian, or German using the databases PubMed, ISI Web of Science, and SCOPUS, without publication time restrictions.

**STUDY ELIGIBILITY CRITERIA:** The study criteria included observational cohort studies and randomized controlled trials of early-onset growth-restricted fetuses (diagnosed before 34 weeks of gestation), with information on the rate of fetal death occurring before 34 weeks of gestation and absent or reversed end-diastolic velocities in the umbilical artery and/or ductus venosus.

**STUDY APPRAISAL AND SYNTHESIS METHODS:** For quality assessment, 2 reviewers independently assessed the risk of bias using the Newcastle-Ottawa Scale for observational studies and the Cochrane Collaboration's tool for randomized trials. For the meta-analysis, odds ratio for both fixed and random-effects models (weighting by inverse of variance) were used. Heterogeneity between studies was assessed using  $\tau^2$ ,  $\chi^2$  (Cochrane Q), and  $I^2$  statistics. Publication bias was assessed by a funnel plot for meta-analyses and quantified by the Egger method.

**RESULTS:** A total of 31 studies were included in this meta-analysis. The odds ratios for fetal death (random-effects models) were 3.59 (95% confidence interval, 2.3–5.6), 7.27 (95% confidence interval, 4.6–11.4), and 11.6 (95% confidence interval, 6.3–19.7) for growth-restricted fetuses with umbilical artery absent end-diastolic velocities, umbilical artery reversed end-diastolic velocities, and ductus venosus absent or reversed end-diastolic velocities, respectively. There was no substantial heterogeneity among studies for any of the analyses.

**CONCLUSION:** Early-onset growth-restricted fetuses with either umbilical artery or ductus venosus absent or reserved end-diastolic velocities are at a substantially increased risk for fetal death.

**Key words:** Doppler, ductus venosus, fetal death, fetal growth restriction, perinatal mortality, umbilical artery

chronic reactive vasoconstriction of the tertiary stem villi<sup>10</sup> are assumed to result in upstream modifications in the flow velocity of the umbilical artery. The result is an augmented pulsatile wave-form signifying an increased impedance.

In extreme cases, this is manifested as absent or reversed end-diastolic

velocity associated with critically low umbilical flow before 34 weeks of gestation.<sup>11</sup> These cases represent end stages of placental histological and functional damage and are associated with an increased risk of perinatal death<sup>12</sup> and long-term abnormal neurodevelopment.<sup>4</sup>

Redistribution of the umbilical venous blood toward the ductus venosus is associated with less fetal growth,<sup>13</sup> and frank growth restriction is an important compensatory mechanism.<sup>14,15</sup> However, the pulsatile waveform of the ductus venosus blood velocity has become an important clinical indicator of hypoxic challenge in severe growth restriction.<sup>16</sup> An augmented atrial contraction wave that is linked to an absent or reversed end-diastolic velocity in the ductus venosus has been associated with an increased risk of perinatal mortality and neonatal morbidity.<sup>17</sup>

However, the single most important prognostic factor in preterm growth restriction is gestational age at delivery.<sup>3,18</sup> The main challenge in management of these pregnancies is timely delivery, in which the risk of fetal death has to be weighed against the risk of neonatal mortality and morbidity. Thus, fetuses are not delivered until the risk of dying in utero surpasses the risk of adverse perinatal outcome because of prematurity.<sup>19</sup> While the risk of neonatal mortality and severe morbidity is well documented in contemporary series on growth-restricted neonates,<sup>3,18,20</sup> the risk of fetal death when Doppler changes are present is still controversial.<sup>18,20</sup>

The objective of this study was to conduct a systematic review and meta-analysis to establish the risks of fetal death in early-onset growth-restricted fetuses with absent or reversed velocity waveforms in the umbilical artery or ductus venosus.

## Materials and Methods

### Eligibility criteria, information sources, search strategy

A systematic search was performed using databases PubMed, ISI Web of Science, and SCOPUS to identify relevant studies published in English, Spanish, French, Italian, or German, without publication date restriction. References of relevant publications were manually searched for additional potentially relevant published studies. The first search was run on Feb. 17, 2017. Afterward an update was extended until June 20, 2017.

This review was carried out adhering to the Meta-analysis Of Observational

Studies in Epidemiology guidelines,<sup>21</sup> and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reporting systematic review and meta-analysis in randomized control trials.<sup>22</sup> The study protocol was agreed between the authors before running the analysis, and one author (T.K.) being external to the group, acted as a reviewer of it.

All abstracts identified were assessed by 2 independent evaluators (J.C. and R.M.), both blinded to authorship, authors' institutions, and study results. Studies meeting inclusion criteria were full text reviewed. A third investigator (F.F.) independently resolved any disagreement between evaluators. In cases of relevant studies with missing information, corresponding authors were reached by e-mail. [Annex 1](#) in the supplemental material details the search strategy and query syntaxes.

### Study selection

Criteria for inclusion in this systematic review were observational cohort studies (retrospective and prospective) and randomized control trials of early-onset growth-restricted fetuses (diagnosed before 34 weeks of gestation), with information on the rate of fetal death occurring before 34 weeks of gestation and on the presence of absent or reversed end-diastolic velocity waveforms in the umbilical artery or the ductus venosus.

### Data extraction

The following data were extracted on a data sheet based on Cochrane Consumers and Communication Review Group's data extraction template: countries in which the study was carried out, study period, inclusion and exclusion criteria, sample size, information on Doppler end-diastolic waveforms in the umbilical artery and ductus venosus, and the frequency of fetal death with each waveform pattern.

The risk of fetal death was analyzed for the following groups: (1) umbilical artery absent end-diastolic velocity; (2) umbilical artery reversed end-diastolic velocity; (3) umbilical artery absent or reversed end-diastolic velocity; and (4) ductus venosus absent or reversed end-diastolic velocity. Studies that for a

given comparison reported no fetal death were excluded. Furthermore, instances of interruption of pregnancy cases were excluded for analysis.

### Quality assessment

Two reviewers (J.C. and R.M.) independently assessed the quality of the selected studies. Quality assessment of observational studies was carried out using the Newcastle-Ottawa Scale.<sup>23</sup> Each study was judged on 3 dimensions: the selection of the study groups; the comparability of the groups; and the ascertainment of the exposure. The quality of randomized studies was assessed with the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials,<sup>24</sup> which consists of 6 questions that addresses sequence generation, allocation concealment, blinding, incomplete data, reporting bias, and other biases.

Answers with regard to bias were categorized to low risk, high risk, and unclear risk. Results from these questions were graphed and assessed using Review Manager (computer program; version 5.3, 2014, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

### Statistical analysis

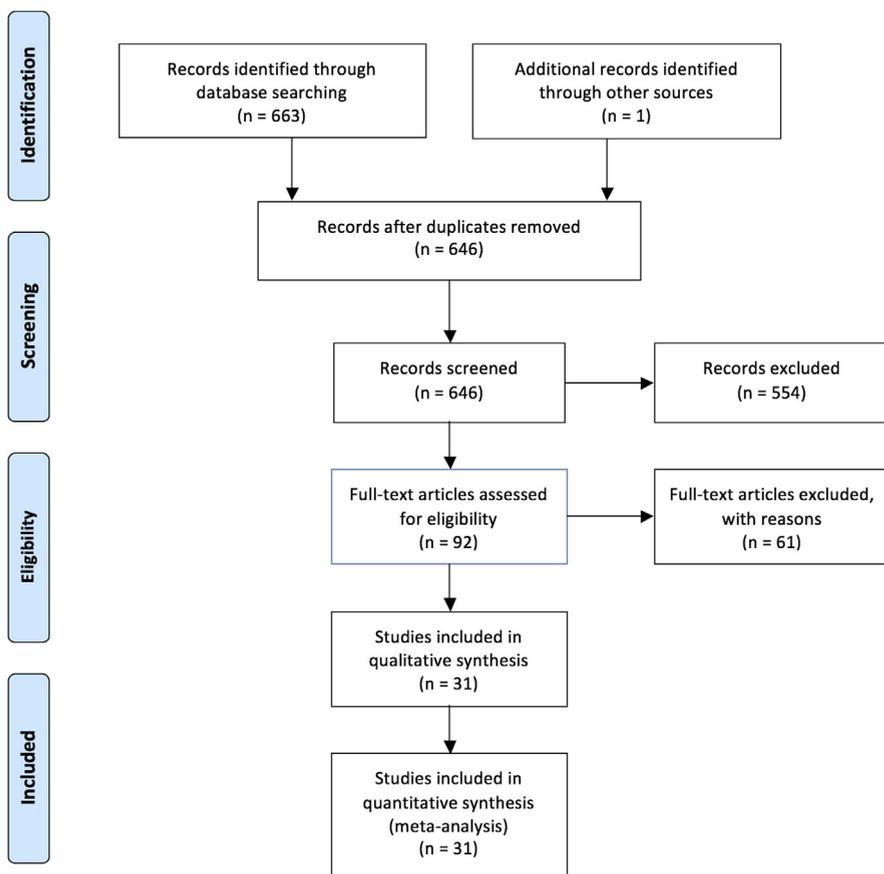
Extracted results were pooled in a meta-analysis. The meta-analysis was performed by computing odds ratios (ORs) using both fixed and random-effects models (weighting by inverse of variance). Between-study heterogeneity was assessed using  $\tau^2$ ,  $\chi^2$  (Cochrane Q), and  $I^2$  statistics.

According to the Cochrane handbook, the heterogeneity measured by  $I^2$  was interpreted as nonimportant (<30%), moderate (30–60%), or substantial (>60%).<sup>25</sup> Results were presented using forest plots.

An influence analysis was performed to ascertain the results of the meta-analysis by excluding each of the individual studies. Publication bias was assessed by a funnel plot for meta-analysis and quantified by the Egger method.<sup>26,27</sup>

A meta-regression procedure of the log-OR was performed to evaluate the

**FIGURE 1**  
PRISMA flow chart: Summary of evidence search and selection



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

contribution of mean gestational age at delivery and mean birthweight on the association between ductus venosus absent or reversed end-diastolic velocity and fetal death.

Statistical analysis was conducted using STATA software for Mac (version 15, Stata Corp, College Station, TX) (module meta<sup>28</sup>) and R (version 3.1.2, The R Foundation for Statistical Computing) (package meta, version 4.2<sup>29</sup>).

## Results

### Study selection

A total of 663 studies were identified by database searching, with 1 additional study included manually. Of these, 92 studies were eligible for full-text review. After the review, 31 studies were retained for analysis (28 cohort studies<sup>12,30-56</sup> and 3 randomized control trials<sup>20,57,58</sup>). Figure 1 depicts the review flow diagram.

The following authors were reached and they provided aggregated data on their published studies: Monier et al, 2017<sup>56</sup>; Cruz-Lemini et al, 2012<sup>52</sup>; Cosmi et al. 2005<sup>12</sup>; Turan et al, 2011<sup>51</sup>; the Growth Restriction Intervention Trial (GRIT) Study Group<sup>20</sup> (Annex 2 in the supplemental material details the shared information). The characteristics of the included articles are described in Supplemental Table 1.

### Risk of bias of the included studies

Among the cohort studies, 4 were considered as having a low risk of bias, while 8 had medium risk because they either had no study controls for each Doppler pattern or the analyzed exposure (abnormal Doppler pattern) was present at the start of the study. Finally, 16 had a high risk of bias, and all of them shared a combination of lack of representativeness

of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, exposure present at the start of the study, or the lack of study controls for each Doppler pattern.

Table 1 tabulates the risk of bias of the observational studies included in the meta-analysis, according to the Newcastle-Ottawa Scale.<sup>23</sup> On the other hand, the risk of bias for randomized control trials was assessed according to Cochrane's tool designed for this purpose and it is depicted in the Supplemental Figures 1 and 2.

### Synthesis of results

A total of 5909 Doppler assessments (and 336 fetal deaths) were included in the analysis.

### Umbilical artery absent end-diastolic velocity and fetal death

The weighted OR of umbilical artery absent end-diastolic velocity for fetal death was 3.59 (2.29–5.62), with no differences between the fixed and the random-effects models. Figure 2 shows the forest plot for the individual and overall OR for fetal death in cases with umbilical artery absent end-diastolic velocity. No significant heterogeneity was found among studies.

Influence analysis showed that the exclusion of 1 study<sup>56</sup> resulted in a 26% increased weighted OR (Supplemental Table 2). The funnel plot (Supplemental Figure 3) did not suggest the existence of publication bias. Likewise, the Egger k-coefficient was not significant (1.30, 95% confidence interval [CI], –1.12 to 2.73;  $P = .069$ ), further making unlikely a publication bias. Additionally, separate analyses were performed for observational and randomized studies (Supplemental Figures 4 and 5).

### Umbilical artery reversed end-diastolic velocity and fetal death

Under the random-effects models, the weighed OR of umbilical artery reversed end-diastolic velocity for fetal death was 7.27 (4.61–11.44;  $P < .001$ ). Figure 3 shows the forest plot for the individual and overall ORs for fetal death in cases with umbilical artery reversed end-diastolic velocity. The tau<sup>2</sup> (0.291;

**TABLE 1**  
**Newcastle-Ottawa scale for risk of bias assessment for observational studies**

Study	Selection				Comparability		Outcome			Stars	
	Author	Year	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Study controls for umbilical artery/ductus venosus absent end diastolic velocity	Study controls for umbilical artery/ductus venosus reverse end diastolic velocity	Assessment of outcome		Long-enough follow-up
Battaglia et al <sup>30</sup>	1993	*	*	*	*	*		*	*	*	7
Valcamonico et al <sup>31</sup>	1994	*	*	*	*	*	*	*	*	*	7
Ozcan et al <sup>32</sup>	1998	*	*	*	*	*		*	*	*	8
Madazli et al <sup>33</sup>	2001	*	*	*	*	*		*	*	*	8
Hofstaetter et al <sup>34</sup>	2002	*	*	*	*	*		*	*	*	8
Soregaroli et al <sup>35</sup>	2002	*	*	*	*	*	*	*	*	*	9
Baschat et al <sup>36</sup>	2003	*	*	*	*	*		*	*	*	7
Ertan et al <sup>37</sup>	2003		*	*	*	*		*	*	*	6
Bilardo et al <sup>38</sup>	2004	*	*	*	*	*		*	*	*	7
Figueras et al <sup>39</sup>	2004	*	*	*	*	*		*	*	*	8
Cosmi et al <sup>12</sup>	2005	*	*	*	*	*		*	*	*	7
Schwarze et al <sup>40</sup>	2005	*	*	*	*	*		*	*	*	7
Mari et al <sup>41</sup>	2007		*	*	*	*		*	*	*	6
Crispi et al <sup>42</sup>	2008	*	*	*	*	*		*	*	*	7
Hernandez-Andrade et al <sup>43</sup>	2008	*	*	*	*	*	*	*	*	*	8
Picconi et al <sup>44</sup>	2008	*	*	*	*	*		*	*	*	7
Rizzo et al <sup>45</sup>	2008	*	*	*	*	*	*	*	*	*	8
Brodzski et al <sup>46</sup>	2009	*	*	*	*	*		*	*	*	7
Robertson et al <sup>47</sup>	2009	*	*	*	*	*		*	*	*	7
Shand et al <sup>48</sup>	2009	*	*	*	*	*	*	*	*	*	9
Spinillo et al <sup>49</sup>	2009	*	*	*	*	*	*	*	*	*	9
Benavides-Serralde et al <sup>50</sup>	2011	*	*	*	*	*	*	*	*	*	8

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(continued)

**TABLE 1**  
Newcastle-Ottawa scale for risk of bias assessment for observational studies (continued)

Study	Selection			Comparability		Outcome					
	Year	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Study controls for umbilical artery/ductus venosus absent end diastolic velocity	Study controls for umbilical artery/ductus venosus reverse end diastolic velocity	Assessment of outcome	Long-enough follow-up	<10% lost to follow-up	Stars
Turan et al <sup>51</sup>	2011	*	*	*	*	*	*	*	*	*	7
Cruz-Lemini et al <sup>52</sup>	2012	*	*	*	*	*	*	*	*	*	7
Abdelhalim et al <sup>53</sup>	2014	*	*	*	*	*	*	*	*	*	9
Crimmins et al <sup>54</sup>	2014	*	*	*	*	*	*	*	*	*	8
Frauensschuh et al <sup>55</sup>	2015	*	*	*	*	*	*	*	*	*	5
Monier et al <sup>56</sup>	2017	*	*	*	*	*	*	*	*	*	7

Star indicates that cells with a star indicate that the corresponding item is addressed satisfactorily in the publication in question.  
Caradoux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

$P = .06$ ) and  $Q$ -value (28.8) suggested heterogeneity and the  $I^2$  (36%) quantified it as moderate.

Influence analysis showed that the exclusion of 1 study<sup>56</sup> resulted in a 13.4% increased weighted OR (Supplemental Table 3). The funnel plot (Supplemental Figure 6) did not suggest the existence of publication bias. Likewise, the Egger  $k$ -coefficient was not significant (0.1, 95% CI, -1.16 to 1.36;  $P = .868$ ). Additionally, separate analyses were performed for observational and randomized studies (Supplemental Figures 7 and 8).

**Umbilical artery absent or reversed end-diastolic velocity and fetal death**

Under the random-effects models, the weighed OR of umbilical artery absent or reversed end-diastolic velocity for fetal death was 6.80 (4.52–10.24;  $P < .001$ ). Figure 4 shows the forest plot for the individual and overall ORs for fetal death in cases with umbilical artery absent or reversed end-diastolic velocity.  $Tau^2$  (0.22;  $P = .14$ ), and the  $Q$ -value (31.49) suggests an absence of important heterogeneity, also implied by the  $I^2$  value of 24%.

Influence analysis showed that the exclusion of any of 2 studies<sup>35,56</sup> resulted in a 12.3% and 11.3% increased weighted OR, respectively (Supplemental Table 4). The funnel plot for publication bias assessment is shown in Supplemental Figure 9. The Egger  $k$ -coefficient method for publication bias was not significant (0.678; -0.25 to 1.61;  $P = .147$ ). Additionally, separate analyses were performed for observational and randomized studies (Supplemental Figures 10 and 11).

**Ductus venosus absent or reversed end-diastolic velocity and fetal death**

Under the random-effects models, the weighed OR of ductus venosus absent or reversed end-diastolic velocity for fetal death was 11.16 (6.31–19.73;  $P < .001$ ). Figure 5 shows the forest plot for the individual and overall ORs for fetal death in cases with ductus venosus absent or reversed end-diastolic velocity. The  $tau^2$  (0.521;  $P = .019$ ),  $Q$ -value (25.52), and the  $I^2$  (49%) showed a moderate heterogeneity between studies.

Influence analysis showed that the exclusion of 1 study<sup>54</sup> results in a 12.6% increased OR (Supplemental Table 5). The Egger k-coefficient was  $-1.01$  (95% CI,  $-3.25$  to  $1.22$ ;  $P = .341$ ), suggesting a lack of publication bias. The funnel plot for visually assessing publication bias is depicted in Supplemental Figure 12. Additionally, separate analyses were performed for observational and randomized studies (Supplemental Figures 13 and 14).

The meta-regression procedure showed that neither mean gestational age at delivery (estimate,  $-0.14$ ;  $P = .58$ ) nor mean birthweight (estimate,  $-0.001$ ;  $P = .54$ ) significantly explained the variability of the effect of ductus venosus absent or reversed end-diastolic velocity on fetal death. Supplemental Figures 15 and 16 show the bubble graphs with the fitted meta-regression line of the mean gestational age at delivery and mean birthweight.

### Comment

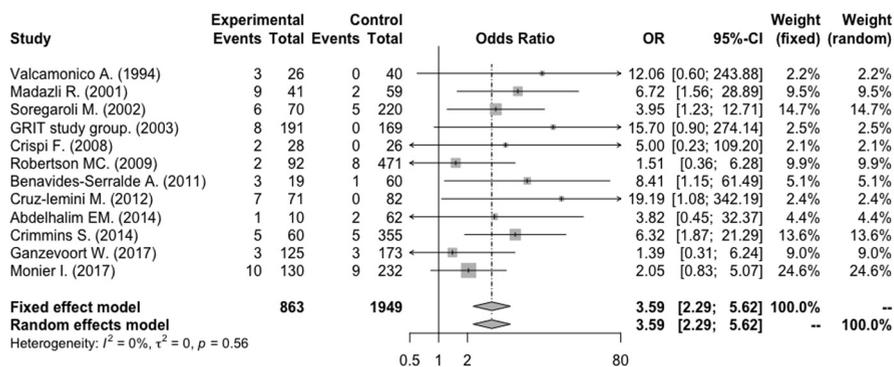
In the management of early-onset growth-restricted fetuses with severe Doppler abnormalities, the fine balance of the risk of fetal death (if left in utero) and the risk of prematurity (if delivered) guides the decision on the gestational age to deliver, aiming at maximizing survival without major sequelae.

While there are contemporary series reporting the risks of prematurity (infant mortality and severe morbidity) among fetal growth-restricted babies with severe Doppler abnormalities,<sup>3,18,20</sup> the risk of fetal death for different Doppler patterns has not been well described. This risk has often been stated within individual studies, which may not necessarily reflect the risk of the broad spectrum of fetuses exhibiting Doppler abnormalities. With 5909 Doppler evaluations analyzed, this meta-analysis depicts the association between umbilical artery and ductus venosus with absent or reverse end-diastolic velocity waveforms and the risk of fetal death among fetuses with early-onset growth restriction.

Only a few well-designed prospective studies have been conducted that allow establishing the risk of perinatal death for individual Doppler abnormalities.

**FIGURE 2**

### OR of umbilical artery absent end diastolic velocity for fetal death



Forest plot of the odds ratio of umbilical artery absent end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random effects model).

CI, confidence interval; OR odds ratio.

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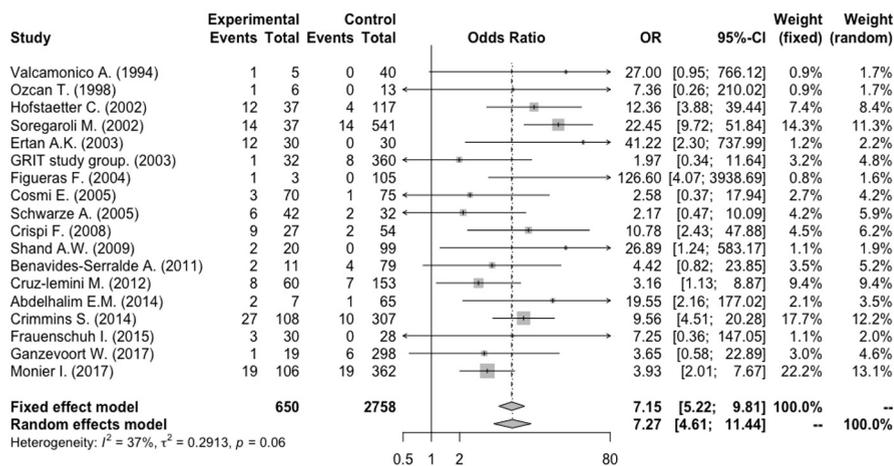
Good evidence comes from 2 randomized studies. The first, the GRIT study,<sup>20</sup> compared immediate vs delayed delivery in growth-restricted fetuses below 36 weeks of gestation and demonstrated that early delivery to avoid fetal death was counterbalanced by neonatal death and neurological sequelae. However, antenatal surveillance was not standardized; and, therefore, reported rates

of perinatal death have been found higher than expected.

More recently, the Trial of Randomized Umbilical and Fetal Flow in Europe study<sup>3</sup> aimed to describe perinatal morbidity and mortality in early-onset fetal growth restriction based on time of antenatal diagnosis and delivery. They found better-than-expected perinatal outcomes in this high-risk group of

**FIGURE 3**

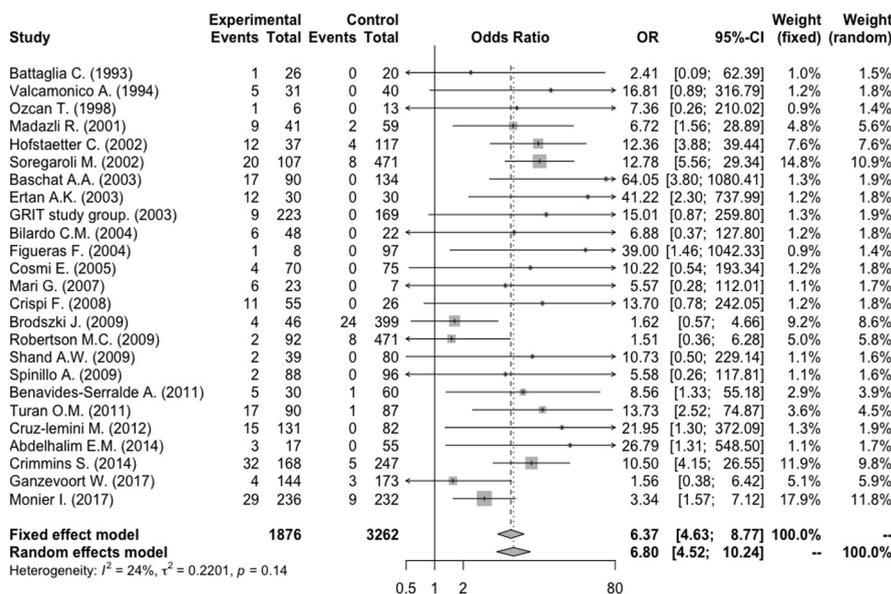
### OR of umbilical artery reverse end diastolic velocity for fetal death Forest plot of the odds ratio of umbilical artery reverse end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random effects model)



CI, confidence interval; OR odds ratio.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

**FIGURE 4**  
**OR of umbilical artery absent or reverse end diastolic velocity**



Forest plot of the odds ratio of umbilical artery absent or reverse end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model).

CI, confidence interval; OR odds ratio.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

fetuses (an overall probability of survival without major morbidity of approximately 70%), which could be attributed to good adherence to a management protocol. This underscores the importance of standardizing the prenatal care

of these pregnancies, in particular in defining the optimal gestational age for delivery.

The results of this meta-analysis can be used to guide the decision on the gestational age to delivery to maximize

intact survival. Our pooled data on the fetal death rate in fetuses with umbilical artery absent end-diastolic velocity yields a risk of fetal death of 6.8% (59 of 863). This risk is outweighed by the risks of infant mortality or severe morbidity, as reported in the Trial of Randomized Umbilical and Fetal Flow in Europe study, at 33–34 weeks.

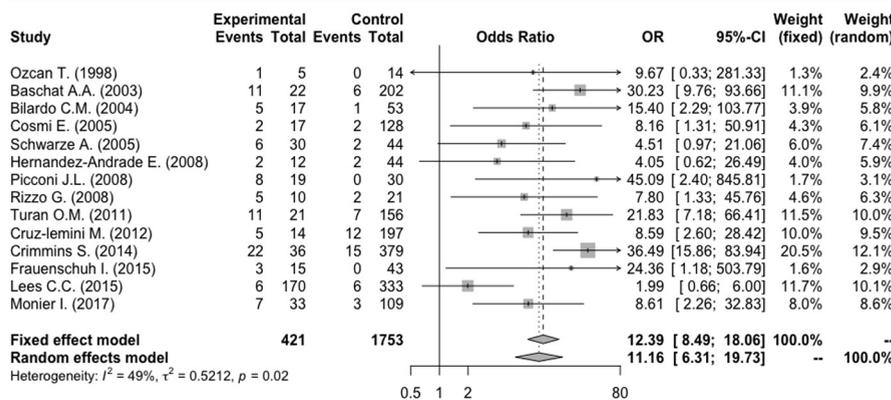
For cases with umbilical artery reversed end-diastolic velocity or ductus venosus absent or reversed end-diastolic velocity, the pooled risks of fetal death (19% [72 of 376] and 20% [77 of 377], respectively) are higher than the risk of neonatal mortality or severe morbidity from 30 weeks onward. Only 5 studies<sup>12,32,45,52,56</sup> separately reported risks for absent and reversed end-diastolic velocities in the ductus venosus; thus, a meta-analysis was not attempted with these groups separated. Among them, the risk of fetal death of cases with ductus venosus reversed end-diastolic velocity was 46% (21 of 46). This risk is outweighed by the risks of prematurity at  $\leq 28$  weeks.

Our analysis has several strengths. First, we carried out an extensive and systematic literature search without time restrictions. Second, the 31 studies collectively enrolled a notable number of fetal deaths ( $n = 336$ ) among a large number with Doppler evaluations ( $n = 5909$ ). Third, for the umbilical artery, we were able to separately estimate the risks of fetal death for cases with absent and with reversed end-diastolic velocities.

Nonetheless, we also acknowledge some limitations. First, because we included only studies of early-onset growth-restricted fetuses requiring delivery before 34 weeks, the applicability is restricted to this period of pregnancy, the reason being that umbilical artery Doppler does not reliably reflect placental insufficiency beyond this gestational age.<sup>59</sup>

Second, the small number of studies separately reporting risks for absent and reversed end-diastolic velocities in the ductus venosus prevented us from carrying out separate meta-analyses, and we had to combine both patterns into 1 single category. The argument can also be made that with better equipment and

**FIGURE 5**  
**OR of ductus venosus absent or reverse end diastolic velocity**



Forest plot of the odds ratio of ductus venosus absent or reverse end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random effects model).

CI, confidence interval; OR odds ratio.

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skills, zero velocity would be reported less, and, consequently, a technical issue (skills and equipment) decides how many cases with absent end-diastolic velocity are identified.

Third, the included studies were hampered by clinical heterogeneity because case definition, types of antenatal testing, and frequency of these tests varied widely among studies. However, it could be argued that this is an area of ongoing research and that just recently a consensus definition has been reached.<sup>60</sup> Nonetheless, the selection criteria of our study could be reasonably assumed to capture reasonably this recent definition.

Fourth, timely delivery and fetal death are competing factors. Thus, differences in management could also account for the heterogeneity we found in the studies reporting risks in fetuses with ductus venosus absent or reversed end-diastolic velocities. The meta-regression performed on these studies does not seem to indicate such risk of work-up bias.

Fifth, only series in which the Doppler status has been concealed to the clinicians should have been included; however, there were few studies with concealed Doppler assessment,<sup>12,30-32,34,35,38,44,45</sup> none of which were recent. For ethical reasons, newer studies with such a design are unlikely to be carried out.

Finally, among cases with umbilical artery absent or reversed end-diastolic velocities, one quarter concomitantly have ductus venosus absent or reversed end-diastolic velocities.<sup>36</sup> The resolution of information reported in the included studies does not allow ascertaining the risk for fetal death of umbilical artery reversed end-diastolic velocity with and without ductus venosus absent or reversed end-diastolic velocity. Conversely, the proportion of cases with ductus venosus absent or reversed end-diastolic velocities and positive diastolic flow in the umbilical artery is negligible.<sup>36</sup>

In conclusion, early-onset growth-restricted fetuses with either umbilical artery/ductus venosus absent or reversed end-diastolic velocities are at a substantially increased risk for fetal death. The risks reported in this meta-analysis may

be useful for counseling pregnancies with early-onset growth restriction on the optimal gestational age for delivery. ■

#### ACKNOWLEDGMENT

Our sincere thanks go to the following authors and study groups for sharing aggregated data of their publications: the GRIT study group; the Epipage-2 Study Group; Erich Cosmi et al; Turan et al, and, Cruz-Lemini et al. We also thank S. Lobmaier for collaborating with the translation and extraction of data from articles in German.

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### Annex 1: Supplemental material: search strategy

#### Selected keywords

death, Doppler, ductus venosus, fetal Doppler, fetal growth restriction, growth retardation, growth restriction, intrauterine growth restriction, mortality, small for gestational age, stillbirth, umbilical artery

#### PUBMED query

(mortality OR stillbirth OR death) AND Doppler AND fetal AND (ductus venosus OR umbilical artery) AND (growth retardation OR growth restriction OR IUGR OR FGR OR SGA OR small for gestational age OR small-for-gestational age OR small-for-gestational-age) AND (English [la] OR French [la] OR Spanish [la] OR Italian [la] OR German [la]) NOT review [pt] NOT review [ti] NOT meta-analysis [ti]

Total yield: 320 articles

#### SCOPUS query

(mortality OR stillbirth OR death) AND doppler AND fetal AND (ductus venosus OR umbilical artery) AND (growth retardation OR growth restriction OR iugr OR fgr OR sga OR small for gestational age OR small-for-gestational age OR small-for-gestational-age) AND NOT review [title] AND NOT meta-analysis [title] AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "cp") AND (LIMIT-TO (SUBJAREA, "MEDI") OR LIMIT-TO (SUBJAREA, "HEAL") AND (LIMIT-TO (LANGUAGE, "English") OR LIMIT-TO (LANGUAGE, "German") OR LIMIT-TO (LANGUAGE, "Spanish") OR LIMIT-TO (LANGUAGE, "Italian").

Total yield: 268 articles

#### ISI web of Science query

TS = ([mortality OR stillbirth OR death] AND Doppler AND fetal AND [ductus venosus OR umbilical artery] AND [growth retardation OR growth restriction OR IUGR OR FGR OR SGA OR small for gestational age OR small-for-gestational age OR small-for-gestational-age]).

Refined by languages: (English OR German OR French OR Spanish OR unspecified) AND [excluding] databases: (MEDLINE) AND [excluding] document types: (Review OR Editorial).

Time span: all years.

Search language = Auto

Total yield: 75 articles

#### Search time frame

The first search was run on Feb. 17, 2017. Afterward, an update was extended until June 20, 2017.

## Annex 2: Supplementary material Aggregated data were provided by the authors of the following studies included in the meta-analysis

- Monier I, Ancel P-Y, Ego A, et al. Fetal and neonatal outcomes of preterm infants born before 32 weeks of gestation according to antenatal versus postnatal assessments of restricted growth. *Am J Obstet Gynecol* 2017;216:516.e1-10.<sup>56</sup>

Study population: 2919 singleton nonanomalous infants 24–31 weeks of gestational age from the EPIPAGE 2 study.

### Umbilical artery and Ductus venosus for fetal death among suspected fetal growth restriction/small-for-gestational-age infants

Variable	Suspected fetal growth restriction/small-for-gestational-age infants	
	Fetal death n (% <sup>a</sup> )	Livebirths n (% <sup>a</sup> )
Total	82 (11.8)	502 (81.2)
Umbilical artery		
Normal	7 (9.1)	153 (30.5)
Elevated Doppler index	2 (2.5)	70 (13.8)
Absent end-diastolic velocity	10 (11.9)	120 (23.8)
Reversed end-diastolic velocity	19 (22.4)	87 (17.4)
Missing	44 (54.0)	72 (14.5)
Ductus venosus		
Normal	2 (2.5)	98 (19.6)
Elevated Doppler index	1 (1.4)	8 (1.6)
Absent a-wave	3 (3.5)	8 (1.6)
Reversed a-wave	4 (4.5)	18 (3.6)
Missing	72 (88.1)	370 (73.6)

<sup>a</sup> Weighted percentage.

- Cruz-Lemini M, Crispi F, Van Mieghem T, et al. Risk of perinatal death in early-onset intrauterine growth restriction according to gestational age and cardiovascular Doppler indices: a multicenter study. *Fetal Diagn Ther* 2012;32:116-22.<sup>52</sup>

Study population: 222 singletons nonanomalous early-onset (<34 weeks) suspected fetal growth restriction.

\* There are more cases than reported in the original paper because some were excluded from the initial analysis because of incomplete data on other variables different from umbilical artery and ductus venosus).

<b>Umbilical artery and ductus venosus for fetal death among suspected fetal growth restriction</b>		
<b>Variable</b>	<b>Suspected fetal growth restriction</b>	
	<b>Fetal death n (%<sup>a</sup>)</b>	<b>Live births n (%<sup>a</sup>)</b>
Total	18 (8.1)	204 (91.9)
Umbilical artery		
Present end-diastolic velocity	0 (0)	82 (40.2)
Absent end-diastolic velocity	7 (38.8)	64 (31.4)
Reversed end-diastolic velocity	8 (44.4)	52 (25.5)
Missing	3 (16.6)	6 (2.9)
Ductus venosus		
Present a-wave	10 (55.6)	188 (92.2)
Absent a-wave	2 (11.1)	3 (1.5)
Reversed a-wave	5 (27.8)	9 (4.4)
Missing	1 (5.6)	4 (2.0)

<sup>a</sup> Weighted percentage.

- GRIT Study Group. A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. *BJOG* 2003;110:27-32.<sup>20</sup>

Study population: 392 singleton pregnancies randomized before 34 weeks.

<b>Umbilical artery and Ductus venosus for fetal death</b>		
<b>Variable</b>	<b>Fetal death</b>	
	<b>n (%<sup>a</sup>)</b>	<b>Live births n (%<sup>a</sup>)</b>
Total	9 (2.2)	383 (97.7)
Umbilical artery		
Present end-diastolic velocity	0 (0.0)	169 (44.1)
Absent end-diastolic velocity	8 (88.8)	183 (47.7)
Reversed end-diastolic velocity	1 (1.1)	31 (8.1)

<sup>a</sup> Weighted percentage.

- Cosmi E, Ambrosini G, D'Antona D, Saccardi C, Mari G. Doppler, cardiotocography, and biophysical profile changes in growth-restricted fetuses. *Obstet Gynecol* 2005;106:1240-5.<sup>12</sup>

Study population: 145 fetuses with an estimated weight below the 10th percentile and abnormal umbilical artery pulsatility index.

Variable	Suspected fetal growth restriction	
	Fetal death n (% <sup>a</sup> )	Live births n (% <sup>a</sup> )
Total	4 (2.8)	141 (97.2)
Umbilical artery		
Positive end-diastolic velocity	0 (0.0)	74 (52.4)
Absent end-diastolic velocity	1 (0.2)	0 (0.0)
Reversed end-diastolic velocity	3 (0.8)	67 (47.5)
Ductus venosus		
Present a-wave	2 (0.5)	126 (89.3)
Absent or reversed a-wave	2 (0.5)	15 (10.3)

<sup>a</sup> Weighted percentage.

- Turan OM, Turan S, Berg C, et al. Duration of persistent abnormal ductus venosus flow and its impact on perinatal outcome in fetal growth restriction. *Ultrasound Obstet Gynecol* 2011;38:295-302.<sup>52</sup>

Gestational age at diagnosis of the whole cohort of growth restricted babies:

- Mean: 31.7 weeks
- Range: 24.6 - 38.4 weeks

Gestational age at delivery of those fetal deaths with Umbilical artery absent or reversed end-diastolic velocity:

- Mean: 27.6 weeks
- Range: 24.6 - 30.6 weeks

Gestational age at delivery of those fetal deaths with Ductus venosus absent or reversed end-diastolic velocity:

- Mean: 28 weeks
- Range: 24.6 - 30.6 weeks

All ductus venosus with absent or reversed end-diastolic velocity had umbilical artery absent or reversed end-diastolic velocity.

**SUPPLEMENTAL FIGURE 1**  
**Risk of bias summary of included randomized studies**

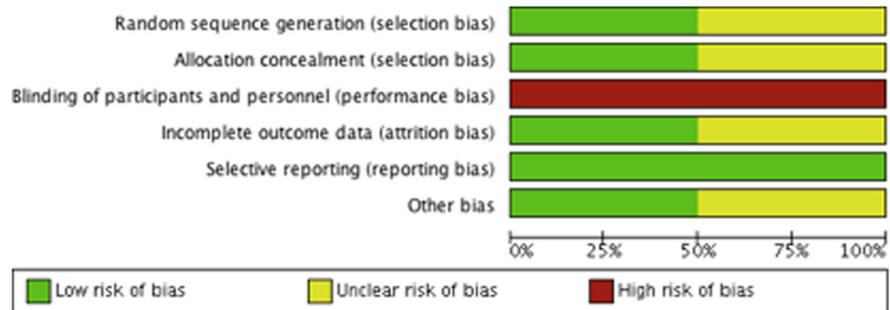
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
GRIT 2003	?	?	-	?	+	?
TRUFFLE 2015	+	+	-	+	+	+

This is a review of authors' judgments about each risk of bias item for each included study.

GRIT, Growth Restriction Intervention Trial Study Group; TRUFFLE, Trial of Randomized Umbilical and Fetal Flow in Europe.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL FIGURE 2**  
**Risk of bias graph of included randomized studies**

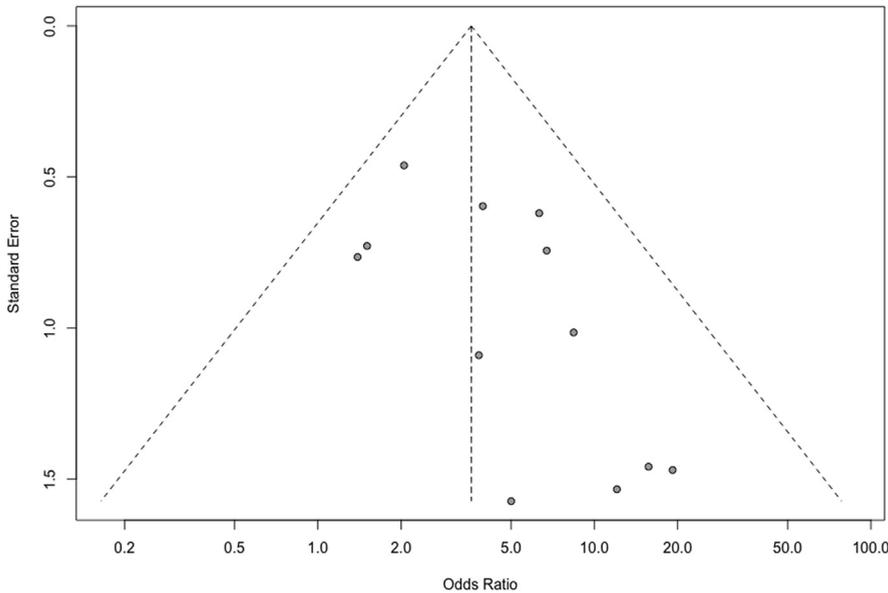


This is a review of review authors' judgments about each risk of bias item presented as percentages across all included studies.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL FIGURE 3**

**Funnel plot for umbilical artery absent end-diastolic velocity**

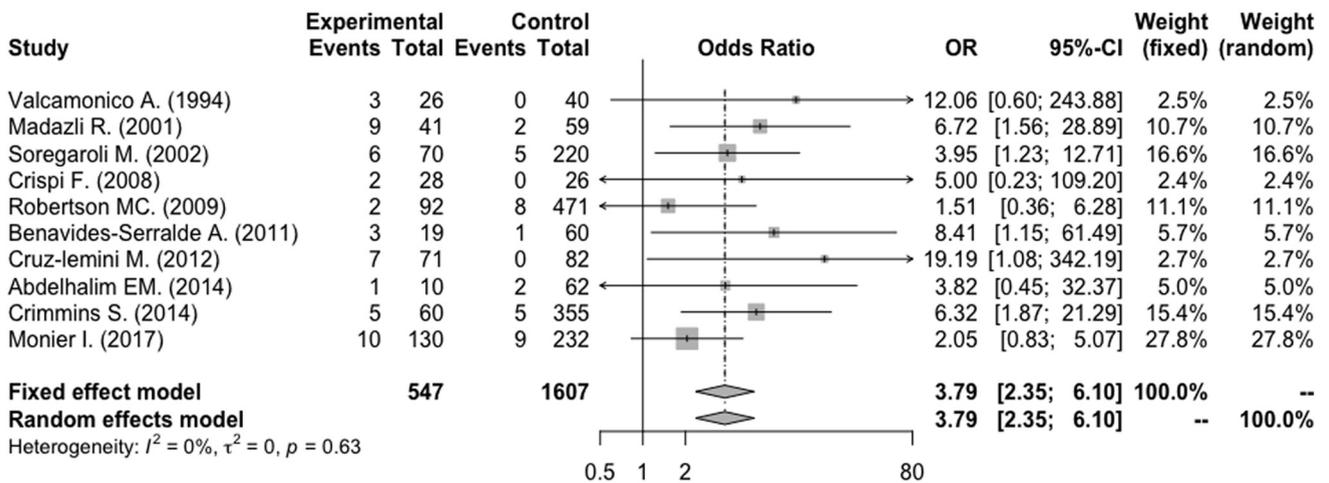


This is a funnel plot with pseudo 95% confidence limits for umbilical artery absent end diastolic velocity.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

**SUPPLEMENTAL FIGURE 4**

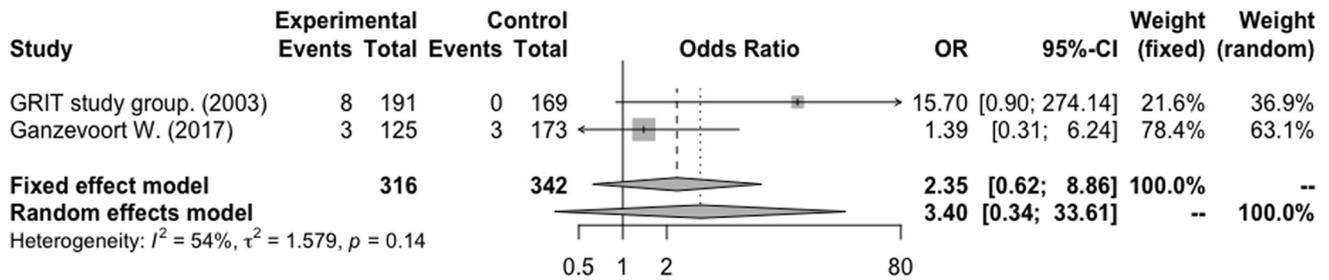
**Forest plot of of umbilical artery absent end-diastolic velocity**



Forest plot of the odds ratio of umbilical artery absent end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only cohort studies.

CI, confidence interval; OR, odds ratio.

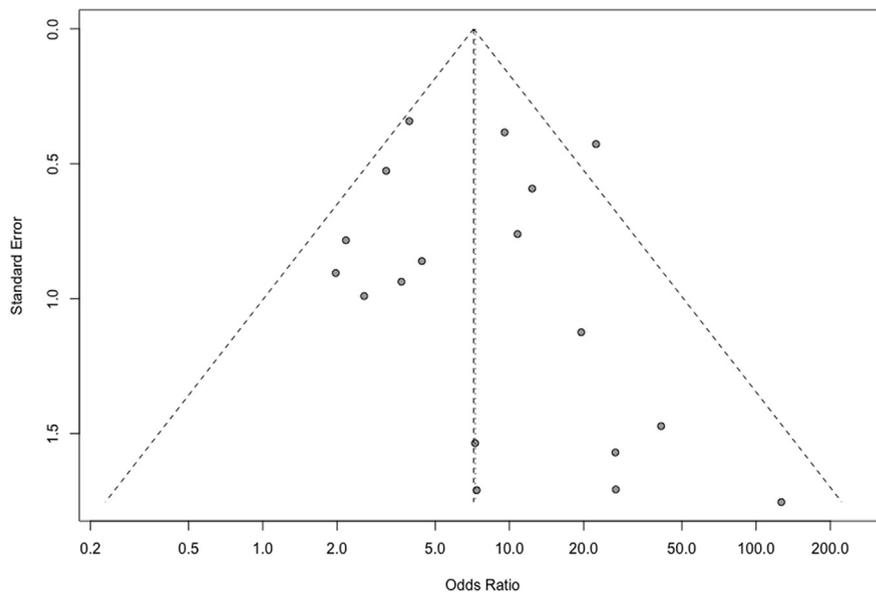
Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

**SUPPLEMENTAL FIGURE 5****Forest plot of of umbilical artery absent end-diastolic velocity**

Forest plot of the odds ratio of umbilical artery absent end-diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only randomized studies.

CI, confidence interval; GRIT, Growth Restriction Intervention Trial; OR, odds ratio.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

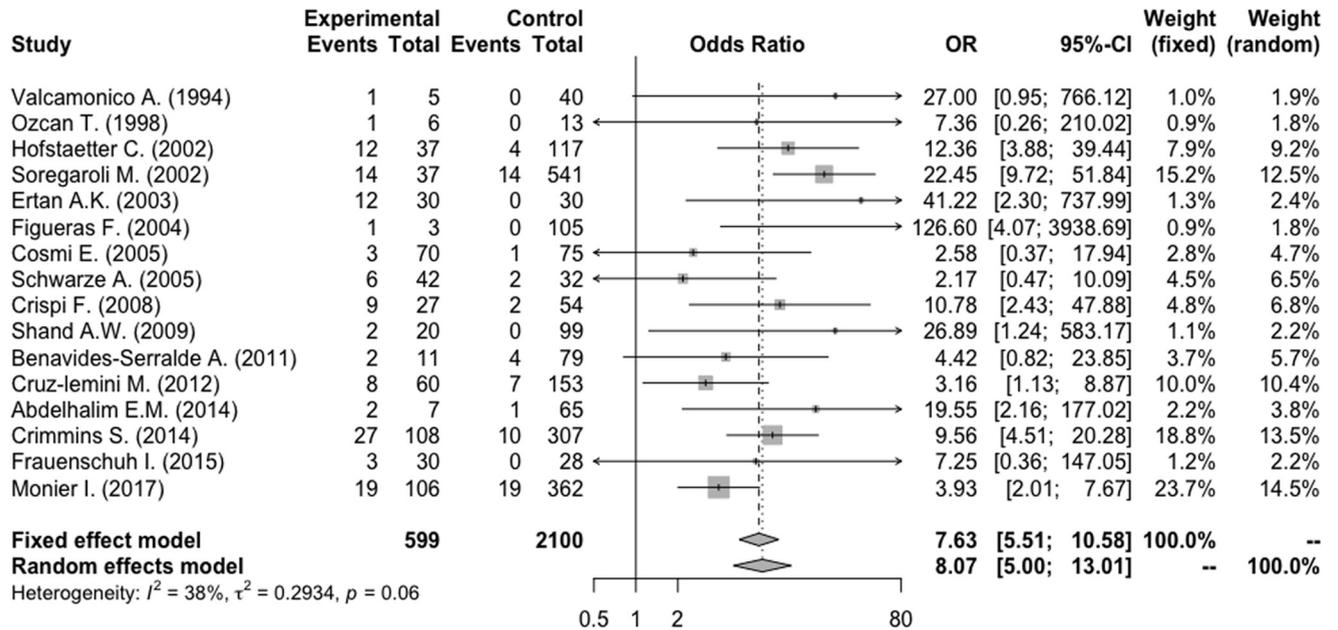
**SUPPLEMENTAL FIGURE 6****Funnel plot for umbilical artery reverse end-diastolic velocity**

Funnel plot with pseudo 95% confidence limits for umbilical artery reverse end diastolic velocity.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL FIGURE 7**

**Forest plot of umbilical artery reverse end-diastolic velocity for fetal death**



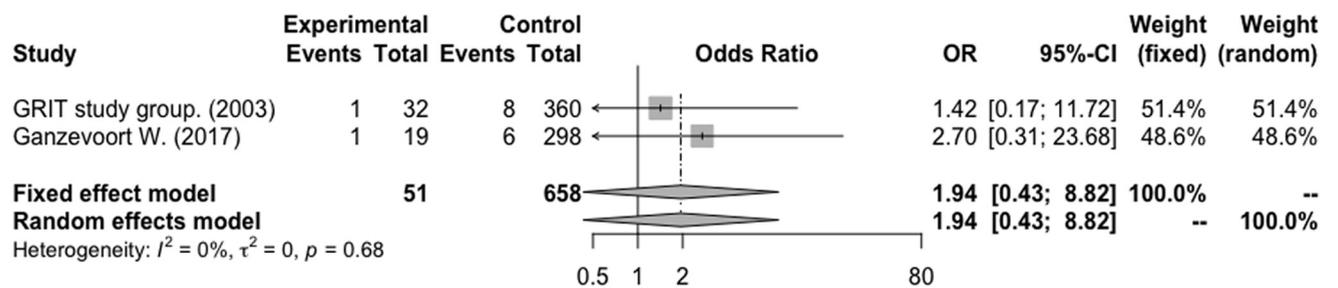
Forest plot of the odds ratio of umbilical artery reverse end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only cohort studies.

CI, confidence interval; OR, odds ratio.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

**SUPPLEMENTAL FIGURE 8**

**OR of umbilical artery reverse end-diastolic velocity for fetal death**



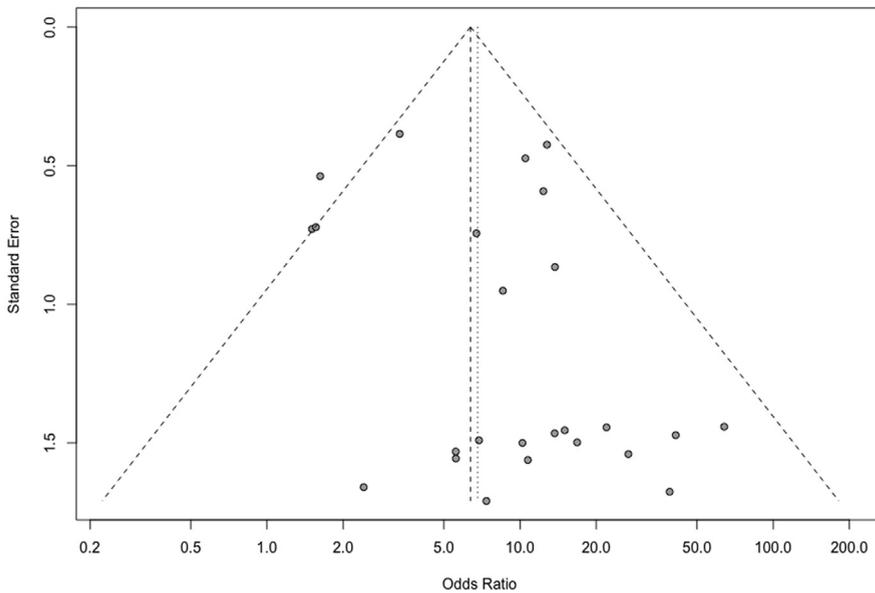
Forest plot of the odds ratio of umbilical artery reverse end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only randomized studies.

CI, confidence interval; GRIT, Growth Restriction Intervention Trial; OR, odds ratio.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

**SUPPLEMENTAL FIGURE 9**

**Funnel plot for umbilical artery absent or reverse end-diastolic velocity**

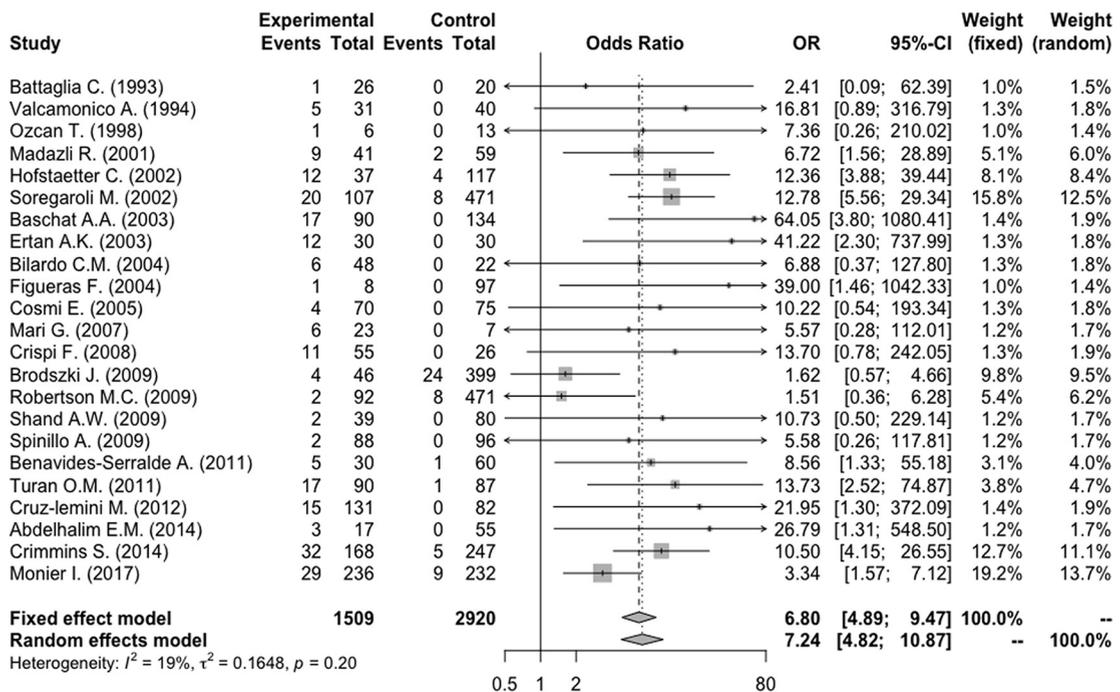


This shows a funnel plot with pseudo 95% confidence limits for umbilical artery absent or reverse end-diastolic velocity.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL FIGURE 10**

**Forest plot of umbilical artery absent or reverse end-diastolic velocity**

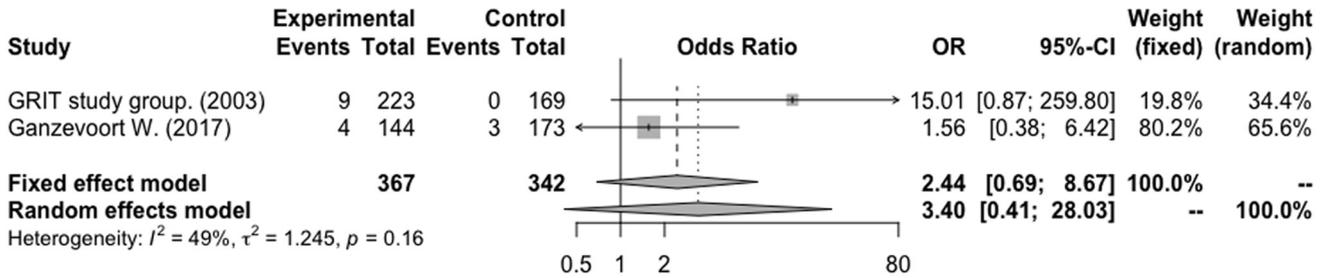


Forest plot of the odds ratio of umbilical artery absent or reverse end diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only cohort studies.

CI, confidence interval; OR, odds ratio.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

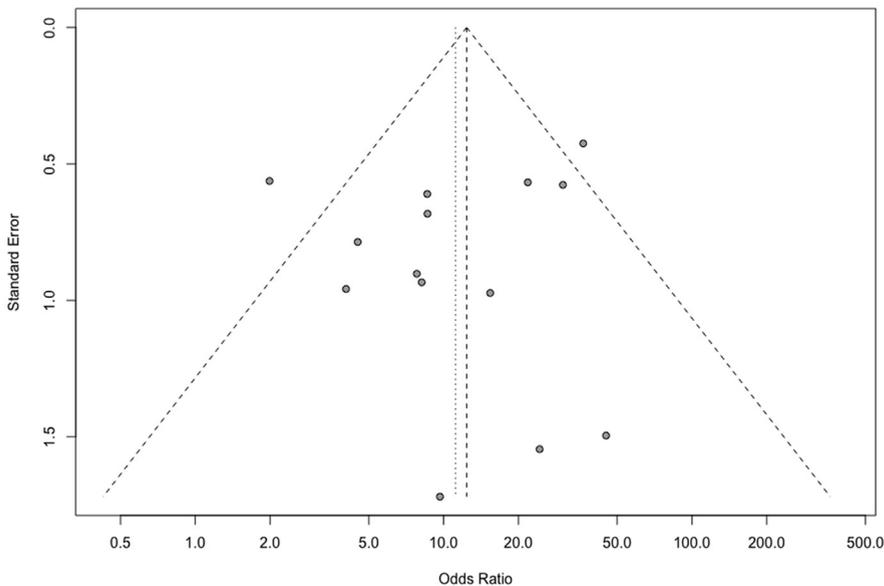
**SUPPLEMENTAL FIGURE 11**  
**Forest plot umbilical artery absent or reverse end-diastolic velocity**



This figure shows a forest plot of the odds ratio of umbilical artery absent or reverse end-diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only randomized studies.

CI, confidence interval; GRIT, Growth Restriction Intervention Trial; OR, odds ratio.  
 Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

**SUPPLEMENTAL FIGURE 12**  
**Funnel plot for ductus venosus absent or reverse end-diastolic velocity**

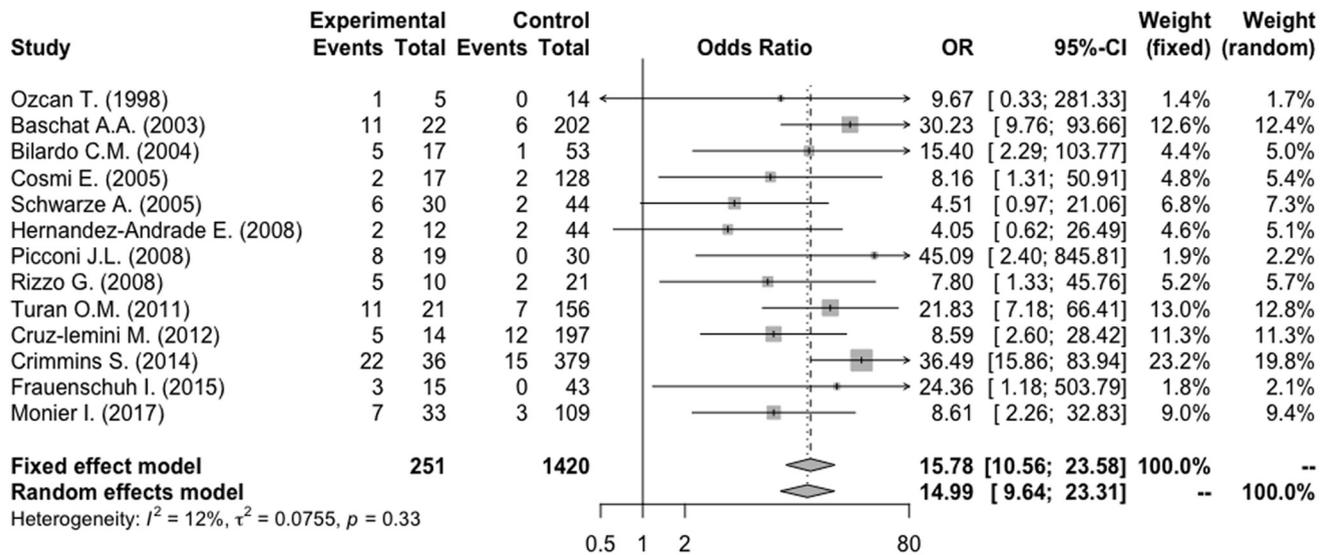


Funnel plot with pseudo 95% confidence limits for ductus venosus absent or reverse end diastolic velocity.

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

**SUPPLEMENTAL FIGURE 13**

**Forest plot of ductus venosus absent or reverse end-diastolic velocity**



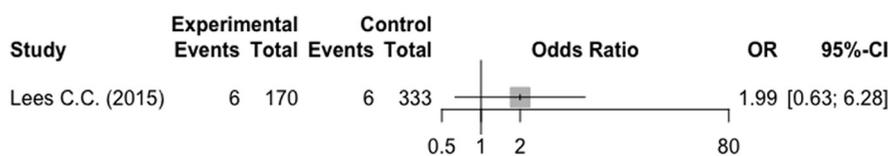
Forest plot of the odds ratio of ductus venosus absent or reverse end-diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only cohort studies.

CI, confidence interval; OR, odds ratio.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL FIGURE 14**

**Forest plot of ductus venosus absent or reverse end-diastolic velocity**



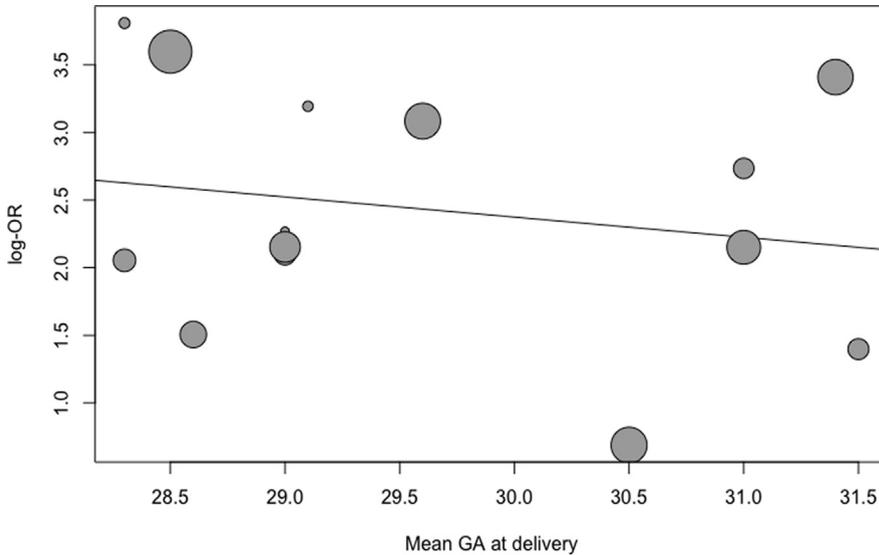
The figure shows the forest plot of the odds ratio of ductus venosus absent or reverse end-diastolic velocity for fetal death (weighted by the inverse of the variance under fixed and random-effects model) considering only randomized studies.

CI, confidence interval; OR, odds ratio.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL FIGURE 15**

**Bubble of gestational age on diastolic velocity**



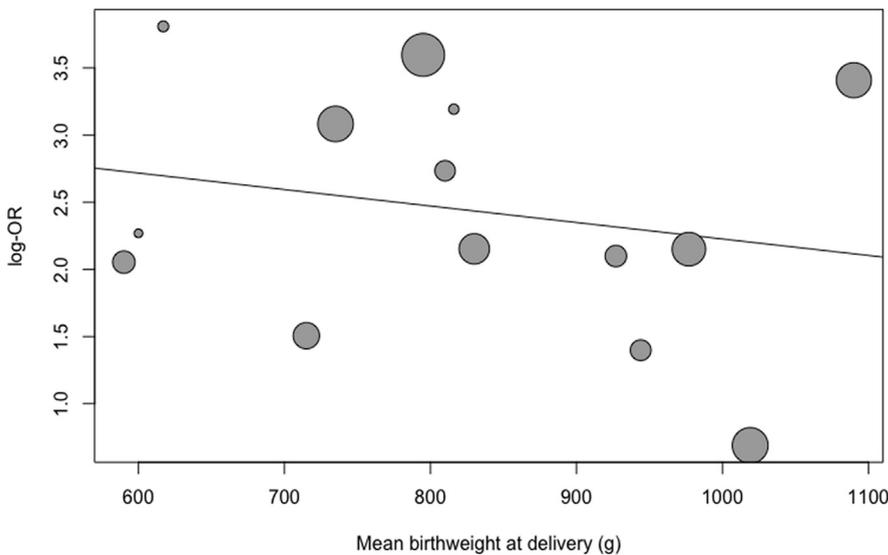
Bubble graph with the fitted meta-regression line of the mean gestational age at delivery against the OR for fetal death of the studies on ductus venosus absent or reverse end diastolic velocity.

GA, gestational age; OR, odds ratio.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL FIGURE 16**

**Bubble graph of birthweight on diastolic velocity**



This figure shows the bubble graph with the fitted meta-regression line of the mean birthweight against the OR for fetal death of the studies on ductus venosus absent or reverse end-diastolic velocity.

OR, odds ratio.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTAL TABLE 1**  
**Characteristics of the studies included in the meta-analysis**

Author	Year of publication	Country	Design	Study period	Inclusion criteria	Exclusion criteria	n	Vessel
Battaglia et al <sup>30</sup>	1993	Italy	Prospective cohort	January 1988 to November 1991	<ul style="list-style-type: none"> <li>• Singleton pregnancies</li> <li>• Amniotic fluid &lt;2 cm</li> <li>• &gt;2 SD in umbilical artery Doppler flow velocity-waveforms</li> <li>• Abdominal circumference &lt;5th centile</li> </ul>	<ul style="list-style-type: none"> <li>• Fetal structural or chromosomal abnormalities</li> <li>• Maternal diabetes</li> </ul>	46	Umbilical artery
Valcamonico et al <sup>31</sup>	1994	Italy	Prospective cohort	January 1989 to June 1990	<ul style="list-style-type: none"> <li>• Estimated fetal weight &lt; 2 SD</li> <li>• Information on Doppler flow evaluation</li> </ul>	<ul style="list-style-type: none"> <li>• x</li> </ul>	31	Umbilical artery
Ozcan et al <sup>32</sup>	1998	United States	Prospective cohort	June 1994 to February 1997	<ul style="list-style-type: none"> <li>• Normal fetal anatomy</li> <li>• Fetal weight &lt;5th centile</li> <li>• Doppler waveform estimations within 2 weeks from delivery</li> </ul>	<ul style="list-style-type: none"> <li>• Neonates with a birthweight &gt;5th centile</li> <li>• Fetal structural or chromosomal abnormalities after delivery</li> </ul>	19	Umbilical artery/ductus venosus
Madazli et al <sup>33</sup>	2001	Turkey	Prospective cohort	.	<ul style="list-style-type: none"> <li>• Singleton pregnancies</li> <li>• Fetal abdominal circumference &lt;2 SD</li> </ul>	<ul style="list-style-type: none"> <li>• Fetal structural or chromosomal abnormalities</li> </ul>	100	Umbilical artery
Hofstaetter et al <sup>34</sup>	2002	Germany	Prospective cohort	5.5 years	<ul style="list-style-type: none"> <li>• Singleton pregnancies</li> <li>• Estimated fetal weight below 10th centile</li> </ul>	<ul style="list-style-type: none"> <li>• Fetal structural or chromosomal abnormalities</li> </ul>	146	Umbilical artery
Soregaroli et al <sup>34</sup>	2002	Italy	Retrospective cohort	1991–1999	<ul style="list-style-type: none"> <li>• Singleton pregnancies</li> <li>• Fetal abdominal circumference &lt;2 SD</li> <li>• Information of fetal biometry, amniotic fluid and fetal-maternal Doppler velocimetry</li> </ul>	<ul style="list-style-type: none"> <li>• x</li> </ul>	578	Umbilical artery
Baschat et al <sup>36</sup>	2003	United States	Prospective cohort	December 1994 to June 2001	<ul style="list-style-type: none"> <li>• Delivery prior to 37 completed weeks of gestation</li> <li>• Birthweight &lt;10th percentile</li> <li>• Pulsatility index umbilical artery &gt;2 SD above the mean for gestational age</li> </ul>	<ul style="list-style-type: none"> <li>• Maternal diabetes</li> <li>• Fetal structural or chromosomal abnormalities</li> <li>• Twin gestation</li> </ul>	224	Umbilical artery/ductus venosus
Ertan et al <sup>37</sup>	2003	Germany	Cohort	10 year period	<ul style="list-style-type: none"> <li>• Umbilical artery or fetal aorta absent or reverse end diastolic velocity at the time of delivery</li> <li>• Perinatal outcome</li> </ul>	<ul style="list-style-type: none"> <li>• Fetal structural or chromosomal abnormalities</li> </ul>	30	Umbilical artery

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

(continued)

## SUPPLEMENTAL TABLE 1

## Characteristics of the studies included in the meta-analysis (continued)

Author	Year of publication	Country	Design	Study period	Inclusion criteria	Exclusion criteria	n	Vessel
GRIT Study Group <sup>20</sup>	2003	Belgium	RCT	.	<ul style="list-style-type: none"> <li>• Singleton or multiple pregnancies where the responsible clinician was uncertain whether to deliver the baby immediately</li> <li>• Gestational age between 24 and 36 weeks</li> <li>• Recorded waveform of umbilical artery Doppler</li> </ul>	<ul style="list-style-type: none"> <li>• x</li> </ul>	392	Umbilical artery
Bilardo et al <sup>38</sup>	2004	The Netherlands/ United Kingdom	Cohort	.	<ul style="list-style-type: none"> <li>• Singleton pregnancies</li> <li>• &lt; 33 weeks of gestation</li> <li>• Abdominal circumference &lt;5th centile</li> </ul>	<ul style="list-style-type: none"> <li>• x</li> </ul>	70	Umbilical artery / Ductus venosus
Figueras et al <sup>39</sup>	2004	Spain	Prospective cohort	June 1998 to December 1999	<ul style="list-style-type: none"> <li>• Pregnancies &gt; 26 weeks</li> <li>• Fetal weight &lt;5th centile</li> </ul>	<ul style="list-style-type: none"> <li>• x</li> </ul>	108	Umbilical artery
Cosmi et al <sup>12</sup>	2005	Italy	Prospective cohort	2001 to 2004	<ul style="list-style-type: none"> <li>• Fetal weight &lt;10th centile</li> <li>• Umbilical artery pulsatility index &gt;2</li> <li>• Normal fetal anatomy</li> <li>• Absence of maternal pathology</li> <li>• Delivery before 32 weeks of gestation</li> <li>• Forward umbilical artery diastole</li> <li>• Forward ductus venous diastolic flow</li> <li>• At least 3 consecutive Doppler measurements before delivery</li> <li>• Last Doppler measurement obtained within 24 hours from delivery</li> </ul>	<ul style="list-style-type: none"> <li>• Abnormal fetal anatomy</li> <li>• Maternal pathology</li> <li>• Pulsation in umbilical vein</li> <li>• Amniotic fluid index &lt;5 cm</li> </ul>	145	Umbilical artery/ductus venosus
Schwarze et al <sup>40</sup>	2005	Germany	Retrospective cohort	1999–2004	<ul style="list-style-type: none"> <li>• Birthweight &lt;10th centile</li> <li>• Absent or reverse end-diastolic velocity in umbilical artery</li> <li>• Delivered before 34 weeks of gestation</li> </ul>	<ul style="list-style-type: none"> <li>• Multiple pregnancies</li> <li>• Fetal structural abnormalities</li> </ul>	74	Umbilical artery/ductus venosus

Caradeux. Doppler changes and risk of fetal death. Am J Obstet Gynecol 2018.

(continued)

## SUPPLEMENTAL TABLE 1

## Characteristics of the studies included in the meta-analysis (continued)

Author	Year of publication	Country	Design	Study period	Inclusion criteria	Exclusion criteria	n	Vessel
Mari et al <sup>40</sup>	2007	Italy	Retrospective cross-sectional	.	<ul style="list-style-type: none"> <li>Fetal weight &lt;3rd centile</li> <li>Umbilical artery pulsatility index &gt;95th centile</li> <li>Normal anatomy</li> <li>Middle cerebral artery examination within 8 days before delivery of fetal demise</li> <li>Deliveries before 33 weeks of gestation</li> </ul>	<ul style="list-style-type: none"> <li>Fetal structural or chromosomal abnormalities</li> </ul>	30	Umbilical artery
Crispi et al <sup>42</sup>	2008	United Kingdom	Cohort	.	<ul style="list-style-type: none"> <li>Fetal weight &lt;10th centile</li> <li>Umbilical artery pulsatility index &gt;2 SD</li> <li>Fetal death between 24 and 34 weeks</li> </ul>	<ul style="list-style-type: none"> <li>Evidence of fetal infection</li> <li>Structural/ chromosomal abnormalities</li> </ul>	81	Umbilical artery
Hernandez-Andrade et al <sup>43</sup>	2008	Spain	Cohort	.	<ul style="list-style-type: none"> <li>Fetal weight &lt;10th centile</li> <li>Umbilical artery pulsatility index &gt;2 SD</li> <li>Information from ductus venosus, umbilical artery, and middle cerebral artery</li> </ul>	<ul style="list-style-type: none"> <li>x</li> </ul>	56	Ductus venosus
Picconi et al <sup>44</sup>	2008	United States	Retrospective cohort	.	<ul style="list-style-type: none"> <li>Fetal weight &lt; 10th centile</li> <li>Umbilical artery pulsatility index &gt;95th centile</li> <li>Normal anatomy</li> <li>Doppler assessment of the ductus venosus</li> </ul>	<ul style="list-style-type: none"> <li>Fetal infection</li> <li>Fetal structural or chromosomal abnormalities</li> </ul>	49	Ductus venosus
Rizzo et al <sup>45</sup>	2008	Italy	Prospective cohort	March 2006 to May 2008	<ul style="list-style-type: none"> <li>Fetal weight &lt;10th centile</li> <li>Abnormal umbilical artery velocity waveforms during and diastole</li> <li>Successful recordings from both ductus venosus and aortic isthmus</li> </ul>	<ul style="list-style-type: none"> <li>Fetal structural or chromosomal abnormalities</li> <li>Maternal disease</li> </ul>	31	Ductus venosus
Brodzski et al <sup>46</sup>	2009	Sweden	Retrospective cohort	1998–2004	<ul style="list-style-type: none"> <li>Fetuses with absent or reverse end-diastolic velocity in umbilical artery before 30 weeks of gestation</li> <li>Fetal weight &lt;2 SD</li> <li>Live-born delivery before 30 weeks of gestation</li> </ul>	<ul style="list-style-type: none"> <li>Fetal structural or chromosomal abnormalities</li> <li>Absence of twin-to-twin transfusion syndrome</li> </ul>	46	Umbilical artery

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

(continued)

## SUPPLEMENTAL TABLE 1

## Characteristics of the studies included in the meta-analysis (continued)

Author	Year of publication	Country	Design	Study period	Inclusion criteria	Exclusion criteria	n	Vessel
Robertson et al <sup>47</sup>	2009	Australia	Retrospective cohort	July 1998 to January 2006	<ul style="list-style-type: none"> <li>• Singleton pregnancies</li> <li>• Growth-restricted fetuses</li> <li>• Absent end-diastolic flow</li> <li>• Subsequent administration of betamethasone and poststeroid umbilical artery Doppler studies</li> </ul>	<ul style="list-style-type: none"> <li>• x</li> </ul>	92	Umbilical artery
Shand et al <sup>48</sup>	2009	Australia	Retrospective cohort	January 2001 to December 2004	<ul style="list-style-type: none"> <li>• Birthweight ratio of less than 0.85</li> <li>• Umbilical artery Doppler assessment within 7 days of birth</li> </ul>	<ul style="list-style-type: none"> <li>• x</li> </ul>	119	Umbilical artery
Spinillo et al <sup>49</sup>	2009	Italy	Prospective cohort	1997–2006	<ul style="list-style-type: none"> <li>• Fetal abdominal circumference &lt;10th centile</li> <li>• Umbilical artery pulsatility &gt;95th centile</li> <li>• Umbilical artery absent/reversed end-diastolic velocities</li> </ul>	<ul style="list-style-type: none"> <li>• Fetal structural or chromosomal abnormalities</li> </ul>	184	Umbilical artery
Benavides-Serralde et al <sup>50</sup>	2011	Spain	Prospective cohort	April 2007 to December 2009	<ul style="list-style-type: none"> <li>• Singleton pregnancies</li> <li>• Fetal weight &lt;10th centile</li> <li>• High-risk pregnancies</li> </ul>	<ul style="list-style-type: none"> <li>• x</li> </ul>	72	Umbilical artery
Turan et al <sup>51</sup>	2011	United States/ Germany/Italy/The Netherlands/United Kingdom	Prospective cohort	January 2000 to March 2006	<ul style="list-style-type: none"> <li>• Singleton pregnancies</li> <li>• Abdominal circumference &lt;5th percentile</li> <li>• Umbilical artery pulsatility index &gt;2 SD</li> <li>• At least 3 Doppler examinations before delivery</li> </ul>	<ul style="list-style-type: none"> <li>• Fetal structural or chromosomal abnormalities</li> </ul>	177	Umbilical artery/ductus venosus
Cruz-Lemini et al <sup>52</sup>	2012	Spain/Belgium/Chile	Prospective cohort	2 year period	<ul style="list-style-type: none"> <li>• Fetal weight &lt;10th centile</li> <li>• Umbilical artery pulsatility index &gt;95th centile</li> </ul>	<ul style="list-style-type: none"> <li>• Twin pregnancies</li> <li>• Fetal infection</li> <li>• Fetal structural or chromosomal abnormalities</li> </ul>	222	Umbilical artery
Abdelhalim et al <sup>53</sup>	2014	Egypt	Prospective cohort	May 2010 to February 2013	<ul style="list-style-type: none"> <li>• Singleton pregnancies</li> <li>• Scan at 28–38 weeks</li> <li>• High-risk pregnancies for IUGR</li> </ul>	<ul style="list-style-type: none"> <li>• Low-risk pregnancies</li> <li>• Fetal structural or chromosomal abnormalities</li> </ul>	72	Umbilical artery

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

(continued)

## SUPPLEMENTAL TABLE 1

## Characteristics of the studies included in the meta-analysis (continued)

Author	Year of publication	Country	Design	Study period	Inclusion criteria	Exclusion criteria	n	Vessel
Crimmins et al <sup>54</sup>	2014	United States/ Germany	Retrospective cohort	January 2000 to December 2002	<ul style="list-style-type: none"> <li>High-risk pregnancies</li> <li>Fetal weight &lt;10th centile</li> </ul>	<ul style="list-style-type: none"> <li>Fetal structural or chromosomal abnormalities</li> <li>Multiple gestation</li> <li>Fetal infection</li> <li>Unavailability of outcome variables</li> </ul>	987	Umbilical artery/ductus venosus
Frauenschuh et al <sup>55</sup>	2015	Germany	Cohort	1996–2004	<ul style="list-style-type: none"> <li>High-risk singleton pregnancy</li> <li>Growth-restricted fetuses &lt;32 weeks</li> <li>Umbilical artery absent/reversed end-diastolic velocities</li> </ul>	<ul style="list-style-type: none"> <li>Multiple pregnancies</li> <li>Fetal structural or chromosomal abnormalities</li> </ul>	58	Umbilical artery/ductus venosus
Lees et al <sup>57</sup> (TRUFFLE)	2015	Europe (United Kingdom, The Netherlands, Germany, Austria, Italy)	Randomized control trial	January 2005 to October 2010	<ul style="list-style-type: none"> <li>Singleton pregnancies</li> <li>Fetal abdominal circumference &lt;10th centile</li> <li>Umbilical artery pulsatility index &gt;95th centile, with or without reversed or absent end-diastolic velocities</li> <li>Gestational age between 26 and 31.9 weeks</li> <li>Fetal weight &gt;500 g</li> <li>Normal ductus venosus waveform with pulsatility index &lt;95th centile</li> </ul>	<ul style="list-style-type: none"> <li>Delivery known, planned, or impending</li> <li>Women younger than 18 years old</li> <li>Fetal structural or chromosomal abnormalities</li> </ul>	503	Ductus venosus
Ganzevoort et al <sup>58</sup> (TRUFFLE)	2017	Swiss	Retrospective cohort	1998–2004	<ul style="list-style-type: none"> <li>Fetal weigh &lt;2 SD</li> <li>Umbilical artery absent/reversed end-diastolic velocities</li> <li>Delivery &lt;30 weeks of gestation</li> </ul>	<ul style="list-style-type: none"> <li>Fetal structural or chromosomal abnormalities</li> <li>Twin-to-twin transfusion syndrome</li> </ul>	317	Umbilical artery
Monier et al <sup>56</sup>	2017	France	Prospective cohort	2011–2017	<ul style="list-style-type: none"> <li>All deliveries between 22 and 31 weeks</li> <li>Information on Doppler and fetal outcome</li> </ul>	<ul style="list-style-type: none"> <li>Patients with no inform consent or incomplete data</li> </ul>	636	Umbilical artery/ductus venosus

IUGR, intrauterine growth restriction; RCT, randomized controlled trial.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

## SUPPLEMENTAL TABLE 2

## Influence analysis on umbilical artery absent end-diastolic velocity

## IoV random effect model estimation if the study is deleted

Study deleted	OR	95% CI	OR change (%)	Heterogeneity		Relative weights IoV REM, %	
				I <sup>2</sup> , %	P value		
Valcamonico et al <sup>31</sup> (1994)	3.54	2.19	5.72	-2.9	0	NS	2.9
Madazli et al <sup>33</sup> (2001)	3.37	2.05	5.55	-7.4	0	NS	8.8
Soregaroli et al <sup>35</sup> (2002)	3.58	2.14	5.99	-1.8	0	NS	15.1
GRIT Study Group <sup>20</sup> (2003)	3.50	2.16	5.66	-4.0	0	NS	2.6
Crispi et al <sup>42</sup> (2008)	3.61	2.24	5.84	-0.8	0	NS	2.3
Robertson et al <sup>47</sup> (2009)	4.05	2.45	6.65	11.1	0	NS	9.1
Benavides-Serralde et al <sup>50</sup> (2011)	3.47	3.47	5.64	-4.7	0	NS	4.1
Cruz-Lemini et al <sup>52</sup> (2012)	3.48	2.15	5.62	-4.6	0	NS	2.9
Abdelhalim et al <sup>53</sup> (2014)	3.66	2.25	5.92	0.3	0	NS	3.6
Crimmins et al <sup>54</sup> (2014)	3.33	2.00	5.55	-8.6	0	NS	13.9
Ganzevoort et al <sup>58</sup> (2017)	3.99	2.43	6.55	9.5	0	NS	8.6
Monier et al <sup>56</sup> (2017)	4.45	2.57	7.73	22.2	0	NS	26.1

Umbilical artery absent end-diastolic velocity Egger publication bias: \_cons, 1.30, SE, 0.641; t = 2.04, p = .069 (-1.12 to 2.73).

CI, confidence interval; NS, not significant; OR, odds ratio; IoV, Inverse of Variance; REM, Random Effect Model.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

SUPPLEMENTAL TABLE 3

## Influence analysis on umbilical artery reverse end-diastolic velocity

Study deleted	IoV random effect model estimation if the study is deleted				Heterogeneity		Relative weights IoV REM (%)
	OR	95% CI		OR change, %	I <sup>2</sup> , %	P value	
Valcamonico et al <sup>31</sup> (1994)	7.36	4.62	11.71	−1.1	0	.583	2.1
Ozcan et al <sup>32</sup> (1998)	7.50	4.72	11.94	0.8	0	.582	1.9
Hofstaetter et al <sup>34</sup> (2002)	7.04	4.37	11.34	−5.4	0	.609	8.4
Soregaroli et al <sup>35</sup> (2002)	6.11	4.23	8.83	−17.8	0	.490	12.2
Ertan et al <sup>37</sup> (2003)	7.17	4.57	11.24	−3.7	0	.612	2.2
GRIT Study Group <sup>20</sup> (2003)	7.92	5.10	12.30	6.4	0	.627	3.7
Figuera et al <sup>39</sup> (2004)	7.17	4.59	11.19	−3.7	0	.618	1.9
Cosmi et al <sup>12</sup> (2005)	7.65	4.81	12.17	2.8	0	.595	3.3
Schwarze et al <sup>40</sup> (2005)	7.92	5.02	12.49	6.4	0	.613	5.4
Crispi et al <sup>42</sup> (2008)	7.19	4.48	11.54	−3.3	0	.599	5.6
Shand et al <sup>48</sup> (2009)	7.31	4.59	11.63	−1.8	0	.588	2.7
Benavides-Serralde et al <sup>50</sup> (2011)	7.66	4.79	12.26	2.9	0	.596	4.7
Cruz-Lemini et al <sup>52</sup> (2012)	8.16	5.15	12.93	9.7	0	.602	9.8
Abdelhalim et al <sup>53</sup> (2014)	7.19	4.55	11.36	−3.4	0	.602	2.7
Crimmins et al <sup>54</sup> (2014)	7.14	4.31	11.84	−4.0	0	.630	13.4
Frauenschuh et al <sup>55</sup> (2015)	7.44	4.68	11.85	0	0	.580	2.0
Ganzevoort et al <sup>58</sup> (2017)	7.73	4.88	12.25	3.9	0	.602	3.6
Monier et al <sup>56</sup> (2017)	8.40	5.31	13.30	12.8	0	.535	14.6

Umbilical artery reverse end-diastolic velocity Egger Publication Bias,  $\text{I}^2$  cons 0.100, SE, 0.597,  $t = 0.17$ ,  $P = .868$  (−1.16 to 1.36).

CI, confidence interval; OR, odds ratio; IoV, Inverse of Variance; REM, Random Effect Model.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.

SUPPLEMENTAL TABLE 4

## Influence analysis on umbilical artery absent or reverse end-diastolic velocity

Study deleted	IoV random-effect model estimation if the study is deleted				Heterogeneity		Relative weights IoV REM (%)
	OR	95% CI		OR change, %	I <sup>2</sup> , %	P value	
Battaglia et al <sup>33</sup> (1993)	7.31	4.72	11.32	2.0	0	NS	1.4
Valcamonica et al <sup>31</sup> (1994)	7.10	4.58	11.00	-1.0	0	NS	2.1
Ozcan et al <sup>32</sup> (1998)	7.27	4.68	11.29	1.5	0	NS	1.7
Madzali et al <sup>33</sup> (2001)	7.20	4.58	11.30	0.4	0	NS	5.3
Hofstaetter et al <sup>34</sup> (2002)	6.81	4.36	10.63	-5.0	0	NS	7.7
Soregaroli et al <sup>35</sup> (2002)	6.56	4.21	10.21	-8.5	0	NS	11.3
Baschat et al <sup>36</sup> (2003)	6.77	4.46	10.27	-5.6	0	NS	2.4
Ertan et al <sup>37</sup> (2003)	6.90	4.51	10.57	-3.7	0	NS	2.0
GRIT Study Group <sup>20</sup> (2003)	7.09	4.58	10.97	-1.1	0	NS	1.8
Bilardo et al <sup>38</sup> (2004)	7.18	4.63	11.13	0.1	0	NS	1.3
Figueras et al <sup>39</sup> (2004)	7.09	4.57	10.98	-1.1	0	NS	2.0
Cosmi et al <sup>12</sup> (2005)	7.18	4.62	11.15	0.1	0	NS	2.0
Mari et al <sup>41</sup> (2007)	7.18	4.64	11.12	0.2	0	NS	1.0
Crispi et al <sup>42</sup> (2008)	7.09	4.59	10.96	-1.1	0	NS	1.4
Brodzski et al <sup>46</sup> (2009)	7.85	5.50	11.22	9.5	0	NS	8.6
Robertson et al <sup>47</sup> (2009)	7.67	5.13	11.45	6.9	0	NS	5.4
Shand et al <sup>48</sup> (2009)	7.22	4.64	11.23	0.7	0	NS	2.2
Spinillo et al <sup>49</sup> (2009)	7.27	4.68	11.29	1.4	0	NS	1.8
Benavides-Serralde et al <sup>50</sup> (2011)	7.10	4.56	11.05	-1.1	0	NS	3.2
Turan et al <sup>51</sup> (2009)	6.90	4.47	10.66	-3.7	0	NS	3.6
Cruz-Lemini et al <sup>52</sup> (2012)	7.02	4.55	10.82	-2.1	0	NS	1.6
Abdelhalim et al <sup>53</sup> (2014)	7.05	4.55	10.92	-1.6	0	NS	2.4
Crimmins et al <sup>54</sup> (2014)	6.85	4.34	10.81	-4.4	0	NS	10.0
Ganzevoort et al <sup>58</sup> (2017)	7.68	5.08	11.62	7.2	0	NS	5.7
Monier et al <sup>56</sup> (2017)	7.89	5.08	12.27	10.1	0	NS	12.3

Umbilical artery absent or reverse end-diastolic velocity Egger Publication Bias.  $\tau$ -cons, 0.678, SE, 0.451,  $t = 1.50$ ,  $P = .147$  (-0.25 to 1.61).

CI, confidence interval; IoV, inverse of variance; NS, not significant; OR, odds ratio; REM, random effect model.

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SUPPLEMENTAL TABLE 5

## Influence analysis on ductus venosus absent or reverse end-diastolic velocity

Study deleted	IoV random-effect model estimation if the study is deleted				Heterogeneity		Relative weights IoV REM, %
	OR	95% CI	OR change, %	I <sup>2</sup> , %	P value		
Ozcan et al <sup>32</sup> (1998)	12.11	6.67 21.99	1.9	0	NS	2.9	
Baschat et al <sup>36</sup> (2003)	10.62	5.79 19.45	-10.7	0	NS	10.1	
Bilardo et al <sup>38</sup> (2004)	11.48	6.26 21.05	-3.4	0	NS	4.8	
Cosmi et al <sup>12</sup> (2005)	12.08	6.57 22.22	1.6	0	NS	5.5	
Schwarze et al <sup>40</sup> (2005)	12.62	6.90 23.08	6.2	0	NS	7.0	
Hernández-Andrade et al <sup>43</sup> (2008)	12.59	6.95 22.83	5.9	0	NS	5.3	
Picconi et al <sup>44</sup> (2008)	11.35	6.26 20.61	-4.5	0	NS	3.6	
Rizzo et al <sup>45</sup> (2008)	12.00	6.50 22.15	1.0	0	NS	5.9	
Turan et al <sup>51</sup> (2009)	10.96	5.84 20.53	-7.8	0	NS	10.3	
Cruz-Lemini et al <sup>52</sup> (2012)	12.23	6.51 22.95	2.8	0	NS	9.6	
Crimmins et al <sup>54</sup> (2014)	10.04	5.82 17.30	-15.5	0	NS	12.6	
Frauenschuh et al <sup>55</sup> (2015)	11.70	6.40 21.45	-1.5	0	NS	3.8	
Lees et al <sup>57</sup> (2015)	17.17	11.28 26.16	44.4	0	NS	10.2	
Monier et al <sup>56</sup> (2017)	12.06	6.45 22.55	1.4	0	NS	8.4	

Ductus venosus absent or reverse end-diastolic velocity Egger Publication Bias,  $\tau_{cons}$ , -1.01, SE, 1.02,  $t = -0.99$ ,  $P = .341$  (-3.25 to 1.22).

CI, confidence interval; NS, not significant; OR, odds ratio; IoV, Inverse of Variance; REM, Random Effect Model.

Caradeux. Doppler changes and risk of fetal death. *Am J Obstet Gynecol* 2018.



# Outcome in early-onset fetal growth restriction is best combining computerized fetal heart rate analysis with ductus venosus Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe

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## Introduction

Advances in neonatal care over the last few decades have resulted in improved survival of preterm infants even at very early gestational ages.<sup>1</sup> However, morbidity, neurological impairment, and decrements in intellectual and social performance are still prevalent and strongly associated with gestational age at birth.<sup>2,3</sup> The situation becomes even more critical if prematurity is determined by the need to rescue the fetus from an unfavorable intrauterine environment—as is the case in placental insufficiency. The outcome of these infants will not only depend on the degree of prematurity but also on the severity of fetal growth restriction (FGR).<sup>4-6</sup> Given

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**BACKGROUND:** Early-onset fetal growth restriction represents a particular dilemma in clinical management balancing the risk of iatrogenic prematurity with waiting for the fetus to gain more maturity, while being exposed to the risk of intrauterine death or the sequelae of acidosis.

**OBJECTIVE:** The Trial of Umbilical and Fetal Flow in Europe was a European, multicenter, randomized trial aimed to determine according to which criteria delivery should be triggered in early fetal growth restriction. We present the key findings of the primary and secondary analyses.

**STUDY DESIGN:** Women with fetal abdominal circumference <10th percentile and umbilical pulsatility index >95th percentile between 26-32 weeks were randomized to 1 of 3 monitoring and delivery protocols. These were: fetal heart rate variability based on computerized cardiotocography; and early or late ductus venosus Doppler changes. A safety net based on fetal heart rate abnormalities or umbilical Doppler changes mandated delivery irrespective of randomized group. The primary outcome was normal neurodevelopmental outcome at 2 years.

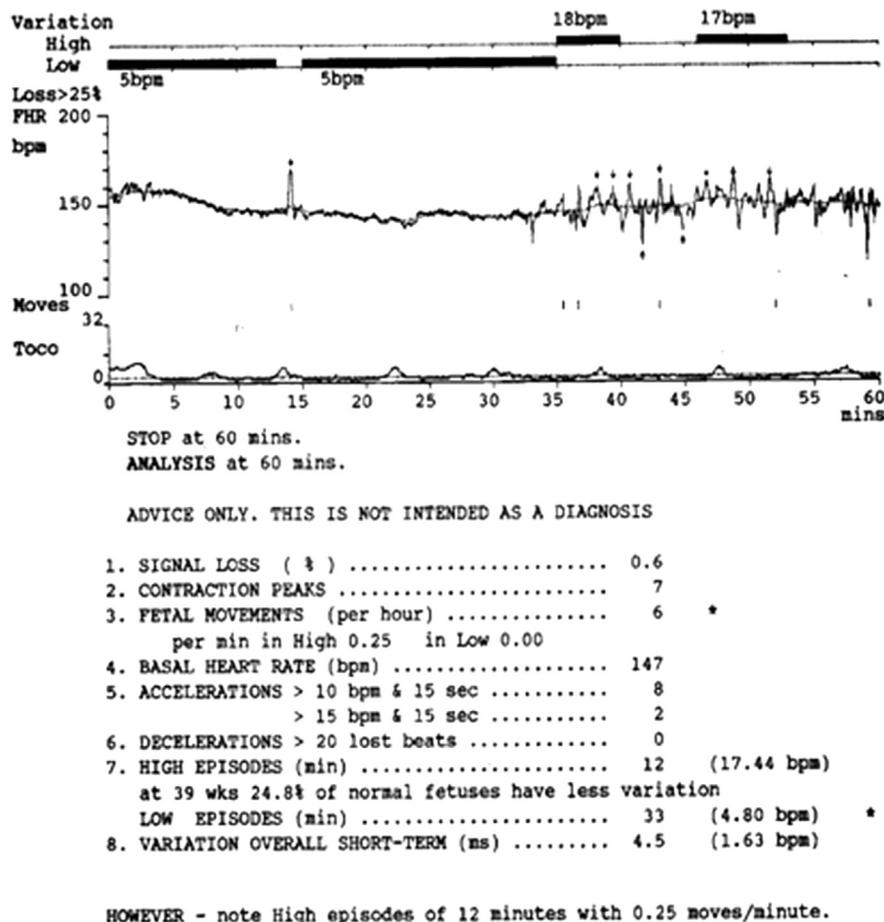
**RESULTS:** Among 511 women randomized, 362/503 (72%) had associated hypertensive conditions. In all, 463/503 (92%) of fetuses survived and cerebral palsy occurred in 6/443 (1%) with known outcome. Among all women there was no difference in outcome based on randomized group; however, of survivors, significantly more fetuses randomized to the late ductus venosus group had a normal outcome (133/144; 95%) than those randomized to computerized cardiotocography alone (111/131; 85%). In 118/310 (38%) of babies delivered <32 weeks, the indication was safety-net criteria: 55/106 (52%) in late ductus venosus, 37/99 (37%) in early ductus venosus, and 26/105 (25%) in computerized cardiotocography groups. Higher middle cerebral artery impedance adjusted for gestation was associated with neonatal survival without severe morbidity (odds ratio, 1.24; 95% confidence interval, 1.02–1.52) and infant survival without neurodevelopmental impairment at 2 years (odds ratio, 1.33; 95% confidence interval, 1.03–1.72) although birthweight and gestational age were more important determinants.

**CONCLUSION:** Perinatal and 2-year outcome was better than expected in all randomized groups. Among survivors, 2-year neurodevelopmental outcome was best in those randomized to delivery based on late ductus venosus changes. Given a high rate of delivery based on the safety-net criteria, deciding delivery based on late ductus venosus changes and abnormal computerized fetal heart rate variability seems prudent. There is no rationale for delivery based on cerebral Doppler changes alone. Of note, most women with early-onset fetal growth restriction develop hypertension.

**Key words:** antepartum surveillance, cardiotocography, intrauterine growth restriction, neurodevelopmental handicap, perinatal outcome, Trial of Umbilical and Fetal Flow in Europe, umbilical artery Doppler

FIGURE 1

## Computerized cardiotocography readout



One-hour recording of the fetal heart rate (FHR) with computerized Dawes and Redman analysis. Bullet point 8 in the figure shows short-term variation used in the Trial of Umbilical and Fetal Flow in Europe as the cardiocotography criterion for deciding upon delivery in severe fetal growth restriction.

FHR, fetal heart rate; IVC, inferior vena cava; SVC, superior vena cava; toco, tocography.

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that no targeted treatment exists for FGR, delivery is the only intervention that can prevent severe hypoxemia and acidosis, and eventually intrauterine death. Thus, optimal monitoring and timing of delivery remains crucial in the management of early-onset FGR.<sup>7</sup>

The issue of timing of delivery had first been addressed by the Growth Restriction Intervention Trial, which reported on 587 babies.<sup>8,9</sup> This study randomized women with compromised small babies to immediate delivery or expectant management, based on equipoise of the clinician regarding optimal management. Early reports indicated that an expectant

policy (time to delivery 4.9 days) seemed associated with a more favorable neuro-developmental outcome than immediate delivery (0.9 days). At school age, however, no difference was found between immediate or delayed delivery.<sup>10</sup> From this or other studies there is no clear evidence to support delayed above early delivery.<sup>11</sup> A significant limitation of the Growth Restriction Intervention Trial was that neither gestational limits nor clinical criteria for monitoring and timing of delivery were defined. The only entry criterion for the study was the clinician's uncertainty on whether to deliver or continue the pregnancy.

Monitoring early FGR and timing delivery has been undertaken in a variety of ways, including biophysical profile scoring<sup>12</sup> and umbilical artery (UA) Doppler,<sup>13</sup> although there is little evidence underlying the use of either technique. Different UA Doppler patterns identify different degrees of impaired placental function. Absent end-diastolic velocities (AED) or reversed end-diastolic velocities (RED) indicate impairment of the fetoplacental circulation and presage fetal deterioration.<sup>13</sup> Longitudinal studies conducted on high-risk pregnancies have shown that the transition from AED to RED may be slow and gradual in early FGR, nevertheless, both AED and RED have been associated not only with increased fetal and neonatal mortality but also with a higher incidence of long-term neurological impairment when compared with FGR fetuses with positive end-diastolic velocities in the umbilical circulation.<sup>14,15</sup>

Since the early 2000s, attention has moved to assessment of the ductus venosus (DV) (Figures 1 and 2) and computerized cardiocotography (cCTG) analysis of fetal heart rate short-term variation (STV) to guide timing of delivery in FGR (Figure 3).<sup>16</sup> A longitudinal observational study of FGR fetuses monitored by Doppler and cCTG showed that <32 weeks' gestation, DV Doppler abnormalities (Figure 4) in some cases preceded the onset of a low STV, and that continuing pregnancy until the cCTG becomes abnormal in these cases was associated with a significantly higher perinatal mortality and worse composite perinatal outcome.<sup>17</sup> In particular, mortality was higher if both DV and cardiocotography (CTG) were abnormal than when only one was abnormal. Another multicenter study on a large cohort of FGR pregnancies followed up longitudinally also demonstrated that intact survival increased by 1-2% for every extra day spent in utero up to 32 weeks.<sup>18</sup> The balance in early-onset FGR is between, on the one hand, prolonging pregnancy to reduce prematurity-related complications, and in the other, timely intervention, to prevent mortality and limit morbidity.<sup>19-21</sup>

The issue of how to monitor and when to deliver in early-onset FGR has until recently been informed by little evidence. Indeed, in a seminal opinion 15 years ago the inconsistencies in management of severe FGR with different monitoring strategies—biophysical profile, venous Doppler, and fetal heart rate changes—were highlighted.<sup>7</sup>

The Trial of Umbilical and Fetal Flow in Europe (TRUFFLE) was designed to answer the question of which methodologies should be used to monitor and according to which criteria deliver fetuses with early-onset FGR.<sup>22</sup> In doing so, the TRUFFLE study compared 2 techniques in the monitoring and timing of delivery in early-onset (26–32 weeks) FGR. These were DV Doppler and cCTG from which the fetal heart STV can be ascertained. Both abnormalities of DV and cCTG-STV have been found to be closely associated with fetal hypoxia/acidemia.<sup>17,23–25</sup> Given expert uncertainty on the ideal trigger for intervention, the DV Doppler group was split into 2 arms: less severe (early) and more severe (late) abnormalities. In the 2 Doppler DV groups, safety-net criteria were used to trigger delivery based on the finding of very low cCTG-SVT. The presence of spontaneous, repetitive decelerations on CTG and/or deteriorating maternal condition prompted delivery in all 3 groups. After 32 weeks gestational age, pregnancy was managed according to local protocols.<sup>26</sup> In this review we will discuss the study design and results with relevance to their implementation in clinical practice.

### The definition of early-onset FGR

As smallness of the fetus can be constitutional, due to fetal malformations, chromosomal abnormalities, and infections,<sup>19,20</sup> the population in the TRUFFLE study was restricted to impaired fetal growth considered to be of uteroplacental origin. The inclusion criteria were singleton pregnancies with fetal abdominal circumference (AC) <10th percentile, gestational age between 26<sup>+0</sup>–31<sup>+6</sup> weeks, and UA Doppler pulsatility index >95th centile.<sup>22,26</sup> The American Congress of Obstetricians and Gynecologists and

Royal College of Obstetricians and Gynecologists definition of growth restriction is based only on AC or estimated fetal weight (EFW) <10th percentile.<sup>21,27</sup> This definition includes patients with failure of growth not dependent on uteroplacental function and thus includes also fetuses with smallness not directly related to placental insufficiency.<sup>19,20</sup> In the TRUFFLE study, the definition of AC <10th percentile and umbilical impedance >95th percentile was arrived at through expert consensus of the investigator group in 2002. This has stood the test of time and with minor variation represents the combination of parameters that are closely related to perinatal morbidity (PORTO)<sup>28</sup> and a recent Delphi consensus (Delphi refers to the process by which expert opinion is focused towards a conclusion in a stepwise, iterative way).<sup>29</sup>

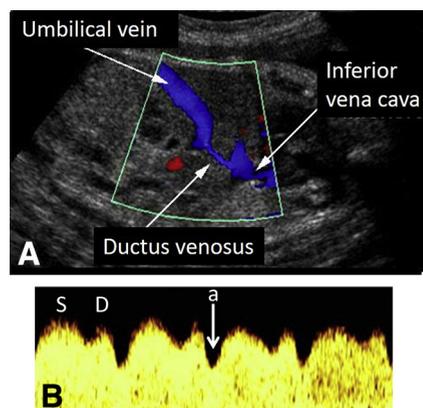
The 26<sup>+0</sup> and 31<sup>+6</sup> weeks' range was chosen as representing where maximum uncertainty existed, given uncertainty of outcomes at gestational ages <26 weeks and with a fetal weight <500 g and the low incidence of severe neonatal complications ≥32 weeks of gestation.<sup>30</sup>

### Monitoring techniques and criteria for delivery

The standard of care in maternal-fetal medicine units in Europe formed the basis of management for the study. Given the lack of a universally accepted protocol for monitoring these pregnancies and criteria for timing delivery, the aim of TRUFFLE was to compare the outcome in the survivors of FGR pregnancies at 2 years of age when the timing of delivery was based on different monitoring techniques, namely cCTG-STV or DV Doppler.

The cCTG (Figure 1) reflect changes in fetal sympathetic, parasympathetic activity and chemoreceptors occurring during the process of hypoxic deterioration in placental FGR.<sup>23,24</sup> The increase in DV pulsatility index with progression to absent and reverse flow velocities of the a-wave (atrial contraction) (Figures 2 and 3) is typically seen only in severe and early gestational age FGR fetuses.<sup>16,18,31,32</sup> After 32 weeks,

**FIGURE 2**  
Ductus venosus imaging and waveform



(A) Two-dimensional and color Doppler imaging of ductus venosus (DV). (B) Normal second-trimester DV waveform. S-wave indicates systole, D-wave diastole and a-wave denotes late diastole (atrial contraction). Vertical arrow shows positive flow.

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abnormal CTG (late decelerations, reduced variability) will almost invariably precede DV abnormalities.<sup>16</sup> Hypoxemia and acidemia result in altered sympathetic and parasympathetic activity, hence in decreased fetal heart rate variation, reflected by a lower cCTG-STV.<sup>23,24</sup> Late (shallow) decelerations are indicative of a chemoreceptor-mediated response to fetal acidemia and of a direct depression effect of acidemia on myocardial tissue.<sup>25</sup>

### Randomization arms

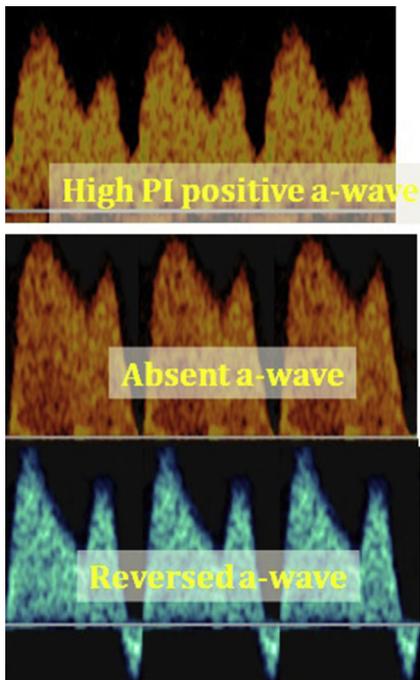
Patients were randomized into 3 arms for the decision to deliver:

1. Abnormal cCTG-STV (<3.5 milliseconds at 26<sup>+0</sup>–28<sup>+6</sup> weeks and <4 milliseconds at 29<sup>+0</sup>–31<sup>+6</sup> weeks).
2. Early DV Doppler abnormalities: pulsatility index >95th percentile.
3. Late DV Doppler abnormalities: absent or reversed a-wave.

### Safety-net criteria for delivery

In cases randomized to DV changes, the trigger for delivery was a cCTG-STV <2.6 milliseconds at 26<sup>+0</sup>–28<sup>+6</sup> weeks

**FIGURE 3**  
Ductus venosus Doppler  
velocimetry waveforms



Progression (from top to bottom) from increased pulsatility index (PI), to absent and reversed flow during a-wave. Positive (forward) and negative (reversed) flow are denoted.

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and  $<3$  milliseconds at  $29^{+0}$ - $31^{+6}$  weeks. Spontaneous repeated persistent decelerations on CTG represented a safety-net criterion in all 3 trial arms. At gestations  $>32$  weeks, the policy for delivery was based on local protocols. RED in the UA was recommended as a reason to deliver the fetus  $>32$  weeks but was permissible  $>30$  weeks; AED,  $>34$  weeks but permissible  $>32$  weeks.

#### Maternal indications for delivery

Maternal indications for delivery were considered as independent of fetal condition, randomization arm, and gestational age.<sup>22,26</sup>

#### Primary outcome

Given the high rate of perinatal survival even in early preterm infants, the primary outcome was not based on perinatal mortality and morbidity. Instead,

the study was powered on a primary outcome of survival without cerebral palsy or neurosensory impairment, or with a Bayley III developmental score<sup>33</sup> of  $>85$ , at 2 years of age.<sup>26</sup>

#### Secondary outcomes

Secondary outcomes were perinatal mortality, and neonatal and infant morbidity and mortality.

#### Patient characteristics

The TRUFFLE study cohort consisted of 511 women recruited of 542 eligible for study inclusion. The mean maternal age was 31 years, 63% were nulliparous, 84% were Caucasian, with a mean body mass index of  $25 \text{ kg/m}^2$ . No differences in demographic features were reported in the 3 trial arms. Hypertensive disorders of pregnancy were either already present at recruitment or developed during the observational period in 50% of cases with no difference between the 3 randomization arms<sup>26</sup> and complicated 73% of the pregnancies by the time of delivery. Comparing these data with the incidence of pregnancy hypertension, chronic hypertension, and preeclampsia in the general population,<sup>34</sup> it was apparent that the population entering the TRUFFLE study was destined for uteroplacental impairment from an early gestational age. Hypertensive disease, preeclampsia, and severe FGR is strongly associated with abnormal uterine artery Doppler velocimetry, although this parameter was not required for study inclusion.<sup>35</sup>

#### Results: fetal and neonatal risks of early FGR

##### Mortality

The mean gestational age at delivery was 30.7 weeks and neonatal weight was 1019 g.<sup>22</sup> Antenatal death occurred in 12 cases (2.4%), including 5 cases where parents declined consent to delivery. In spite of the severity of FGR, 92% babies survived to discharge. These results are more favorable than those previously reported from observational studies.<sup>4,18</sup>

##### Morbidity

Severe morbidity among live births was present in 24% of infants and 5% of neonates died in the perinatal period.

Overall, 71% of survivors were discharged from the neonatal wards without severe morbidity. The most common causes of early neonatal morbidity were sepsis (18%) and bronchopulmonary dysplasia (10%). Relatively infrequent were germinal matrix hemorrhage (2%) and cystic periventricular leukomalacia (1%).<sup>26</sup>

#### 2-year Survival and neurodisability

Of all women recruited to the study, there were nonsignificant differences in survival without infant neurodisability at 2 years: 77% for the cCTG group, 84% for the early DV group, and 85% for the late DV group ( $P = .09$ ); this analysis included all deaths. However, among the survivors in a predefined primary analysis, the percentage of infants without neurodevelopmental impairment at 2 years of age, corrected for prematurity, was significantly higher (95%) in the late DV group compared to the cCTG arm (85%). In the same arm (late DV changes, ie, 0 or reversed a-wave) the better neurological outcome was associated with a small and nonsignificant excess of antenatal deaths.<sup>26</sup>

#### Middle cerebral artery Doppler and outcome

Normalized for gestation using z-scores, middle cerebral artery (MCA) pulsatility index and umbilicocerebral ratio at inclusion were associated with 2-year survival with normal neurodevelopmental outcome (odds ratio [OR], 1.33; 95% confidence interval [CI], 1.03–1.72, and OR, 0.88; 95% CI, 0.78–0.99, respectively) as were gestation at delivery and birthweight p50 ratio (OR, 1.41; 95% CI, 1.20–1.66, and OR, 1.86; 95% CI, 1.33–2.60, respectively).<sup>36</sup>

#### Safety-net deliveries $<32$ weeks

The TRUFFLE protocol applied up to 32 weeks. In those delivered  $<32$  weeks, the safety-net criteria triggered delivery in 38% of cases: 52% of 106 cases in the late DV group, 37% of 99 cases in the early DV group, and 25% of 105 cases in the cCTG-SVT group. Other fetal or maternal indications accounted for 30% of all deliveries  $<32$  weeks.<sup>37</sup>

## Discussion

### The TRUFFLE findings in context

Overall, outcomes for very preterm fetuses with FGR were much better than previously assumed: 82% of children with known outcome survived without neurological impairment. With the exception of cerebral ultrasound abnormalities, commonly used neonatal morbidity criteria are poor markers of later neurodevelopmental outcome. Indeed, 2-year neurodevelopmental impairment was not preceded by any component of composite neonatal morbidity in 56% of cases.<sup>38</sup> Gestational age at both study entry and delivery were strongly related to morbidity and mortality. Thus, specific morbidity/mortality tables in relation to gestational age at entry in the study and gestational age at delivery can be used for accurate parental counseling. The most important independent determinants of the composite adverse outcome (death or severe morbidity) were the presence of maternal hypertensive disease, low gestational age, and a low EFW at study inclusion.

### Implications for clinical practice

Optimal timing of delivery of the early FGR fetus is achieved by monitoring with both DV and cCTG-STV. In those randomized to the late DV group there was better neurological outcome in surviving children, with nonsignificantly higher antenatal mortality. The latter was unlikely to be due to the lower cCTG-STV safety-net criteria in the DV randomization arm compared to those of the cCTG arm, as in 6 of the 7 cases fetal death would have been inevitable even had they been allocated to another randomization arm. Hence, delivery should be undertaken when the a-wave in the DV reaches the 0 line (absent a-wave) or when there is a pathologically low STV. This lower cCTG-STV cut-off was chosen assuming that STV of 2.6 milliseconds is the lowest cut-off clinically appropriate given the high chance of hypoxemia/acidemia below this level.<sup>24,39</sup> The presence of spontaneous, repetitive fetal heart rate decelerations or maternal indications

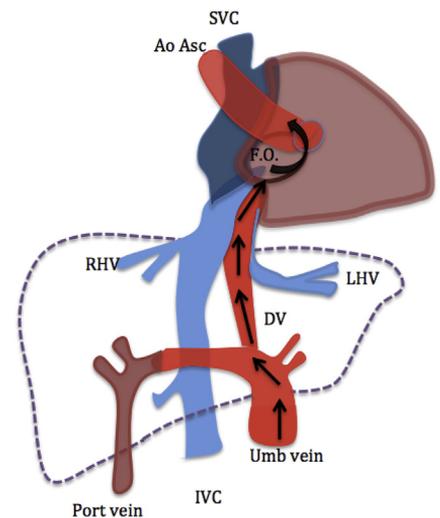
should trigger delivery independently of DV and cCTG-STV evaluation. Monitoring frequency of DV Doppler evaluation and cCTG was not established by the study, however it is reasonable to suggest frequent monitoring of cCTG and DV Doppler with a sliding scale from at least every 2-3 days to daily, based on the severity of FGR and UA Doppler abnormalities.

A subanalysis of babies delivered <32 weeks' gestation, in other words those whose management was strictly defined by the protocol, showed that more than one third delivered based on safety-net criteria, and another one third for other fetomaternal reasons.<sup>38</sup> Hence, in clinical practice, a significant proportion of fetuses will be delivered because of cCTG-STV abnormalities, even before DV changes occur. However, overall data from the TRUFFLE trial<sup>22,26</sup> and subanalyses<sup>37</sup> show a better outcome by the integrated use of both DV and cCTG-STV.

### Variability of measurements

There is considerable biological variation in Doppler measurements and we did not formally assess this in the TRUFFLE study. Our recommendation is that Doppler measurements should be performed by experienced clinicians and the pulsatility index should be repeated at least 3 times at each assessment to verify uniformity of findings. It is still a subject of a debate as to whether maternal steroid administration to promote fetal lung maturation affects UA Doppler (pseudonormalization of absent flow in the UA)<sup>40</sup> and fetal heart rate. The day-to-day risk of an abnormally low cCTG-STV prompting delivery was 5%, and not predictable by the previous cCTG-STV.<sup>41</sup> TRUFFLE used 2 different cut-offs: in the cCTG arm (STV <3.5 and 4 milliseconds at <29 and 29-32 weeks, respectively) and as a safety-net in the DV arm (STV <2.6 and 3.0 milliseconds at <29 and 29-32 weeks, respectively).<sup>26</sup> Although not mandated by the protocol, the majority of participating centers undertook daily CTG monitoring. In the case of maternal hypertension and/or HELLP syndrome, we

**FIGURE 4**  
Fetal central venous circulation



Fetal central venous circulation: highly oxygenated blood coming from placenta reaches liver through umbilical (Umb) vein. About 40% is shunted directly to heart through ductus venosus (DV); the rest is directed to the right liver lobe. DV, left hepatic vein (LHV), and right hepatic vein (RHV) drain into inferior vena cava (IVC). Highly oxygenated blood in DV forms jet streaming preferentially from right to left atrium through foramen ovale (FO), and through left ventricle and ascending aorta (Ao Asc) to fetal brain.

Frusca. TRUFFLE study of early fetal growth restriction. *Am J Obstet Gynecol* 2018.

advise repeating assessments more frequently, since fetal deterioration may occur very rapidly.

### Delivery >32 weeks

Although the TRUFFLE study stopped recruiting at 32 weeks, many of the pregnancies continued beyond that gestation, if the criteria for delivery were not yet met. TRUFFLE did not investigate which Doppler criteria should be used for delivering these fetuses. However, Doppler evaluation of the UA becomes increasingly more important with advancing gestation. RED flow may always prompt delivery >32 weeks and AED >34 weeks. Beyond 34 weeks it is unusual to observe an AED pattern and delivery is often then triggered by other fetal criteria. From these gestational ages

decisions as to the timing of delivery will take into account the maternal condition, fetal growth, and EFW and should be left to the clinical judgment of the managing team. Given the current interest in the fetal adaptive response to chronic hypoxemia assessed by Doppler of the MCA pulsatility index and its ratio with the UA (cerebroplacental ratio),<sup>42</sup> we undertook a secondary analysis of MCA Doppler in the TRUFFLE cohort. MCA Doppler did not add useful information for clinical management of these pregnancies.<sup>36</sup>

### Conclusion

The optimal management of early FGR fetuses should integrate clinical, Doppler, and cCTG parameters to ensure safe deferral of delivery for the fetus and the mother, or a timely intervention.<sup>43</sup> Centers formerly acting upon cCTG-STV alone should be aware that severe anomalies in the DV, when they precede cCTG abnormalities, are an indication for undertaking delivery. Alternatively, when the DV is still normal, they can confidently defer delivery, provided the cCTG-STV remains above the safety-net cut-off level. Non-cCTG assessment does not allow an objective assessment of fetal heart rate variability and, although its utility was not tested in this study, is not recommended for this reason. Although TRUFFLE did not specifically investigate monitoring frequency, cCTG-STV and Doppler of UA and DV should be undertaken with increasing frequency after the onset of AED in the UA, with more intensive monitoring in case of rapid deterioration. In summary, a predefined and agreed-upon protocol, based on or similar to that of TRUFFLE,<sup>22</sup> is likely to lead to optimal perinatal and infant outcome. ■

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# Diagnosis and surveillance of late-onset fetal growth restriction



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By consensus, late fetal growth restriction is that diagnosed >32 weeks. This condition is mildly associated with a higher risk of perinatal hypoxic events and suboptimal neurodevelopment. Histologically, it is characterized by the presence of uteroplacental vascular lesions (especially infarcts), although the incidence of such lesions is lower than in preterm fetal growth restriction. Screening procedures for fetal growth restriction need to identify small babies and then differentiate between those who are healthy and those who are pathologically small. First- or second-trimester screening strategies provide detection rates for late smallness for gestational age <50% for 10% of false positives. Compared to clinically indicated ultrasonography in the third trimester, universal screening triples the detection rate of late smallness for gestational age. As opposed to early third-trimester ultrasound, scanning late in pregnancy (around 37 weeks) increases the detection rate for birthweight <3rd centile. Contrary to early fetal growth restriction, umbilical artery Doppler velocimetry alone does not provide good differentiation between late smallness for gestational age and fetal growth restriction. A combination of biometric parameters (with severe smallness usually defined as estimated fetal weight or abdominal circumference <3rd centile) with Doppler criteria of placental insufficiency (either in the maternal [uterine Doppler] or fetal [cerebroplacental ratio] compartments) offers a classification tool that correlates with the risk for adverse perinatal outcome. There is no evidence that induction of late fetal growth restriction at term improves perinatal outcomes nor is it a cost-effective strategy, and it may increase neonatal admission when performed <38 weeks.

**Key words:** fetal growth restriction, infant, late-onset disorders, newborn, small-for-gestational age, term birth

## Definition of “late-onset” fetal growth restriction

Late fetal growth restriction (FGR) is usually defined as that diagnosed >32 weeks of pregnancy. One study<sup>1</sup> showed

that a cut-off of 32 weeks at diagnosis or 34 weeks at delivery maximized the clinical differences between early- and late-onset FGR, in terms of perinatal mortality (7.1% vs 0%;  $P < .001$ ), adverse perinatal outcome (13.4% and 4.6%;  $P < .001$ ), and association with preeclampsia (35.1% vs 12.1%;  $P < .001$ ). More recently, a survey was conducted on 45 experts aiming at reaching consensus on the definition of late vs early FGR.<sup>2</sup> There was good agreement (89%) in defining late FGR as that diagnosed >32 weeks.

While in early-onset FGR the typical pattern of deterioration progresses from escalating abnormalities in Doppler parameters to abnormal biophysical parameters,<sup>3,4</sup> in late-onset FGR there is a common pattern of normal or minimally elevated umbilical Doppler indices with mildly abnormal cerebral Doppler, but

without obvious cardiovascular changes beyond these findings.<sup>5,6</sup> Contrary to early-onset FGR, in late-onset FGR the association with preeclampsia is weak.<sup>7</sup> The Table shows the main differential features between both clinical subtypes.

Another major source of terminological confusion is the distinction between pathologically and constitutionally small fetuses. By convention, both clinical forms have been termed as “fetal growth restriction” and constitutional “smallness for gestational age” (SGA), respectively. Whereas FGR represents a pathological condition (mainly associated with placental insufficiency<sup>8</sup>) associated with adverse perinatal outcome, constitutional smallness is associated with near-normal perinatal outcomes as it represents the lowest end of the size spectrum of normal fetuses.

## Short- and long-term consequences of late FGR

### Neonatal and infant consequences

Approximately one third of the medically indicated late preterm births are complicated with FGR.<sup>9</sup> Late FGR is associated with cesarean delivery for fetal distress, neonatal acidosis, and admission to the neonatal unit.<sup>10</sup> The association with harder hypoxic events emerges when large cohorts are analyzed. Mendez-Figueroa et al,<sup>11</sup> in a cohort of 5416 term, uncomplicated pregnancies with SGA (birthweight [BW] <10th centile) found a higher incidence of neonatal death (1.1 vs 0.4/1000 births; adjusted odds ratio [OR], 2.56; 95% confidence interval [CI], 1.83–3.57). In another recent study, Chauhan et al<sup>12</sup> evaluated in a cohort of 115,502 uncomplicated pregnancies of nonanomalous singletons born at term the association between SGA (<10th centile of BW;  $n = 4983$ ) and hypoxic composite neonatal morbidity including 5-minute Apgar score <5 (prevalence among SGA 0.4%), hypoxic

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ischemic encephalopathy (prevalence 0.4%), seizures (prevalence 0.1%), and neonatal death (prevalence 0.1%). After adjusting for potential confounders, hypoxic composite neonatal morbidity was significantly higher in SGA (1.1%) compared with normally grown babies (0.7%; adjusted relative risk [RR], 1.44; 95% CI, 1.07–1.93). A large case-control study<sup>13</sup> including 493 babies with cerebral palsy born  $\geq 35$  weeks found severe smallness (BW  $< 2$  SD) to be associated with an OR of 4.81 (95% CI, 2.7–8.5).

It has been shown by spectroscopy that late SGA fetuses<sup>14</sup> and, to a greater extent, late FGR infants<sup>15</sup> (defined by BW  $< 3$ rd centile or Doppler abnormalities) have brain metabolite differences vs normally grown babies that are correlated with later neurodevelopment. A meta-analysis<sup>16</sup> on neurodevelopment in term SGA babies including 28 studies (7861 SGA babies) found that SGA-born infants had 0.32 SD poorer (95% CI, 0.25–0.38) standardized neurodevelopmental scores.

### Long-term consequences

At long term, the effects of SGA are more difficult to disentangle from other environmental factors. However, a recent cohort<sup>17</sup> (n = 1,100,980) study that adjusted for maternal and paternal educational level found that term SGA was significantly associated with an increased risk of poor school performance at the time of graduation from compulsory school (grades  $< 10$ th percentile), with adjusted OR and 95% CI ranging from 1.85 (1.65–2.07) for severe SGA ( $< 3$  SD of BW) to 1.5 (1.43–1.58) for moderate SGA (BW  $-2$  to  $-3$  SD). In a subanalysis, all BW groups were associated with an increased risk of poor school performance among boys with short stature (10.1% of those individuals born with a BW  $< 2$  SD) compared to those with nonshort stature. Finally, it has been suggested that fetal programming also operates in term SGA babies,<sup>18</sup> predisposing them to a higher incidence of metabolic syndrome. Another recent large cohort study<sup>19</sup> on 49,927 female nurses found that term SGA ( $< 10$ th centile of BW) was associated with an increased risk of adult-onset (diagnosed

<b>TABLE</b>		
<b>Main differential features between both clinical phenotypes of fetal growth restriction</b>		
	<b>Early FGR</b>	<b>Late FGR</b>
Prevalence <sup>7</sup>	0.5–1%	5–10%
Challenge <sup>10</sup>	Management (gestational age at delivery)	Detection and diagnosis
Evidence of placental disease <sup>1,7,a</sup>	High 70% Abnormal umbilical Doppler 60% Association with preeclampsia Severe angiogenic disbalance	Low <10% Abnormal umbilical Doppler 15% Association with preeclampsia Mild angiogenic disbalance
Pathophysiology and oxygen delivered to brain <sup>6</sup>	Hypoxia +/+ Systemic cardiovascular adaptation	Hypoxia +/- Central cardiovascular adaptation
Clinical impact <sup>10</sup>	High mortality and morbidity	Low mortality/morbidity + high prevalence = large etiological fraction of adverse outcomes

*FGR, fetal growth restriction.*

<sup>a</sup> Crispi F, Dominguez C, Llubra E, Martin-Gallan P, Cabero L, Gratacos E. Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction. *Am J Obstet Gynecol* 2006;195:201-7.

*Figueras. Late-onset fetal growth restriction. Am J Obstet Gynecol* 2018.

$> 30$  years) diabetes mellitus (OR, 2.42; 95% CI, 1.44–4.07, adjusted for body mass index and parental history of diabetes).

### Placental histopathological findings in late FGR

Placentas from FGR fetuses delivered at term have significantly increased frequencies of uteroplacental vascular lesions (especially infarcts) compared to normal controls, although the incidence of such lesions is much lower than in preterm FGR.<sup>20-22</sup> Furthermore, it has been reported that compared to normal term pregnancies, placentas from FGR at term may have an increased incidence of other villous lesions including fibrosis, hypovascularity, and avascularity, suggestive of fetal thrombotic events.<sup>23</sup> Hence, differences in placental histopathological findings between late and early FGR are more quantitative (in severity and extension) rather than qualitative.<sup>24</sup> A series of 142 placentas from singleton SGA pregnancies born  $> 34$  weeks with normal umbilical artery (UA) Doppler velocimetry found that 54.2% had placental weights  $< 3$ rd

percentile (compared to 9.9% of 142 placentas from normally grown babies;  $P < .001$ ). Only 21.8% (31/142) of SGA placentas were free of histological abnormalities, while it was 74.6% (106/142) in the normally grown group ( $P < .001$ ). In the abnormal SGA placentas (111/142) there were a total of 161 lesions (classified according standardized criteria<sup>25</sup>) attributable to maternal underperfusion in 64% (103/161), fetal underperfusion in 15.5% (25/161), and inflammation in 20.5% (33/161). Interestingly, those pregnancies with signs of underperfusion<sup>25</sup> had a significantly higher incidence of emergency cesarean delivery for nonreassuring fetal status (44.1% vs 21.4%, respectively;  $P = .013$ ) and neonatal metabolic acidosis at birth (33.3% vs 14.3%, respectively;  $P = .023$ ) than did those without signs of underperfusion.<sup>26</sup> Furthermore, neonatal morbidity (as assessed by the Morbidity Assessment Index For Newborns score<sup>27</sup>) differed significantly between those with and without placental signs of underperfusion (89 vs 0, respectively;  $P = .025$ ). Finally, 83 infants of the same cohort were followed up for 2-year

neurological assessment<sup>28</sup> when adjusted neurodevelopmental outcomes (Bayley scale) were significantly poorer in births involving placental underperfusion (relative to SGA infants without these signs) for all 3 domains of the Bayley scale: cognitive (105.5 vs 96.3, adjusted  $P = .03$ ), language (98.6 vs 87.8, adjusted  $P < .001$ ), and motor (102.7 vs 94.5, adjusted  $P = .007$ ). The adjusted ORs of abnormal cognitive, language, and motor competencies in instances of underperfusion were 9.3-, 17.5-, and 1.44-fold higher, respectively, differing significantly for the former 2 domains.

### Screening for late SGA

Since failure to achieve growth potential is a concept difficult to gauge, fetal size is used as a proxy, with all its limitations. Therefore, traditionally, a SGA fetus has been regarded as equivalent of FGR. However, a distinction between FGR (with an increased risk of perinatal complications) and low-risk SGA would be desirable.

### The importance of diagnosing late small fetuses

An audit on 1543 cases of perinatal death (>28 weeks of gestational)<sup>29</sup> revealed that a failure to detect FGR accounted for 10% of the avoidable cases (those in which panel agreement was met that suboptimal care contributed to the fatal outcome), although no stratification was provided for late vs early FGR. A large study<sup>30</sup> reported a significantly increased risk of fetal death in SGA delivered >37 weeks compared to those delivered in the 37th week (47/10,000; 95% CI, 34.6–62.5 vs 21/10,000; 95% CI, 13.0–32.1; RR, 2.2; 95% CI, 1.3–3.7). Another study including 92,218 singletons found fetal death rates of 9.7 vs 18.9/1000 with antenatally detected vs nondetected FGR.<sup>31</sup> Gestational age in both groups differed by only 10 days (270 vs 280 days), which underscores the relevance of detection and timely delivery.

### Early screening

First- or second-trimester screening with uterine Doppler velocimetry, biochemical markers (angiogenic factors), and maternal characteristics may detect

early-onset growth restriction in up to 90%.<sup>7</sup> However, late-onset growth restriction is still largely unpredicted. Most studies addressing first-trimester screening for late FGR, used SGA as a proxy, reporting detection rates (DR) for a 10% of false positives ranging from 25% (with only uterine artery [UtA] Doppler velocimetry)<sup>32</sup> to 51% (combining maternal characteristics, blood pressure, uterine Doppler velocimetry, pregnancy-associated plasma protein-A, and placental growth factor).<sup>33</sup> At first trimester, prediction of late FGR (when defined as severe smallness [ $<3$ rd centile] or the presence of Doppler signs suggestive of placental insufficiency) was better than prediction of late SGA (for a 10% of false-positive rate 65.8% [95% CI, 64.8–66.8] vs 23% [95% CI, 18.8–27.2]).<sup>7,34</sup> Prediction for late FGR with preeclampsia was only slightly better (nonsignificantly) than for normotensive FGR (for a 10% of false positives, 70.2% [95% CI, 56–81.4] vs 63.5% [95% CI, 58.4–68.3]. At second trimester, a combination of fetal biometry, estimated fetal weight (EFW) <10th centile, and abnormal uterine Doppler velocimetry or cerebroplacental ratio (CPR) (which combines UA and middle cerebral artery [MCA] pulsatility indices) only detected 20.1% of late SGA for 25% of false positives.<sup>35</sup> Similarly, in a large series<sup>36</sup> of 8024 pregnancies (nulliparous women) uterine Doppler velocimetry (elevated pulsatility index) was evaluated at 16–22+6 weeks showing limited performance in predicting BW <5th centile: (DR of 45.5% for 25% of false positives). Incorporating maternal age, early pregnancy body mass index, race/ethnicity, smoking status prior to pregnancy, chronic hypertension, and pregestational diabetes in the prediction model resulted in only modest improvements. Finally, combining maternal characteristic, first-trimester blood pressure, and second-trimester biometrics and uterine Doppler velocimetry, 43.3% of DR for 10% of false positives has been reported.<sup>37</sup> Therefore, early screening for late FGR is of limited value.

### Fundal height

In low-risk pregnancies, serial measurements of symphysis-fundal height (SFH)

is recommended as a simple and inexpensive screening tool.<sup>38,39</sup> Only 1 randomized controlled trial<sup>40</sup> addressed the incremental yield of fundal height measurement over abdominal palpation, showing a nonsignificant improvement of 32% (95% CI, –8% to 90%) in detecting neonatal SGA. Furthermore, the meta-analysis of 34 studies (most of them hospital-based, which may bias the results toward overoptimistic performance) showed a DR of SFH for SGA of ~60% for a false-positive rate of ~15%, concluding that the method is unsuitable for primary screening.<sup>41</sup> Although SFH determination is of limited value in routine obstetrical care, it continues to be the only physical examination screening test available. Furthermore, the studies do not report separate information on early and late clinical subtypes, nor differentiate between SGA and FGR.

### Ultrasound fetal biometry

A meta-analysis of randomized trials failed to demonstrate benefit from routine third-trimester scan.<sup>42</sup> It may be argued that the older pooled data hold limited contemporary validity. Technology and expertise in the 1970s and 1980s do not translate legitimately into current practice. The most recent study<sup>43</sup> was dated 2003 and it claimed a 30% reduction in SGA. Some of studies also relied on outdated surrogates of fetal growth or formulas to EFW.<sup>44,45</sup> Furthermore, many of the studies involved no change in management if a diagnosis of FGR was made, which does not reflect current practice.

A total of 13 series<sup>37,46–57</sup> on routine ultrasound screening that performed the scan at a mean gestational age >32 weeks have been published since 2012, including a total of 22,927 pregnancies with 1776 SGA babies. SGA was variably defined as BW <10th centile or <5th centile. The summary receiver operating characteristic curve showed an area under the curve of 88.2% (95% CI, 85.4–91%) (Figure 1 and Appendix). For a false-positive rate of 10%, the resulting DR was 70% (95% CI, 62–78%). Only in 1 study<sup>37</sup> FGR (severe smallness or abnormal Doppler

velocimetry) was addressed (including 1303 pregnancies and 83 FGR), showing a DR of 74.4% (CI, 63.6–83.4%) for 10% of false positives.

The main questions for the use of ultrasound in the detection of small fetuses are: (1) whether it must be systematic or only focused on a selected population by high-risk factors; (2) which is the optimal parameter, ie, EFW, abdominal circumference (AC), or both; and (3) what the optimal gestational age would be.

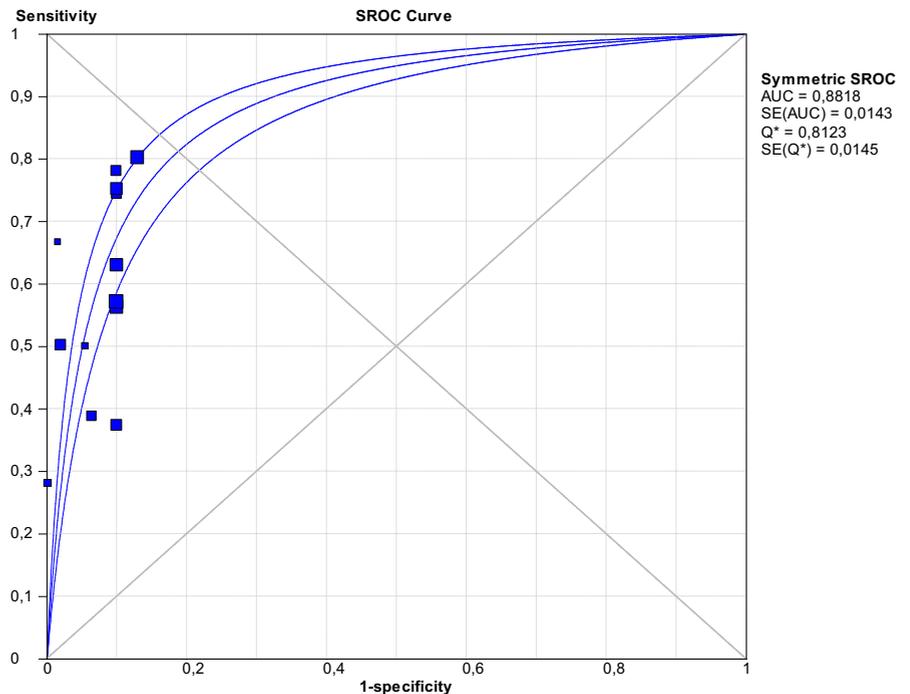
### Systematic vs selective ultrasound

Serial scanning is recommended in high-risk pregnancies,<sup>38,39</sup> based on expert opinion. Although up to 25% of the maternity population fall into the category that would require serial scanning based on risk factors,<sup>58</sup> the DR for SGA of such a strategy is <50%.<sup>59</sup> A large prospective study<sup>57</sup> has been published involving 3977 nulliparous women, in which serial scanning was performed at 28, 32, and 36 weeks and the results were concealed to participants and treating clinicians. This series reported that universal screening triples the DR of SGA as compared with screening based on clinical risk factors (from 69 [20%] of 352, to 199 [57%] of 352). Several factors could account for the variability of the reported performances of third-trimester ultrasound screening, such as baseline risk of the population, the gestational age at scan (being the performance better late in the third trimester<sup>47,56</sup>), and the parameter used for growth assessment AC alone vs EFW.

### EFW vs AC

While the American Congress of Obstetricians and Gynecologists supports only the use of EFW <10th percentile, the Royal College of Obstetricians and Gynecologists supports the use of AC <10th percentile as an additional criterion.<sup>38,39</sup> Indeed, a recent systematic review and meta-analysis on this issue<sup>60</sup> found that AC is comparable to EFW in predicting SGA. The largest prospective study<sup>46</sup> (including 5515 singleton pregnancies routinely scanned at 35–37 weeks) favors EFW over individual biometric measures: for a

**FIGURE 1**  
Performance of routine ultrasound screening for the prediction of late SGA



Summary receiver operating characteristic curve (SROC)\* of studies on routine ultrasound for smallness for gestational age screening performed at mean gestational age >32 weeks. \*Random (DerSimonian method) effects model: Walter SD. Properties of summary receiver operating characteristic (SROC) curve for diagnostic test data. The methodology used to construct the data can be found in Stat Med 2002;21:1237-56.

AUC, area under curve; SGA, small for gestational age.

Figueras. Late-onset fetal growth restriction. *Am J Obstet Gynecol* 2018.

5% of false-positive rate the detection for severe SGA (<3rd centile) requiring delivery within 2 weeks of assessment (that could be considered a proxy for FGR) was 83.3% (95% CI, 67.2–93.6) for a combination of fetal biometrics (AC, head circumference, and femur length) plus maternal characteristics and 91.7% (95% CI, 77.5–98.2) for EFW plus maternal characteristics. Individual performance of each biometric measure was not provided.

### Optimal gestational age for screening

A meta-analysis of randomized trials failed to demonstrate benefit from routine third-trimester scan.<sup>42</sup> However, of the included studies only 3 of them<sup>43,45,61</sup> (contributing only 12% of subjects overall) performed the scan >34 weeks. Therefore, the relevance of this meta-analysis to current clinical practice

could be questionable. A recent randomized study<sup>56</sup> compared in low-risk pregnancies routine screening at 32 (n = 1272) vs 36 (n = 1314) weeks. For FGR at birth (<10th customized centile at birth), the false-positive rates for both strategies were similar (6.4% vs 8.2%), but the DR were superior at 36 vs 32 weeks' gestation (38.8% vs 22.5%;  $P = .006$ ). Likewise, for severe smallness (<3rd customized centile at birth), for a similar rate of false positives (8.5% vs 8.7%), DR was superior at 36 vs 32 weeks' gestation (61.4% vs 32.5%;  $P = .008$ ). Two prospective studies<sup>46,62</sup> carried out on the same population showed that while universal screening (maternal characteristics plus EFW) at 30–34 weeks had a DR of 65% (10% of false positives) of 1727 babies born with a BW <5th centile, at 34–37 weeks the DR was 80% (10% of false positives) of 278.

## SGA vs FGR

Once the diagnosis of a small fetus has been established, the next step is the differential diagnosis between FGR and constitutional smallness. Indeed, SGA represent a heterogeneous population that comprises fetuses that fail to achieve their growth potential mainly due to placental insufficiency along with a fraction of the small babies who are only are constitutionally small (ie, they have a low growth potential). Further complexity is added by the fact that histological<sup>63</sup> and biochemical<sup>64</sup> signs of placental insufficiency can occur in apparently uncomplicated pregnancies with normal fetal/neonatal weight.

The distinction between pathological (FGR) and constitutional smallness is clinically relevant because of the correlation with perinatal outcome. Whereas FGR represents a pathological condition associated with adverse perinatal outcome, SGA babies are associated with near-normal perinatal outcomes. While conceptually FGR and SGA are different conditions, their clinical differentiation is difficult.

## The diagnosis of severe SGA based on biometric parameters

Pilliod et al<sup>65</sup> analyzed a retrospective cohort of all births in the United States during 2005 ( $n = 3,349,816$  non-anomalous singletons), as recorded in a national database. An increase in the number of fetal deaths  $>37$  weeks was reported, mainly for those babies  $<3$ rd centile: while the risk of fetal death (per 10,000 at-risk pregnancies) at 36 and 37 weeks were 21.4 and 18.7, respectively, it was 23.2, 32.3, 32.4, and 58 at 38, 39, 40, and 41 weeks, respectively. A prospective cohort of 132 term SGA fetuses with normal umbilical, uterine, and cerebral Doppler velocimetry found that very-low EFW centile ( $<3$ rd centile) predicted a higher risk of adverse perinatal outcome.<sup>66</sup> In addition, the follow-up of a cohort of 292 late SGA babies found that severe smallness ( $<3$ rd centile) was the most predictive factor for neurological problems at 2 years of life as defined by an abnormal score in the Ages and Stages Questionnaire (ASQ) (OR, 3.6; 95% CI, 1.5–8.8).<sup>67</sup> Thus, severe

smallness by itself could be seen as a stand-alone criterion for FGR. Fetuses with severe smallness are over-represented among the prenatally suspected late SGA fetuses ( $\sim 30\%$ ) because they are more likely to be detected antenatally.<sup>7,57,68</sup>

## Velocity of biometric parameters

Some reports<sup>69–72</sup> in high-risk populations have shown that defective longitudinal fetal growth is associated with adverse perinatal outcome. In these series, “high-risk” was variably defined by maternal characteristics (age  $>35$  years, smoking), obstetric history (previous FGR or hypertensive diseases), or EFW/AC  $<10$ th centile.

Several recent studies used serial ultrasound evaluations of fetal growth as a strategy to improve diagnosis of FGR. The first, conducted by Sovio et al<sup>57</sup> in a large cohort of 3977 unselected nulliparous women, found a significant association of second- to third-trimester growth velocity to the occurrence of adverse outcome. Upon stratification, the association remained only significant for those cases ( $n = 560$ ) with EFW  $<10$ th centile (RR, 1.96; 95% CI, 1.21–3.19). The effect of SGA on adverse outcome was significantly modified by the presence of low growth velocity, to a greater extent than by the presence of abnormal umbilical or uterine Doppler velocimetry.

On the other hand, Karlsen et al,<sup>73</sup> in a prospective cohort of 211 pregnancies at risk of SGA (24.6% of them with an EFW  $<5$ th centile), aimed at evaluating whether the use of conditional growth centiles could improve the prediction of adverse outcome. This method uses a previous measurement to condition individualized ranges for the subsequent measurement.<sup>74</sup> Using a 5th centile threshold, for adverse outcome, the specificity of 78% (95% CI, 70–84%) using size centile as a predictor was improved to 94% (95% CI, 89–97%) when conditional growth centile was added to the model, whereas the sensitivity was not significantly changed (60% [95% CI, 49–69%] vs 39% [95% CI, 30–50%]). The combination of growth velocity with Doppler

parameters for predicting adverse outcome was not explored in this series.

In a series<sup>75</sup> of 308 nulliparous women who subsequently gave birth to adequate-for-gestational age infants, reduced growth velocity between 28–36 weeks’ (EFW decline  $>30$  centiles) was found associated with abnormal CPR (RR, 2.80; 95% CI, 1.25–6.25) and nonsignificantly with UA pH  $<7.15$  (RR, 2.34; 95% CI, 0.89–6.14). However, the predictive performance of reduced fetal growth was poor (for abnormal CPR, DR of 23% [95% CI, 9–43.7] for 8.2% of false positives; and for pH  $<7.15$ , DR of 21% [95% CI, 6.1–45.6] for 9% of false positives).

Also recently, we reported on a cohort of 472 SGA-suspected fetuses that longitudinal growth assessment from diagnosis to delivery does not add to other Doppler parameters in predicting adverse perinatal outcome.<sup>76</sup> Indeed, recent evidence on retrospective series<sup>77,78</sup> shows that there is a correlation between growth velocity and the umbilical/cerebral Doppler. However, when the association to adverse outcomes has been addressed, only the Doppler parameter remained independently associated.<sup>77</sup>

There is not a clear definition of slow growth. A recent consensus on the definition of late FGR<sup>2</sup> proposed defining slow growth when AC/EFW crosses 50 centiles between 2 measurements (for instance, from the 75th centile in a first measurement to the 25th centile in second measurement). However, it could be argued that this definition is arbitrary and lacking interval time frame: the same amount of decline over a short time interval would be seen as more concerning. Despite fetal growth, velocity assessment is an intuitive notion that is in keeping with how postnatal growth assessment is performed; the evidence supporting its use is unclear.

## Doppler parameters

There is a sizable body of evidence showing that the UA velocimetry does not reliably reflect placental insufficiency and does not reliably predict adverse outcome in late-onset FGR.<sup>5,69,79</sup> It is intriguing that while most cases of

late-onset SGA present histological signs of placental underperfusion (mainly vascular occlusion and villous hypoplasia),<sup>80</sup> this is not reflected in the UA Doppler. One could speculate that the degree of the extension is what accounts for this finding. Indeed, animal<sup>81</sup> and mathematical<sup>82</sup> experimental models of placental vessel obliteration have suggested that UA Doppler becomes abnormal only if an extensive part of the placenta is involved. Since the UA velocimetry is not a sensitive parameter to detect late forms of FGR, other Doppler measures have been explored to reflect the fetal adaptation to placental insufficiency.

The use of MCA Doppler in this setting is supported by recent studies that have demonstrated that 15-20% of term SGA fetuses with normal UA Doppler have reduced impedance in MCA blood flow, and that this sign is associated with poorer perinatal outcome<sup>83,84</sup> and neurobehavior, both at birth<sup>85</sup> and at 2 years of age.<sup>86</sup> Furthermore, the CPR, which combines the pulsatility index of the MCA and UA, has been demonstrated to be more sensitive to hypoxia (defined as a reduced partial pressure of oxygen [pO<sub>2</sub>] in the arterial system) than its individual components<sup>87</sup> and it correlates better with adverse outcome.<sup>88-90</sup> In addition to these brain Doppler parameters, abnormal UtA Doppler has been associated with an increased risk of intra-partum fetal distress, emergency cesarean delivery, and admission to intensive care unit.<sup>84,91,92</sup>

### Combination of fetal biometry and Doppler velocimetry

A model combining severe smallness (ie, EFW <3rd centile) with Doppler parameters (CPR and UtA) remarkably improves the risk profiling (for neonatal acidosis, 11.7% of 307 vs 5% of 202 in SGA without criteria,  $P = .009$ ; for cesarean delivery for nonreassuring fetal status 29.3% vs 7.9%,  $P < .001$ )<sup>93</sup> without excessive technical sophistication; the estimation of the fetal weight is an integrated part of the third-trimester echography and Doppler interrogation of the UA, MCA, and UtA is easily

accomplished in the majority of cases. Such an algorithm allows profiling the general population of late SGA fetuses in 2 risk-differing groups. While small fetuses with moderate growth restriction (>3rd centile) and normal placental function on both the fetal (normal CPR) and maternal (normal uterine Doppler) sides are classified as low-risk SGA and managed as constitutionally small babies, those with either severe smallness or Doppler evidence of placental dysfunction are considered high-risk FGR. Among late FGR babies, further evidence is needed to determine what the contribution is of each component of the high-risk FGR definition into the overall performance.

Interestingly, a study comparing routine induction at 37 weeks for all SGA detected cases with selective induction only for those classified as FGR according to the previously mentioned criteria (EFW <3rd centile, CPR and UtA) showed not only less intervention (cesarean delivery rate of 25% of 143 vs 40% 138;  $P < .06$ ) but also improved neonatal outcomes (composite neonatal morbidity of 9% vs 22%;  $P < .01$ ).<sup>94</sup> In this series, the qualifying criteria for FGR were EFW <3rd centile in 35.9% (101/281), an abnormal uterine Doppler velocimetry in 31% (29/93), an abnormal CPR in 19.6% (55/281), and first-trimester low pregnancy-associated plasma protein-A in the remaining 5% (14/281).

It is likely that in future years maternal blood biomarkers are incorporated as a diagnostic criterion of FGR in composite algorithms, as a marker of placental involvement.<sup>95</sup> Indeed, it has been shown in late-onset FGR that the angiogenic factors correlate with placental findings secondary to underperfusion.<sup>96,97</sup>

### Can FGR be present in normally grown babies?

It is biologically implausible that all cases of placental insufficiency occur in babies with BW <10th percentile. In fact, perinatal mortality remains higher in babies between the 10th-50th percentile of BW,<sup>98</sup> suggesting that a proportion of cases of placental insufficiency exhibit

growth within normal ranges. There is evidence showing that normally growing babies with abnormal CPR have a higher frequency of placental insufficiency as determined by abnormal UtA Doppler.<sup>99</sup> There is evidence coming from large retrospective series on pregnancies attended in a tertiary center that abnormal CPR is associated with perinatal morbidity<sup>77,100</sup> and mortality,<sup>101</sup> independently of BW. Furthermore, some smaller prospective series on low-risk populations also suggest this notion.<sup>102</sup> However, the clinical application of these findings remains to be determined. The largest prospective series on unselected pregnancies failed to find predictive value of CPR adverse outcome when performed at 30-34<sup>103</sup> or 35-37<sup>104</sup> weeks. Therefore, even if CPR is a marker of placental insufficiency independent of size, the effectiveness of a strategy based on CPR assessment in the overall population is still to be proven.<sup>105</sup>

### Antepartum surveillance

Contrary to early-onset FGR, late-onset FGR is not associated with a progression of hemodynamic changes, and fetuses only exceptionally display Doppler changes in the UA or ductus venosus. However, progression to severe fetal deterioration and even fetal death can occur rapidly. Evidence from animal models<sup>106</sup> shows that prolongation of pregnancy renders to significant growth restriction (14% fetal weight reduction) and hypoxia (evaluated by magnetic resonance imaging and immunohistochemistry) because of differential loss of placental mass rather than any compromise in fetoplacental blood flow. This finding validates the inability of UA Doppler to safely monitor such fetuses.

This might be explained by reduced tolerance to hypoxia of the term in comparison with the preterm fetus and the more common presence of uterine contractions. Therefore, the strategy in the management of late-onset FGR is essentially based on risk assessment. Concerning surveillance, a relevant notion is that the status low-risk vs high-risk, and consequently the recommended management, can change after

an initial diagnosis, and for these reasons serial measurements of the biometrics and Doppler are recommended.

There is evidence from 1 randomized trial<sup>107</sup> that when compared with monitoring every 2 weeks, twice-a-week monitoring results in more inductions (82% of 70 vs 66% of 54;  $P = .02$ ), without any improvement in the perinatal outcomes. Thus, the standard of care for those low-risk SGA would be this latter regimen. However, in late-onset FGR such definition of “low-risk SGA” could not be reliably trusted on the umbilical Doppler, because it does not reflect any progression from diagnosis to delivery.<sup>5</sup> Therefore, some other monitoring markers are needed.

### Serial growth assessment

Ultrasound growth assessment should not be performed more frequently than every 2 weeks because the inherent error associated with ultrasonographic measurements can preclude an accurate assessment of growth.<sup>108</sup> The advantage of longitudinal over cross-sectional assessment has not been clearly demonstrated.

### Amniotic fluid volume

In a large randomized controlled trial on late SGA,<sup>109</sup> one third had oligohydramnios, as defined by an amniotic fluid index  $<5$ . However, compared with the single deepest vertical pocket, the amniotic fluid index results in an overdiagnosis of oligohydramnios.<sup>110</sup> In a prospective series of pregnancies with oligohydramnios and FGR,<sup>111</sup> the fetal growth centile remained stable over the 8 weeks following the diagnosis, suggesting that the oligohydramnios is not reflecting any risk of progression. Furthermore, a meta-analysis<sup>112</sup> of 18 trials showed an association with abnormal 5-minute Apgar, but not with acidosis or perinatal death in SGA (RR, 1.6; 95% CI, 0.9–2.6). Because of the limited evidence, the inclusion of oligohydramnios assessment in management protocols of SGA/FGR is not recommended.

### Brain Doppler

Hypoxemia secondary to placental insufficiency sets into motion

phenomena of circulatory redistribution mainly characterized by the centralization of blood flow. The better oxygenated blood goes toward the most vital organs (brain, heart, adrenals), while vasoconstriction limits the blood's arrival at the organs considered less indispensable. This constellation of changes is known as hemodynamic redistribution. Among them, Doppler MCA assessment has been the most widely studied parameter. Figure 2 shows the progression of changes in the MCA.

Longitudinal studies in late-onset SGA cases have shown that MCA becomes abnormal in about 15% of the cases.<sup>5</sup> It has been shown<sup>83,113</sup> that in near-term SGA fetuses, MCA could be useful to predict adverse outcome, independently of the UA Doppler. Remarkably, a study where clinicians were blinded to the Doppler indices compared SGA babies with normal and abnormal MCA, reporting 6 times as many instances of emergent cesarean delivery for fetal distress (29% vs 4.8%;  $P < .001$ ) and a 3-fold increased risk of neonatal metabolic acidosis (7.6% vs 2.4%;  $P = .03$ ) at labor induction.<sup>114</sup> This is a relevant issue because according current guidelines,<sup>38,39</sup> labor induction at term is the current standard of care of late-onset SGA. Therefore, while an association exists between abnormal MCA and adverse outcome that would justify its use as surveillance tool, this sign is rather a late manifestation, with acceptable specificity but low sensitivity for clinical applicability.<sup>90</sup>

Due to increased impedance in the placental vasculature in combination with a decrease in cerebral resistance secondary to vasodilation, the ratio between the MCA and UA (ie, the CPR) is decreased even with UA and MCA values very close to normal.<sup>89</sup> Consistently, animal models demonstrated that this ratio is better correlated with hypoxia than its individual components.<sup>87</sup> In late SGA fetuses, CPR becomes abnormal in ~20% of cases.<sup>5,94</sup> The CPR improves the sensitivity of UA and MCA alone, because it is already decreased when its individual components are still within normal ranges.<sup>87,88</sup> A recent systematic

review<sup>90</sup> found that in fetuses with SGA born  $>32$  weeks of gestational age, CPR (9 studies) adds value to assessment over MCA (8 studies) in predicting adverse outcomes. Therefore, the CPR could be seen as the primary surveillance tool in late SGA. Several references have been published on CPR and different cut-offs have been used in the literature.<sup>115</sup> A CPR calculator that included most used references is available at: <http://www.ajog.org/pb/assets/raw/Health%20Advance/journals/y mob/CPR/index.htm>.

### Uterine Doppler

Uterine Doppler is a noninvasive surrogate of the placental function of the maternal compartment. In late SGA it has been found to be associated with a higher frequency of placental signs of maternal underperfusion.<sup>116</sup> Figure 3 shows the spectrum of abnormalities in the UTA waveform.

Interestingly, about a third of pregnancies with abnormal third trimester uterine Doppler had normal values at the beginning of the pregnancy, and this group still has an exceedingly high incidence (~30%) of placenta-related diseases.<sup>117</sup> This suggests that the uterine Doppler has the potential advantage of capturing placental insufficiency from differing pathways: that resulting from defective trophoblastic invasion early in pregnancy, but also that emerging late in pregnancy and probably related to other pathological mechanisms.

At diagnosis, late SGA with abnormal uterine Doppler has a 2-fold increased risk (62.7% vs 34.6%;  $P < .01$ ) of developing abnormal brain Doppler indices before induction of labor.<sup>118</sup> This may be of value in planning the timing of fetal surveillance. In addition, serial uterine Doppler assessment as a surveillance tool has doubtful value because longitudinal studies fail to show any progression from diagnosis to delivery.<sup>5</sup>

### Timing and mode of delivery

Several guidelines recommend delivery at 37–38 weeks.<sup>38,39</sup> This recommendation is based on the findings of the DIGITAT study,<sup>109</sup> in which 650 women with SGA  $>36$  weeks were randomized to

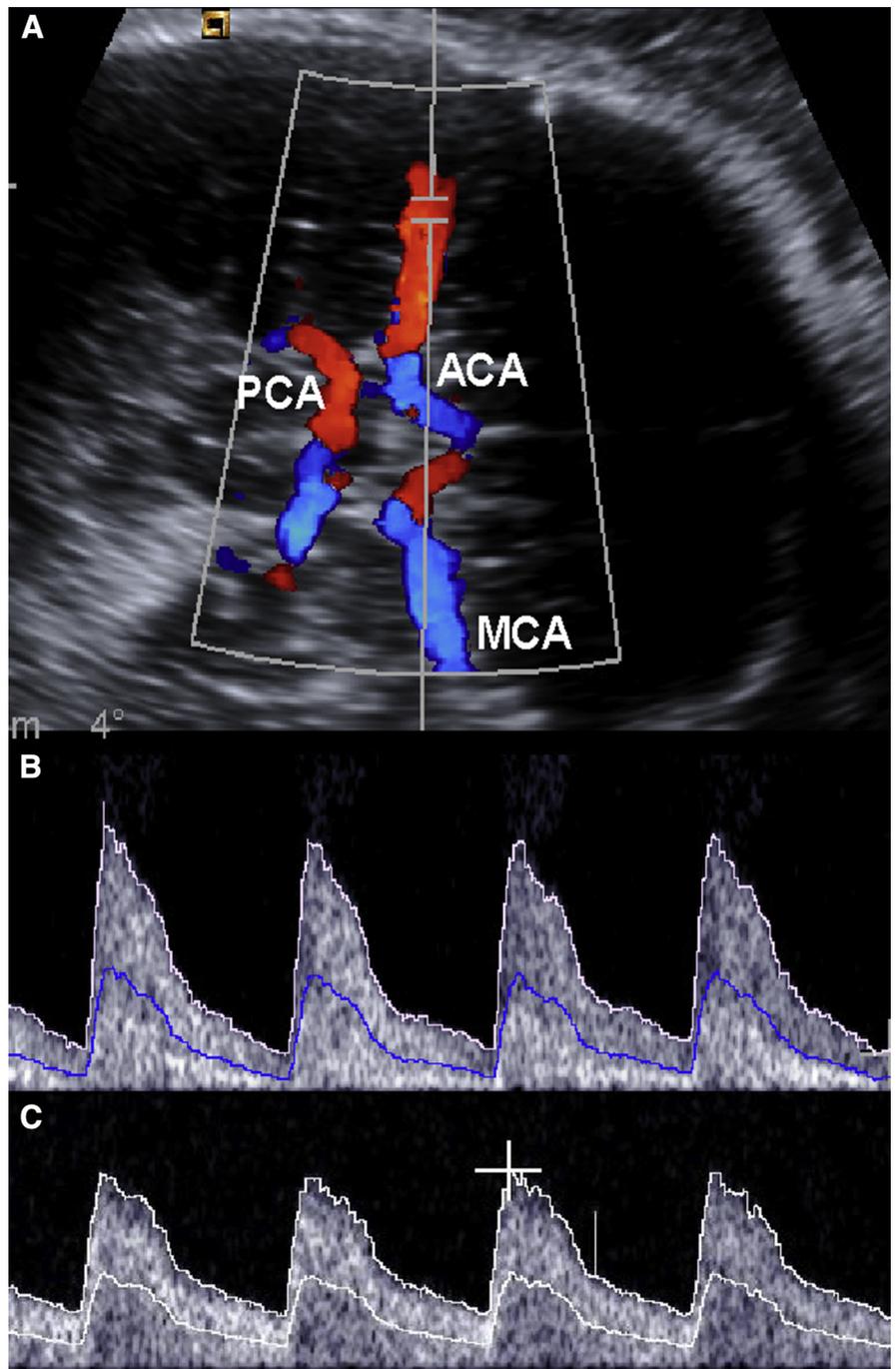
induction or expectant management. Induction group infants were delivered 10 days earlier (266 vs 277 days; mean difference  $-9.9$  days; 95% CI,  $-11.3$  to  $-8.6$ ) and weighed 130 g less (mean difference  $-130$  g; 95% CI,  $-188$  to  $-71$  g) than babies in the expectant monitoring group. There was no difference in the perinatal outcomes except that women in the expectant group had a 2-fold increase in risk of developing preeclampsia (3.7% of 321 vs 7.9% of 329; mean difference  $-4.2$ ; 95% CI,  $-7.7$  to  $-0.6$ ). A total of 17/321 (5.3%) infants in the induction group experienced the composite adverse neonatal outcome, compared with 20/329 (6.1%) in the expectant monitoring group (difference  $-0.8\%$ , 95% CI,  $-4.3$  to  $3.2\%$ ). This was defined as 5-minute Apgar  $<7$ , UA pH  $<7.05$ , or admission to neonatal intensive care. The prevalence of these outcomes was 9/650 (1.4%), 14/567 (2.5%), and 22/650 (3.4%), respectively.

In a secondary analysis,<sup>119</sup> a higher percentage of neonatal admissions was found after induction  $<38$  weeks' gestational age: 125 (61%) admissions vs 92 (44%) after expectant management, difference 16% (95% CI, 6.7–26%;  $P = .001$ ). This suggests that if induction is considered, it is reasonable to delay until 38 weeks. Cesarean deliveries were performed on 45 (14.0%) mothers in the induction group and 45 (13.7%) in the expectant monitoring group (difference 0.3%, 95% CI,  $-5.0$  to 5.6%).

After a response rate of  $\sim 50\%$ , 2-year evaluation was performed of neurodevelopment (ASQ) and neurobehavior (Child Behavior Checklist [CBCL]). A total of 27% of 274 infants had an abnormal score on the ASQ and 13% of 265 on the CBCL. Results of the ASQ and the CBCL did not differ between expectant and induction arms.<sup>67</sup> The most predictive factors for abnormal ASQ was a BW  $<2.3$  centile (OR, 3.6; 95% CI, 1.5–8.8).

A health economics analysis<sup>120</sup> demonstrated that both strategies (induction vs expectant management) generated comparable costs: on average €7106 per patient for the induction group (N = 321) and €6995 for the

**FIGURE 2**  
Middle cerebral artery Doppler changes



Color Doppler assessment of middle cerebral artery (MCA) **A**, at level of circle of Willis and flow velocity waveforms **B**, in control fetus with normal waveform and **C**, in growth-restricted fetus with high diastolic velocities and decreased pulsatility index.

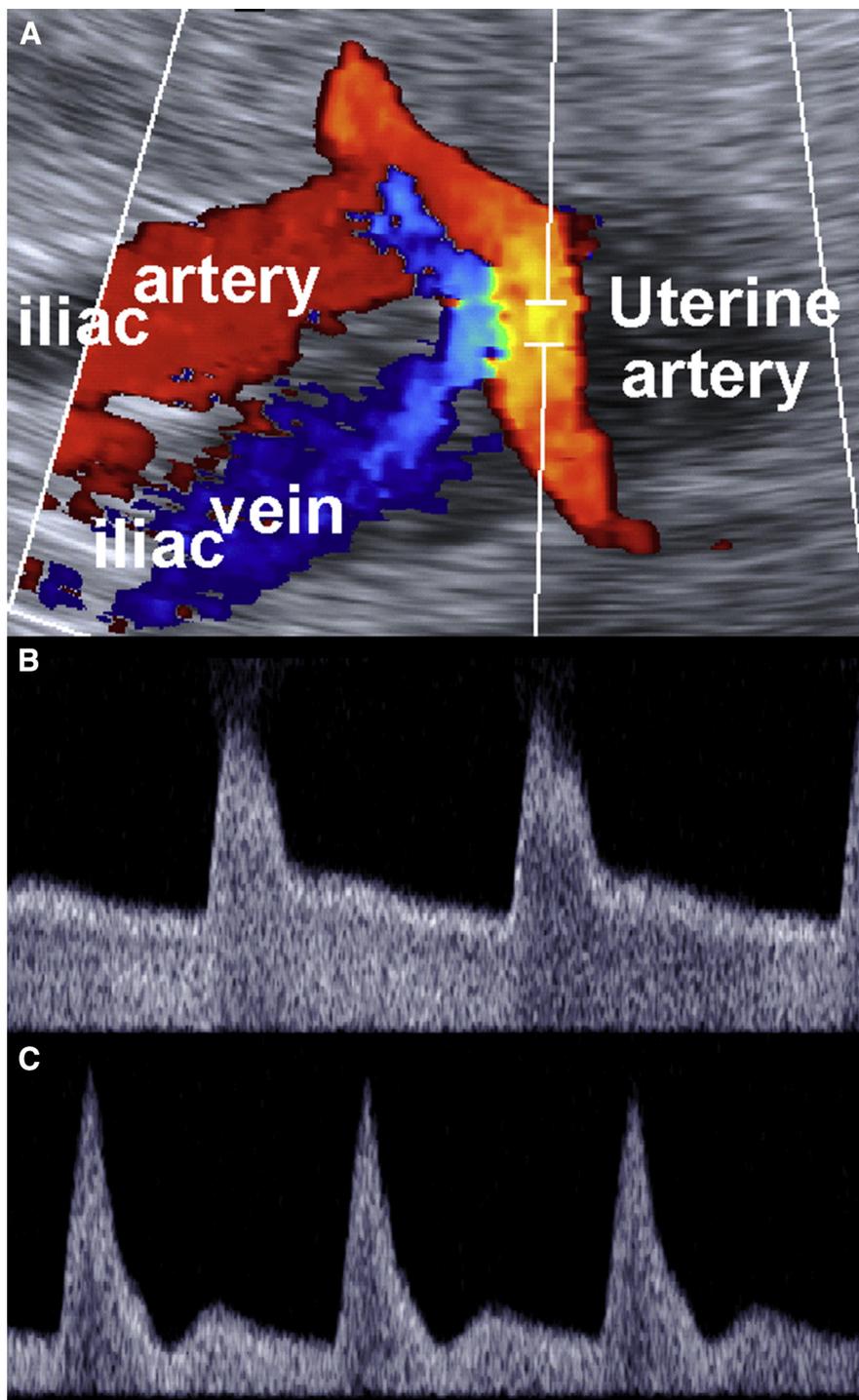
ACA, anterior cerebral artery; PCA, posterior cerebral artery

Figueras. Late-onset fetal growth restriction. *Am J Obstet Gynecol* 2018.

expectant management group (N = 329) with a cost difference of €111 (95% CI, €1296–1641).

In the DIGITAT study all SGA fetuses were managed under a common protocol without any attempt to differentiate

**FIGURE 3**  
**Uterine artery Doppler changes**



Site of insonation of uterine artery with color Doppler **A**, at crossover of iliac artery. **B**, Normal and **C**, abnormal (increased impedance to flow with early diastolic notching) waveforms.

*Figueras. Late-onset fetal growth restriction. Am J Obstet Gynecol 2018.*

between low-risk SGA and high-risk FGR. As discussed above, a combination of biometric and Doppler parameters allows profiling a subgroup of fetuses that concentrates most instances of adverse outcomes.<sup>10</sup> While

delivery of high-risk FGR at 38 weeks is justified, a more expectant management could be offered to low-risk SGA.

An observational study<sup>94</sup> compared a strategy of systematic induction of late SGA at 37 weeks ( $n = 138$ ) with risk stratification and induction indicated by severe smallness, abnormal CPR, or abnormal uterine Doppler velocimetry ( $n = 143$ ). The incidence of neonatal composite adverse outcomes was lower after selective induction (9% vs 22%;  $P < .01$ ). This was defined as the presence of at least 1 of the following conditions: Apgar  $<7$  at 5 minutes, cord arterial pH  $<7.10$ , hypoglycemia (blood glucose  $<2.5$  mmol/L), and ventilation. The individual prevalence of these outcomes was 3/281 (1.1%), 5/98 (5%), 25/240 (10.4%), and 28/281 (10%), respectively. Furthermore, neonatal admission was also more frequent after systematic induction (13% vs 42%;  $P < .01$ ). Furthermore, cesarean delivery rates (25% vs 40%;  $P = .06$ ) were lower after selective induction. This study suggests that protocol-based management of SGA babies may improve outcomes and that identification of moderate SGA should not alone prompt delivery.

### Conclusions

First- or second-trimester screening strategies provide limited DR for late SGA. At third trimester, universal screening triples the DR of late SGA compared to clinically indicated scanning. As opposed to early third-trimester ultrasound, scanning late in pregnancy (around 37 weeks) increases the DR for BW  $<3$ rd and 10th centile.

UA Doppler velocimetry alone does not provide good differentiation between low-risk SGA and high-risk FGR. A combination of biometric parameters (with severe smallness usually defined as EFW or AC  $<3$ rd centile) with Doppler criteria of placental insufficiency (either in the maternal [uterine Doppler] or fetal [CPR] compartments) offers a classification tool that correlates with the risk for adverse perinatal outcome. For surveillance purposes, CPR is sensitive to reflect progression from diagnosis until term.

There is no evidence that induction of late FGR at term improves the perinatal outcomes nor is it a cost-effective strategy, and it may increase neonatal admission when performed <38 weeks. ■

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## Appendix

Systematic review of studies on routine ultrasound screening performing the scan at a mean gestational age >32 weeks

Query syntax:

((("diagnostic imaging"[Subheading] OR ("diagnostic"[All Fields] AND "imaging"[All Fields]) OR "diagnostic imaging"[All Fields] OR "ultrasound"[All Fields] OR "ultrasonography"[MeSH Terms] OR "ultrasonography"[All Fields] OR "ultrasound"[All Fields] OR "ultrasonics"[MeSH Terms] OR "ultrasonics"[All Fields]) OR US[All Fields] OR ("radionuclide imaging"[MeSH Terms] OR ("radionuclide"[All Fields] AND "imaging"[All Fields]) OR "radionuclide imaging"[All Fields] OR "scan"[All Fields]) OR ultrasonographic[All Fields] OR ("diagnostic imaging"[Subheading] OR ("diagnostic"[All Fields] AND "imaging"[All Fields]) OR "diagnostic

imaging"[All Fields] OR "ultrasonography"[All Fields] OR "ultrasonography"[MeSH Terms])) AND (SGA [All Fields] OR ("Proc Int Conf Autom Face Gesture Recognit"[Journal] OR "fgr"[All Fields] OR "Fungal Genet Rep"[Journal] OR "fgr"[All Fields]) OR (("Small"[Journal] OR "small"[All Fields]) AND gestational[All Fields] AND ("Age"[Journal] OR "age"[All Fields] OR "Age (Omaha)"[Journal] OR "age"[All Fields] OR "Age (Dordr)"[Journal] OR "age"[All Fields] OR "Adv Genet Eng"[-Journal] OR "age"[All Fields]))) AND ((detection[All Fields] AND ("J Rehabil Assist Technol Eng"[Journal] OR "rate"[All Fields])) OR ("sensitivity and specificity"[MeSH Terms] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity and specificity"[All Fields] OR "sensitivity"[All Fields])) AND (("pregnancy trimester, third"[MeSH Terms] OR

("pregnancy"[All Fields] AND "trimester"[All Fields] AND "third"[All Fields]) OR "third pregnancy trimester"[All Fields] OR ("third"[All Fields] AND "trimester"[All Fields]) OR "third trimester"[All Fields]) OR 3rd[All Fields])

Inclusion criteria:

Population: low-risk or nonselected pregnancies

Predictor: estimated fetal weight or abdominal circumference

Outcome: smallness for gestational age or fetal growth restriction

Design: observational (prospective or retrospective cohorts) or interventional  
Mean gestational age at ultrasound >32 weeks

Publication date ≥2012

Sources: PubMed

Query results: 132 Studies, of which 13 met the inclusion criteria after review of full-text document by 2 independent reviewers (J.C. and F.F.).



# A placenta clinic approach to the diagnosis and management of fetal growth restriction

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## Introduction

The concept of a placenta clinic, providing comprehensive medical and surgical care for a wide spectrum of disorders, has developed in several academic centers worldwide over the past 20 years. Success is based on interdisciplinary management in a hospital-based tertiary care environment led by maternal-fetal medicine subspecialists working with nurse practitioners, internal medicine subspecialties and gynecologic surgeons with support from neonatal pediatrics, perinatal pathology, magnetic resonance imaging (MRI), reproductive genetics, obstetrical anesthesia, and perinatal psychiatry. These resources offer an enhanced model of care in the context of suspected fetal growth restriction (FGR), and are especially useful for women with pre-existing hypertension, complex obstetrical backgrounds, or other medical comorbidities that place women at higher risk of placental pathology. By placing a focus on the prenatal diagnosis of placental diseases, this approach aids the distinction between a healthy small for gestational age

Effective detection and management of fetal growth restriction is relevant to all obstetric care providers. Models of best practice to care for these patients and their families continue to evolve. Since much of the disease burden in fetal growth restriction originates in the placenta, the concept of a multidisciplinary placenta clinic program, managed primarily within a maternal-fetal medicine division, has gained popularity. In this context, fetal growth restriction is merely one of many placenta-related disorders that can benefit from an interdisciplinary approach, incorporating expertise from specialist perinatal ultrasound and magnetic resonance imaging, reproductive genetics, neonatal pediatrics, internal medicine subspecialties, perinatal pathology, and nursing. The accurate diagnosis and prognosis for women with fetal growth restriction is established by comprehensive clinical review and detailed sonographic evaluation of the fetus, combined with uterine artery Doppler and morphologic assessment of the placenta. Diagnostic accuracy for placenta-mediated fetal growth restriction may be enhanced by quantification of maternal serum biomarkers including placenta growth factor alone or combined with soluble fms-like tyrosine kinase-1. Uterine artery Doppler is typically abnormal in most instances of early-onset fetal growth restriction and is associated with coexistent preeclampsia and underlying maternal vascular malperfusion pathology of the placenta. By contrast, rare but potentially more serious underlying placental diagnoses, such as massive perivillous fibrinoid deposition, chronic histiocytic intervillitis, or fetal thrombotic vasculopathy, may be associated with normal uterine artery Doppler waveforms. Despite minor variations in placental size, shape, and cord insertion, placental function remains, largely normal in the general population. Consequently, morphologic assessment of the placenta is not currently incorporated into current screening programs for placental complications. However, placental ultrasound can be diagnostic in the context of fetal growth restriction, for example in Breus' mole and triploidy, which in turn may enhance diagnosis and management. Several examples are illustrated in our figures and supplementary videos. Recent advances in the ability of multiparameter screening and intervention programs to reduce the risk of severe preeclampsia will likely increase efforts to deliver similar improvements for women at risk of fetal growth restriction. Placental pathology is important because the underlying pathologies associated with fetal growth restriction have a wide range of recurrence risks. Rare conditions such as massive perivillous fibrinoid deposition or chronic histolytic intervillitis may recur in >50% of subsequent pregnancies. Postpartum care in a placenta-focused program can provide effective counseling for modifiable maternal risk factors, and can assist in planning future pregnancy care based on the pathologic basis of fetal growth restriction.

**Key words:** angiogenic growth factors, Doppler, fetal growth restriction, pathology, placenta, small for gestational age, ultrasound

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(SGA) fetus and a fetus at risk of perinatal complications due to FGR. Comprehensive electronic medical records are a key component of care, ensuring accurate interpretation of gestational age-dependent ultrasound observations, integration of ambulatory

care, and seamless transition into inpatient care, delivery, and postpartum follow-up. Integration of multiparameter screening for FGR is an emerging important component of available software.<sup>1</sup> Clinic-based website resources can also be used to enhance

**TABLE 1**  
**Risk factors for impaired fetal growth**

Risk factor	Population	Type of fetal growth impairment	Strength of association (95% CI)
Use of assisted reproductive techniques	Declercq et al, <sup>3</sup> 2015 Longitudinal cohort study N = 334,628 Pregnancies from unselected obstetric population	Low birthweight <2500 g SGA	aOR 1.26 (1.08–1.41) aOR 1.10 (0.96–1.27)
Loss of co-twin	Prömpeler et al, <sup>4</sup> 1994 Retrospective cohort study N = 43 Twin pregnancies with single fetal death	SGA	22% Incidence in surviving twin
Heavy first-trimester vaginal bleeding	Saraswat et al, <sup>5</sup> 2010 Systematic review N = 14 studies included	Low birthweight <2500 g SGA	OR 1.83 (1.48–2.28) OR 1.54 (1.18–2.00)
Increased nuchal translucency	Kumar et al, <sup>6</sup> 2017 Prospective cohort study N = 2168 Unselected singleton pregnancies	SGA	OR 1.72 (1.07–2.77)
Low PAPP-A: <1st percentile, <0.29 MoM Low PAPP-A: <5th percentile, <0.38 MoM Free β-hCG: <1st percentile, <0.21 MoM	Krantz et al, <sup>7</sup> 2004 Prospective cohort study N = 8012 Pregnancies from unselected obstetric population	SGA	OR 5.4 (2.8–10.3), PPV 24.1% OR 2.7 (CI 1.9–3.9), PPV 14.1% OR 2.7 (1.3–5.9), PPV 14.3%
Low PAPP-A alone: <5% of values for gestational age, <0.4 MoM High AFP: >5% of values for gestational age [>1.7 MoM] and low PAPP-A	Smith et al, <sup>8</sup> 2006 Multicenter prospective cohort N = 8483 Unselected singleton pregnancies in early pregnancy ≤14 wk gestation	SGA	OR 2.8 (2.0–4.0) OR 8.5 (3.6–20.0)
Low PIGF: <5th percentile, <12 pg/mL	Crovetto et al, <sup>1</sup> 2016 Nested case-control study within prospective cohort study N = 9150 Unselected singleton pregnancies	Early-onset FGR <34 wk Late onset FGR ≥34 wk	AUC 0.925 (0.872–0.977) DR 86.4% (85.7–87.1) at FPR 10% AUC 0.761 (0.726–0.796) DR 65.8% (64.8–66.8)
Discrepancy between crown-rump length measurements and accurate menstrual history by 2–6 d	Smith et al, <sup>9</sup> 1998 Retrospective cohort study N = 4229 Healthy unselected singleton pregnancies	Low birthweight <2500 g SGA <5th percentile	RR 1.8 (1.3–2.4) RR 3.0 (2.0–4.4)

AFP, alpha-fetoprotein; aOR, adjusted odds ratio; AUC, area under curve; CI, confidence interval; DR, detection rate; FGR, fetal growth restriction (<10th percentile due to underlying pathology); FPR, false positive rate; hCG, human chorionic gonadotropin; MoM, multiples of median; OR, odds ratio; PAPP, pregnancy-associated plasma protein; PIGF, placenta growth factor; PPV, positive predictive value; RR, relative risk; SGA, small for gestational age (<10th percentile of birthweight unless range stated otherwise).

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patient understanding of placenta-related diseases.<sup>2</sup>

### Diagnostic evaluation in suspected FGR

#### Review of pregnancy history and prior test results

Fetal growth assessment begins with assignment of gestational age, ideally using ultrasound measurements from the first or early second trimesters.

Subsequent biometry data are then used to review the trajectory of growth. Several risk factors for SGA birth or FGR that include the use of assisted reproductive technologies, loss of a co-twin, heavy first-trimester vaginal bleeding, increased nuchal translucency, abnormal screening analyte data, and crown-rump length discrepancy are listed in Table 1.<sup>1,3-9</sup> Accurate dating is essential for establishing the subsequent

diagnosis of either a healthy SGA fetus or a fetus with growth restriction.<sup>10</sup> Relevant maternal comorbidities should be noted and addressed, in particular chronic hypertension, diabetes, and elevated body mass index. Prior uterine surgeries are relevant in subsequent planning of mode of delivery. Obtaining a travel history (to Zika virus-affected areas) is also relevant to the evaluation of a suspected

**TABLE 2**  
**Maternal substance use and fetal growth outcomes**

Risk factor	Population	Type of growth impairment	Strength of association (95% CI)
Alcohol $\geq$ 1 alcoholic beverage [12 g]/d until pregnancy was known	Jaddoe et al, <sup>12</sup> 2007 Population-based prospective cohort study N = 7141 Cohort: Women in early gestation <18 wk	Low birthweight <2500 g	OR 4.81 (1.10–21.08)
Marijuana	Warshak et al, <sup>13</sup> 2015 Retrospective cohort study N = 6468 Cohort: Singletons >20 wk gestation	SGA	aOR 1.30 (1.03–1.62)
Cocaine	Gouin et al, <sup>14</sup> 2011 Meta-analysis N = 31 studies	Low birthweight <2500 g SGA	OR 3.66 (2.90–4.63) OR 3.23 (2.43–4.30)
Cigarettes	McCowan et al, <sup>15</sup> 2009 Prospective cohort study N = 2504 Cohort: Healthy nulliparous women	SGA	OR 1.76 (1.03–3.02)

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; SGA, small for gestational age (<10th percentile of birthweight).

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FGR pregnancy.<sup>11</sup> Maternal substance use of alcohol, marijuana, cocaine, and cigarette smoking all increase the risk of low birthweight (<2500 g) or SGA deliveries (Table 2).<sup>12–15</sup> Finally, the results of any additional pregnancy tests, such as invasive microarray genetic data, fetal anatomical assessment, and previous pregnancy reports (especially for placental pathology), are reviewed.

### Biometry, anatomy, and amniotic fluid

Ultrasound imaging begins with fetal biometry and a review of anatomy. A variety of formulas exist to estimate fetal weight.<sup>16</sup> Appropriate selection among available formulas is important when there is fetal asymmetry (elevated head circumference/abdominal circumference ratio with short femurs) at <33 weeks with abnormal umbilical artery Doppler,<sup>17</sup> because in this context incorporation of femur length (FL) can lead to significant (>10%) underestimation of fetal weight. In a study of 43 early-onset FGR pregnancies delivered at <33 weeks, incorporation of FL underestimated birthweight by 8% when  $\leq$ 27 weeks, and by 15% at 28–33 weeks.<sup>18</sup> Therefore, selecting an appropriate formula without FL is important when deriving the estimated fetal weight in suspected early-onset FGR pregnancies

that have an elevated head circumference/abdominal circumference ratio for gestational age. A second important consideration is gestational age assignment in early-onset FGR in the absence of first-trimester ultrasound dating; in this context, gestational age was accurately predicted throughout the second trimester ( $\pm$ 3 days in 97.5%, n = 40) by measurement of the transcerebellar diameter,<sup>19</sup> which is therefore an important measurement to make. Amniotic fluid volume assessment is relevant to making a diagnosis of FGR; oligohydramnios is a feature of placenta-mediated FGR, while some fetal malformations and chromosomal abnormalities are associated with excess amniotic fluid.<sup>20</sup>

Careful reevaluation of fetal anatomy is necessary for evaluation of all non-placental causes of FGR since, at a population-based level, congenital birth defects confer a 2.6 relative risk (RR) for birth of an SGA neonate.<sup>21</sup> In this context, some findings, such as echogenic bowel<sup>22</sup> or short FL, may be consistent with placental FGR rather than aneuploidy or other fetal causes of FGR<sup>18,23</sup>; short femurs associated with FGR may be distinguished from most skeletal dysplasias by noting normal bone morphology, continued femur

elongation, and normal shape in the remaining long bones, chest wall, and skull. Careful evaluation of cardiac anatomy is important, since a range of congenital cardiac malformations are associated with suspected FGR. In a population-based study, congenital heart disease was associated with birthweight <10th percentile, especially tetralogy of Fallot (RR, 4.6; 95% confidence interval [CI], 3.1–6.8), atrial septal defect (RR, 3.8; 95% CI, 3.4–4.2), and coarctation of the aorta (RR, 3.5; 95% CI, 2.4–5.1).<sup>21</sup> Some cardiac defects specifically reduce fetal brain growth, especially hypoplastic heart syndrome and large ventriculoseptal defects.<sup>24</sup> A range of fetal brain abnormalities is more common in FGR pregnancies. One third of triploidy fetuses diagnosed in the second trimester exhibit bilateral ventriculomegaly.<sup>25</sup> Acquired brain injury is surprisingly common in early-onset FGR. In a prospective single-center series of 90 FGR pregnancies delivered at 28–34 weeks with abnormal umbilical artery Doppler, 40% had immediate postnatal evidence of brain injury (intraventricular hemorrhage, periventricular leukomalacia) in comparison with 12% in a gestational age-matched control group.<sup>26</sup> Vasodilation of the middle cerebral artery accompanied by

TABLE 3

## Ultrasound-derived maximum placental dimensions in second trimester

Wk	N	Variable	Mean $\pm$ SD, cm	IQR	5th–95 <sup>th</sup> centiles
20	270	Thickness	2.48 $\pm$ 0.48	2.2–2.7	1.8–3.4
		Curve-linear length	18.11 $\pm$ 2.84	16.2–119.5	14.4–23.1
21	404	Thickness	2.55 $\pm$ 0.56	2.2–2.9	2.9–3.5
		Curve-linear length	18.92 $\pm$ 2.96	16.8–20.7	20.7–24.1
22	182	Thickness	2.68 $\pm$ 0.66	2.2–3.1	3.1–3.9
		Curve-linear length	19.42 $\pm$ 3.27	16.9–21.2	21.2–26.1

IQR, interquartile range (25th–75th centile).

Table values adapted with permission from Wright et al.<sup>37</sup>

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retrograde aortic isthmus flow conferred the greatest risk (67%) of acquired brain injury. Such lesions are challenging to identify with prenatal ultrasound; consequently, fetal MRI may emerge as a clinically useful modality to define brain anatomy in the context of early-onset FGR, especially when brain abnormalities or intracranial hemorrhage are suspected on ultrasound. Fetal MRI can also estimate fetal brain oxygen delivery and consumption<sup>27</sup> and may be able to detect ischemic brain injury by diffusion-weighted imaging.<sup>28</sup>

### Uterine artery Doppler

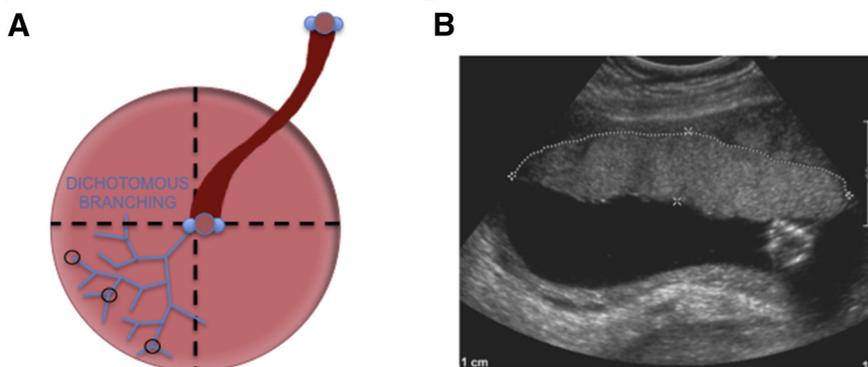
The uterine arteries selectively vasodilate during pregnancy, directing the increased cardiac output to the uterus. Doppler assessment of the proximal arteries demonstrates this phenomenon, with declining mean pulsatility index (PI) values as pregnancy advances; we use the reference range provided by Gomez et al<sup>29</sup> for clinical interpretation of the mean PI value across gestation. Uterine artery Doppler (UtAD) assessment is an attractive concept to screen for FGR in the second trimester,<sup>30</sup> since

the majority of early-onset FGR pregnancies exhibit a postnatal pathology diagnosis of maternal vascular malperfusion (MVM) of the placenta, associated with bilateral high-resistance notched waveforms.<sup>31</sup> Normally the waveform is assessed on both sides, but can be omitted on the opposite side of a lateral placenta to avoid false-positive mean PI results.<sup>32</sup> In large cohort studies of unselected women, UtAD achieves insufficient precision as a screening test to deliver improved outcomes for suspected FGR pregnancies. The Uterine Test to Detect Preeclampsia (UTOPIA) trial randomized 11,667 to a fetal anatomical ultrasound with or without UtAD at 19–23 weeks, where women in the screened group with an abnormal UtAD (mean PI >90th percentile) received enhanced surveillance.<sup>30</sup> Moderate sensitivity (60%) was achieved for the prediction of FGR and delivery <34 weeks, with sensitivity reducing to 24% for FGR and delivery  $\geq$ 34 weeks, and 18% for SGA births. Despite significantly greater interventions such as corticosteroid use (RR, 1.79; 95% CI, 1.4–2.3) and induction of labor (RR, 1.36; 95% CI, 1.07–1.72), no significant improvements in either perinatal or maternal outcomes was demonstrated. A similar conclusion was reached in the Nulliparous Pregnancy Outcomes Study of 8024 women, where UtAD was performed at 16–21 weeks as a screening test for SGA birth across all gestational ages at the fifth centile, achieving a modest 45% sensitivity using a mean PI  $\geq$ 0.98.<sup>33</sup> A smaller US cohort made similar conclusions.<sup>34</sup> UtAD may be incorporated within multiparameter models, comprising clinical risk factor and biomarkers, to predict placental disease or associated adverse clinical outcomes in the second trimester,<sup>35–37</sup> but are not sufficiently precise to recommend for use in low-risk pregnancies.

UtAD may likewise be integrated into similarly designed first-trimester screening algorithms to predict adverse pregnancy outcomes related to SGA birth.<sup>38</sup> This approach may become more popular following the recent publication of a substantial reduction (odds

FIGURE 1

## Normal placental sonographic findings in second trimester



**A**, In optimal placental development, placenta is circular, with central 3-vessel cord. Umbilical artery branches (blue circles) ramify across chorionic plate in dichotomous fashion (shown in 1 quadrant). Individual villous trees form below each branch point and therefore form even in periphery of disc (open circles). **B**, Sonographic measurement of maximum placental length at 21 weeks using curve-linear method at basal plate (+ – +), and maximum placental thickness (x – x) at 21 weeks of gestation. See [Supplementary Video 1](#). Reference range for placental dimensions at 20+0 to 23+6 weeks' gestation is shown in [Table 3](#).

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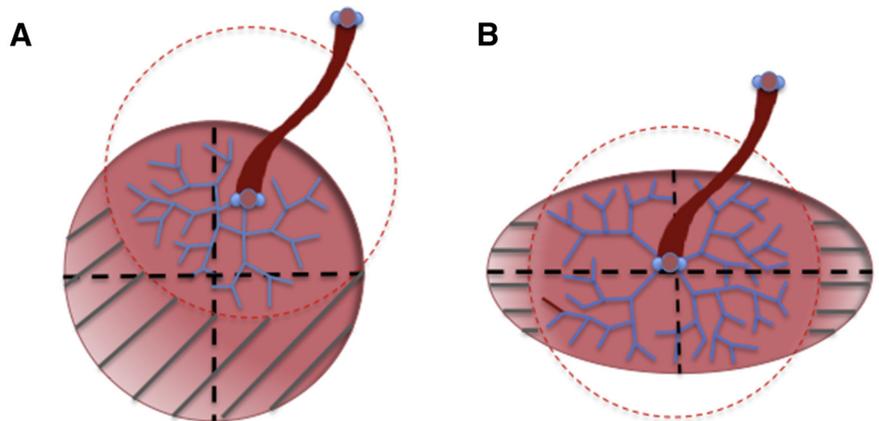
ratio [OR], 0.38; 95% CI, 0.2–0.74) in the incidence of preterm preeclampsia following administration of aspirin (150 mg/d) to screen-positive women, although in this study aspirin did not improve birthweight.<sup>39</sup> In a diagnostic setting, UtAD has prognostic utility in women with abnormal biomarker data in the second trimester.<sup>40,41</sup> Abnormal UtAD may normalize during the second trimester, which is a favorable observation since outcomes are improved in comparison with women that exhibit persistently abnormal waveforms.<sup>42</sup> Third-trimester UtAD is not an effective screening tool in unselected pregnancies,<sup>43</sup> but may aid identification of a placental basis for suspected FGR.

### Placental morphologic assessment

Visualization of the placenta by ultrasound is a logical adjunct to UtAD because a majority of placentas examined following extreme preterm births with preeclampsia or FGR are small and grossly abnormal.<sup>44-46</sup> The simplest method uses 2-dimensional ultrasound to measure maximum placental length, thickness, overall placental shape, and cord insertion.<sup>37,47-49</sup> Normal placental findings in the second trimester are summarized in [Table 3](#)<sup>37</sup> and illustrated in [Figure 1](#) and [Supplementary Video 1](#). Descriptive associations have been demonstrated between gross abnormalities in placental size, shape, and cord insertion and adverse perinatal outcomes including FGR.<sup>50,51</sup> Increased placental thickness confers an increased risk of perinatal complications, but the implication of this finding depends on the underlying pathology. A single-center Japanese study in 3183 women demonstrated an increased OR (1.8; 95% CI, 1.2–2.8) of SGA at birth where thickness was >95th centile for gestation, but did not report placenta pathology data.<sup>52</sup> Placental morphologic assessment can improve screening accuracy for FGR but is of insufficient value to justify its cost in low-risk populations,<sup>36</sup> since variations in placental size and shape have relatively weak associations with birthweight<sup>37,53</sup> ([Figure 2](#)). In high-risk pregnancies with bilateral abnormal UtAD waveforms at 19-23 weeks, the finding of

**FIGURE 2**

**Minor variations in placental anatomy that impair overall efficiency (fetal-placental weight ratio at birth)**

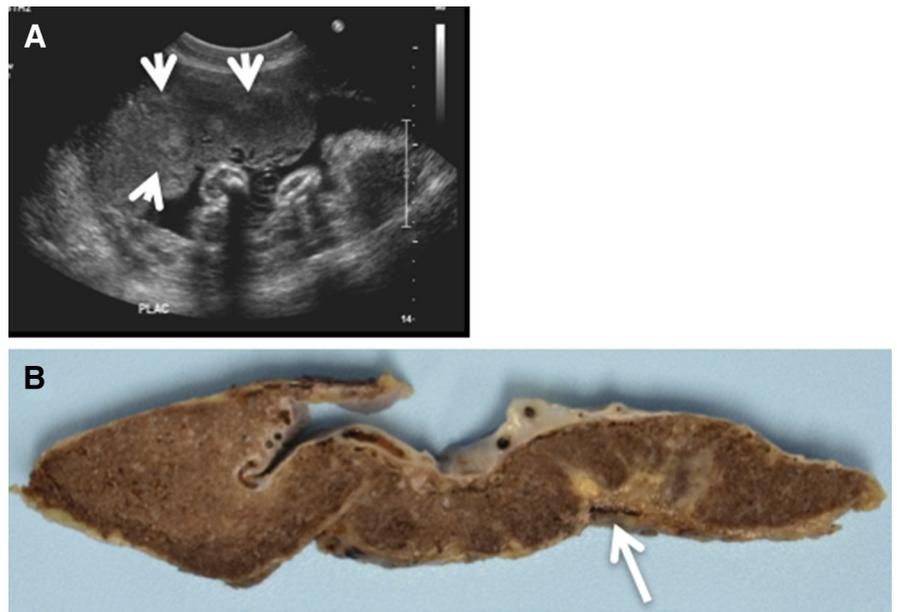


**A**, Eccentric cord insertion: as cord insertion is placed more eccentrically chorionic tissue on opposing edge may become less vascularized due to attenuated chorionic plate vascular branching in opposite quadrant. **B**, Elliptical placenta: similar phenomenon may occur at lateral margins of elliptical placenta. Such alterations in placental shape and cord insertion alone account for only ~10% of variation found in birthweight.

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**FIGURE 3**

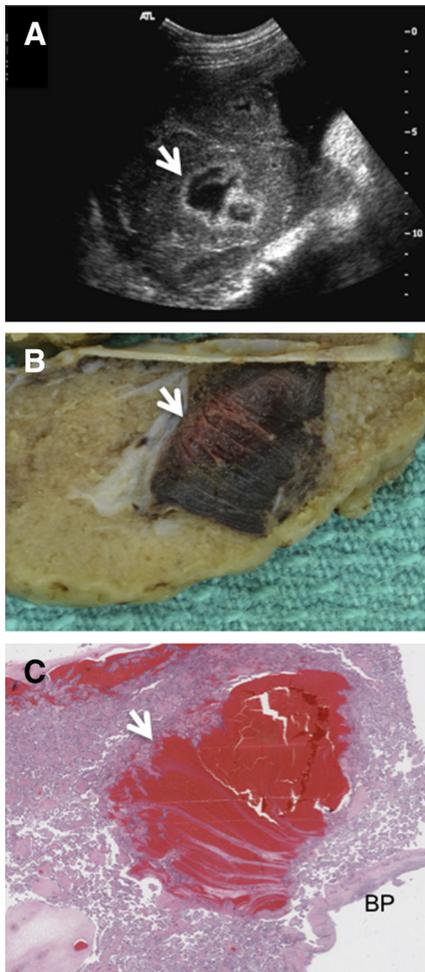
**Placental infarction**



**A**, Multiple echo-dense lesions (arrowheads) within anterior placenta in fetal growth restriction pregnancy with bilateral abnormal uterine artery Doppler waveforms and early-onset preeclampsia at 31 weeks of gestation. **B**, Corresponding central slice of fixed placenta with infarct arising from basal plate region (arrow). See [Supplementary Video 5](#).

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**FIGURE 4**  
Intervillous thrombosis

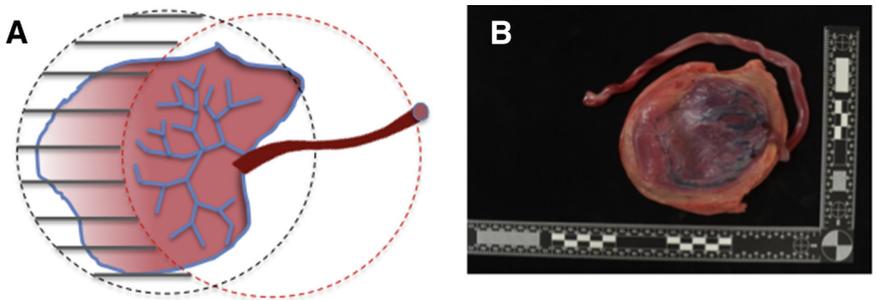


**A**, Ultrasound image of placenta showing echogenic cystic lesion; note crenated white rim surrounding black center (arrowhead). **B**, Following fixation and serial sectioning, this lesion is identified as intervillous thrombus. Note laminated layers of blood (arrowhead). **C**, Corresponding hematoxylin-eosin photomicrograph. Note lesion is within intervillous space of placental parenchyma. Isolated intervillous thrombi are common and of no functional significance. If numerous, they may contribute to pathogenesis of fetal growth restriction. Contrast with infarction (Figure 3), which is associated with decidual vasculopathy of basal plate (BP). See [Supplementary Video 6](#).

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abnormal placental shape (thickness/length ratio  $>0.5$  or thickness  $>4$  cm) increased the odds of early-onset FGR (OR, 4.7; 95% CI, 1.4–15.1).<sup>54</sup>

**FIGURE 5**  
Severe maternal vascular malperfusion placental pathology



**A**, Combination of asymmetrically small placenta (dashed black circle indicates expected placental disc size). Note eccentric cord insertion and zone of chorionic plate vascular arborization centered on this point (dashed red circle). Overlapping area of vascularized placenta (blue surface branching pattern) indicates severe chorion regression. **B**, Representative case at 23 weeks of gestation with severe preeclampsia, cardiac failure, fetal growth restriction stillbirth, and HELLP syndrome with bilateral abnormal uterine artery Doppler. Serial sections of fixed placenta demonstrated multiple infarcts and histologic features of uteroplacental vascular insufficiency in placental villi.

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Three-dimensional ultrasound is a more complex approach, but can derive placental volume and shape in early pregnancy at the time of the nuchal translucency examination.<sup>55,56</sup> A recent systematic review of 5 studies (302/5411 pregnancies with a subsequent diagnosis of SGA) using 3-dimensional placental volume to predict SGA birth showed inadequate screening test characteristics (sensitivity 25%, specificity 90%).<sup>57</sup> The method has similar performance characteristics to second-trimester UtAD to screen for FGR.<sup>58</sup> Presently, the assessment of placental morphology is not recommended in low-risk pregnancies, since variations in size and shape are common in normal pregnancy. The Collaborative Perinatal Project involving 24,152 births in the United States demonstrated that placental morphological characteristics observed following birth accounted for 39% of birthweight variation.<sup>59</sup> Examples of minor sonographic variations are illustrated in [Supplementary Videos 2 to 4](#).

### Mechanisms of placental injury

The most common mechanism of pathologic injury to the placenta resulting in FGR is via ischemia-reperfusion insults to the developing placental villi.<sup>60</sup> This concept was recently

reviewed in detail.<sup>61</sup> The pathophysiology is initiated by failed physiologic transformation of the spiral artery branches of the uteroplacental arteries,<sup>62</sup> restricting maternal blood flow into the intervillous space.<sup>63</sup> This state of MVM is identified sonographically by the combination of a small placenta and bilateral abnormal UtAD waveforms.<sup>37,54</sup> Persistent ischemia-reperfusion damages the developing placental villi, causing the histologic features of MVM, which include multifocal infarction<sup>31,45,64</sup> and formation of syncytial knots, with excess production and secretion of the antiangiogenic protein soluble fms-like tyrosine kinase (sFlt)-1 in syncytial knots<sup>65,66</sup> and suppression of syncytiotrophoblast secretion of the proangiogenic placenta growth factor (PlGF).<sup>67,68</sup> Consequently, abnormal circulating angiogenic ratios of sFlt-1 and PlGF correlate with the extent of placental MVM pathology.<sup>69</sup> However, combining angiogenic factors with UtAD to screen for FGR in early pregnancy in unselected women does not currently achieve clinically useful diagnostic precision; in a Spanish 1:2 matched case-control study, 24/46 SGA births were predicted in a model combining ultrasound and PlGF (sensitivity 52% at 10% false-positive rate).<sup>38</sup>

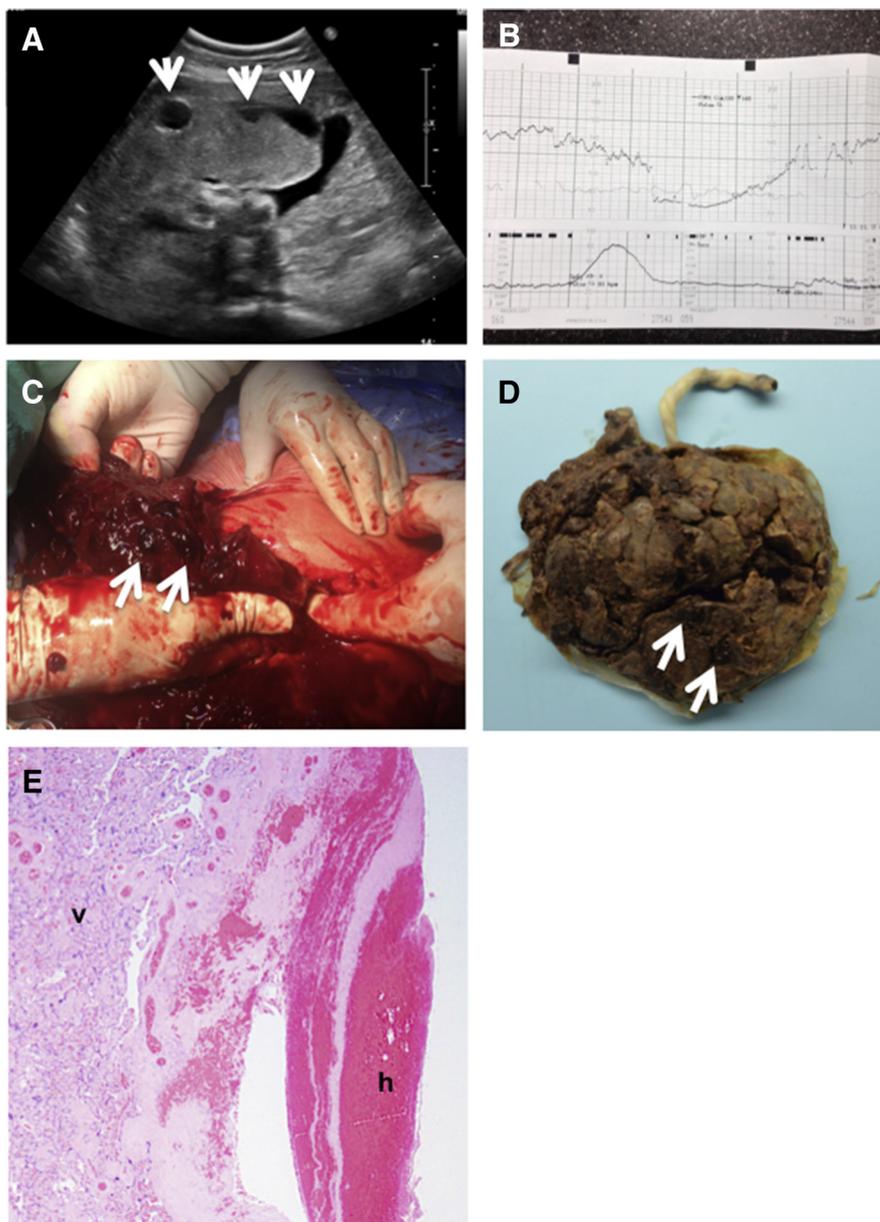
Multifocal placental infarction is found following delivery in almost 80% of early-onset FGR pregnancies with abnormal UtAD waveforms, implying substantial loss of functional placental tissue.<sup>31</sup> The ability to effectively detect widespread placental injury in this context may be of prognostic importance. One retrospective series of 60 early-onset FGR pregnancies demonstrated this concept by predicting stillbirth (17/21, sensitivity 81%, positive predictive value [PPV] 52%) when placental morphology and UtAD waveforms were both abnormal.<sup>44</sup> However, placental infarcts are challenging to identify using ultrasound because they are solid, and thus relatively similar in appearance to normal placental tissue. In a subsequent study of 60 high-risk pregnancies with abnormal UtAD, where placental infarction was found in 24/43 (56%) of placentas examined after delivery, the anticipated sonographic abnormality (echogenic basally located lesions) (Figure 3 and Supplementary Video 5), found in 15 placental images, had only a 33% PPV (21% sensitivity) for infarction.<sup>54</sup>

By contrast, less pathologically important lesions such as intervillous thrombi are more readily identified as they have a crenated white rim and a black center indicating laminated hemorrhage (Figure 4 and Supplementary Video 6), hence their description as echogenic cystic lesions.<sup>70</sup> Measurement of maternal serum PIGF in this setting may aid the interpretation of suspicious placental ultrasound findings, especially if UtAD is abnormal. Given the inherent variations in placental size and shape, the prenatal diagnosis of MVM placental pathology is most confidently made using a combination of abnormal UtAD and a small or morphologically abnormal placenta, and may be supported by low (<100 pg/mL) or very low (<12 pg/mL) maternal PIGF levels (Figure 5).<sup>71</sup>

Major retroplacental hemorrhage (abruption) is readily identifiable by ultrasound when large, but in practice is rarely observed because the disruption of

**FIGURE 6**

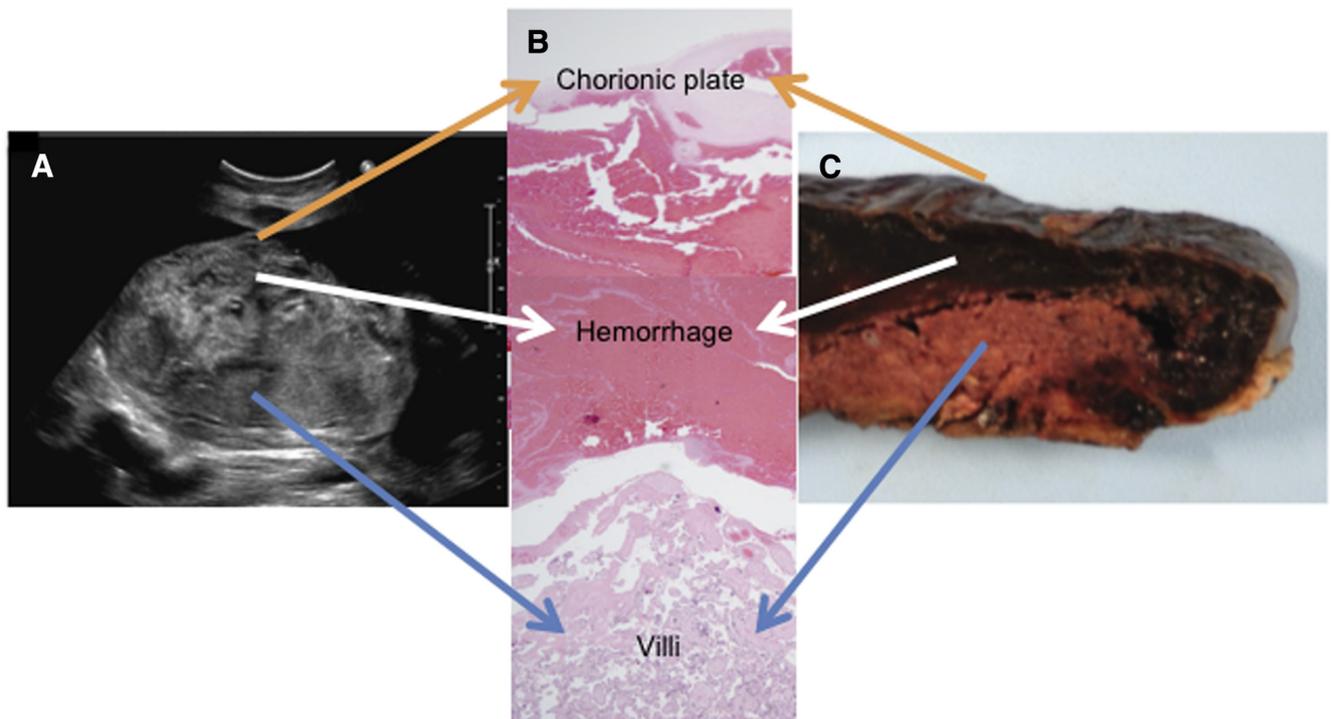
**Chronic placental abruption complicating fetal growth restriction at 33 weeks' gestation**



Patient presented to triage with reduced fetal movements but no abdominal pain. **A**, Ultrasound examination showed 3 areas of placental separation (arrowheads). Absent end-diastolic flow velocity was noted in umbilical arteries and nonstress test was reactive. Patient was admitted and corticosteroids were given. **B**, Cesarean delivery was performed >24 hours due to severe fetal heart rate deceleration in response to Braxton-Hicks contraction. **C**, Retroplacental hematomas were found at delivery (arrows). **D**, Placenta was small (225 g and third-fifth percentile at 33 weeks) with peripheral cord insertion 1.7 cm from disc margin and maternal surface was disrupted by hematomas (arrows). **E**, Low-power hematoxylin-eosin–stained micrograph showing maternal hemorrhage (h) compressing overlying placental villi (v). See Supplementary Video 7.

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**FIGURE 7**  
**Breus' mole**



Sonographic findings of posterior placenta with **A**, extensive echogenic layers at chorionic plate location suggestive of hemorrhage above normal placental tissue. **B**, Low-power micrograph and **C**, gross findings showing laminated hemorrhage between chorionic plate and functional placental villous tissue confirm sonographic appearance. See [Supplementary Video 8](#).

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the maternal-fetal interface triggers a clinical emergency ([Supplementary Video 7](#)). Small retroplacental hematomas may evolve chronically and be visible by ultrasound ([Figure 6](#)). Hemorrhage may also be found in the placental margins, but should be distinguished from the physiologic marginal sinus where intervillous blood reenters the systemic venous circulation ([Supplementary Video 2](#)). Rarely, hemorrhage may be seen where large portions of the membranes detach from the uterine wall.<sup>72</sup>

The perinatal risk from this range of placental lesions depends upon the amount of residual normally functioning placental tissue, combined with knowledge of the uterine and umbilical arterial Doppler waveforms. A good example of this concept is in the diagnosis and evaluation of prognosis in Breus' mole, a condition associated with

severe FGR, where layers of hemorrhage accumulate directly under the chorionic plate, underlying at least 50% of the chorionic plate surface<sup>73</sup> ([Figure 7](#) and [Supplementary Video 8](#)). In this scenario, the parallel observation of normal placental villous tissues below the laminated blood is a favorable prognostic sign for perinatal survival.<sup>73</sup> The site of major hemorrhage is also relevant, as it may be entirely within the membranes, away from the placental disc, or alternatively may physically disrupt placental attachment. Another diagnostic placental abnormality is the typical findings in triploidy, with increased thickness and a uniform microcystic appearance accompanied by severe asymmetric early-onset FGR.<sup>74</sup>

#### **Chorion regression**

Progressive tissue infarction is a characteristic manifestation of the MVM

disease category, but is only one manifestation of the disease spectrum. A second major disease process in MVM is termed "chorion regression."<sup>75</sup> This refers to poor early formation of the definitive placenta (chorion frondosum) at the expense of the membranes (chorion leave).<sup>76</sup> The reduced placental attachment site is then associated with low levels of pregnancy-associated plasma protein-A at the 11- to 13-week first-trimester screening window<sup>77</sup> and may evolve to reveal a small placenta with an eccentric or 2-vessel cord ([Figure 8](#) and [Supplementary Video 9](#)). In this setting, as pregnancy advances, the placenta may become "wobbly" or "floppy" due to poor development of the placental villi, likely corresponding to the histologic appearance of distal villous hypoplasia ([Supplementary Video 10](#)) or may even become hyperinflated, appearing very large with an acutely

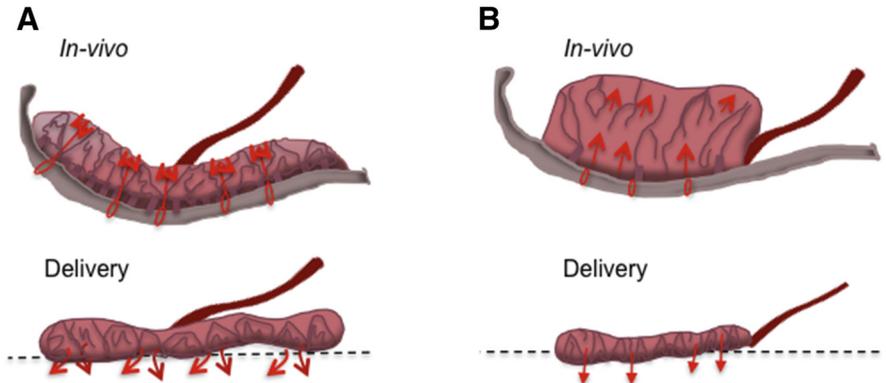
**FIGURE 8**  
Chorion regression



Small fundal placenta (dashed line; curve-linear length 12 cm) at 22 weeks' gestation in 25-year-old woman with false-positive first-trimester screening test for trisomy 21, due to low pregnancy-associated plasma protein-A (0.18 multiples of median). Note marginal cord insertion (arrow). Early-onset fetal growth restriction developed despite bilateral normal uterine artery Doppler waveforms (inset). See [Supplementary Video 9](#).

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**FIGURE 9**  
Placental deflation following delivery



**A**, Normal placenta is expanded in vivo by perfusion of intervillous space via spiral arteries and chorionic and basal plates are maintained in parallel by subset of villous trees that anchor to basal plate (5 anchoring villi). **B**, Subset of pregnancies with chorion regression exhibit placental hyperinflation whereby chorionic plate bulges dramatically into uterine cavity. Following delivery, expanded structure collapses and pathologic examination often shows features of distal villous hypoplasia, therefore loss of normal anchoring villi needed to contain normal placental shape. This phenomenon develops during second trimester, confounding utility of placental volume as component of screening for fetal growth restriction. See [Supplementary Videos 10 and 11](#).

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convex chorionic plate due to distension of the intervillous space by maternal blood<sup>78</sup> ([Figure 10](#) and [Supplementary Video 11](#)).

### Circulating proangiogenic and antiangiogenic placenta-derived proteins

The circulating proangiogenic placenta-derived protein, PIGF, is an important new clinical test that is becoming more available, as well as more widely used to treat women with suspected preeclampsia, given its superior diagnostic accuracy and positive health economic analysis data from the United Kingdom<sup>79,80</sup> and the United States.<sup>81-83</sup> These tests have the potential to improve the diagnosis and management of pregnancies with suspected FGR due to the association of low circulating PIGF is associated with placenta-mediated FGR.<sup>71</sup> Normal circulating PIGF rises progressively during pregnancy to a plateau around 22 weeks.<sup>71</sup> In the second trimester, low levels of PIGF have superior screening performance in comparison with many

potential biomarkers to predict placenta-related complications.<sup>84</sup> In a prospective cohort of 274 women with suspected preeclampsia presenting at 20-34 weeks' gestation, low circulating PIGF (<100 pg/mL) had high sensitivity to detect SGA births ( $n = 96$ ) below third customized birthweight centile (sensitivity 93%, negative predictive value [NPV] 90%), which was superior to fetal weight estimation by ultrasound (sensitivity 71%, NPV 79%).<sup>85</sup> An earlier multicenter study by the same group, of 592 women with reduced symphysis-fundal height measurements, found that combining PIGF with ultrasound biometry increased the sensitivity from 58-69% for the detection of customized growth at the third centile (with the same 93% NPV).<sup>86</sup> As an adjunct to multiparameter screening for placental dysfunction in the second trimester, PIGF offers only modest gains and is therefore not recommended in low-risk pregnancies.<sup>37,87</sup>

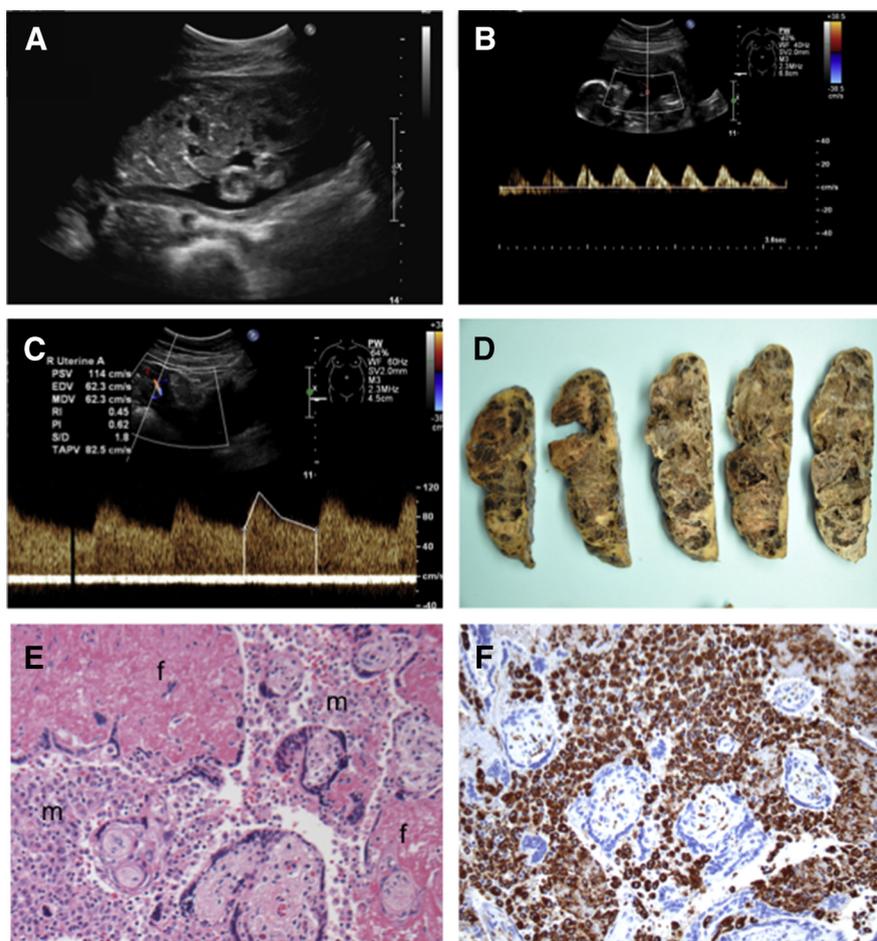
PIGF testing in the context of FGR may be augmented by comeasurement of

the sFlt-1 soluble receptor antagonist to vascular endothelial growth factor. Combined together as a ratio test, these biomarkers are predictive of the placental pathology termed "maternal vascular malperfusion."<sup>69</sup> In a recent Japanese cohort of 34 normotensive preterm FGR cases, an elevated sFlt-1/PIGF ratio (>86) predicted subsequent pregnancy duration, with only 42% (vs 92% with a ratio <86) remaining pregnant 14 days later.<sup>88</sup> In a cohort of 110 subjects with suspected preeclampsia at <34 weeks, a high sFlt-1/PIGF ratio was strongly predictive of adverse outcomes.<sup>89</sup> The ongoing European EVERREST cohort study will determine the prognostic value of PIGF among a range of potentially useful prognostic markers of severe FGR identified <27 weeks' gestation.<sup>90</sup>

### Safety of corticosteroids in early-onset FGR

Consideration of corticosteroid administration for fetal lung maturation is an important component of management in FGR, especially for patients with more

**FIGURE 10**  
**Nonmaternal vascular malperfusion pathology in early-onset fetal growth restriction (FGR)**



Normotensive woman referred at 28 weeks with suspected FGR and previous 22-week stillbirth. **A**, Ultrasound-confirmed asymmetric FGR, accompanied by thick placenta with diffusely abnormal texture, **B**, absent end-diastolic flow velocity waveforms in umbilical arteries, yet **C**, bilateral normal uterine artery Doppler waveforms. **D** to **F**, Placental findings demonstrating massive perivillous fibrinoid deposition of placenta (maternal floor infarction) accompanied by chronic histiocytic intervillitis. **D**, Gross findings in serial sections of fixed placenta demonstrated extensive replacement of villous tissue with lacelike pale fibrinoid material. **E**, Representative hematoxylin-eosin section at medium power showing confluent pink staining in areas of fibrinoid (f) while intervillous space is occupied by numerous histiocytes/macrophages (m). **F**, Positive staining (brown) for CD68 confirms identity of intervillous cells as histiocytes/macrophages. CD3 staining (not shown) showed additional infiltration by T-lymphocytes.

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severe early-onset disease associated with hypertension and abnormal umbilical artery Doppler, and now including women identified with very low PIGF (<12 pg/mL)<sup>71,85</sup> or abnormal sFlt-1/PIGF ratios.<sup>69,88</sup> Corticosteroids pose a specific challenge in the context of severe FGR with abnormal umbilical

artery and fetal Doppler waveforms. In sheep, fetal hypoxemia is associated with lactic acidosis,<sup>91</sup> which is exacerbated directly following steroid administration.<sup>91</sup> The human preterm FGR fetus is also at risk of lactic acidosis,<sup>92</sup> especially if fetal ductus venosus Doppler waveforms are abnormal.<sup>93</sup> Consequently, if

metabolic acidosis is present, it may be exacerbated following maternal beta-methasone administration. Curiously, >50% of FGR fetuses with absent end-diastolic flow in the umbilical arteries will exhibit a temporary improvement in umbilical artery Doppler waveforms in response to steroid administration, which is a favorable sign and may persist for 7-10 days.<sup>94</sup> In 1 study of 19 FGR fetuses, 10 exhibited a favorable umbilical artery Doppler response, whereas in the remaining 9 cases, 5 showed no improvement, 2 had a subsequent still birth, and 2 had severe fetal acidosis at cesarean delivery.<sup>95</sup> A more recent larger study of 93 fetuses showed that a third will not show any improvement in umbilical artery Doppler following steroid administration, and have a worse prognosis than the majority with improvements in end-diastolic flow velocity.<sup>96</sup> We interpret these data to imply that enhanced fetal monitoring, either daily as an inpatient, or >48 hours in an ambulatory setting, is justified when administering corticosteroids in this context. Ideally, all early-onset FGR fetuses should receive prenatal steroids prior to delivery; rarely this is not possible, for example if spontaneous decelerations occur due to placental abruption (Figure 6).

### Social work and mental health support

Women with preterm FGR pregnancies, along with their families, may be subjected to substantial emotional stress, particularly when the fetal prognosis appears poor or highly uncertain. Pre-existing poor mental health may exacerbate these concerns and are considered to be significant comorbidities in FGR pregnancies.<sup>97,98</sup> In our experience, around 25% of our placenta clinic patients at risk of FGR access our perinatal mental health services. Continuity of psychosocial care into the postpartum period is important because of the uncertain neonatal prognosis in preterm FGR birth. Dedicated clinic nurse practitioners can provide this ongoing support prior to a 6- to 8-week postpartum visit, when clinical issues summarized in Table 2 can be addressed.

## Importance of placental pathology

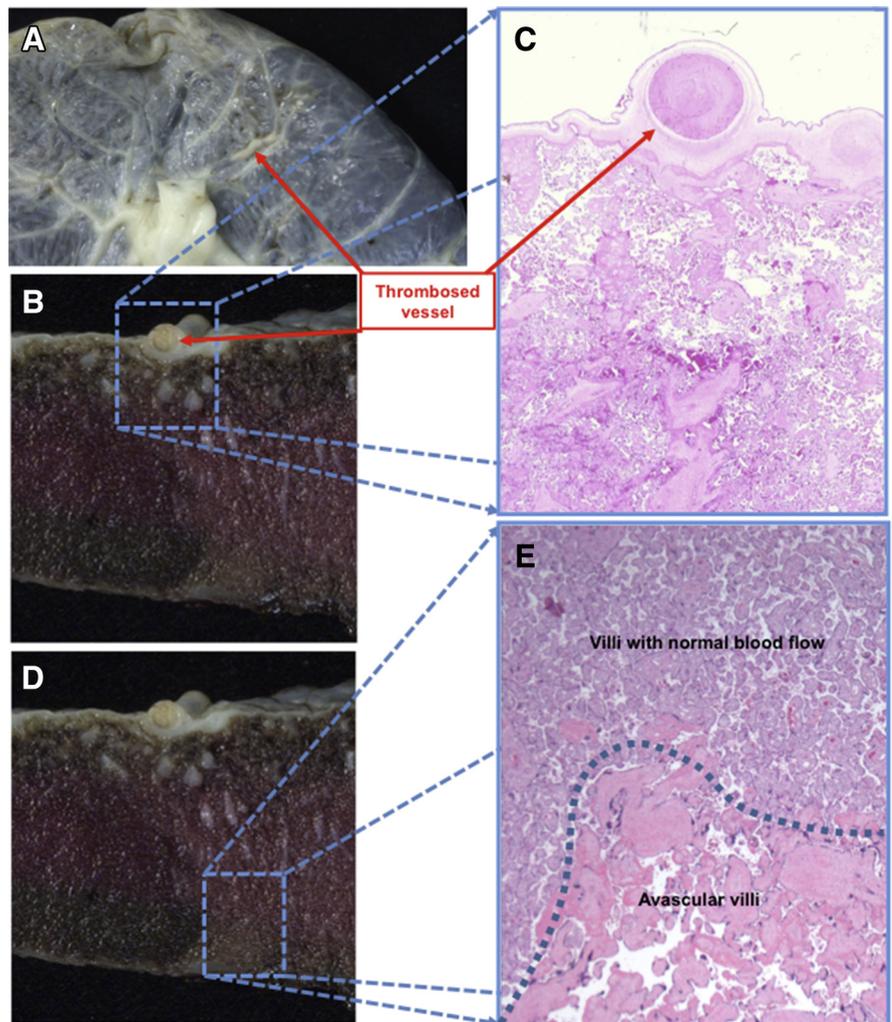
### MVM placental pathology

Placental pathology may be very informative in FGR by providing an understanding of the pathogenic mechanisms underlying growth restriction. International consensus was recently achieved on nomenclature and diagnostic criteria relevant to FGR.<sup>99</sup> The most common placental pathology diagnosis in FGR is MVM, a disease category defined by findings that include a small placenta, the presence of infarcts (Figure 3), and histologic abnormalities of the placental villi, including syncytial knot formation and distal villous hypoplasia (Figures 5, 8, and 9). A recent prospective cohort study of 856 healthy nulliparous women noted an 8% incidence of MVM, although interestingly only 50% of affected pregnancies had an adverse pregnancy outcome.<sup>37</sup> Multiple diagnostic features of MVM increased the PPV for FGR, consistent with recent cohort data from Detroit, where the severity of FGR and degree of imbalance in circulating angiogenesis-regulating proteins correlated with the severity of MVM.<sup>69</sup> The majority of placentas following delivery for severe FGR, especially with coexistent preeclampsia, will show MVM.<sup>31</sup> In subsequent pregnancies, low-dose aspirin treatment (150 mg/day) may not reduce the risk of FGR; however, it significantly reduces the risk of recurrent preterm preeclampsia.<sup>39</sup>

Placental pathology no longer guides considerations to prescribe low-molecular-weight heparin (LMWH) in subsequent pregnancies following a diagnosis of placental MVM. LMWH has formerly been prescribed on the basis of being considered a placental anticoagulant, but in 1 pilot randomized control trial it had no effect on placental pathology.<sup>100</sup> Furthermore, maternal genetic thrombophilia is not associated with placental infarction<sup>101</sup> and is no longer considered pathogenic in the context of FGR.<sup>102</sup> Two recent high-quality randomized controlled trials indicate that LMWH confers no additional benefit in addition to aspirin for the prevention of FGR associated with the risk of recurrent preeclampsia.<sup>103,104</sup>

**FIGURE 11**

**Fetal thrombotic vasculopathy with mild fetal growth restriction at 38 weeks of gestation**



At cesarean delivery, newborn had patchy skin necrosis involving arm. Review of placental pathology revealed **A**, fetal surface vessels suspicious for thrombosis and **B**, placental cross-section with **C**, corresponding hematoxylin-eosin (H&E) histology showing thrombosis within chorionic plate vessel. **D**, Slightly pale basal region of same placental cross-section (note that central red band is fixation artifact) shows **E**, corresponding H&E histology demonstrating avascular villi in distal/basal portions of villous tree beneath occluded vessel.

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### Non-MVM placental disease

Screening programs for preeclampsia<sup>39</sup> and FGR<sup>38</sup> incorporate UtAD assuming that impaired uteroplacental blood flow is a unifying underlying disease pathogenesis. However, as illustrated in Figures 8 to 10 and in Supplementary Videos 9 to 11, significant FGR and associated placental pathology may occur with normal UtAD waveforms. In

a single-center retrospective cohort study of 196 pregnancies with early-onset FGR, 10% exhibited normal UtAD waveforms and their placentas at delivery were significantly more likely to show massive perivillous fibrinoid deposition (MPVFD)<sup>105</sup> (also called “maternal floor infarction”) (21% vs 7%) or chronic intervillitis<sup>106</sup> (16% vs 1%) compared to women with bilateral

abnormal UtAD waveforms.<sup>31</sup> Both are rare placental diseases but have a high recurrence rate >70%,<sup>107,108</sup> considerably greater than for MVM (Figure 10). No effective treatment plan in future pregnancies has been developed for chronic intervillitis, although pravastatin may be effective for MPVFD.<sup>109</sup> Since neither is a perfusion-related disorder, the demonstration of normal midpregnancy UtAD waveforms will not exclude disease recurrence. Interestingly, maternal serum PIGF was demonstrated to be substantially depressed at 20-30 weeks in 11 pregnancies subsequently shown to have MPVFD following delivery.<sup>110</sup> Another non-MVM, non-perfusion-related placental pathology is villitis of unknown etiology,<sup>111</sup> which shows recurrence rates of 10-37%, and is more likely to be recurrent when severe and high grade.<sup>111-113</sup> In contrast, low-grade villitis of unknown etiology affecting a small proportion of villi is relatively common and typically has no clinical implications. Any of these 3 diagnoses will help inform counseling about recurrence rates and prognosis, and in the context of recurrent pregnancy losses with documented MPVFD or chronic histiocytic intervillitis, discussion of future pregnancy options could include in vitro fertilization and surrogacy for women with recurrent losses despite trying all available medical options.

A final disease category associated with FGR is fetal vascular malperfusion (previously called “fetal thrombotic vasculopathy”) where portions of the placental villous tree lack fetal vascular perfusion. A major cause of fetal vascular malperfusion is intermittent or partial cord compression resulting in scattered thrombosis of regions of the distal vascular tree<sup>114,115</sup> (Figure 11). Rarely, cord obstruction can be identified by ultrasound. Since most cord anomalies and entanglement are considered sporadic,<sup>116</sup> the recurrence risk for FGR in this context is minimal.

### Placental health screening to direct care in a future pregnancy

When FGR occurs in the context of a known or presumed MVM, low-dose

aspirin each evening starting at 12 weeks' gestation is recommended for any future pregnancy, especially if preeclampsia was present, since at-risk women given aspirin 150 mg/d had a substantial reduction in recurrence of preterm-onset preeclampsia.<sup>39</sup> Interestingly, this large trial demonstrated no reduction in the risk of FGR (at the third or fifth centiles for birthweight), although earlier meta-analysis data predicted that aspirin would prevent FGR.<sup>117</sup> Therefore, the most recent evidence suggests that aspirin may be ineffective in reducing the recurrence risk of normotensive FGR.<sup>39</sup> Likewise, 2 recent trials exploring the adjunct use of prophylactic doses of LMWH found no reduction in the rates of recurrence of preterm preeclampsia or coexistent FGR for at-risk populations.<sup>103,104</sup> Also, the vasodilatory effect of the drug sildenafil was shown in a randomized control trial to be ineffective in preventing severe FGR in high-risk women.<sup>118</sup> Additional drugs with potential to prevent severe preeclampsia, and therefore potentially any associated FGR, include proton pump inhibitors,<sup>119</sup> statins,<sup>120</sup> metformin,<sup>121</sup> hydroxychloroquine,<sup>122</sup> and melatonin.<sup>123</sup> With the exception of melatonin, none have been shown to prevent FGR.<sup>124</sup> ■

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# Antenatal glucocorticoids, magnesium sulfate, and mode of birth in preterm fetal small for gestational age



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A diagnosis of fetal growth restriction and subsequent preterm birth is associated with increased risks of adverse perinatal and neurodevelopmental outcomes and potentially long-lasting effects to adulthood. Most such cases are associated with placental insufficiency and the fetal response to chronic intrauterine hypoxemia and nutrient deprivation leads to substantial physiological and metabolic adaptations. The management of such pregnancies, especially with respect to perinatal interventions and birth mode, remains an unresolved dilemma. The benefits from standard interventions for threatened preterm birth may not be necessarily translated to pregnancies with small-for-gestational-age fetuses. Clinical trials or retrospective studies on outcomes following administration of antenatal glucocorticoids and magnesium sulfate for neuroprotection when preterm birth is imminent either have yielded conflicting results for small-for-gestational-age fetuses, or did not include this subgroup of patients. Experimental models highlight potential harmful effects of administration of antenatal glucocorticoids and magnesium sulfate in the pregnancies with fetal small for gestational age although clinical data do not substantiate these concerns. In addition, heterogeneity in definitions of fetal small for gestational age, variations in the inclusion criteria, and the glucocorticoid regime contribute to inconsistent results. In this review, we discuss the physiologic adaptations of the small-for-gestational-age fetus to its abnormal in utero environment in relation to antenatal glucocorticoids; the impact of antenatal glucocorticoids and intrapartum magnesium sulfate in pregnancies with fetal small for gestational age; the current literature on birth mode for pregnancies with fetal small for gestational age; and the knowledge gaps in the existing literature.

**Key words:** birth route, corticosteroid, fetal growth restriction, neonate, neuroprotection, preterm

## Introduction

Fetal growth restriction (FGR) refers to fetuses not attaining biologically determined growth potential.<sup>1</sup> To date, the most widely used correlate of FGR has been an estimated fetal weight <10th

percentile for gestational age (GA), otherwise known as small for GA (SGA).<sup>2-4</sup> Strictly speaking, FGR requires serial studies to document a change in growth trajectory while SGA is diagnosed largely based on birthweight

or estimated fetal weight for GA. In the majority of cases, fetal SGA is due to a spectrum of chronic placental disease, commonly described by clinicians as “placental insufficiency.”<sup>5</sup> Other causes of fetal SGA include genetic disorders, congenital anomalies, or infections.<sup>5</sup> Fetal SGA is associated with stillbirth, adverse neonatal outcomes, altered neurological and cognitive development, and potentially cardiovascular and endocrine diseases in adulthood, with significant social and economic implications.<sup>6-10</sup> Fetal SGA fetuses undergo substantial physiologic adaptation in response to fetal hypoxemia and nutrient deprivation<sup>11-13</sup> and thus may render standard perinatal and intrapartum interventions such as antenatal glucocorticoids or intrapartum magnesium sulfate less effective or ineffective and at times harmful.<sup>14-16</sup> Not surprisingly, management of pregnancies with FGR likely to deliver at preterm gestation remains an unresolved dilemma and there is subsequent wide variation in clinical practice. These variations include array of surveillance methods and very different parameters considered in contemplating management decisions such as timing of birth.<sup>3,17-19</sup>

In this article, we review: (1) the physiologic adaptations of SGA fetuses in relation to antenatal glucocorticoids; (2)

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the impact of antenatal glucocorticoids and intrapartum magnesium sulfate for pregnancies with fetal SGA likely to deliver at preterm gestation; and (3) the mode of birth after suspected fetal SGA.

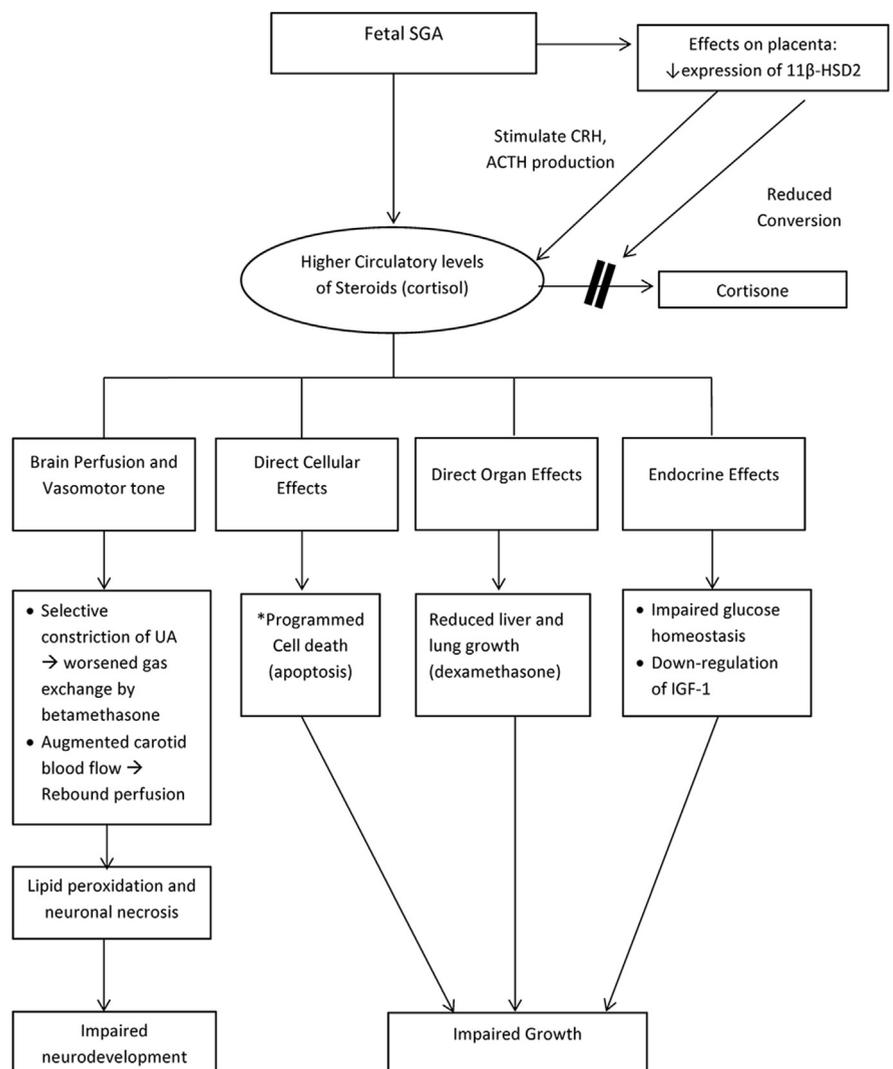
### Fetal SGA and antenatal glucocorticoids

#### Overview of benefits and concerns of antenatal glucocorticoid use in preterm births

Antenatal glucocorticoids administration to improve newborn outcomes has become the mainstay of prophylactic treatment before anticipated preterm birth.<sup>20,21</sup> In otherwise healthy fetuses, antenatal glucocorticoids promote pulmonary surfactant synthesis and secretion, enhance structural maturation of the alveoli to support postnatal lung function, increase lung compliance, and generate an enhanced response to postnatal surfactant treatment.<sup>22</sup> Glucocorticoids also have similar maturational effects on other fetal organs including the brain, kidneys, and intestine.<sup>22</sup> A Cochrane review of 30 studies concluded that a single course of antenatal glucocorticoids prior to preterm birth was associated with a reduction in neonatal mortality (risk ratio [RR], 0.69; 95% confidence interval [CI], 0.59–0.81), respiratory distress syndrome (RR, 0.66; 95% CI, 0.56–0.77), intraventricular hemorrhage (RR, 0.55; 95% CI, 0.40–0.76), necrotizing enterocolitis (RR, 0.50; 95% CI, 0.32–0.78), need for mechanical ventilation (RR, 0.68; 95% CI, 0.56–0.84), and systemic infections in the first 48 hours after birth (RR, 0.60; 95% CI, 0.41–0.88).<sup>20</sup> Currently a single course of glucocorticoids is recommended for pregnant women between 24<sup>0</sup> weeks (or 23<sup>0</sup> weeks, based on a family's decision regarding resuscitation) and 33<sup>6</sup> weeks of GA who are at risk of preterm birth within 7 days, including for those with ruptured membranes and multiple gestations.<sup>23</sup> For decades, it has been assumed that chronic intrauterine stress that occurs in tandem with fetal SGA may cause prolonged stimulation of adrenal gland, accelerate pulmonary maturation, and thus result in a lower risk for respiratory distress

#### FIGURE

#### Pathophysiological changes associated with fetal SGA in relation to antenatal glucocorticoids



ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; HSD2, hydroxysteroid dehydrogenase type 2; IGF, insulin-like growth factor; UA, umbilical artery.

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syndrome than appropriate-for-GA neonates.<sup>24</sup> This rationale implies that growth-restricted fetuses may not benefit from antenatal corticosteroids in contrast with appropriately grown fetuses.

#### Pathophysiological changes associated with fetal SGA in relation to antenatal glucocorticoids

The effects of glucocorticoids are complex in the setting of fetal SGA, and both basic and translational science studies

have raised specific concerns in this regard (Figure).

First, chronic fetal stress associated with fetal SGA stimulate placental corticotropin-releasing hormone release.<sup>25</sup> Corticotropin-releasing hormone,<sup>26</sup> adrenocorticotropic hormone,<sup>26</sup> and cortisol levels<sup>27</sup> are all significantly elevated in fetal SGA in a graded manner as shown in studies where the degree of hypoglycemia in fetuses correlated with the extent of placental vascular compromise.<sup>28</sup> Circulating levels of glucocorticoids can

regulate vasomotor tone, brain perfusion, the response to exogenous steroids, and glucose homeostasis after birth. On the other hand, elevations of cortisol down-regulate insulin like growth factor-I activity and may therefore have additional negative impacts on linear growth.<sup>29</sup> Second, fetal SGA is associated with reduced expression and function of 11 $\beta$ -hydroxysteroid dehydrogenase type 2 in the placenta,<sup>30,31</sup> an enzyme in the pathway for conversion of cortisol to cortisone. Reduced cortisol to cortisone conversion leads to excessive transplacental transfer of maternal endogenous cortisol to the fetus.<sup>14,32</sup> Third, elevated fetal cortisol levels, coupled with increased dosage (relative to fetal weight) or a more prolonged exposure to glucocorticoids, result in a switch in fetus from a state when cellular proliferation is needed for growth and cell differentiation to a state of programmed cell death.<sup>15,33</sup> Studies have demonstrated decreased fetal growth velocity and weight gain in both animal models and in neonates after glucocorticoids exposure,<sup>34,35</sup> although the minor effect of corticosteroids on fetal growth velocity is transient and potentially does not affect long-term growth.<sup>36</sup> Fourth, there is conflicting evidence on the effect of exogenous glucocorticoids on lung growth and surfactant protein expression in different animal models of intrauterine growth restriction.<sup>14</sup> Despite transient improvement in umbilical artery end-diastolic flow in preterm fetal SGA following glucocorticoids administration,<sup>37-39</sup> the net effect may be neutral. Fifth, dexamethasone seems to be more potent in eliciting nongenomic effects than betamethasone in fetus as shown by a greater reduction in lung and liver weight after repetitive doses of dexamethasone.<sup>15,33</sup> However, betamethasone might also selectively constrict the umbilical arteries and exacerbate these preexisting abnormalities in transplacental gas exchange.<sup>40</sup> Thus, both these agents have positive and negative effects and there is debate in literature regarding which agent might be better in these circumstances.<sup>20</sup> Finally, Miller et al<sup>41</sup> demonstrated that SGA fetuses displayed augmented carotid blood flow reperfusion in response to maternal betamethasone in comparison

with healthy fetuses; this rebound perfusion correlated with lipid peroxidation and higher neuronal necrosis.

In summary, SGA carries major consequences for not only somatic growth, but also for regulation of the endocrine, respiratory, and cardiovascular systems. With the adaptive changes in the physiology of SGA fetuses, the efficacy and safety of the antenatal glucocorticoids have been questioned.

#### **Antenatal corticosteroid use for pregnancies with fetal SGA: evidence from human studies**

There are conflicting results from studies addressing the efficacy of antenatal corticosteroids to improve preterm birth outcomes for SGA fetuses (Table).

Bernstein et al<sup>42</sup> examined the association among SGA neonates, receipt of antenatal glucocorticoids, and neonatal outcomes in very low birthweight neonates in the Vermont Oxford Network database. They reported that antenatal glucocorticoid administration was associated with significantly lower risks of adverse outcomes in SGA neonates, and benefits were similar to that in non-SGA neonates.<sup>42</sup> A population-based study from the Israel Neonatal Network reported that antenatal glucocorticoids therapy was associated with significantly reduced mortality and morbidities among preterm SGA neonates.<sup>43</sup> A retrospective cohort study from the Canadian Neonatal Network revealed that, for preterm SGA neonates, exposure to antenatal corticosteroids 1-7 days before birth was associated with decreased odds of neonatal mortality and major morbidity, similar in magnitude to that observed among GA-matched non-SGA neonates.<sup>44</sup> A follow-up study of SGA neonates born between 26-32 weeks' gestation suggested that survival without disability or handicap at 2 years' corrected age was increased in children who received betamethasone as fetuses, compared with children who did not receive betamethasone, although there was a statistically significant negative effect of betamethasone on subsequent somatic growth<sup>45</sup> (Table).

In contrast, some studies reported no effects of antenatal corticosteroids on neonatal morbidity or mortality among SGA infants.<sup>46-49</sup> van Stralen et al,<sup>46</sup> in a retrospective cohort study, reported that the prevalence of adverse neonatal outcomes did not differ between severely preterm SGA fetuses with and without exposure to antenatal corticosteroids. Ley et al<sup>48</sup> and Elimian et al<sup>47</sup> also reported no additional benefits for mortality and short-term morbidities in SGA exposed to antenatal corticosteroids. Mitsiakos et al<sup>49</sup> identified that SGA fetuses exposed to antenatal corticosteroids exhibited a higher incidence of severe global delay (those who scored 2 SD below average in all parameters in Griffiths test) than the nonexposed group (Table).

#### **Gaps of knowledge and recommendations**

In summary, the results published so far regarding the benefits of antenatal corticosteroids in the fetal SGA subgroup are inconsistent, likely because of heterogeneity in the definitions, inclusion criteria, and the steroid regime for SGA.<sup>50</sup> To date, there are no randomized studies specifically designed to assess the effect of antenatal corticosteroids in fetal SGA. The efficacy considerations are based on prospective or retrospective cohorts and small case-control studies.<sup>15</sup> In daily clinical practice, SGA fetuses frequently become exposed to exogenous corticosteroids when preterm birth is anticipated.<sup>15</sup> The following gaps of knowledge need to be urgently addressed in future clinical studies: (1) what are the neonatal morbidities associated with exposure of SGA fetuses to repeated courses of antenatal corticosteroids; (2) what are the immediate safety issues for fetal monitoring when corticosteroids are given to mothers of preterm SGA fetuses; and (3) what are the neurocognitive outcomes associated with SGA fetuses exposed to a single course of antenatal glucocorticoids. The science of impact of multiple glucocorticoid courses is an additional area of research as many of these neonates may

**TABLE**  
**Major studies of role of antenatal corticosteroid in growth-restricted fetuses**

Study	Methods	Mortality	RDS	Grade III or IV IVH	NEC	PDA	Composite outcome	Developmental outcome	Physical growth
Ley et al, <sup>48</sup> 1997	Retrospective cohort; single-center study from 1985 through 1994 of 234 SGA infants born <33 wk GA	GC exposed vs nonexposed group: OR, 0.5 (95% CI, 0.21–1.32)	GC exposed vs nonexposed group: OR, 1.2 (95% CI, 0.62–2.34)	NR	NR	NR	NR	NR	NR
Elimian et al, <sup>47</sup> 1999	Retrospective cohort; single-center study from 1990 through 1997 of 220 SGA infants with BW <1750 g	GC exposed vs nonexposed group: 7.9% vs 7.0%; <i>P</i> = .78	GC exposed vs nonexposed group: 27.0% vs 24.2%; <i>P</i> = .67	NR	GC exposed vs nonexposed group: 1.6% vs 1.9%; <i>P</i> = .99	GC exposed vs nonexposed group: 14.3% vs 6.4%; <i>P</i> = .06	NR	NR	NR
Bernstein et al, <sup>42</sup> 2000	Retrospective cohort study from 1991 through 1996 of 1720 singleton SGA infants of 501–1500 g BW at 25–30 wk GA	<sup>a</sup>	OR for GC exposed 0.70 vs OR for unexposed 0.51	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>
Schaap et al, <sup>45</sup> 2001	Case-control (1:1); 2 tertiary care centers from 1984 through 1991 of 124 SGA infants at 26–31 wk GA	GC exposed vs nonexposed group: 15% vs 24%; <i>P</i> = .20	GC exposed vs nonexposed group 37% vs 40%; <i>P</i> = .80	GC exposed vs nonexposed group: 13% vs 15%; <i>P</i> = 1.0	NR	NR	NR	Survival without disability or handicap at 2 y corrected age in GC vs non-GC exposed group (82% vs 65%; OR, 3.2 (95% CI, 1.1–11.2); no differences in behavior problems (43% vs 45%; OR, 0.9 (95% CI, 0.4–2.1)	Growth in <10th centiles in GC exposed vs nonexposed group (29% vs 7%; OR, 5.1 (95% CI, 1.4–23.8)
van Stralen et al, <sup>46</sup> 2009	Retrospective cohort; single-center study from 2001 through 2005 of 88 singleton SGA infants <34 wk GA or BW <1500 g	Non-GC vs GC group: 12% vs 9%; <i>P</i> = .73	Non-GC vs GC group: 50% vs 42%; <i>P</i> = .44	NR	Non-GC vs GC group: 6% vs 6%; OR, 1.02 (95% CI, 0.18–5.79)	Non-GC vs GC group: 18% vs 19%; OR, 0.92 (95% CI, 0.37–2.29)	Non-GC vs GC group: 24% vs 28%; <i>P</i> = .62 <sup>b</sup>	NR	NR

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(continued)

**TABLE**  
**Major studies of role of antenatal corticosteroid in growth-restricted fetuses** (continued)

Study	Methods	Mortality	RDS	Grade III or IV IVH	NEC	PDA	Composite outcome	Developmental outcome	Physical growth
Mitsiakos et al, <sup>49</sup> 2013	Retrospective cohort; single-center study of 149 severe SGA (BW <3rd percentile) singletons born 24–31 <sup>6/7</sup> wk GA	GC exposed vs nonexposed group: 21.8% vs 14.5%; <i>P</i> = .29	GC exposed vs nonexposed group: 51.7% vs 58%; <i>P</i> = .51	GC exposed vs nonexposed group: 3.4% vs 4.8%; <i>P</i> = .69	GC exposed vs nonexposed group: 11.5% vs 8%; <i>P</i> = .59	GC exposed vs nonexposed group: 48% vs 50%; <i>P</i> = .87	NR	GC exposed vs nonexposed group: severe global delay: 6% vs 0%; <i>P</i> = .19	NR
Riskin-Mashiah et al, <sup>43</sup> 2016	Retrospective cohort; multicenter study of 1771 singleton SGA VLBW infants of 24–31 wk GA	GC exposed vs nonexposed group: 19.3% vs 32.2%; <i>P</i> < .0001	GC exposed vs nonexposed group: 68.0% vs 72.3%; <i>P</i> = .08	GC exposed vs nonexposed group: 6.5% vs 11.0%; <i>P</i> = .003	GC exposed vs nonexposed group: 8.2% vs 10.9%; <i>P</i> = .07	NR	GC exposed vs nonexposed group: 43.4% vs 54.1%, <i>P</i> < .0001 <sup>c</sup>	NR	NR
Melamed et al, <sup>44</sup> 2016	Retrospective cohort; Canadian Neonatal Network from 2010 through 2014 of 918 singleton SGA infants born 24 <sup>0/7</sup> –33 <sup>6/7</sup> wk GA	GC exposed vs nonexposed group: 7% vs 12%; <i>P</i> = .01	GC exposed vs nonexposed group: 52% vs 46%; <i>P</i> = .09	NR	GC exposed vs nonexposed group: 4% vs 3%; <i>P</i> = .56	NR	GC exposed vs nonexposed group: 28% vs 30%; <i>P</i> = .56 <sup>d</sup>	NR	NR

BW, birthweight; CI, confidence interval; GA, gestational age; GC, glucocorticoids; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NR, not reported; OR, odds ratio; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; SGA, small for gestational age; VLBW, very low birthweight.

<sup>a</sup> Maternal prenatal GC administration was associated with significant reductions in risks of RDS (OR, 0.51; 95% CI, 0.44–0.58), IVH (OR, 0.67; 95% CI, 0.61–0.73), severe IVH (OR, 0.50; 95% CI, 0.43–0.57), and death (OR, 0.54; 95% CI, 0.48–0.62)—only NEC among outcomes evaluated was not reduced in association with use of prenatal GC therapy—these benefits of prenatal GC therapy were similar among infants with intrauterine growth restriction and normally grown infants, and ORs listed represent pooled ORs;

<sup>b</sup> Adverse neonatal outcome: defined as presence of at least 1 of following: neonatal death, severe cerebral lesions, or major neonatal disorders (moderate or severe bronchopulmonary dysplasia, NEC grade ≥II, and retinopathy of prematurity stage ≥III);

<sup>c</sup> Composite adverse outcome: death or any major morbidity including bronchopulmonary dysplasia, IVH grades 3–4, periventricular leukomalacia, NEC, and retinopathy of prematurity grades 3–4; <sup>d</sup> Composite neonatal outcome: neonatal mortality or one of the following neonatal morbidities including bronchopulmonary dysplasia, severe brain injury defined as grade 3 or 4 IVH or periventricular leukomalacia, retinopathy of prematurity defined as stage 3 or higher.

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pass the routine window of benefit of 7 days before birth.

Based on the current clinical evidence, it is reasonable to give a single course of glucocorticoids to pregnant women with growth-restricted fetuses who are at risk of preterm birth within 7 days; however, this intervention needs to be combined with enhanced fetal surveillance.<sup>51</sup> There is insufficient evidence to conclude whether repeated or rescue antenatal corticosteroids administration is beneficial or harmful for this group of infants. Furthermore, existing data in the literature do not allow us to recommend either betamethasone or dexamethasone as the preferable corticosteroid, which may be answered when results of an ongoing trial are available, although this trial is not exclusively focused on FGR fetuses.<sup>52</sup>

### Fetal SGA and magnesium sulfate

Both preterm birth and fetal SGA are associated with higher risk of cerebral palsy.<sup>53</sup> Neurodevelopmental morbidities associated with preterm birth include cerebral palsy, developmental delay, hearing and visual deficits, and behavioral issues. Animal studies revealed abnormal neuronal migration, reduced numbers of neurons in the hippocampus and the cerebellum, and retarded dendritic and axonal growth in preterm fetuses as potential reasons for neurological and behavioral deficits.<sup>54,55</sup> Perinatal brain injury in preterm neonates is related to both white matter and neuronal injury and is suspected in part to be secondary to the release of proinflammatory cytokines and oxygen-free radicals.<sup>56</sup> Fetal SGA has been shown to be associated with a severe reduction in cortical growth and a significant decrease in cell number in the future cortex.<sup>57</sup> Magnesium sulfate administered during the intrapartum period exerts neuroprotective effects presumably through the following mechanisms: competitively reducing intracellular calcium entry, blocking glutamate and other excitatory neurotransmitter receptors responsible for neuronal death, and modulating the actions of proinflammatory cytokines and oxygen-free radicals.<sup>58-61</sup> It is readily transferred

across the placenta into fetal circulation within an hour of administration and has therefore prompted investigators to assess its role in fetal neuroprotection.

Following the publication of several major clinical trials assessing the efficacy of intrapartum magnesium administration,<sup>62-65</sup> a Cochrane review confirmed the neuroprotective role of magnesium sulfate given to women at risk of preterm birth, with reduced risk of cerebral palsy (RR, 0.68; 95% CI, 0.54–0.87) and substantial gross motor dysfunction (RR, 0.61; 95% CI, 0.44–0.85).<sup>66</sup> In all, 63 women needed to be treated with intrapartum magnesium sulfate to prevent 1 child from developing cerebral palsy. A recently published individual participant data meta-analysis, again, yielded a similar conclusion regarding the impact of antenatal magnesium sulfate to reduce the combined risk of fetal/infant death or cerebral palsy, and the benefit is seen regardless of the reason for preterm birth.<sup>67</sup> Furthermore, antenatal magnesium sulfate exposure was independently associated with a decreased risk (odds ratio, 0.18; 95% CI, 0.049–0.65) of magnetic resonance imaging–detected cerebellar hemorrhage in preterm infants of <33 weeks' gestation.<sup>68</sup> However, some concerns have been expressed regarding the potential for intestinal injury following administration of magnesium sulfate.<sup>69</sup> A large population-based study reported no association between antenatal exposure to magnesium sulfate and necrotizing enterocolitis or spontaneous intestinal perforation in extremely preterm infants after adjustment for confounding variables, including SGA.<sup>70</sup> Guidelines from professional societies recommend that magnesium sulfate administration should be considered for women with imminent preterm birth, although there are variations in the upper limit of GA for which it has been suggested (<32 vs <30 weeks).<sup>56,71-73</sup> Important to the context of this review is that none of the recommendations specify magnesium sulfate administration guidelines when fetal SGA is suspected.

None of the clinical trials specifically analyzed the outcomes of pregnancies

expressed to magnesium sulfate with fetal SGA.<sup>62,64,65,74,75</sup> It is not currently known if administration of magnesium sulfate to pregnancies with fetal SGA can reverse the consequences of adverse brain growth as some of the processes for neuronal injury described above may already have been established especially if fetal Doppler abnormalities are already present.<sup>76</sup> Higher borderline cord blood ionized magnesium levels were observed in term growth-restricted fetuses compared with healthy term newborns,<sup>55</sup> although the mechanism for this increase was incompletely understood. Additional intrapartum administration could in theory lead to toxic levels of magnesium in SGA fetuses and could on the contrary be neurotoxic.<sup>54</sup>

By contrast, magnesium is reported to suppress production of inflammatory cytokine and chemokine levels in preterm fetuses, and have vasodilatory effects that potentially improve uterine blood flow,<sup>77</sup> which is affected in pregnancies with SGA fetuses.<sup>78</sup> Roman et al,<sup>77</sup> in a rat model, reported that continuous oral maternal magnesium supplementation throughout gestation was accompanied by a significant decrease in the incidence of fetal SGA. Gao and Zou<sup>79</sup> reported that subcutaneous administration of magnesium to maternal rats with induced fetal SGA by exposure to smoking led to a dose-dependent improvement in fetal weight, an effect thought to be due to conserved placental function secondary to decreased in apoptosis of trophoblasts via reduced expression of caspase-3.

### Gaps of knowledge and recommendations

In summary, there is insufficient evidence to recommend for or against the administration of magnesium sulfate for neuroprotection to women at risk of preterm birth with a SGA fetus. At this point, evidence is lacking with respect to the following: (1) the effectiveness and safety profile of magnesium sulfate for neuroprotection in pregnancies carrying a fetus suspected of having fetal SGA; (2) the GA below which this therapy should be offered; (3) the optimal loading and

maintenance doses; (4) the impact of magnesium sulfate administration on early neurodevelopmental outcomes among preterm fetal SGA; and (5) the effect of magnesium sulfate administration on neurodevelopmental outcomes >2 years of age, especially learning disabilities and developmental coordination disorder in pregnancies affected by fetal SGA.

## Fetal SGA and mode of birth

### Near-term fetal SGA

The main challenge in the management of pregnancies with fetal SGA is to predict which fetuses can tolerate induction of labor (IOL) safely and which fetuses should have a planned cesarean birth. Among term appropriately grown fetuses, planned cesarean birth is not recommended <39<sup>0</sup> weeks' gestation due to the higher risk of respiratory complications compared to vaginal births.<sup>80</sup> The DIGITAT trial randomized 650 pregnancies with suspected fetal SGA (defined as an estimated fetal weight <10th centile) at 36-38 weeks' gestation to birth by IOL or to delayed birth (mean 10 days) with fetal monitoring.<sup>81</sup> At randomization, >97% in each arm had normal umbilical artery Doppler waveforms. The rates of cesarean birth (14% vs 13.7%) were very similar in both arms of the study and were mostly performed for suspected fetal compromise (82% vs 89%). Predefined composite neonatal outcomes were similar in both arms (5.3% vs 6.1%). These data suggest that near-term fetuses with suspected fetal SGA and normal umbilical artery Doppler can safely tolerate IOL.

In a single-center retrospective study of 836 women with suspected fetal SGA and a significantly higher emergency cesarean birth rate of 43%, the rate of neonatal admission was higher with attempted vaginal birth (43% vs 29%) than in women who had a planned cesarean birth.<sup>82</sup> These findings contrast with a secondary analysis of the Cesarean Section Registry of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, which reported that SGA infants born to women who had a trial of labor before

cesarean birth exhibited no difference in neonatal outcomes compared with those delivered by planned repeat cesarean birth (adjusted RR, 0.99; 95% CI, 0.88–1.12).<sup>83</sup> These findings may not apply to smaller newborns, since only 15-23% of SGA neonates in the 2 arms of the study were born at preterm gestation.<sup>83</sup>

Several tests of fetal well-being have the potential to identify a subset of near-term SGA fetuses that may benefit from planned cesarean delivery. The oxytocin challenge test (OCT) was developed in the pre-Doppler era, as a tool to avoid stillbirth and reduce the risk of severe fetal acidosis at vaginal birth by performing cesarean births in women exhibiting a positive test.<sup>84</sup> In 2003, a prospective Scandinavian study addressed the role of the OCT to direct mode of birth in 84 term fetuses with suspected FGR.<sup>85</sup> Pregnancies with absent end-diastolic flow in the umbilical arteries were excluded and underwent cesarean birth directly. Nineteen (23%) women in the cohort had a positive OCT that, by hospital protocol, also resulted in planned cesarean birth. Interestingly, umbilical artery Doppler waveforms did not predict the OCT result. Furthermore, among the remainder, the success of attempted vaginal birth (69% with abnormal vs 78% with normal waveforms) was also not predicted by umbilical artery Doppler. Several investigators, for example the multicenter PORTO group,<sup>3</sup> that prospectively evaluated >1100 pregnancies with suspected FGR, reported limited diagnostic utility of umbilical artery Doppler to predict adverse perinatal outcomes, which aligns with recent findings in a mouse model of SGA stillbirth at term.<sup>86</sup>

The human near-term fetus protects oxygen delivery to the brain in the face of progressive hypoxemia by increasing cerebral blood flow.<sup>87</sup> This redistribution of fetal cardiac output is recognized noninvasively by increased diastolic flow velocities in the middle cerebral arteries (MCA), which reduces the waveform pulsatility index (PI).<sup>88</sup> The ratio of the PI in the MCA/umbilical artery is termed the "cerebroplacental ratio" (CPR). A subsequent PORTO group

analysis identified the superiority of an abnormal CPR (<1.0) in comparison with umbilical artery Doppler to predict adverse perinatal outcomes.<sup>89</sup> Unfortunately, no specific data on mode of birth were presented, nor on the strength of the relationship between Doppler findings, fetal weight estimation, or the subsequent risk of emergency cesarean birth. A subsequent large retrospective cohort study demonstrated the association between CPR and an increased risk of operative birth for fetal compromise.<sup>90</sup> In Barcelona, among longitudinal Doppler studies of 171 late-onset fetal SGA cases, MCA Doppler was superior to umbilical artery Doppler for the subsequent prediction of birth due to an abnormal biophysical profile.<sup>91</sup> In 2011, the Scandinavian group reported the introduction of MCA Doppler into their protocol to manage term pregnancies with suspected fetal SGA, again excluding attempted vaginal delivery in pregnancies with highly abnormal umbilical artery Doppler waveforms.<sup>92</sup> OCT remained a gold standard test for planned cesarean birth, however MCA Doppler was not predictive of an abnormal OCT. The investigators justified ongoing use of the OCT to direct mode of birth due to the low (3%) overall rate of low Apgar scores and acidosis and a 63% successful vaginal birth rate. The OCT is not widely used as a discrete test of fetal well-being. However, as the cervical catheter option for IOL near term is gaining some popularity, and is increasingly combined with oxytocin,<sup>93</sup> then in a pragmatic sense OCTs are being performed when vaginal delivery is being attempted in near-term SGA pregnancies.

To guide clinicians using the above ultrasound information to manage pregnancies with late-onset FGR, a decision tool has been developed to predict the risk of perinatal morbidity and cesarean birth from analysis of a cohort of 509 pregnancies.<sup>94</sup> Any of 3 criteria (CPR <10th centile; estimated fetal weight <3rd centile; uterine artery Doppler mean PI >95th centile) resulted in a 3- to 4-fold increased risk of emergency cesarean birth (29% vs 8%). Birth decision algorithms for pregnancies

complicated by FGR have also been proposed by French<sup>95</sup> and Irish<sup>18</sup> clinicians. These are largely based on expert opinions rather than high-level evidence. Not surprisingly, there are significant variations in the recommendations and their grading across various practice guidelines.<sup>18</sup>

### Preterm FGR

When FGR is suspected in earlier gestations, it commonly is associated with abnormal uterine artery Doppler, high rates of absent/reversed end-diastolic flow in the umbilical arteries, and significant placental pathology.<sup>78</sup> The severity of placenta-mediated FGR presenting with these placental Doppler findings commonly results in progressive alterations in both MCA and ductus venosus Doppler waveforms that correlate with progressive degrees of fetal hypoxia.<sup>96</sup> Uterine contractions in this context have been shown to provoke abnormal flow patterns in the uterine and umbilical arteries<sup>97-99</sup> and thus the reported rates of cesarean birth typically are >80%.<sup>100</sup> Consequently, many centers now use absent/reversed end-diastolic flow as an indication for elective cesarean birth in this context.<sup>101</sup> Interestingly, the TRUFFLE trial, comparing safety of monitoring of the preterm FGR fetus by ductus venosus Doppler and computerized nonstress test, did not standardize mode of birth and did not report rates of cesarean birth.<sup>102</sup> Data from National Center for Health Statistics identified cesarean birth rates of 50-67% for SGA neonates and 22-38% for appropriate-for-GA neonates of 26-32 weeks of gestation in vertex presentation.<sup>103</sup> Cesarean birth was associated with a survival advantage for preterm SGA neonates between 26-30 weeks' gestation after adjustment for sociodemographic and medical factors (odds ratio, 2.8; 95% CI, 2.2-3.5).<sup>103</sup> However, confounding by indication cannot be ruled out.

### Conclusions

Despite substantial advances in neonatal care, many unresolved issues remain regarding key decisions for the optimal management of pregnancies

complicated by SGA fetuses, especially when preterm delivery is contemplated. Substantial physiologic adaptations made by the preterm SGA fetus to an unfavorable environment have the potential to render proven beneficial treatments questionable in management of preterm birth in fetal SGA, such as antenatal glucocorticoids and magnesium sulfate for neuroprotection. Such interventions deserve specific evaluation in suspected fetal SGA. The widespread application of fetal Doppler studies in the assessment of preterm SGA fetuses has resulted in improved clinical outcomes, largely from improved prenatal diagnosis and in utero transfer of such pregnancies to tertiary care facilities. Despite substantial advances in effective noninvasive fetal monitoring methods to safely prolong pregnancy, especially the application of fetal Doppler studies, the ultimate obstetric intervention of delivery mode has surprisingly received minimal attention. Further research is encouraged to aid clinicians in the decision between IOL and planned cesarean birth for the pregnancies with suspected SGA fetus. Standardization of definitions, monitoring methods, and the design of adequately powered studies are urgently needed to further improve outcomes in these high-risk pregnancies. Questions regarding: (1) neonatal morbidities and neurocognitive outcomes associated with SGA fetuses exposed to single or repeated courses of antenatal corticosteroids; and (2) effectiveness and safety profile of magnesium sulfate for neuroprotection in pregnancies carrying a fetus suspected of having fetal SGA need to be addressed in future clinical studies. ■

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# The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction



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Fetal growth restriction and related placental pathologies such as preeclampsia, stillbirth, and placental abruption are believed to arise in early pregnancy when inadequate remodeling of the maternal spiral arteries leads to persistent high-resistance and low-flow uteroplacental circulation. The consequent placental ischaemia, reperfusion injury, and oxidative stress are associated with an imbalance in angiogenic/antiangiogenic factors. Many interventions have centered on the prevention and/or treatment of preeclampsia with results pertaining to fetal growth restriction and small-for-gestational-age pregnancy often included as secondary outcomes because of the common pathophysiology. This renders the study findings less reliable for determining clinical significance. For the prevention of fetal growth restriction, a recent large-study level meta-analysis and individual patient data meta-analysis confirm that aspirin modestly reduces small-for-gestational-age pregnancy in women at high risk (relative risk, 0.90, 95% confidence interval, 0.81–1.00) and that a dose of  $\geq 100$  mg should be recommended and to start at or before 16 weeks of gestation. These findings support national clinical practice guidelines. In vitro and in vivo studies suggest that low-molecular-weight heparin may prevent fetal growth restriction; however, evidence from randomized control trials is inconsistent. A meta-analysis of multicenter trial data does not demonstrate any positive preventative effect of low-molecular-weight heparin on a primary composite outcome of placenta-mediated complications including fetal growth restriction (18% vs 18%; absolute risk difference, 0.6%; 95% confidence interval, 10.4–9.2); use of low-molecular-weight heparin for the prevention of fetal growth restriction should remain in the research setting. There are even fewer treatment options once fetal growth restriction is diagnosed. At present the only management option if the risk of hypoxia, acidosis, and intrauterine death is high is iatrogenic preterm birth, with the use of peripartum maternal administration of magnesium sulphate for neuroprotection and corticosteroids for fetal lung maturity, to prevent adverse neonatal outcomes. The pipeline of potential therapies use different strategies, many aiming to increase fetal growth by improving poor placentation and uterine blood flow. Phosphodiesterase type 5 inhibitors that potentiate nitric oxide availability such as sildenafil citrate have been extensively researched both in preclinical and clinical studies; results from the Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction consortium of randomized control clinical trials are keenly awaited. Targeting the utero-placental circulation with novel therapeutics is another approach, the most advanced being maternal vascular endothelial growth factor gene therapy, which is being translated into the clinic via the doEs Vascular endothelial growth factor gene therapy safEly impRove outcome in seveRe Early-onset fetal growth reSTriction consortium. Other targeting approaches include nanoparticles and microRNAs to deliver drugs locally to the uterine arterial endothelium or trophoblast. In vitro and in vivo studies and animal models have demonstrated effects of nitric oxide donors, dietary nitrate, hydrogen sulphide donors, statins, and proton pump inhibitors on maternal blood pressure, uteroplacental resistance indices, and angiogenic/antiangiogenic factors. Data from human pregnancies and, in particular, pregnancies with fetal growth restriction remain very limited. Early research into melatonin, creatine, and N-acetyl cysteine supplementation in pregnancy suggests they may have potential as neuro- and cardioprotective agents in fetal growth restriction.

**Key words:** aspirin, creatine, esomeprazole, fetal growth restriction, intrauterine growth restriction, low-molecular-weight heparin, melatonin, N-acetylcysteine nitric oxide donor, pravastatin, preeclampsia, sildenafil, small for gestational age, vascular endothelial growth factor gene therapy

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Dr David is a shareholder in Magnus Growth, a company that is aiming to take a therapy for fetal growth restriction into the clinic. Dr Groom reports no conflict of interest.

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Fetal growth restriction (FGR) describes a group of conditions in which a fetus fails to reach its full growth potential. FGR is difficult to define and measure and so small for gestational age (SGA), defined by birthweight percentile, is often used as the most reliable surrogate marker. FGR and SGA may be caused by fetal issues such as chromosomal anomalies, genetic syndromes, and fetal infection; maternal disease; environmental toxins including cigarette

smoking; and the most common cause, uteroplacental insufficiency. This article will focus on preventative and treatment options for FGR due to uteroplacental insufficiency.

During early pregnancy trophoblast invasion of the maternal spiral arteries remodels and disrupts their smooth muscle layer, creating a low-resistance and high-flow uteroplacental circulation capable of efficient gaseous and nutrient exchange for optimal fetal growth.<sup>1</sup> Inadequate or abnormal trophoblast invasion results in incomplete remodeling of the spiral arteries and persistence of a high-resistance and low-flow circulation.<sup>2,3</sup>

It is hypothesized that this results in a sequence of events including reduced placental perfusion, placental ischemia and reperfusion injury<sup>4</sup>; oxidative stress<sup>5</sup>; an imbalance in angiogenic factors<sup>6-8</sup>; vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), with antiangiogenic factors; soluble fms-like tyrosine kinase 1 (sFlt-1); and soluble endoglin and an increased frequency of atherosclerosis in the placental bed.<sup>9</sup>

Clinically these events present as the placenta-mediated complications of pregnancy: FGR, preeclampsia, placental abruption, and late pregnancy loss. Placental bed biopsies in pregnancies affected by FGR and preeclampsia confirm that there is a major defect in myometrial spiral artery remodeling that is linked to these clinical parameters.<sup>10-12</sup>

The ongoing adverse in utero environment associated with FGR ultimately may lead to hypoxic damage and stillbirth. With no proven therapeutic interventions available planned early birth must be considered and offered once a fetus reaches a viable gestational age and size. However, preterm birth then adds further morbidity and mortality risk to an already compromised neonate.

There is an urgent need to identify early in pregnancy those women at most risk of developing FGR to investigate and offer preventative therapies. Once FGR is diagnosed, other strategies will be required to improve fetal growth and well-being, which may allow iatrogenic delivery to be delayed and/or to

ameliorate the harm of the hypoxic intrauterine environment.

### Prevention of FGR

#### Aspirin and other antiplatelet agents

The release of sFlt-1 and soluble endoglin<sup>6,7</sup> into the maternal circulation causes endothelial dysfunction, a feature of the placenta-mediated complications of pregnancy and in particular preeclampsia, and an imbalance in vasoactive factors such as endothelin,<sup>13</sup> nitric oxide,<sup>14</sup> and prostacyclin,<sup>15</sup> resulting in reduced vasodilatation and increased vasoconstriction.

Aspirin has a number of effects at the vascular level that may prevent FGR (Figure). For many years it was understood that aspirin suppresses the production of prostaglandins and thromboxanes through its irreversible inactivation of the cyclooxygenase enzyme. Thromboxane is a powerful vasoconstrictor and prothrombotic antiplatelet agent. Low-dose, long-term aspirin use irreversibly blocks the formation of thromboxane A<sub>2</sub> in platelets, inhibiting platelet aggregation. More recently, novel cytoprotective and antioxidant mechanisms of aspirin have been observed that are independent of cyclooxygenase inhibition. Aspirin acetylates endothelial nitric oxide synthase, leading to nitric oxide release from the vascular endothelium.<sup>16</sup> In addition, aspirin increases the activity of heme oxygenase-1 in endothelial cells to catabolize heme, which leads to a reduction in oxidative stress, injury, and inflammation.<sup>17</sup>

Most aspirin studies have centred on preeclampsia as a primary outcome measure, with FGR included as a secondary outcome only. The volume and quality of evidence, however, does allow meaningful interpretation and implementation of findings.

This year there was simultaneous publication of systematic reviews based on study-level meta-analysis<sup>18</sup> and individual patient data meta-analysis<sup>19</sup> of randomised trials of aspirin and other antiplatelet agents that included 20,909 and 32,217 women, respectively. Both analyses supported preexisting evidence that aspirin provides a modest risk

reduction for FGR and SGA (less than the fifth or less than the 10th percentile) at birth (individual patient data analysis relative risk, 0.90, 95% confidence interval [CI] 0.81-1.00).<sup>19</sup> The difference in the conclusions of these meta-analyses arose from assessment of gestational age at initiation of therapy, before or after 16 weeks (Table 1).

The individual patient data meta-analysis found that low-dose aspirin and other antiplatelet agents had a consistent effect on preeclampsia, regardless of whether treatment was started before or after 16 weeks gestation.<sup>19</sup> Data specific to FGR support earlier initiation of therapy where possible. In the study-level meta-analysis, there was a dose-response relationship for SGA when treatment was initiated  $\leq 16$  weeks, favoring a dose of 100–150 mg.<sup>18</sup>

Studies demonstrating circadian effects of aspirin on plasma renin activity<sup>20</sup> and urinary excretion of cortisol, dopamine, and norepinephrine<sup>21</sup> as well as clinical trials that show a circadian effect of aspirin to treat prehypertension<sup>22</sup> and mild hypertension<sup>23</sup> in nonpregnant adults suggest timing of daily dosing should be considered, particularly with reference to the prevention of preeclampsia.

Two small randomized trials in pregnancy have found that evening but not morning administration of aspirin is associated with a reduction in ambulatory blood pressure,<sup>24,25</sup> and in one of these trials, a reduction in the incidence of preeclampsia and FGR was also seen.<sup>24</sup> The circadian mechanism of action in the prevention of FGR seems less clear. However, if recommending daily aspirin therapy, it seems prudent to recommend evening dosing.

Most national and international guidelines recommend a 100–150 mg aspirin dose to prevent FGR and SGA pregnancy in women at high risk.<sup>26</sup> However, patient selection and accurate identification of those at most risk of FGR is not clear because, like most studies of therapies for the prevention of placenta-mediated complications of pregnancy, prediction studies have been more focussed on preeclampsia rather

than FGR. This is highlighted by a recent large, multicenter, randomized trial of aspirin to prevent preterm preeclampsia.

The Aspirin for Evidence-Based Preeclampsia Prevention trial used a complex algorithm including maternal factors, mean arterial pressure, uterine artery Doppler pulsatility index, and maternal serum biomarkers (maternal serum pregnancy-associated plasma protein A and placental growth factor) to identify women at high risk. Although aspirin use was associated with a reduction in preterm preeclampsia, rates of SGA less than the 10th, less than the fifth, or less than the third percentiles were unchanged,<sup>27</sup> suggesting alternative prediction models are required before being able to truly assess the effect of aspirin on those at highest risk.

### Heparin and low-molecular-weight heparin

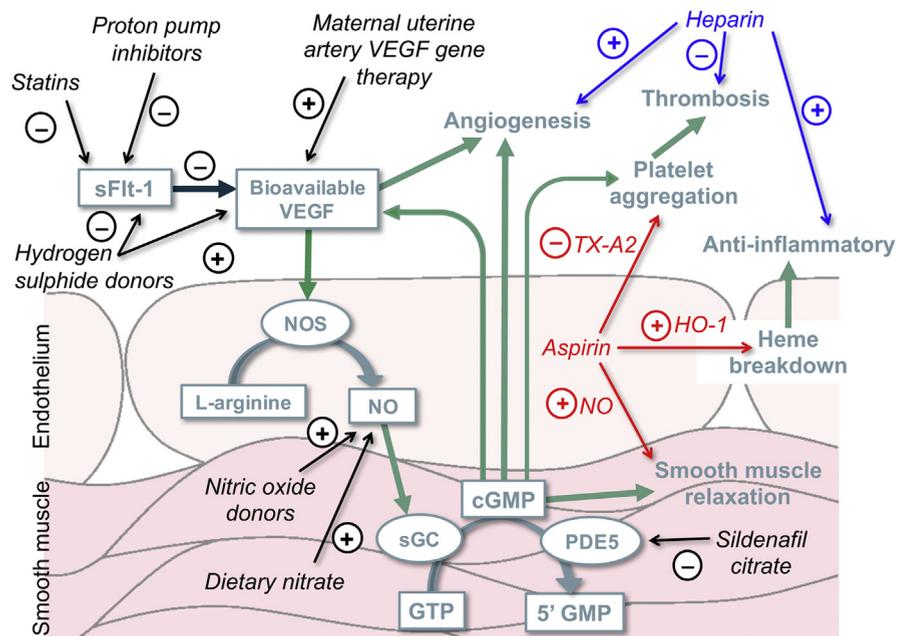
Unfractionated heparin and low-molecular-weight heparin (LMWH) are commonly used in pregnancy for thromboprophylaxis and the treatment of venous thromboembolism. More recently LMWH is preferred to unfractionated heparin and appears safe and effective for these indications.<sup>28</sup> Unfractionated heparin and LMWH do not cross the placenta<sup>29</sup> and thus pose little direct risk to the fetus.

Initial interest in heparins to prevent placental pathology centered on their anticoagulant properties and presumed ability to prevent placental thrombosis and subsequent infarction leading to miscarriage. In vitro and in vivo data suggest heparins have a variety of other biological properties including antiinflammatory,<sup>30</sup> complement inhibition,<sup>31</sup> and anti-tumor<sup>32</sup> actions as well as being proangiogenic<sup>33-37</sup> (Figure). These additional effects may positively influence trophoblast development and invasion, making them potential candidates for the prevention of placenta-mediated complications of pregnancy including FGR.

### Preclinical studies of unfractionated heparin and LMWH on angiogenesis

In vitro studies using placental villous explants found that both unfractionated heparin and LMWH promote

**FIGURE**  
Sites of action of interventions under investigation to treat FGR



Sites of action at vascular smooth muscle and endothelium of the interventions under investigation to treat FGR.

*cGMP*, cyclic guanosine monophosphate; *5' GMP*, guanosine monophosphate; *PDE5*, phosphodiesterase type 5 inhibitor; *GTP*, guanosine-5'-triphosphate; *HO-1*, heme oxygenase-1; *NO*, nitric oxide; *NOS*, nitric oxide synthase; *sFlt-1*, soluble fms-like tyrosine kinase 1; *sGC*, soluble guanylate cyclase; *TX-A2*, thromboxane A2; *VEGF*, vascular endothelial growth factor.

Groom. Therapeutic interventions in fetal growth restriction. *Am J Obstet Gynecol* 2018.

angiogenesis.<sup>33,34,36</sup> The mechanism of action is unclear, but enhanced expression of matrix metalloproteinases may be contributory.<sup>38</sup> However, there are inconsistencies in the in vitro study results with some demonstrating suppression of trophoblast invasion,<sup>39</sup> particularly when heparin is used at therapeutic levels.<sup>40</sup> Further caution is raised by the finding of elevated sFlt-1 concentration and impaired VEGF signaling in endothelial cells when placental villi are exposed to LMWH at therapeutic doses,<sup>41</sup> although this was most significant in healthy early and term pregnancy placentae but not in placentae from pregnancies with preeclampsia and/or FGR.

### Clinical studies of LMWH

In vivo use of LMWH appears to have a more positive effect on markers of angiogenesis. When used in pregnancy for anticoagulation, serum PIGF concentration is increased and there is a lower

sFlt-1/PIGF ratio compared with gestation-matched controls,<sup>37</sup> and in a small randomized trial of women at high risk of preeclampsia, plasma levels of PIGF were elevated 1 and 3 hours after LMWH administration, not seen in women at similar risk receiving placebo.<sup>35</sup>

The effect of heparin therapy on uteroplacental circulation is less clear. In a small open-label study of women with gestational hypertension, treatment with LMWH reduced the uterine artery resistance index.<sup>42</sup> However, more sustained use of LMWH in a randomized control trial of LMWH and aspirin vs aspirin alone found no differences in uterine artery Doppler resistance index at 22–24 weeks or in umbilical artery Doppler pulsatility index at 22–24 weeks and later gestational ages.<sup>43</sup>

Because early evidence suggested a relatively strong association between inherited thrombophilias and preeclampsia and FGR, initial randomized

TABLE 1

**Effect of gestational age at initiation of aspirin therapy for prevention of FGR or SGA at birth**

	Relative risk	95% CI
Study-level meta-analysis <sup>53</sup> (FGR), wks		
≤16	0.56	0.44–0.70
>16	0.95	0.86–1.05
IPD meta-analysis <sup>54</sup> (SGA), wks		
<16	0.76	0.61–0.94
≥16	0.95	0.84–1.08

Study level meta-analysis<sup>53</sup> used FGR as outcome to assess fetal size, defined as birthweight <10th or <5th percentile for gestational age or similar definition. The IPD meta-analysis<sup>54</sup> used SGA as outcome to assess fetal size; SGA at birth was as defined by individual trialists, including centile charts and cutoff point used. FGR, fetal growth restriction; IPD, individual patient data; SGA, small for gestational age.

Groom. *Therapeutic interventions in fetal growth restriction. Am J Obstet Gynecol* 2018.

trials of heparin focused specifically on populations of women with or without thrombophilia.<sup>44-46</sup> More recent evidence from prospective cohort studies suggests any association of thrombophilia and placenta-mediated complications, if present, is only weak,<sup>47</sup> so more recent trials have included women regardless of thrombophilia status. Many trials have diverse inclusion criteria identifying women not only at high risk of FGR and preeclampsia but also earlier pregnancy complications such as recurrent miscarriage and non-placenta-related conditions such as venous thromboembolism.

Results of early randomized trials were encouraging and suggested that heparin could reduce the risk of preeclampsia and FGR.<sup>44,45</sup> But a positive effect of LMWH was not seen consistently across all published trials,<sup>44-46,48-52</sup> possibly reflecting the heterogeneity of the populations being examined, the type of LMWH being used, prolonged trial recruitment phases,<sup>44,46</sup> and early trial discontinuations.<sup>45,48</sup>

A study-level meta-analysis of 6 trials (848 women) demonstrated LMWH (included trials used enoxaparin, dalteparin, and nadroparin) was associated with a reduction in a composite outcome (preeclampsia, birthweight <10<sup>th</sup> percentile, placental abruption, or pregnancy loss >20 weeks), 18.7% vs 42.9% (relative risk, 0.52, 95% CI, 0.32–0.86), with similar risk

reductions for a number of secondary outcomes including SGA <10th percentile and less than the fifth percentile.<sup>53</sup> However, there were high levels of heterogeneity across trials and trials of higher-quality suggested no treatment effect.

The same authors have subsequently completed an individual patient data meta-analysis including 5 trials from the study-level meta-analysis and 3 additional trials (963 women).<sup>54</sup> Again, a composite primary outcome (early-onset or severe preeclampsia, SGA less than the percentile, placental abruption, and late pregnancy loss after 20 weeks) was used but with no difference seen between those treated and those untreated, 14% vs 22% (relative risk, 0.64, 95% CI, 0.36–1.11).

Reviewing all trial data of LMWH therapy was associated with a reduction in SGA <10th percentile and less than the fifth percentile but not less than the third percentile. However, trial quality also had an impact on these results, with heterogeneity seen between single-center and multicenter trials; there was no effect of LMWH seen when considering only data from multicenter trials (Table 2).

In a subgroup analysis, including only women with a history of a SGA infant, LMWH was not associated with any reduction in the composite primary outcome. These meta-analyses did not

include subgroup analysis by type of LMWH used but a further study-level meta-analysis including fewer participants (403 women in 5 heterogeneous trials) has compared dalteparin and enoxaparin use. Both types of LMWH were associated with a reduction in preeclampsia, but only dalteparin was effective in reducing the incidence of FGR.<sup>55</sup>

Since the publication of the 2016 individual patient data meta-analysis,<sup>54</sup> 2 further multicenter trials have been published. The Heparin-Preeclampsia<sup>49</sup> and Enoxaparin for Preeclampsia and Intrauterine Growth Restriction (EPPI)<sup>52</sup> trials included only women at high risk of placenta-mediated pregnancy complications, with or without inherited thrombophilia.

The EPPI trial included a higher proportion of women with a prior history of an SGA infant than most other trials.<sup>52</sup> Both trials reported no difference in rates of composite primary outcomes (maternal death, perinatal death, preeclampsia, placental abruption, and/or SGA <10th percentile in the Heparin-Preeclampsia trial and preeclampsia and/or SGA less than the fifth percentile in the EPPI trial) or any secondary outcomes specific to fetal growth.

These recent trials add significant participant numbers (n = 406) and show consistent results with the conclusion of the published individual patient data meta-analysis, that LMWH does not reduce the risk of recurrent placenta-mediated pregnancy complications in at-risk women. If LMWH therapy is protective for the recurrence of placenta-mediated pregnancy complications, then the effect is likely to be modest and, if present, possibly confined to certain subgroups only or specific types of LMWH.

Currently LMWH therapy for the prevention of FGR should be limited to the research setting. Before any future trials are undertaken, further research is required to accurately phenotype women deemed to be at the highest risk to better identify those who may benefit from treatment.

## Treatment of FGR

### Phosphodiesterase type 5 inhibitors

Phosphodiesterase type 5 inhibitors block the phosphodiesterase enzyme preventing the inactivation of the intracellular second-messenger cyclic guanosine monophosphate within vascular smooth muscle cells, which potentiates the action of nitric oxide leading to vasodilatation. Maternal spiral arteries that have not undertaken complete remodeling early in pregnancy have intact or partially intact muscular layers and so potentially remain responsive to nitric oxide and amenable to vasodilatation. The majority of work investigating phosphodiesterase type 5 inhibitors and FGR has used sildenafil, but more recently other agents, including the longer-acting tadalafil, have been studied [Table 3](#).

### Preclinical studies

In vitro studies show that when compared with healthy control vessels, myometrial small arteries from pregnancies affected by FGR have increased vasoconstriction and reduced vaso-relaxation; preincubation with sildenafil ameliorates this difference.<sup>56</sup>

Work in animal models predominantly support the theory of improved fetal growth with maternal sildenafil use, however, interestingly raises some questions over the mechanism of action. In the catechol-O-methyl transferase (COMT<sup>-/-</sup>) knockout mouse model of preeclampsia and FGR,<sup>57</sup> sildenafil in maternal drinking water in late pregnancy normalises pup growth measures and abnormal umbilical artery Doppler flow indices when compared with untreated catechol-O-methyl transferase (COMT<sup>-/-</sup>) controls.<sup>58</sup> However, this beneficial effect on fetoplacental blood flow and fetal growth was not associated with increased uterine artery blood flow.

Sildenafil use also increased pup weight in an alternative mouse model of FGR that has a normal vascular phenotype.<sup>59</sup> Alterations in placental weight may be an alternative to vasodilatation as the mechanism of action, a theory that is further supported by studies in ovine models of FGR. In maternal nutrient-restricted FGR sheep pregnancy,

**TABLE 2**  
**Primary and fetal growth outcomes from individual patient data meta-analysis of LMWH trials for the prevention of recurrence of placenta-mediated pregnancy complications**

Variables	All trials			Multicenter trials			Single-center trials			Absolute difference (95% CI), P value
	LMWH	No LMWH	Absolute difference (95% CI), P value	LMWH	No LMWH	Absolute difference (95% CI), P value	LMWH	No LMWH	Absolute difference (95% CI), P value	
Primary composite outcome <sup>a</sup>	62/444 (14%)	95/433 (22%)	-8.0% (-17.3 to 1.4) P = .09	47/263 (18%)	47/255 (18%)	-0.6% (-10.4 to 9.2) P = .91	15/181 (8%)	48/178 (27%)	-18.7% (-21.6 to -15.7) P < .0001	
SGA <10th percentile	61/444 (14%)	94/429 (22%)	-8.2% (-5.4 to -0.1) P = .009	47/263 (18%)	53/251 (21%)	-3.2% (-9.6 to 3.1) P = .32	14/181 (8%)	41/178 (23%)	-15.3% (-19.1 to -11.5) P < .0001	
SGA <fifth percentile	27/443 (6%)	38/429 (9%)	-2.8% (-5.4 to -0.1) P = .042	22/262 (8%)	23/251 (9%)	-0.8% (-3.7 to 0.2) P = .61	5/181 (3%)	15/178 (8%)	-5.7% (-6.1 to -5.2) P < .0001	
SGA <third percentile	13/443 (3%)	12/249 (3%)	0.1% (-1.9 to 2.2) P = .89	13/262 (5%)	9/251 (4%)	1.4% (-1.3 to 4.1) P = .32	0/181	3/178 (2%)	<sup>b</sup>	

Data are extracted from Rodger et al., 2016.<sup>54</sup> Data are expressed as a number (percentage). CI, confidence interval; LMWH, low-molecular-weight heparin; SGA, small for gestational age.  
<sup>a</sup> Primary composite outcome includes early-onset or severe preeclampsia or SGA less than the fifth percentile or placental abruption or pregnancy loss ≥20 weeks' gestation; <sup>b</sup> Expected counts were less than 5, so no formal testing was performed.  
 Groom. *Therapeutic interventions in fetal growth restriction*. *Am J Obstet Gynecol* 2018.

**TABLE 3**  
**Summary of progress of experimental treatments for fetal growth restriction**

Experimental treatment	Method of administration	Potential mechanisms of action	Current stage of investigation
Phosphodiesterase type 5 inhibitors	Oral	Selective vascular smooth muscle relaxation and vasodilatation	Phase II/III clinical trials
Maternal VEGF gene therapy	Injected into uterine arteries or applied to outside of vessels	Local vasodilatation and angiogenesis	Phase I/IIa clinical trial
Nanoparticles	Intravenous injection	Uterine blood flow, placental function	Preclinical
microRNAs	Intravenous injection	Uterine blood flow, placental function	Preclinical
Statins	Oral	Antiinflammatory, antioxidant, and angiogenesis	Phase II/III clinical trials (for preeclampsia only)
Nitric oxide donors	Oral	Selective vascular smooth muscle relaxation and vasodilatation	Phase II nonrandomized (for preeclampsia only)
Hydrogen sulphide	Oral	Selective vascular smooth muscle relaxation and vasodilatation	Preclinical
Proton pump inhibitors	Oral	Angiogenesis	Phase II/III clinical trials (for preeclampsia only)
Melatonin	Oral	Antioxidant	Phase II nonrandomized
Creatine	Oral	Cellular energy homeostasis	Preclinical
N-acetylcysteine	Oral	Selective vascular smooth muscle relaxation and vasodilatation	Phase II randomized (for preeclampsia only)

VEGF, vascular endothelial growth factor.

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sildenafil increased fetal growth and amino acid availability. In addition, when FGR was created in sheep using uterine artery embolization, sildenafil improved placental and lamb weight and ameliorated the increased umbilical artery resistance but with no effect on maternal myometrial vessel resistance.<sup>60</sup> Not all preclinical studies, however, have demonstrated positive effects of sildenafil treatment on FGR, with some animal models showing no effect and others showing negative and potentially harmful effects.<sup>61,62</sup>

### Clinical studies

Several case reports and a small randomized trial of sildenafil to selectively reduce pulmonary vascular resistance in pregnant women with pulmonary arterial hypertension demonstrate improved maternal cardiorespiratory performance and echocardiography status with better neonatal outcomes.<sup>63-66</sup> It also appears to be a useful adjunctive therapy for

persistent pulmonary hypertension of the newborn.<sup>67,68</sup> Use in pregnancy and the early neonatal period for these indications have not raised safety concerns.

Two small randomized trials have studied sildenafil treatment of preeclampsia in which 30–60% of participants had coexisting FGR.<sup>69,70</sup> Both trials demonstrated positive effects on maternal blood pressure, and in one trial sildenafil was associated with an increase in the mean prolongation of pregnancy (14.4 days vs 10.4 days,  $P = .008$ ). No differences were seen in the measures of fetal growth, but compared with placebo, uterine and umbilical artery Doppler pulsatility index was reduced 24 hours after commencing sildenafil.<sup>70</sup>

More specific to FGR pregnancies, a single-dose, randomized, placebo-controlled trial showed that 2 hours after ingestion of 50 mg sildenafil, there was reduced resistance in the umbilical artery and increased resistance in the fetal middle cerebral artery, showing it

can influence the fetoplacental circulation.<sup>71</sup> To date, more prolonged use of sildenafil to treat FGR has been reported only in case reports<sup>72,73</sup> and a small case-control study.<sup>74</sup>

In this open study, 10 women with early-onset FGR received 25 mg three times daily sildenafil and were compared with 17 matched untreated control women. A higher proportion of women taking sildenafil had an increased posteligibility fetal abdominal circumference growth velocity (90% vs 41%, odds ratio, 12.9, 95% CI, 1.3–126) with a tendency toward improved survival and intact survival to hospital discharge. However, it should be noted that the sildenafil-treated group were eligible for the study an average of 10 days later and delivered an average of 9 days after those untreated, delivering at a time (<28 weeks) when gestational age is likely to be the most significant predictor of outcome.

These limited human pregnancy studies to date have not raised specific concerns of maternal and/or fetal side effects. However, sildenafil does have a side effect profile including most commonly headache, flushing, dyspepsia, nasal congestion, and impaired vision and blurred vision.<sup>75</sup> Fetal effects are less well known. Sildenafil is likely to cross the placenta, so effects, in particular, on pulmonary vasculature and cerebral blood flow,<sup>71</sup> must be considered.

In addition, some animal studies suggest a detrimental rather positive effect on uterine blood flow and fetal well-being,<sup>61</sup> and although any delay in delivery is hoped to improve long-term outcome, ongoing exposure to a hostile in utero environment has potential to cause greater harm than that caused by preterm delivery.

The results of randomized trials of sildenafil and other phosphodiesterase type 5 inhibitors are keenly awaited. The international Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction (STRIDER) Consortium includes 5 placebo-controlled randomized trials in the United Kingdom,<sup>76</sup> New Zealand and Australia,<sup>77</sup> The Netherlands,<sup>78</sup> Canada,<sup>79</sup> and Ireland.<sup>80</sup> These trials have been conceived and designed through an international collaboration and include women with early-onset FGR. Although independently funded and executed, shared data management systems and outcomes will allow assessment in prospectively planned systematic reviews including individual patient data meta-analyses.<sup>81</sup>

Trials in the United Kingdom and New Zealand and Australia have completed participant recruitment and results are expected soon. Both these trials have childhood outcome studies underway to assess surviving children at the age of 2–3 years and provide important data on longer-term neurological and cardiometabolic outcomes.

### Maternal VEGF gene therapy

An alternative approach to treating FGR is to increase the levels of VEGF in the maternal uterine arteries, thus improving local vasodilatation and

angiogenesis (Figure). This can be achieved with an adenoviral (Ad) gene therapy vector, either injected into the uterine arteries or applied to the outside of the vessels, which produces short-term VEGF expression (Ad.VEGF). This technique, called therapeutic angiogenesis, has been trialed extensively for coronary artery ischaemia and is now reaching phase 3 trials.<sup>82</sup>

Studies in large and small FGR animal models have confirmed the efficacy of this approach for improving fetal growth before birth. In normal sheep pregnancy, injection of Ad.VEGF ( $1 \times 10^{11}$  particles), compared with injection of a control nonvasoactive vector, increased uterine artery volume blood flow within 7 days of injection, and long term, this increase in flow persisted for at least 4 weeks until the end of gestation.<sup>83–85</sup>

The mechanism is mediated via short-term VEGF expression detectable in the perivascular adventitia of the treated vessels. This is associated with increased endothelial nitric oxide synthase expression, which results in reduces vascular constriction. In the long term, there is vascular remodeling, with a reduced intima to media ratio, increased endothelial cell proliferation in the perivascular adventitia of injected vessels, and reduced uterine artery contractile response. Importantly, there was no evidence of vector spread or expression in fetal tissues and no effect of the vector on maternal or fetal hemodynamic measures.

In FGR sheep and guinea pig models, fetal growth velocity is increased, and fewer fetuses are affected by severe FGR at birth.<sup>86–89</sup> There appears to be amelioration of the brain-sparing effect in FGR fetuses of treated pregnancies, with a lower brain to liver weight ratio by ultrasound measurement and at birth. Offspring born after treated FGR pregnancies have higher postnatal lean tissue mass, a faster growth rate, and improved cardiovascular phenotype.

In the clinical context, vector delivery into the uterine arteries could be achieved through interventional radiology, which is used as a prophylactic measure before delivery in women at high risk of postpartum hemorrhage.<sup>90</sup> While this is more invasive than administering oral

medication, it has the potential advantage of targeting vasoactive changes to the maternal uteroplacental circulation.

The doEs Vascular endothelial growth factor gene therapy safely improve outcome in severe Early-onset fetal growth reSTriction (EVERREST) Project, which started in 2013, aims to carry out a phase I/IIa clinical trial to assess the safety and efficacy of maternal uterine artery Ad.VEGF gene therapy for severe early-onset FGR.<sup>91</sup> The project, funded by the European Union, involves a multinational, multidisciplinary consortium, including experts in bioethics, fetal medicine, fetal therapy, obstetrics, and neonatology.

A bioethical study found no absolute ethical, regulatory, or legal objections to the use of maternal gene therapy in pregnancy, with patients welcoming the development of new drugs for this untreatable disease.<sup>92</sup> The consortium is performing a prospective observational study of pregnancies with severe early-onset FGR to define their trial inclusion criteria, which is likely to recruit those women who are most at risk of an intrauterine death or neonatal death between 22 and 27 weeks of gestation.<sup>93</sup>

### Nanotechnology and other uteroplacental targeting strategies to treat FGR

There are a number of other novel strategies emerging that could target drugs or particles to the uteroplacental circulation and/or the trophoblast with the aim of improving uterine blood flow, placental function, or both (Table 3). Tumor-homing peptide sequences CGKRRK (Cys-Gly-Lys-Arg-Lys) and iRGD (Cys-Arg-Gly-Asp-Lys-Gly-Pro-Asp-Cys) bind selectively to the placental surface of humans and mice and do not interfere with normal development. By coating nanoparticles with these sequences, cargoes of proteins such as insulin-like growth factor 2 can be delivered specifically to the placenta.<sup>94</sup>

Insulin-like growth factors promote placental cell proliferation and survival and facilitate the placental uptake of glucose and amino acids. In the placenta-specific insulin-like growth factor 2 knockout mouse model of late-onset FGR<sup>95</sup> such nanoparticle

insulin-like growth factor 2 treatment improved fetal weight.<sup>96</sup> Recently a novel nitric oxide donor (SE175) encapsulated into targeted liposomes has been delivered systemically to the endothelial nitric oxide synthase knockout mouse, which exhibits impaired uteroplacental blood flow and FGR,<sup>97</sup> leading to increased fetal weight and a mean spiral artery diameter and a decrease in the placental weight, indicative of improved placental efficiency.<sup>98</sup>

Another approach has used mitochondria-targeted antioxidant MitoQ bound to nanoparticles to localize and prevent oxidative stress in the placenta.<sup>99</sup> Finally, targeted micro-RNA treatment to the placenta may enhance intrinsic placental growth signaling. miR-145 and miR675 have previously been identified as negative regulators of placental growth. When applied to human first-trimester trophoblast explants, conjugates of the placental homing placental homing peptide CCGKRRK with these peptide-microRNAs enhanced cytotrophoblast proliferation.<sup>100</sup> These approaches will need careful study from a safety and efficacy perspective, but they look promising for a targeted FGR treatment.

### Potential drug therapies for FGR

Investigation of new drug therapies remains at the preclinical or very early clinical phases and has focused on treatment of preeclampsia rather than FGR. Statins are lipid-lowering medications with antiinflammatory, antioxidant, and angiogenic properties (Figure). Within small animal models of preeclampsia, pravastatin reduces levels of sFlt-1 and maternal hypertension and increases VEGF and fetal weight.<sup>101,102</sup>

In a single nonrandomized study including 21 women with antiphospholipid syndrome and treated with aspirin and LMWH, the addition of pravastatin in 11 women after the onset of preeclampsia and/or FGR appeared to delay delivery and improve pregnancy outcomes compared with 10 women who did not receive pravastatin.<sup>103</sup>

In the Statins to Ameliorate early onset Preeclampsia randomized trial (STAMP), which completed recruitment

in 2014,<sup>104</sup> birthweight is included as a secondary outcome but results are still awaited. A further multicenter pilot study in the United States is expected to have completed recruitment at the end of 2018, with a rate of SGA included as a secondary outcome.<sup>105</sup>

Nitric oxide relaxes vascular smooth muscle cells, resulting in vasodilatation (Figure). In women with preeclampsia, short-term treatment with a nitric oxide donor, isosorbide dinitrate, reduces maternal blood pressure<sup>106,107</sup> and lowers resistance in umbilical artery<sup>107,108</sup> and uterine artery<sup>107</sup> Doppler waveforms. No randomized trials of nitric oxide donors have included long-term therapy or been sufficiently powered to assess any effect on pregnancy outcomes.

Hydrogen sulphide, like nitric oxide, is a gas that produces vasodilatation by acting on smooth muscle cell adenosine triphosphate-sensitive potassium channels, while its angiogenic effects appear to be mediated by VEGF and the VEGF receptor 2 (Figure).<sup>109</sup> In a sFlt-1-induced hypertensive, proteinuric rat model, sodium hydrosulfide treatment resulted in elevated VEGF levels and reduced sFlt-1 levels.<sup>110</sup> Further work is now needed to investigate the therapeutic potential of hydrogen sulphide donors in poor placentation.

### Repurposing drugs for FGR, proton pump inhibitors

Because the development of new drugs or the testing of unused drugs for the treatment of FGR pregnancy is difficult and costly, the repurposing of existing drugs that have a known safety profile in pregnancy is an exciting area. Proton pump inhibitors such as esomeprazole have long-term safety data about the treatment of gastric reflux in pregnancy. In vitro studies show proton pump inhibitors decrease sFlt-1 and soluble endoglin and improve markers of endothelial dysfunction (Figure),<sup>111</sup> while esomeprazole reduces blood pressure in a preeclampsia transgenic mouse model that overexpresses sFlt-1.<sup>111</sup> The randomized placebo-controlled Preeclampsia Intervention with Esomeprazole (PIE) trial will assess esomeprazole to treat

early-onset preeclampsia; however, limited secondary neonatal outcomes do not include measures of fetal growth.<sup>112</sup>

### Preventing the adverse outcomes of FGR

Amelioration of the adverse effects of FGR before delivery is an important therapeutic option. When the risks of hypoxia, acidosis, and intrauterine death are deemed high and the fetus is considered to have reached a viable gestational age and size, iatrogenic preterm birth should be offered. Timely antenatal administration of corticosteroids for fetal lung maturation<sup>113-115</sup> and magnesium sulphate for neuroprotection<sup>113,116</sup> is required to prepare for birth with careful consideration of the most appropriate mode of delivery.<sup>117</sup> FGR is associated with long-term neurodevelopmental and cardiac impairment, likely because of oxidative stress.<sup>118-122</sup> Interventions are now being developed to ameliorate this antenatal insult.

### Melatonin

Melatonin, an endogenous lipid-soluble hormone produced by the pineal gland, exerts its powerful antioxidant effect directly by scavenging reactive oxygen species and indirectly by increasing the expression of antioxidant enzymes such as glutathione peroxidase and glutathione reductase. Melatonin crosses the placenta<sup>123</sup> and the fetal blood brain barrier<sup>124</sup> and hence has potential to protect the developing fetal brain and heart from damage by oxidative stress.

In an ovine model of FGR, maternal administration of melatonin protects against cardiac infarct and coronary artery stiffness, cerebral white- and gray-matter injury, and abnormal cerebrovascular development, with improvement in some early neurological outcomes in the offspring. A safety study of melatonin in 6 women with early-onset FGR (4 mg twice daily for the duration of pregnancy) found no fetal<sup>125-127</sup> or maternal safety concerns. Cord blood levels of melatonin were higher and placental malondialdehyde concentrations, a marker of oxidative stress, were lower in the melatonin-treated

group compared with the control untreated women.<sup>126</sup> Trials of efficacy to support melatonin as a neuro- and cardioprotective agent<sup>128</sup> are awaited. A single ongoing study in women at risk of imminent preterm delivery (not specific to FGR)<sup>129</sup> may provide additional information.

### Creatine

Creatine is a naturally produced amino acid derivative that facilitates recycling of adenosine triphosphate and is essential for cellular energy production. Because creatine can cross the placenta, maternal supplementation may increase fetal intracellular creatine and prolong cellular energy homeostasis during hypoxia, potentially providing protection for the brain and other organs in FGR pregnancies.

Maternal dietary creatine supplementation in a spiny mouse model with late-gestation hypoxic injury increases neonatal survival after birth hypoxia and prevents hypoxic damage to the brain, kidney, and skeletal muscle.<sup>130-132</sup> Studies in larger animal models with more prolonged hypoxic injury are ongoing. Low maternal serum and urine creatine levels have been associated with poor fetal growth,<sup>133</sup> but no randomized trials of maternal dietary creatine supplementation in humans have been undertaken.<sup>134</sup>

### N-acetylcysteine

N-acetylcysteine scavenges reactive oxygen species and forms the antioxidant glutathione, thereby counteracting oxidative stress and increasing the bioavailability of nitric oxide.<sup>135</sup> Studies in a rat model of preeclampsia and FGR found that N-acetylcysteine alleviated a rise in maternal blood pressure and increased pup brain weight.<sup>136</sup> In a guinea pig model of maternal chronic hypoxia, administration of N-acetylcysteine did not affect pup weight but did ameliorate oxidative stress responses to hypoxia in the fetal liver.<sup>137</sup> However, a small double-blind, randomized controlled trial found that oral N-acetylcysteine did not stabilize the process of established severe preeclampsia or improve neonatal outcome.<sup>138</sup> Further

studies are needed to investigate whether N-acetylcysteine may prevent fetal complications of FGR.

### Implications for practice

Currently clinicians have limited ability to enhance placentation and prevent FGR, partly due to the paucity of proven therapeutic options but also our inability to accurately identify those at highest risk. A 100–150 mg evening dose of aspirin commenced prior to 16 weeks' gestation provides a modest risk reduction in women at risk using conventional obstetric history–based risk factors.

There are no proven treatments of FGR that will improve fetal growth or outcome once it is diagnosed. The only intervention clinicians can offer is iatrogenic preterm birth with timely administration of maternal corticosteroids and magnesium sulphate to improve neonatal outcome after early preterm birth. Several potential new therapies are on the horizon, but many of these are being primarily investigated for preeclampsia therapy with FGR as a secondary outcome only. It is important that clinicians wait for the results of appropriately designed and powered randomized controlled trials specific to FGR, which include information on meaningful longer-term outcomes before extrapolating positive preclinical and early clinical study findings into clinical practice. ■

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## OBSTETRICS

# The satisfactory growth and development at 2 years of age of the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards cohort support its appropriateness for constructing international standards



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**BACKGROUND:** The World Health Organization recommends that human growth should be monitored with the use of international standards. However, in obstetric practice, we continue to monitor fetal growth using numerous local charts or equations that are based on different populations for each body structure. Consistent with World Health Organization recommendations, the INTERGROWTH-21<sup>st</sup> Project has produced the first set of international standards to date pregnancies; to monitor fetal growth, estimated fetal weight, Doppler measures, and brain structures; to measure uterine growth, maternal nutrition, newborn infant size, and body composition; and to assess the postnatal growth of preterm babies. All these standards are based on the same healthy pregnancy cohort. Recognizing the importance of demonstrating that, postnatally, this cohort still adhered to the World Health Organization prescriptive approach, we followed their growth and development to the key milestone of 2 years of age.

**OBJECTIVE:** The purpose of this study was to determine whether the babies in the INTERGROWTH-21<sup>st</sup> Project maintained optimal growth and development in childhood.

**STUDY DESIGN:** In the Infant Follow-up Study of the INTERGROWTH-21<sup>st</sup> Project, we evaluated postnatal growth, nutrition, morbidity, and motor development up to 2 years of age in the children who contributed data to the construction of the international fetal growth, newborn infant size and body composition at birth, and preterm postnatal growth standards. Clinical care, feeding practices, anthropometric measures, and assessment of morbidity were standardized across study sites and documented at 1 and 2 years of age. Weight, length, and head circumference age- and sex-specific z-scores and percentiles and motor development milestones were estimated with the use of the World Health Organization Child Growth Standards and World Health Organization milestone distributions, respectively. For the preterm infants, corrected

age was used. Variance components analysis was used to estimate the percentage variability among individuals within a study site compared with that among study sites.

**RESULTS:** There were 3711 eligible singleton live births; 3042 children (82%) were evaluated at 2 years of age. There were no substantive differences between the included group and the lost-to-follow up group. Infant mortality rate was 3 per 1000; neonatal mortality rate was 1.6 per 1000. At the 2-year visit, the children included in the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards were at the 49th percentile for length, 50th percentile for head circumference, and 58th percentile for weight of the World Health Organization Child Growth Standards. Similar results were seen for the preterm subgroup that was included in the INTERGROWTH-21<sup>st</sup> Preterm Postnatal Growth Standards. The cohort overlapped between the 3rd and 97th percentiles of the World Health Organization motor development milestones. We estimated that the variance among study sites explains only 5.5% of the total variability in the length of the children between birth and 2 years of age, although the variance among individuals within a study site explains 42.9% (ie, 8 times the amount explained by the variation among sites). An increase of 8.9 cm in adult height over mean parental height is estimated to occur in the cohort from low-middle income countries, provided that children continue to have adequate health, environmental, and nutritional conditions.

**CONCLUSION:** The cohort enrolled in the INTERGROWTH-21<sup>st</sup> standards remained healthy with adequate growth and motor development up to 2 years of age, which supports its appropriateness for the construction of international fetal and preterm postnatal growth standards.

**Key words:** development, INTERGROWTH-21<sup>st</sup> fetal growth standards, postnatal growth

Although human growth, from cell to whole body, is recognized as a universal biologic process, some

entrenched views persist regarding fetal growth, in particular that it should be compared with a site-specific rather than prescriptive population. This view is not held by the World Health Organization (WHO) or by the Centers for Disease Control & Prevention,<sup>1,2</sup> which recommend using international neonatal standards. Likewise, such

standards have now been adopted to estimate the burden and consequences of babies being born small for gestational age in low- and middle-income countries.<sup>3</sup>

We have summarized the key statistical, physiologic, ethnic, and genetic evidence relating to this issue.<sup>4,5</sup> Practically, the debate focuses on whether it is

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correct to monitor fetal growth using 1 of the many site-specific charts available. Typically, such charts are based on different populations for each fetal body structure and have been developed at hospital level.<sup>4</sup> These multiple, site-specific charts are references, not international standards that are used commonly in most other areas of biology and medicine.

This neglected aspect of obstetric practice means that clinical decisions are made based on reference charts that were derived from a wide range of different study populations. For example, a woman may have an early gestational age assessment with the use of a fetal crown-rump length chart based on a study of 80 women from Glasgow, Scotland,<sup>6,7</sup> followed by a clinical assessment with the use of a fundal height chart based on 313 women from Cardiff, Wales.<sup>8</sup> Fetal biometry values may then be compared with 1 of many local charts,<sup>9</sup> and, during the same ultrasound scan, estimated fetal weight may be determined from an equation based on 109 fetuses studied in Texas during the 1980s,<sup>10,11</sup> complemented by a recent chart from other US populations.<sup>12</sup>

If the woman requires further assessment, the umbilical Doppler measures are judged with the use of yet another reference population.<sup>13</sup> At birth, the anthropometric measures of the newborn infant could be evaluated with the use of a multiplicity of reference charts, all of which are totally unrelated to the fetal growth charts that were being used just a few weeks earlier.

The INTERGROWTH-21<sup>st</sup> Project aimed to resolve these issues by conducting studies of human growth and development that involved pregnant women who were enrolled at <14 weeks gestation specifically to monitor their fetuses, newborn infants, and children prospectively up to 2 years of age to generate a single set of international standards to make judgements on the growth of all humans.<sup>14</sup> The studies were based conceptually on the WHO prescriptive approach to constructing human growth standards.<sup>15</sup> The study populations across geographically delimited

areas were selected because they had the recommended health, nutrition, and socioeconomic status that was required to construct international standards.<sup>15</sup>

Hence, the INTERGROWTH-21<sup>st</sup> Standards (from maternal weight gain, to pregnancy dating, fetal growth and estimated fetal weight, to brain structures, amniotic fluid volume, umbilical artery Doppler measures, and newborn body composition) are prescriptive because they are based on a cohort of “healthy” pregnancies and babies from the same geographically selected populations in which most of the health and nutritional needs of mothers were met and adequate antenatal care provided.

Nevertheless, the question always remains with studies that are focused on fetal growth as to how “healthy” were these children after birth and during childhood (ie, are they truly healthy?). We took this question seriously very early in the planning of the project and added a clinical and developmental follow-up evaluation<sup>16-18</sup> beyond the customary early neonatal period as a further criterion to support the assertion that INTERGROWTH-21<sup>st</sup> babies represent true standard populations.<sup>19</sup> The key milestone of 2 years of age was identified as a realistic and biologically relevant time point.<sup>20</sup>

Hence, we first compared the INTERGROWTH-21<sup>st</sup> Standards<sup>4,21,22</sup> with the WHO Child Growth Standards.<sup>23</sup> We demonstrated that, during the early neonatal period, the participants who were selected were appropriate and met the WHO prescriptive criteria for optimal growth.<sup>15</sup> We then extended, for the first time in this literature, the prescriptive evaluation by designing the Infant Follow-up Study of the INTERGROWTH-21<sup>st</sup> Project.

This study aimed to evaluate the growth, nutrition, morbidity, and motor development at 2 years of age of the infants who were included in the international fetal and preterm growth standards to reinforce their prescriptive nature against which fetuses and preterm infants worldwide can now be compared.

## Materials and Methods

INTERGROWTH-21<sup>st</sup> was a multi-center, population-based project that was conducted between 2009 and 2016 in 8 locations: Pelotas, Brazil; Turin, Italy; Muscat, Oman; Oxford, UK; Seattle, WA; Shunyi County, Beijing, China; the central area of Nagpur, India, and the Parklands suburb of Nairobi, Kenya.<sup>14,24</sup>

The primary aim of the project was to study growth, health, nutrition, and neurodevelopment from <14 weeks gestation to 2 years of age.<sup>14</sup> In the Fetal Growth Longitudinal Study of the INTERGROWTH-21<sup>st</sup> Project,<sup>21</sup> we recruited women from these 8 populations who initiated antenatal care at <14 weeks gestation and who met the entry criteria of optimal health, nutrition, education, and socioeconomic status.<sup>14</sup>

Gestational age was estimated based on the date of the last menstrual period and corroborated by ultrasound measurement of crown-rump length at 9<sup>+</sup>0 to 13<sup>+</sup>6 weeks gestation with the use of a standard protocol. All fetuses in the Fetal Growth Longitudinal Study were eligible to contribute data to the construction of the international fetal growth standards; all infants who were born at <37 weeks gestation in the Fetal Growth Longitudinal Study were eligible to contribute data to the construction of the international Postnatal Growth Standards for Preterm Infants. At each postnatal visit, a record of any illnesses in the preceding months was noted in addition to anthropometric measurements and a developmental assessment.

Weight, length, and head circumference were obtained within 12 hours (and no >24 hours) of birth on the postnatal wards and at follow-up visits that were scheduled at 1 and 2 years of age ( $\pm 1$  month). Measurements were taken exclusively by the same teams who were trained and standardized at regular intervals for the INTERGROWTH-21<sup>st</sup> Project.<sup>25</sup>

All study sites used the same methods and equipment: electronic scales (Seca, Hangzhou, China) for weight (sensitivity of 10 g to 20 Kg); a specially designed Harpenden infantometer

(Chasmors Ltd, London, UK) for recumbent length, and a metallic non-extendable tape (Chasmors Ltd) for head circumference.<sup>26,27</sup> Measurement procedures were standardized according to WHO recommendations.<sup>28</sup> During the central standardization sessions for anthropometrists, the intra- and inter-observer error of measurement values for recumbent length ranged from 0.3–0.6 cm and for head circumference from 0.2–0.5 cm.<sup>25</sup>

Measurements were taken twice, independently, by 2 of the study anthropometrists. If the difference between the 2 measures exceeded for weight 50 g for newborn infants and  $\leq 100$  g at 1 and 2 years of age (length, 7 mm; head circumference, 5 mm), then both observers independently repeated that measurement a second time and, if necessary, a third time.<sup>25,27</sup>

When the Infant Follow-up Study started, some enrolled children had passed their second birthday already. The families of these children were invited to a follow-up visit with the maximum age at assessment for the child being 27 months. Similarly, those children who already had passed their first birthday, but were  $< 2$  years old, were invited initially for the first visit up to the age of 18 months. In total, only 14% of 1- and 2-year visits occurred outside the protocol-designated age range for assessment.

Detailed information was obtained from the mother about the infant's health, severe morbidities, length of breastfeeding, timing of the introduction of food, feeding practices, and food intake with the use of standardized forms that were produced especially for the project ([www.intergrowth21.org](http://www.intergrowth21.org)).

WHO protocols were followed to assess motor development milestones.<sup>29</sup> We focused on 4 WHO milestones that are less likely to be affected by recall bias: sitting without support, hands and knees crawling, standing alone, and walking alone. Data were collected by trained staff using a form with pictures of the relevant child positions and corresponding definitions. Parents were asked to report the age in months and weeks when they first observed or “never

observed” the milestones (<http://www.intergrowth21.org.uk>).

We collected the same information from parents at 1 and 2 years of age to evaluate the consistency of the reported dates. There were 7965 pairs of values recorded at year 1 and the year 2 interviews, of which 92.6% were identical at both visits. Among the 588 discrepant values, the median difference ranged between  $-1$  week (interquartile range,  $-4.3$ – $4.3$ ) for hands and knees crawling to  $-0.2$  weeks (interquartile range,  $-6.3$ – $2.3$ ) for standing alone. In these cases, after investigation, the values that were obtained at the 1-year visit were used.

Across all study sites, standardized clinical care and feeding practices were implemented based on protocols that were developed by the INTERGROWTH-21<sup>st</sup> Neonatal Group (<http://www.intergrowth21.org.uk>).<sup>30–32</sup> Exclusive breastfeeding up to 6 months was promoted for all babies, with supplementation for preterm infants as recommended.<sup>30,33,34</sup>

Age- and sex-specific z-scores and percentiles were estimated for each child at 2 years of age comparing their weight, length, and head circumference to the WHO Child Growth Standards.<sup>35</sup> Corrected age was used for the preterm subgroup.<sup>36</sup> Four values (3 for weight and 1 for head circumference) were above or below 5 standard deviations (SD) of the mean of the study population and were excluded.

Variance components analysis was performed to calculate the percentage of variance in infant length at birth, 1, and 2 years because of between- and within-site variance. A multilevel mixed effects model was fitted with random intercepts for the study site and individual levels (with individuals nested within sites). The model, which was fitted with unstructured covariance structure, was adjusted by age (after fractional polynomial transformation) and sex. Both age and sex were treated as fixed effects.

We analyzed 2026 mother-father-infant trios to compare the “mean parental height” with a predicted adult height for each infant, defined as twice their length at 2 years of age.<sup>37</sup>

For infants reported to have achieved the milestones, the proportions within the WHO motor development windows of achievement<sup>35</sup> were estimated, and z-scores were calculated by subtraction of the median age of achievement reported in the WHO motor development study from the median age of achievement in our cohort, and division by the SD in the WHO motor development study. Corrected age was used for the preterm subgroup.

The proportion of infants who received breast milk and vitamin and mineral supplements and those who followed a special diet were estimated at 1 and 2 years of age.<sup>38,39</sup>

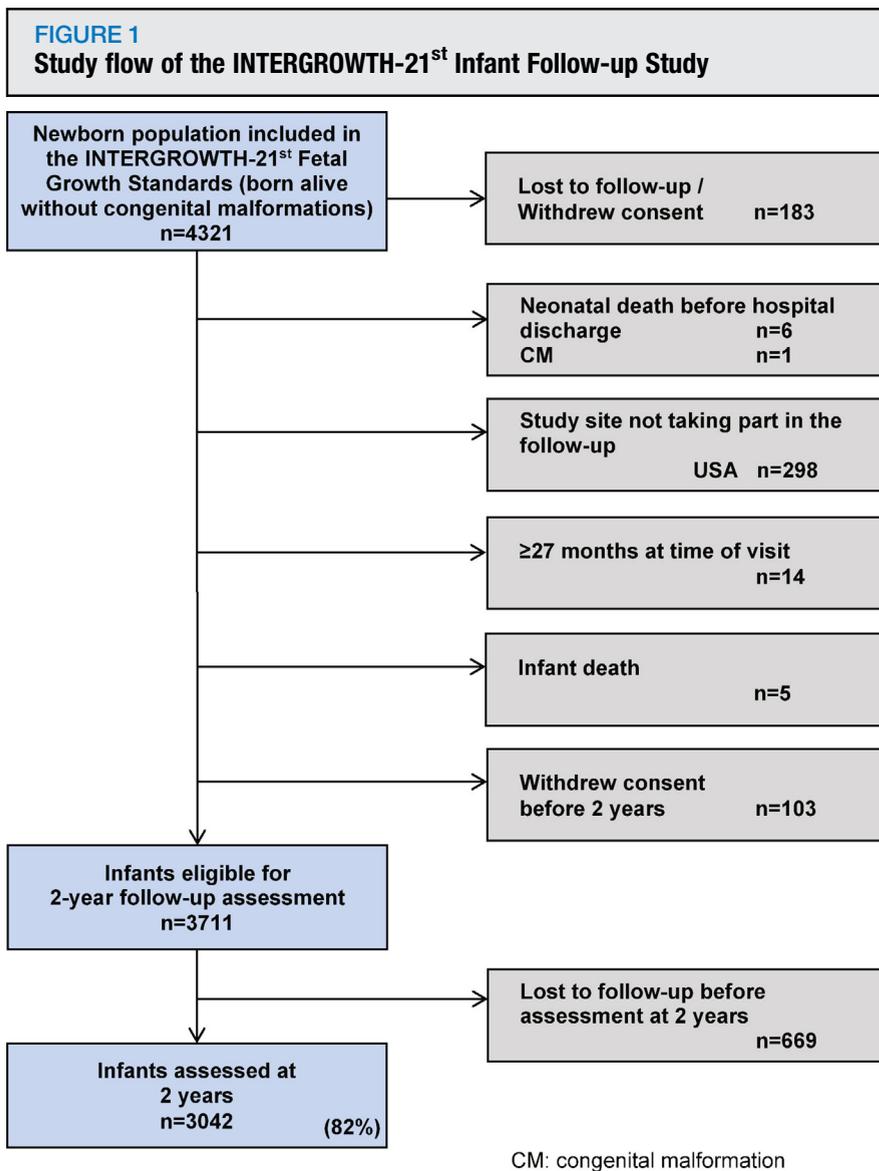
We used Stata software (version 12; StataCorp, College Station, TX). Data were entered locally into the specially developed online data management system (<http://medscinet.com>).<sup>40</sup>

The INTERGROWTH-21<sup>st</sup> Project was approved by the Oxfordshire Research Ethics Committee “C” (reference: 08/H0606/139), the research ethics committees of the individual institutions, and the regional health authorities where the project was implemented. Participants provided written consent to be involved in the study.

## Results

### Population characteristics

There were 4321 singleton newborn infants who were alive at birth without congenital malformations whose mothers were recruited at  $< 14$  weeks gestation and included in the cohort of the international INTERGROWTH-21<sup>st</sup> fetal growth standards.<sup>21</sup> Among these, 183 infants were lost to follow up or withdrew consent during pregnancy; 298 infants were ineligible for the Infant Follow-up Study because the study site in Seattle, WA, could not participate. There were 6 neonatal deaths before hospital discharge (neonatal mortality rate, 1.6/1000 live births), 1 congenital malformation that was detected after birth, and 5 infant deaths, which represented a total infant mortality rate of 3 per 1000 live births. In addition, 103 mothers withdrew consent early in the study. Finally, 14 infants were  $> 27$  months old at the time the follow-up



The chart indicates the cohort that contributed data to the construction of the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards.<sup>21</sup>

CM, congenital malformation; USA, United States of America.

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started; they therefore were not invited to participate. Hence, 3711 newborn infants were eligible for the Infant Follow-up Study, of these, 669 infants were lost to follow up. Thus, the total cohort that was studied comprised 3042 infants (Figure 1) who represented 82% of those eligible (86% for the preterm subgroup, 143/166; Supplementary Figure).

The means ( $\pm$ SD) of the age at which measures were obtained were  $24.4 \pm 1.2$  and  $23.2 \pm 0.7$  months for the total

cohort and the preterm subgroup, respectively; 86% of the 2-year measures were obtained from 23–25 months for the total cohort and 93% were obtained for the preterm subgroup.

The neonatal characteristics of the infants divided into those that completed the 2-year follow-up evaluations ( $n=3042$ ) and those lost to follow up ( $n=669$ ) are presented in Table 1. Both groups were similar in terms of anthropometric measures at birth and neonatal morbidity. A similar comparison within

the preterm subgroup is presented in Table 2.

### Feeding practices

At hospital discharge, 89% of the total cohort and 74% of the preterm subgroup were exclusively breast-milk fed. Similar patterns were seen among the children who were lost to follow-up at 2 years of age. Exclusive breastfeeding was stopped at a median of 5 months (interquartile range, 3–6 months); this was similar in the preterm subgroup. Breastfeeding stopped entirely at a median of 12 months (interquartile range, 6–18 months) for the total cohort and 11 months (interquartile range, 5–18 months) for the preterm subgroup.

In the total cohort, the proportion of children who still were receiving breast milk fell from 59% at 1 year to 11% at 2 years, by which time 34% of the children were formula fed. All children received dairy products of some type (including human milk) at both ages. Food supplements had been given routinely to 33% of children by 1 year and 21% by 2 years. At 1 year of age, 51% of the infants in the preterm subgroup were still receiving breast milk; the figure fell to 8% at 2 years, by which time 34% of children were receiving formula. Food supplements that included vitamins and minerals were given to 36% of the infants in the first year and 28% of the infants by the second year in the preterm cohort. Complementary feeding practices were considered appropriate in terms of diversity, the timing of introduction, and the food variety across sites (Supplementary Tables 1 and 2).<sup>34</sup>

### Postnatal morbidity

The overall morbidity rate in the total cohort was low (Table 3); only 9% of infants were hospitalized (median length of stay, 3 days) in the second year of life. The most frequently reported or diagnosed conditions were acute respiratory infections, diarrhea, and/or gastrointestinal problems with few repeated episodes, skin problems, and febrile episodes. Antibiotics were prescribed on >3 occasions in 10.9% and 15.8% of children in the first and

second years, respectively, which corresponds closely to the rate of reported fever episodes (Table 3). Similar patterns were seen in the preterm subgroup (Table 4). Most of the infants were fully vaccinated in accordance with recommended policies.

### Growth and development from birth to 2 years of age

At 1 year of age, a comparison of the total cohort with the age- and sex-specific WHO Child Growth Standards showed that length and head circumference had a mean  $\pm$  SD z-score of  $0.0 \pm 1.1$  for both measures and that the medians were at the 49th and 48th percentiles of the WHO Child Growth Standards, respectively; for weight, the mean z-score was  $0.2 \pm 1.1$  and median at the 58th percentile.

At the 2-year visit, the growth of the children who were included in the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards plotted almost perfectly onto the WHO Child Growth Standards (ie, 93% for length, 91% for weight [with the expected larger variability], and 92% for head circumference, respectively. Our cohort's values were within the 3rd and 97th cut-off points of the WHO Child Growth Standards (Table 5; Figure 2). For length and head circumference, the mean  $\pm$  SD z-score was  $0.0 \pm 1.1$  for both measures, and the medians were at the 49th and 50th percentiles of the WHO Child Growth Standards, respectively. For weight, the mean  $\pm$  SD z-score was  $0.2 \pm 1.1$ , and median was at the 58th percentile. Figure 2 also shows the 3rd, 50th and 97th percentiles of the distributions of our data (the same percentiles of the WHO Child Growth Standards are included in Figure 2 at years 1 and 2). As shown, the percentiles from our population are almost identical to those of the WHO standards.

At 1 year of age, a comparison of the preterm cohort only with the age- and sex-specific WHO Child Growth Standards at postnatal corrected age, length, and head circumference had a mean z-score of 0.1 for both measures; the medians were at the 52nd percentiles of the WHO Child Growth Standards; for weight, the mean  $\pm$  SD z-score was

**TABLE 1**

**Neonatal characteristics of children who were included in the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards<sup>21</sup> who were evaluated at 2 years of age compared with children who were lost to follow-up**

Characteristic	Evaluated at 2 years of age (n=3042)	Not evaluated at 2 years of age <sup>a</sup> (n=669)
Gestational age at delivery, wk <sup>b</sup>	39.4 $\pm$ 1.4	39.4 $\pm$ 1.4
Birthweight, kg <sup>b</sup>	3.2 $\pm$ 0.5	3.2 $\pm$ 0.5
Birth length, cm <sup>b</sup>	49.1 $\pm$ 2.0	49.2 $\pm$ 2.0
Head circumference, cm <sup>b</sup>	33.7 $\pm$ 1.4	33.9 $\pm$ 1.3
Apgar at 5 min <sup>b</sup>	9.6 $\pm$ 0.6	9.7 $\pm$ 0.6
Age at hospital discharge, d <sup>c</sup>	3 (2–4)	2 (1–4)
Early preterm, <34 wk gestation, n (%)	18 (0.6)	3 (0.4)
Boys, n (%)	1516 (49.8)	324 (48.4)
Neonatal intensive care unit stay >1 d but <3 d, n (%)	160 (5.3)	35 (5.2)
Hyperbilirubinemia, n (%)	137 (4.5)	37 (5.5)
Respiratory distress syndrome, n (%)	51 (1.7)	15 (2.2)
Transient tachypnea of the newborn infant, n (%)	65 (2.1)	15 (2.2)
Exclusive breastfeeding at discharge, n (%)	2698 (88.8)	591 (88.5)

<sup>a</sup> Children lost to follow-up before evaluation at 2 years of age; <sup>b</sup> Data are means $\pm$ standard deviation; <sup>c</sup> Data are given as median (interquartile range).  
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$0.2 \pm 1.1$ , and the median was at the 57th percentile.

At 2 years of age, the growth of the children who were included in the INTERGROWTH-21<sup>st</sup> Preterm Postnatal Growth Standards also plotted similarly onto the WHO Child Growth Standards (Table 6; Figure 2). For length and head circumference, the mean  $\pm$  SD z-scores were  $-0.1 \pm 1.2$  and  $0.0 \pm 1.1$ , respectively, and the median was at the 47th percentile for head circumference of the WHO Child Growth Standards for both measures. For weight, the mean  $\pm$  SD z-score was  $0.2 \pm 1.1$ , and the median was at the 53rd percentile.

The mean postnatal ages, at which the 4 main WHO milestones for gross motor development<sup>29</sup> were achieved for the total cohort and preterm subgroup (chronologic and corrected age) are presented in Figure 3. Both groups

overlapped well for these milestones at the 50th, 3rd, and 97th percentiles of the WHO range for normal term infants. By 2 years of age, >99% of the children had achieved the 4 motor development milestones with >97% within the range of the WHO milestones (data not shown). However, although the preterm subgroup overlapped very well when corrected age was used, they displayed a delay of approximately 1 month in achieving the “walking alone” and “standing alone” milestones, when estimated age after birth was used (Figure 3).

### The variability in children's length among study sites compared with that among individuals within a study site

Maintaining the same analytic approach to the 2-year follow-up data that was

TABLE 2

**Neonatal characteristics of children who were included in the INTERGROWTH-21<sup>st</sup> Preterm Postnatal Growth Standards<sup>22</sup> who were evaluated at 2 years of age compared with children lost to follow-up**

Characteristic	Evaluated at 2 years of age (n=143)	Not evaluated at 2 years of age <sup>a</sup> (n=24)
Gestational age at delivery, wk <sup>b</sup>	35.5±1.6	35.7±1.4
Birthweight, kg <sup>b</sup>	2.5±0.5	2.4±0.5
Birth length, cm <sup>b</sup>	45.7±2.7	45.6±2.3
Head circumference, cm <sup>b</sup>	31.8±1.7	31.8±1.5
Apgar at 5 min <sup>b</sup>	9.2±0.9	9.2±1.2
Age at hospital discharge, d <sup>c</sup>	4 (2–9)	4 (2–7)
Early preterm, <34 weeks gestation, n (%)	19 (13.3)	3 (12.5)
Boys, n (%)	73 (51.0)	8 (33.3)
Neonatal intensive care unit stay >1 but <3 d, n (%)	59 (41.3)	11 (45.8)
Hyperbilirubinemia, n (%)	29 (20.3)	3 (12.5)
Respiratory distress syndrome, n (%)	20 (14.0)	6 (25.0)
Transient tachypnea of the newborn infant, n (%)	23 (16.1)	1 (4.2)
Exclusive breastfeeding at discharge, n (%)	106 (74.1)	19 (79.2)

<sup>a</sup> Children lost to follow-up before evaluation at 2 years of age; <sup>b</sup> Data are given as mean±standard deviation; <sup>c</sup> Data are given as median (interquartile range).

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## Comment

### Main findings

The participants included in the construction of the Fetal Growth Standards, the Newborn Size at Birth and the Preterm Postnatal Growth Standards of the INTERGROWTH-21<sup>st</sup> Project were selected during early pregnancy specifically to generate international standards.<sup>15</sup> The comprehensive data presented here, which describe for the first time the postnatal physical growth, infant mortality rate, morbidity and motor development of the INTERGROWTH-21<sup>st</sup> participants, corroborate that they conformed to the WHO prescriptive approach for the construction of human growth standards. They are a cohort with continuous very low rates of clinical conditions that could affect optimal growth and development.

Our findings reinforce the a priori concept<sup>17</sup> that it is possible to identify a subset of mostly moderate and late preterm infants, with no evidence of intrauterine growth restriction and limited neonatal morbidity,<sup>41</sup> which constitutes an adequate approximation (in terms of growth, health, nutrition, and development) to a prescriptive population for the construction of preterm postnatal growth standards up to 64 weeks postmenstrual age, the time at which they match the WHO Child Growth Standards.<sup>22,23</sup>

### Strengths and limitations of the study in the context of the existing literature

As far as we are aware, this is the first time that a fetal cohort that has been included in longitudinal studies for the specific purpose of constructing prescriptive growth standards has been evaluated up to 2 years of age. Most ultrasound studies that aimed to create reference charts for fetal growth have not reported any postnatal assessment, nor is it likely that such an assessment has been carried out, given the time that has elapsed since these studies were conducted.<sup>9</sup> We selected the 2-year milestone because nutrition indicators that are measured at this age are strongly predictive of adult measures of nutrition,

adopted for the fetus and newborn infant,<sup>4,16,37</sup> we summarized the variability in skeletal growth and size during pregnancy, at birth, and in infancy and childhood (ie, quantifying the variability among study sites, as opposed to that among individuals within a given site). We estimated that the variance among our study sites from birth through 1–2 years of age explains only 5.5% of the total variability in length between birth and 2 years of age; the variance among individuals within a study site explains 42.9% (ie, 8 times the amount after we controlled for age and sex). In Table 7, we compared the present results with the previously published INTERGROWTH-21<sup>st</sup> data from the first trimester of pregnancy to 2 years of age. In all these periods of rapid growth, the variance among sites explains <10% of the total variability in skeletal growth.

### Estimated adult height of the children included in the INTERGROWTH-21<sup>st</sup> fetal growth standards

We estimated the difference between the observed mean parental height and the expected mean adult height (equal to approximately double the mean length at 2 years of age).<sup>37</sup> In the study sites in low-middle income countries (n=1611), an increase in mean expected adult height of 8.9 cm over mean parental height is predicted to occur in a single generation, provided that infants and children are exposed to adequate health, environmental and nutritional conditions from early pregnancy onwards (Figure 4). Conversely, in high-income country sites (N=415), this cohort will be on average 2.2 cm taller than their parents (Figure 4).

human capital, attained height, and intelligence.<sup>42</sup> Before the age of 2 years, it has been shown that children often cross growth percentiles, whereas after this age the phenomenon known as “growth channelization” has been demonstrated, because children tend to grow along the same percentile.<sup>20</sup>

Our unique data are derived from a prospective follow-up evaluation of individuals from 7 different regions of the world from the first trimester of pregnancy to 2 years of age. These findings strengthen the case for the worldwide use of the international INTERGROWTH-21<sup>st</sup> standards that complement the WHO Child Growth Standards in postnatal life. The similarities between the INTERGROWTH-21<sup>st</sup> and WHO studies mean that the size of children, measured at 2 years of age, who were born to healthy mothers, with adequate nutrition, from healthy populations at low risk of adverse pregnancy outcomes, is consistent between the studies and across time.

Other strong features of the study include careful standardization of the outcome measures and the comprehensiveness of the standardized clinical and developmental assessments at 2 years of age.<sup>43</sup> Furthermore, we followed 82% of the children and up to 86% of the pre-term subgroup, which are excellent rates for free-living urban subjects. Baseline similarities between the infants who were evaluated and those lost to follow-up demonstrate that selection bias is very unlikely to have influenced the observed results.

We acknowledge some limitations that relate to practical difficulties of carrying out such a large, multicenter study.

First, the information on morbidity refers mostly to substantive clinical episodes, and data on gross motor development were obtained from parental report rather than direct observation; however, we informed parents about the Infant Follow-up Study protocol at enrolment and asked them to record severe conditions and infant developmental milestones. In addition, parents were encouraged to bring sick children for care to the participating centers;

**TABLE 3**  
**Morbidity in the previous year of children who were included in the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards<sup>21</sup> at 1 and 2 years of age**

Medical condition	1 Year of age (n=2834), n (%)	2 Years of age (n=3042), n (%)
Hospitalized at least once	344 (12.1)	272 (8.9)
Total no. of days hospitalized	3 (1–5) <sup>a</sup>	3 (1–5) <sup>a</sup>
Any prescription made by a healthcare professional	1783 (62.9)	1911 (62.9)
Antibiotics (≥3 regimens)	308 (10.9)	481 (15.8)
Iron/folic acid/vitamin B12/other vitamins	815 (28.8)	430 (14.1)
Up-to-date with local vaccination policies	2607 (92.0)	2903 (95.4)
Otitis media/pneumonia/bronchiolitis	228 (8.0)	293 (9.6)
Parasitosis/diarrhea/vomiting	148 (5.2)	139 (4.6)
Seizures/cerebral palsy/neurologic disorders	9 (0.3)	9 (0.3)
Exanthema/skin disease	456 (16.1)	399 (13.1)
UTI/pyelonephritis	4 (0.1)	10 (0.3)
Fever ≥3 d (≥3 episodes)	293 (10.3)	309 (10.2)
Malaria	13 (0.5)	12 (0.4)
Meningitis	5 (0.2)	0 (0.0)
Other infections that required antibiotics	69 (2.4)	79 (2.6)
Hearing problems	4 (0.1)	3 (0.1)
Asthma	24 (0.8)	42 (1.4)
Cardiovascular problems	9 (0.3)	7 (0.2)
Blindness	6 (0.2)	4 (0.1)
Gastroesophageal reflux	88 (3.1)	9 (0.3)
Any hemolytic condition	14 (0.5)	22 (0.7)
Any malignancy	3 (0.1)	6 (0.2)
Cow's milk protein allergy	NA	21 (0.7)
Food allergies	NA	52 (1.7)
Injury trauma	43 (1.5)	130 (4.3)
Any condition that required surgery	31 (1.1)	34 (1.1)

NA, not applicable (data were not collected at the 1-year follow-up visit); UTI, urinary tract infection.

<sup>a</sup> Data are given as median (interquartile range).

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illness therefore was recorded at the time of the event.

Second, the study outcomes do not extend >2 years of age. This juncture was selected because it is a key time for the detection of postnatal growth faltering,<sup>44,45</sup> and an anthropometric

and clinical evaluation at this age is a very good predictor of subsequent growth. Finally, the Seattle, WA, study site did not participate in the follow-up of children because of logistic issues that were associated with this inner city, highly mobile population. Although they

**TABLE 4**  
**Morbidity of children who were included in the INTERGROWTH-21<sup>st</sup> Preterm Postnatal Growth Standards<sup>22</sup> at 1 and 2 years of age**

Medical condition	1 Year of age (n=154, n (%))	2 Years of age (n=143, n (%))
Hospitalized at least once	34 (22.1)	7 (4.9)
Total number of days hospitalized	5 (3–8) <sup>a</sup>	7 (3–9) <sup>a</sup>
Any prescription made by a healthcare professional	98 (63.6)	72 (50.3)
Antibiotics (≥3 regimens)	31 (20.1)	12 (8.4)
Iron/folic acid/vitamin B12/other vitamins	56 (36.4)	23 (16.1)
Up-to-date with local vaccination policies	139 (90.3)	136 (95.1)
Otitis media/pneumonia/bronchiolitis	13 (8.4)	7 (4.9)
Parasitosis/diarrhea/vomiting	11 (7.1)	10 (7.0)
Seizures/cerebral palsy/neurologic disorders	1 (0.6)	0
Exanthema/skin disease	27 (17.5)	21 (14.7)
UTI/pyelonephritis	0	0
Fever ≥3 d (≥3 episodes)	11 (7.1)	5 (3.5)
Malaria	0	1 (0.7)
Meningitis	0	0
Other infections that required antibiotics	2 (1.3)	4 (2.8)
Hearing problems	0 (0.0)	0
Asthma	2 (1.3)	1 (0.7)
Cardiovascular problems	0	1 (0.7)
Blindness	0	0
Gastroesophageal reflux	6 (3.9)	0
Any hemolytic condition	2 (1.3)	2 (1.4)
Any malignancy	1 (0.6)	0
Cow's milk protein allergy	NA	3 (2.1)
Food allergies	1 (0.6)	3 (2.1)
Injury trauma	1 (0.6)	4 (2.8)
Any condition that required surgery	2 (1.3)	4 (2.8)

NA, not applicable (data were not collected at the 1-year follow-up visit); UTI, urinary tract infection.

<sup>a</sup> Data are given as median (interquartile range).

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represented only 298 newborn infants of more than 4000 in the total cohort and it is very unlikely that they would have affected the overall results presented here, it would have been better to have studied this subsample as well.

The WHO motor development assessment is a simple, pragmatic, and reliable tool to describe normal variation in the achievement of milestones that are reached progressively across infancy. It is especially recommended for studying a large number of infants at the cohort

level, rather than individual level.<sup>35</sup> We have observed that, using chronologic age, gross motor indicators for 2-year-old children who were born preterm (despite being always within WHO recommended windows) are below those of the total cohort by approximately 1 month. This pattern disappears with the use of corrected age (Figure 3). Thus, it is likely that the true range of development in uncomplicated preterm infants is between chronologic and corrected age. However, it is possible that levels of preterm postnatal development may be associated with etiologic phenotypes, as was shown with early neonatal morbidity.<sup>41</sup> We presently are studying these issues in the INTERBIO-21<sup>st</sup> Study, which is the extension to the INTERGROWTH-21<sup>st</sup> Project.

In all the INTERGROWTH-21<sup>st</sup> publications, we have emphasized that the relevant question when comparing growth across populations is whether the variability in skeletal growth within a population (interindividual genetic difference) is larger than the variability among populations (interpopulation genetic difference) when nutritional and health needs are met.

We have used variance components analysis in cohorts that were followed prospectively to identify the proportional contribution of the within and between sites variance components.<sup>4,16,23</sup> We have repeated this analysis for the present article (Table 7). The variance from birth to 2 years of age within a geographic area is 8 times larger than that among geographic areas (Table 7). Hence, it is very unlikely that variability among geographic areas explains >10% of the total variability in infant and child length in healthy, well-nourished, low-risk populations who receive adequate healthcare. These results are in very close agreement with the data from the WHO Child Growth Standards for children <5 years of age, where the variability within study sites explained 70% of the total variance as opposed to a figure of 3.4% that is explained by the between-study sites variability.<sup>23</sup>

This clinical/epidemiologic finding is of great biologic interest because it is

TABLE 5

Anthropometric measures at 2 years of age of children who were included in the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards<sup>21</sup> compared with the World Health Organization Child Growth Standards<sup>a</sup>

Variable	N	INTERGROWTH-21 <sup>st</sup>		World Health Organization Child Growth Standards	
		Mean±standard deviation <sup>b</sup>	Median (interquartile range)	Mean z-score±standard deviation	Median percentile
Weight, kg	3025	12.3±1.7	12.2 (11.1–13.3)	0.2±1.1	58
Length, cm	3010	87.4±3.6	87.3 (85.0–89.7)	0.0±1.1	49
Head circumference, cm	3003	47.8±1.6	47.8 (46.7–48.8)	0.0±1.1	50

<sup>a</sup> Age and gender-specific z-scores and percentiles compared with the World Health Organization Child Growth Standards<sup>23</sup>; <sup>b</sup> Mean values were estimated from raw data.

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consistent with a metaanalysis of 22 genome-wide association studies that showed that the polygenic scores, based on 180 single nucleotide polymorphisms that previously were associated with adult height, explained only a very small proportion of the total variance in birth and infant length (0.13% and 2.95%, respectively).<sup>46</sup>

### Long-term implications

Our 2-year follow-up evaluation of this large cohort of healthy children allowed their mean predicted adult height to be estimated based on the assumption that health, nutritional, and socioeconomic conditions would remain adequate (Figure 4). Thus, the participants in the low-middle income countries sites (and by implication those from other similar countries) are expected to be approximately 8 cm taller as adults than the mean height of their parents; these data are very close to the 6.2–7.8 cm results that were observed in a similar, secondary analysis of the WHO Multicentre Growth Reference Study database.<sup>37</sup> However, because optimal growth largely has been achieved in the parents from high-income country sites, their children are expected to be, on average, only 2.2 cm taller (Figure 4).

Our results confirm a pattern and magnitude of apparent transgenerational “washout”<sup>47</sup> that has previously been described in the Multicentre Growth Reference Study populations.<sup>37</sup> This effect on skeletal growth suggests that a highly sensitive response to environmental changes (eg, better

intrauterine and infant nutrition and healthcare) can occur in 1 generation (ie, in a much shorter timeframe than evolution allows). The mechanisms, which may be mediated by modifications in gene expression that are not linked to DNA sequence changes, are being investigated currently at the molecular level in the INTERBIO-21<sup>st</sup> Study.

The observation that this healthy cohort was at the 58th percentile of the sex-specific weight for age of the WHO Child Growth Standards at 2 years of age has potential implications in describing the natural history of becoming overweight among healthy infants. Because we did not implement any specific nutritional intervention, other than to promote breastfeeding, this weight distribution may represent the initial stages of the overweight epidemic facing many urban children who are exposed to westernized diets. Recent standardized, prospectively collected, fetal data have confirmed the complex effect of nutrition, the environment, migration, and social-cultural issues on fetal growth patterns.<sup>48–50</sup>

The short-term shift in weight distribution in an otherwise healthy population that we have described also reinforces the concept that comparisons among populations to evaluate growth potential should be based on length rather than weight because of its sensitivity to acute influences.

A larger question that goes beyond the scope of this article relates to the timing, velocity, and individual tracking of

growth from conception to 2 years of age vis-à-vis feeding and morbidity in high-risk populations. The exploration of these questions in a longitudinal fashion, including interactions, has considerable statistical complexity, which we are presently investigating in the INTERBIO-21<sup>st</sup> Study.

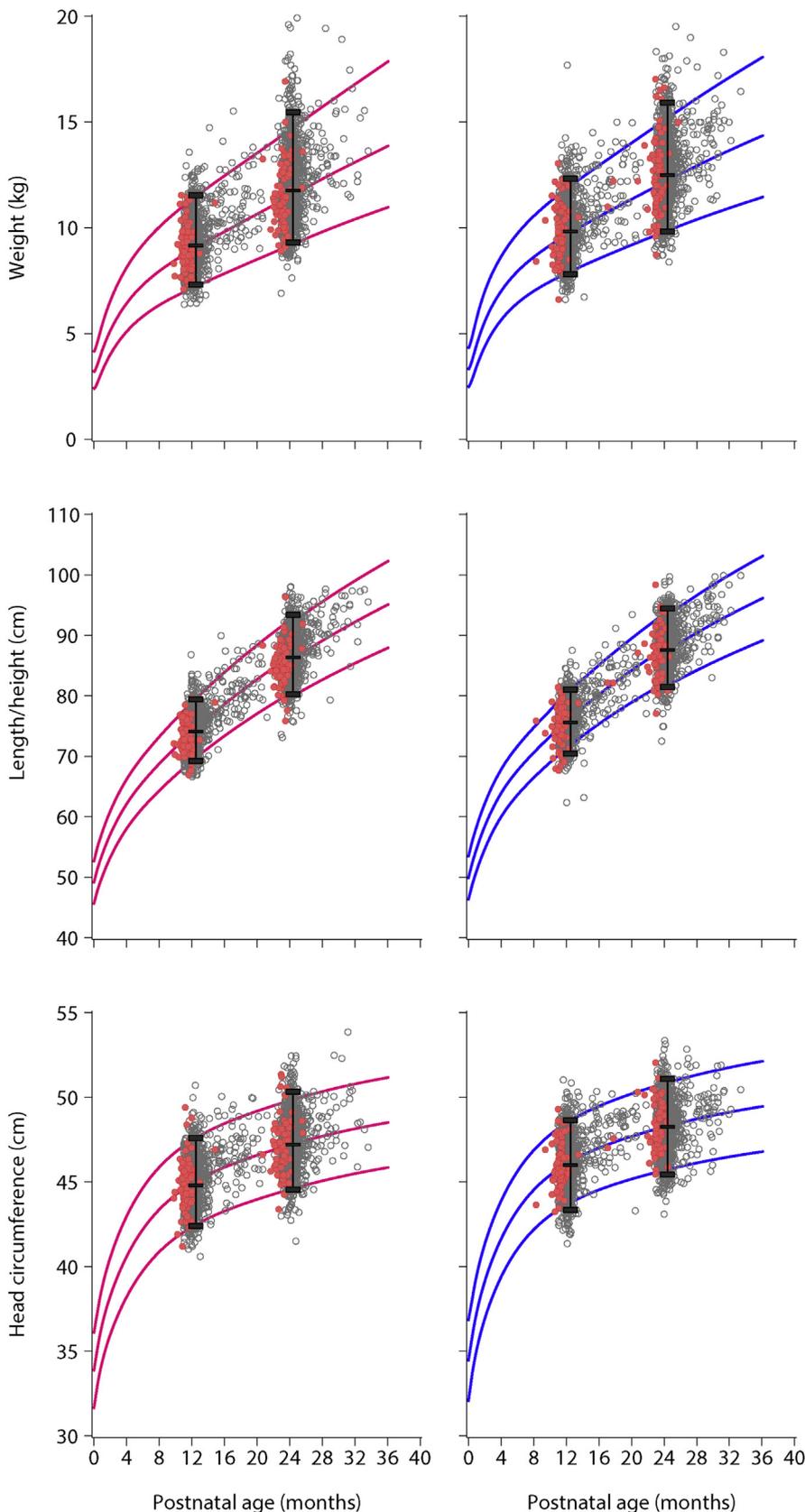
In summary, we have presented evidence that the participants who are enrolled in the international Fetal Growth Standards and the Preterm Postnatal Growth Standards of the INTERGROWTH-21<sup>st</sup> Project and who were selected based on the WHO prescriptive approach for growth standards remain healthy and have adequate growth and development patterns at the key milestone of 2 years of age. This is additional strong confirmation of the sample’s appropriateness for the construction of international growth standards. The INTERGROWTH-21<sup>st</sup> international standards are freely available ([www.intergrowth21.tghn.org](http://www.intergrowth21.tghn.org)) for use worldwide.

### Contributors

J.V. and S.H.K. conceptualized and designed the INTERGROWTH-21<sup>st</sup> Project. J.V., S.H.K., D.G.A., and A.J.N. prepared the original protocol, with later input from A.T.P., L.C.I., F.C.B., and Z.A.B. J.V., A.T.P., L.C.I., A.L., and Z.A.B. supervised and coordinated the project’s overall undertaking. E.S.U., E.O.O., and D.G.A. carried out data management and analysis in collaboration with J.V. R.P., F.C.B., R.O., Y.A.J., E.B., and M.P. collaborated in the overall project and

FIGURE 2

Anthropometric measures at 1 and 2 years of age of the children included in the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards



implemented it in their respective countries. F.G. assisted in the global coordination of the project; L.C.I. and C.C. led the quality control of the anthropometric component, and M.F. and A.S. led the neurodevelopment assessment component. J.V. and S.K. wrote the report with significant contributions by F.G., C.G., C.G.V., F.C.B., and Z.A.B. All coauthors read the report and made suggestions on its content.

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← Data are for children who were included in the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards<sup>21</sup> (grey circles) and children who were included in the Preterm Postnatal Growth Standards<sup>22</sup> (red circles). Values are superimposed onto the 3rd, 50th, and 97th percentiles of the World Health Organization Child Growth Standards<sup>23</sup> (girls [pink lines] and boys [blue lines]). For children born preterm, corrected postnatal age was used.

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TABLE 6

Anthropometric measures at 2 years of age of children who were included in the INTERGROWTH-21<sup>st</sup> Preterm Postnatal Growth Standards<sup>22</sup> compared with the World Health Organization Child Growth Standards<sup>a</sup>

Variable	N	INTERGROWTH-21 <sup>st</sup>		Comparison with World Health Organization Child Growth Standards	
		Mean±standard deviation <sup>b</sup>	Median (interquartile range)	Mean z-score±standard deviation	Median percentile
Weight, kg	142	12.0±1.7	11.7 (10.8–13.2)	0.2±1.1	53
Length, cm	141	86.2±3.7	86.2 (83.8–88.3)	−0.1±1.2	47
Head circumference, cm	140	47.7±1.6	47.6 (46.7–48.6)	0.0±1.1	47

<sup>a</sup> Corrected age was used to obtain age and gender-specific z-scores and percentiles comparing to the World Health Organization Child Growth Standards<sup>23</sup>; <sup>b</sup> Mean values were estimated from raw data.

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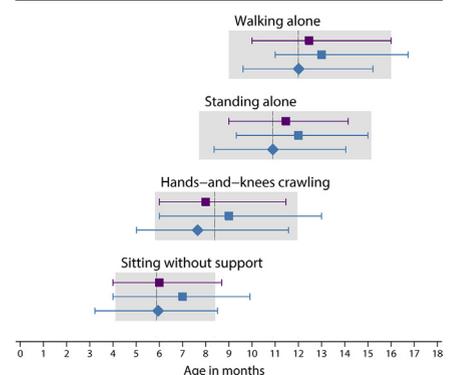
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FIGURE 3

Median age of achievement (3rd and 97th percentiles) of 4 gross motor development milestones



Data are for children who were included in the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards<sup>21</sup> (purple) and children who were included in the INTERGROWTH-21<sup>st</sup> Preterm Postnatal Growth Standards<sup>22</sup> (blue). The diamonds represent the use of corrected age for the children who were born preterm. For comparison, the 3rd and 97th percentiles of achievement<sup>35</sup> for the same milestones are presented in grey (with the median shown as a vertical line).

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TABLE 7

Variance components analysis for fetal, newborn infant, and childhood skeletal growth from the cohort of the INTERGROWTH-21<sup>st</sup> Project

Variance	Fetal ultrasound measures <sup>16</sup> , %		Size at birth <sup>16</sup> (newborn infant length <sup>a</sup> ), %	Infancy/childhood, %	
	1st-trimester fetal crown-rump length <sup>a</sup>	2nd- and 3rd-trimester fetal head circumference		Preterm infant length <sup>22</sup>	Present study length <sup>b</sup>
Among study sites	1.9	2.6	3.5	0.2	5.5
Among individuals within a site	—	18.6	—	57.1	42.9
Residual	98.1	78.8	96.5	42.7	51.6

<sup>a</sup> Variance between individuals for these measures could not be estimated, given the cross-sectional nature of the data; <sup>b</sup> Includes length measurements at birth, 1 and 2 years, controlled for age and sex.

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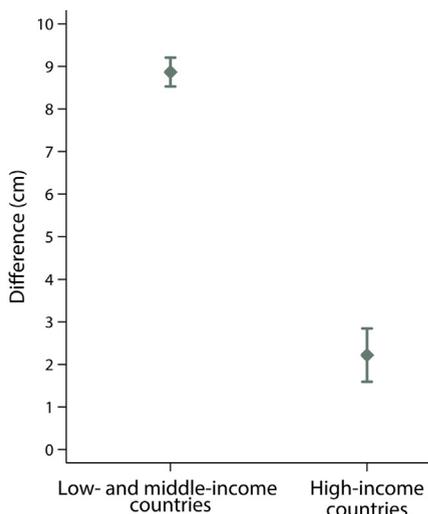
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FIGURE 4

## Expected increase from parental height



Mean (95% confidence interval) difference between estimated adult height (calculated by doubling infant length at 2 years of age) and mean parental height (calculated as the average of maternal and paternal heights) for children who were included in the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards<sup>21</sup> for study sites located in low- and middle-income countries and high-income countries.

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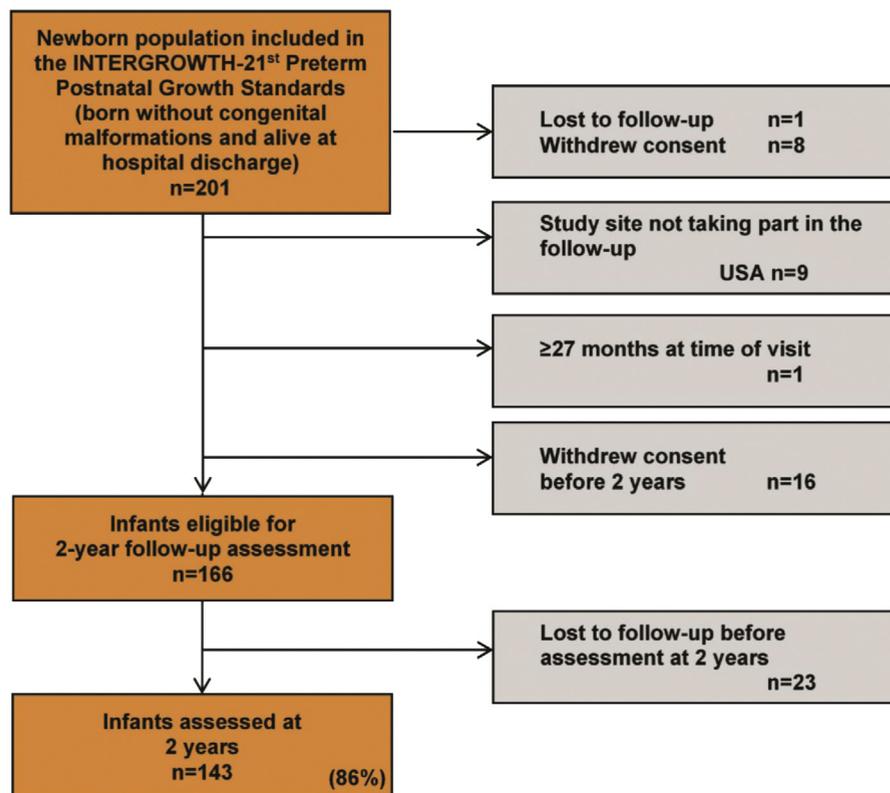
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## SUPPLEMENTARY FIGURE

Study flow of INTERGROWTH-21<sup>st</sup> Preterm Postnatal Follow-up at 2 years

The chart shows the cohort that contributed data to the construction of the INTERGROWTH-21<sup>st</sup> Preterm Postnatal Growth Standards.<sup>22</sup>

Villar et al. Validation of the INTERGROWTH-21<sup>st</sup> fetal growth standards. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTARY TABLE 1****Twenty-four-hour dietary intake of children who were included in the INTERGROWTH-21<sup>st</sup> Fetal Growth Standards<sup>21</sup> at 1 and 2 years of age**

Food group given to the child at least once a day	1 Year of age (n=2832), n (%)	2 Years of age (n=3041), n (%)
Grains, roots, and tubers	2811 (99.3)	3031 (99.7)
Legumes and nuts	1124 (39.7)	1375 (45.2)
Dairy products	2822 (99.6)	3040 (100.0)
Flesh foods	1676 (59.2)	2083 (68.5)
Eggs	575 (20.3)	889 (29.2)
Vitamin-A-rich fruits	1907 (67.3)	1950 (64.1)
Other fruits and vegetables	2606 (92.0)	2863 (94.1)
Fats: spreads/oils	885 (31.3)	1342 (44.1)
Sugars: sweets/sugar products/jelly/sweetened drinks	435 (15.4)	989 (32.5)

Villar et al. Validation of the INTERGROWTH-21<sup>st</sup> fetal growth standards. *Am J Obstet Gynecol* 2018.

**SUPPLEMENTARY TABLE 2****Twenty-four-hour dietary intake for children who were included in the INTERGROWTH-21<sup>st</sup> Preterm Postnatal Growth Standards<sup>22</sup> evaluated at 1 and 2 years of age**

Food group given to the child at least once a day	1 Year of age (n=154)	2 Years of age (n=143)
Grains, roots, and tubers	153 (99.4)	142 (99.3)
Legumes and nuts	54 (35.1)	68 (47.6)
Dairy products	154 (100.0)	143 (100.0)
Flesh foods	95 (61.7)	101 (70.6)
Eggs	35 (22.7)	35 (24.5)
Vitamin-A-rich fruits	104 (67.5)	84 (58.7)
Other fruits and vegetables	130 (84.4)	133 (93.0)
Fats: spreads/oils	34 (22.1)	55 (38.5)
Sugars: sweets/sugar products/jelly/sweetened drinks	14 (9.1)	45 (31.5)

Villar et al. Validation of the INTERGROWTH-21<sup>st</sup> fetal growth standards. *Am J Obstet Gynecol* 2018.

# Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy



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Small for gestational age is usually defined as an infant with a birthweight <10th centile for a population or customized standard. Fetal growth restriction refers to a fetus that has failed to reach its biological growth potential because of placental dysfunction. Small-for-gestational-age babies make up 28-45% of nonanomalous stillbirths, and have a higher chance of neurodevelopmental delay, childhood and adult obesity, and metabolic disease. The majority of small-for-gestational-age babies are not recognized before birth. Improved identification, accompanied by surveillance and timely delivery, is associated with reduction in small-for-gestational-age stillbirths. Internationally and regionally, detection of small for gestational age and management of fetal growth problems vary considerably. The aim of this review is to: summarize areas of consensus and controversy between recently published national guidelines on small for gestational age or fetal growth restriction; highlight any recent evidence that should be incorporated into existing guidelines; and identify future research priorities in this field. A search of MEDLINE, Google, and the International Guideline Library identified 6 national guidelines on management of pregnancies complicated by fetal growth restriction/small for gestational age published from 2010 onwards. There is general consensus between guidelines (at least 4 of 6 guidelines in agreement) in early pregnancy risk selection, and use of low-dose aspirin for women with major risk factors for placental insufficiency. All highlight the importance of smoking cessation to prevent small for gestational age. While there is consensus in recommending fundal height measurement in the third trimester, 3 specify the use of a customized growth chart, while 2 recommend McDonald rule. Routine third-trimester scanning is not recommended for small-for-gestational-age screening, while women with major risk factors should have serial scanning in the third trimester. Umbilical artery Doppler studies in suspected small-for-gestational-age pregnancies are universally advised, however there is inconsistency in the recommended frequency for growth scans after diagnosis of small for gestational age/fetal growth restriction (2-4 weekly). In late-onset fetal growth restriction ( $\geq 32$  weeks) general consensus is to use cerebral Doppler studies to influence surveillance and/or delivery timing. Fetal surveillance methods (most recommend cardiotocography) and recommended timing of delivery vary. There is universal agreement on the use of corticosteroids before birth at <34 weeks, and general consensus on the use of magnesium sulfate for neuroprotection in early-onset fetal growth restriction (<32 weeks). Most guidelines advise using cardiotocography surveillance to plan delivery in fetal growth restriction <32 weeks. The recommended gestation at delivery for fetal growth restriction with absent and reversed end-diastolic velocity varies from 32 to  $\geq 34$  weeks and 30 to  $\geq 34$  weeks, respectively. Overall, where there is high-quality evidence from randomized controlled trials and meta-analyses, eg, use of umbilical artery Doppler and corticosteroids for delivery <34 weeks, there is a high degree of consistency between national small-for-gestational-age guidelines. This review discusses areas where there is potential for convergence between small-for-gestational-age guidelines based on existing randomized controlled trials of management of small-for-gestational-age pregnancies, and areas of controversy. Research priorities include assessing the utility of late third-trimester scanning to prevent major morbidity and mortality and to investigate the optimum timing of delivery in fetuses with late-onset fetal growth restriction and abnormal Doppler parameters. Prospective studies are needed to compare new international population ultrasound standards with those in current use.

**Key words:** clinical management, fetal growth restriction, national guidelines, small for gestational age

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## Introduction

Small for gestational age (SGA) is usually defined as an infant with a birthweight for gestational age <10th centile for a population<sup>1,2</sup> or customized standard.<sup>3,4</sup> These definitions of SGA will include a proportion of babies (18-22%) who are constitutionally small but healthy.<sup>4,5</sup> Fetal growth restriction (FGR)

generally refers to a fetus that has failed to reach its biological growth potential because of placental dysfunction.<sup>6</sup> FGR has considerable overlap with SGA but is more difficult to define in practice, as not all FGR infants have a birthweight <10th centile.<sup>7-9</sup>

Suboptimal fetal growth is important as SGA babies comprise 28-45% of non-anomalous stillbirths.<sup>10,11</sup> Placental insufficiency is a major contributor to the pathophysiology in SGA pregnancies and contributes to the adverse perinatal outcomes.<sup>12</sup> Infants born SGA have higher rates of neurodevelopmental delay, poor school performance, childhood and adult obesity, as well as metabolic disease.<sup>13-18</sup> A limitation of current antenatal care is that the majority of SGA pregnancies are not identified before birth.<sup>19-21</sup> SGA infants recognized before birth who undergo surveillance and timely delivery have a 4- to 5-fold reduction in mortality and/or severe morbidity.<sup>22,23</sup> Therefore, many SGA stillbirths are preventable if detection could be improved and management optimized.

Internationally and regionally, detection of SGA and management approaches can vary considerably. Only 2 previous publications have compared SGA management guidelines between countries.<sup>24,25</sup> The first by Chauhan et al<sup>24</sup> compared the now obsolete 2000 American Congress of Obstetricians and Gynecologists (ACOG) guidelines with the 2002 Royal College of Obstetricians and Gynecologists (RCOG) United Kingdom guidelines and noted that there were considerable variations in content, references cited, and recommendations. More recently, Unterscheider et al<sup>25</sup> compared recommendations made in 4 national guidelines but did not include the New Zealand or the French guideline. The aim of this review is to summarize areas of consensus and controversy between recently published national guidelines on SGA or FGR; to highlight any recent evidence that should be incorporated into existing guidelines; and to identify future research priorities in this field.

## Materials and Methods

Searches through MEDLINE and Google were performed to identify national

guidelines on management of pregnancies complicated by FGR/SGA. MEDLINE searches were undertaken using the terms: “fetal growth retardation/or fetal growth restriction,” “small for gestational age,” and “clinical practice guideline.” The search was confined to articles published from 2010 and published in English. The last search was undertaken on Aug. 7, 2017. Four relevant national guidelines were identified through this process.

The Google searches for national guidelines on diagnosis and management of FGR or SGA identified 3 additional guidelines. The International Guideline Library web site was also searched for fetal growth guidelines, but no additional guidelines were identified from this source. Guidelines published before 2010 were not eligible for inclusion in this review as they did not incorporate recently published evidence.<sup>26</sup>

Each guideline was read by all authors. Summary tables were produced incorporating input from each guideline and included: process for guideline development; definitions, screening, and prevention of SGA; ultrasound surveillance and surveillance after diagnosis of SGA; and timing of delivery. Early-onset SGA (<32 weeks) and late-onset SGA were considered separately as management approaches are different. L.M.M. and N.H.A. developed the tables and checked the tables against the original guideline documents.

## Results

National guidelines from 6 countries were identified that met the above criteria. These were produced in the United States (ACOG<sup>27</sup> and Society for Maternal-Fetal Medicine<sup>28</sup>); the United Kingdom (RCOG<sup>29</sup>); Canada (Society of Obstetricians and Gynecologists of Canada<sup>30</sup>); New Zealand (New Zealand Maternal Fetal Medicine Network<sup>31</sup>); Ireland (Health Service Executive<sup>32</sup>); and France (French College of Gynecologists and Obstetricians<sup>33</sup>). The process for guideline development is summarized in Table 1.

All guidelines highlight the importance of an accurate assessment of gestational age to determine whether

the pregnancy is complicated by FGR or is possibly misdated. The definitions of SGA and FGR, approaches to risk selection, and early screening and prevention are shown in Table 2. There is broad consensus on definitions of SGA and FGR, as birthweight or estimated fetal weight (EFW) <10th centile but 4 of 6 (67%) recommend using a customized EFW<sup>29,31-33</sup> and 2 (33%) recommend using a population reference for EFW.<sup>27,30</sup> Some require other evidence of severity such as abnormal Doppler studies or an EFW <3rd centile to confirm pathological FGR.<sup>29,31-33</sup>

All guidelines comment on the need for early pregnancy risk selection and 5 of 6 (83%) guidelines recommend low-dose aspirin treatment for women with major risk factors for placental insufficiency.<sup>29-33</sup> All guidelines highlight the importance of smoking cessation to prevent SGA and while all recommend that fundal height should be measured in the third trimester, 3 (50%) recommend using customized growth charts,<sup>29,31,32</sup> 2 (33%) recommend use of McDonald rule,<sup>27,30,34</sup> and 1 does not specify a reference.<sup>33</sup>

In Table 3, approaches to third-trimester ultrasound in low- and high-risk women are compared. Five of 6 (83%) agree that there is no current evidence to support routine third-trimester scanning<sup>27,29-32</sup> and 4 of 6 (67%) specify that women with major risk factors should have serial scans in the third trimester.<sup>27,29,31,32</sup> There is also unanimous agreement about the importance of undertaking umbilical artery (UA) Doppler studies in suspected SGA pregnancies as this has been shown to reduce perinatal mortality<sup>35</sup> and no guideline currently incorporates recommendations on utility of third-trimester biomarkers.

Approaches to surveillance and timing of birth in late-onset SGA/FGR ( $\geq 32$  weeks) are summarized in Table 4. Four of 6 (83%) recommend undertaking cerebral Doppler studies<sup>29-31,33</sup> and using the information to influence management. There is considerable inconsistency in terms of recommended frequency of ongoing growth scans after diagnosis of SGA/FGR (2-4 weekly), fetal surveillance

methods (most recommend undertaking cardiocography [CTG]), and timing of delivery. In late-onset FGR with abnormal Doppler studies (raised UA, uterine artery, or reduced cerebral Doppler indices) or EFW <3rd centile the majority (5 of 6, 83%) recommend delivery at 37-38 weeks.<sup>27,29,31-33</sup> When Doppler studies are normal the recommendation varies between delivery at 37<sup>29</sup>-40 weeks.<sup>31</sup>

Management approaches in early-onset SGA/FGR (<32 weeks) are described in Table 5. Not surprisingly there is universal agreement about use of corticosteroids before birth that is likely to occur at <34 weeks 0 days, however the RCOG alone recommends corticosteroids up to 35 weeks 6 days.<sup>29</sup> Four of 6 (67%) recommend use of magnesium sulfate for neuroprotection before very preterm delivery,<sup>27,31-33</sup> with gestation of administration varying from <30<sup>31</sup> to 32-33 weeks.<sup>33</sup> Regarding timing of delivery for preterm FGR with absent or reversed end-diastolic velocity the recommendations for timing of delivery vary from 32<sup>29</sup>-34 weeks<sup>27,28,31-33</sup> and 30<sup>32</sup>-34 weeks,<sup>33</sup> respectively, with the majority (4 of 6, 67%)<sup>29,31-33</sup> specifying that cesarean delivery should be undertaken with this severe Doppler abnormality. The commonest criterion for deciding when to deliver, based on fetal grounds, was a computerized antenatal CTG (3 of 6, 50%),<sup>29,32,33</sup> which includes a real-time automated assessment of short-term fetal heart rate variability (Table 5).

A summary of recommendations where >50% consensus between SGA guidelines is achieved is presented in Table 6.

**Comment**

**Areas where there is potential for improved convergence between SGA guidelines**

*Definitions of FGR.* All guidelines recommended that EFW <10th centile is an appropriate definition of FGR, with some requiring additional parameters to confirm pathological growth restriction. Incorporation of a measure of reduced growth velocity was inconsistent, included in 4 of 6 guidelines (67%),<sup>29,31-33</sup> but often without a specific definition. A recently published Delphi survey on

TABLE 1 Existing national small-for-gestational-age guidelines	
Title	ACOG Practice bulletin no. 134: fetal growth restriction; SMFM Clinical guideline: Doppler assessment of fetus with intrauterine growth restriction from CNGOF
Sponsoring organization	ACOG, SMFM Fetal growth restriction and intrauterine growth restriction: guideline for clinical practice from CNGOF
Investigation and management of small-for-gestational-age fetus	RCOG
Guideline for management of suspected small-for-gestational-age singleton pregnancies and infants >34 wk' gestation	NZMFMN
Intrauterine growth restriction: screening, diagnosis, and management	SOGC
Fetal growth restriction – recognition, diagnosis, and management	Institute of Obstetricians and Gynecologists Royal College of Physicians of Ireland and Health Service Executive
ACOG Practice bulletin no. 134: fetal growth restriction; SMFM	ACOG, SMFM
Year	2013, Updated 2014
Country	United Kingdom
Development process	Developed by committee peer reviewed by professional groups and experts
Year	2013, Updated 2014
Country	New Zealand
Development process	Developed by MFM specialists and neonatologists; endorsed by clinical directors of obstetrics and gynecology
Year	2014, Updated 2017
Country	Ireland
Development process	Written by 3 experts in field, peer reviewed and endorsed by clinical advisory group
Year	2012 SMFM, 2013 ACOG
Country	United States
Development process	Developed by ACOG committee
Year	2015
Country	France
Development process	Organizing committee for guideline development appointed by CNGOF

ACOG, American Congress of Obstetricians and Gynecologists; CNGOF, French College of Gynecologists and Obstetricians; MFM, maternal fetal medicine; NZMFMN, New Zealand Maternal Fetal Medicine Network; RCOG, Royal College of Obstetricians and Gynecologists; SMFM, Society for Maternal-Fetal Medicine; SOGC, Society of Obstetricians and Gynecologists of Canada.  
McCowan. Evidence-based national guidelines for management of suspected fetal growth restriction. *Am J Obstet Gynecol* 2018.

**TABLE 2**  
**Definitions, screening, and prevention for small-for-gestational-age pregnancies**

Country	United Kingdom	New Zealand	Canada	Ireland	United States	France
Definition of SGA	Birthweight <10th customized centile	EFW or birthweight <10th customized centile	EFW <10th population centile	EFW <10th customized centile	Birthweight <10th population centile	EFW or birthweight <10th population centile
Definition of FGR on ultrasound	EFW <10th customized centile, or AC <10th population centile	EFW <10th customized centile or AC ≤5th population centile	EFW <10th or AC <10th population centiles	EFW <10th customized centile	EFW <10th population centile	EFW <10th customized centile
Definition of high-risk FGR/IUGR	EFW <3rd centile	EFW <3rd centile, abnormal UA, uterine artery, MCA or CPR Doppler	Not specified	EFW <3rd, abnormal UA Doppler, oligohydramnios or reduced interval growth	Not specified	Evidence of reduced/arresting of growth with or without abnormal UA or cerebral Doppler, oligohydramnios
Reduced growth velocity in definition of FGR	Change in AC of <5 mm over 14 d	AC or EFW crossing centiles: >30% reduction	Not mentioned	If EFW >10th centile with “poor interval growth”	Not mentioned	Inadequate growth without being SGA
Risk assessment at booking?	Yes	Yes	Yes	Yes	Yes	Yes
Early pregnancy biomarkers	PAPP-A <0.415 MoM—major risk; use of PAPP-A for population screening not recommended	If PAPP-A <0.2 MoM major risk factor; use of PAPP-A for population screening not recommended	If ≥2 serum parameters of aneuploidy screen abnormal (threshold unspecified) increased SGA risk	Low PAPP-A <0.4 MoM risk factor for FGR	No evidence for improved outcome	Not discussed
Uterine artery Doppler for high-risk women?	At 20 wk if ≥3 minor risk factors	At 20–24 wk in high-risk women	At 19–23 wk in women with risk factors	Not recommended	No evidence for improved outcome	Not discussed
Fundal height measurement	Serial fundal height on customized chart from 24 wk; ultrasound if <10th centile, slow or static growth	Serial fundal height on customized chart from 26 wk; ultrasound if reducing velocity or fundal height <10th centile	Serial fundal height—if less than gestation (wk) by >3 cm, ultrasound scan recommended	Serial fundal height on customized chart if available	Serial fundal height at every visit—ultrasound if >3 cm discrepancy with gestation	Serial fundal height screening from 22 wk leading to ultrasound if abnormal—reference chart not specified
Prevention: low-dose aspirin	Low-dose aspirin <16 wk in women with risk factors for preeclampsia	Women at high risk of growth restriction, consider low-dose aspirin 100 mg daily starting <20 wk	Low-dose aspirin for prior preeclampsia, growth restriction, or ≥2 SGA risk factors	Low-dose aspirin 75 mg daily for major SGA risk factors at <16 wk; consider heparin in individual cases	Insufficient evidence to recommend	Low-dose aspirin if previous: preeclampsia <34 wk or FGR <5th centile; 100–160 mg nocte start <16 wk
Prevention: smoking cessation and other interventions	Smoking cessation; no evidence for dietary measures	Smoking cessation in early pregnancy	Smoking cessation—any stage in pregnancy	Smoking cessation—any stage in pregnancy	Tobacco modifiable risk factor; no evidence for bed rest or dietary measures	Smoking cessation and support to become alcohol and drug free before pregnancy; limit multiple pregnancy in assisted reproductive technology; no evidence for bed rest

AC, abdominal circumference; CPR, cerebroplacental ratio; EFW, estimated fetal weight; FGR, fetal growth restriction; IUGR, intrauterine growth restriction; MCA, middle cerebral artery; MoM, multiples of median; PAPP, pregnancy-associated plasma protein; SGA, small for gestational age; UA, umbilical artery.

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definition of FGR, that incorporated responses from 45 experts, reached a consensus definition of early- and late-onset FGR diagnosed before birth.<sup>6</sup> For late FGR ( $\geq 32$  weeks), 2 solitary parameters (abdominal circumference [AC] or EFW  $< 3$ rd centile) and 4 contributory parameters (EFW or AC  $< 10$ th centile, AC or EFW crossing centiles by  $> 2$  quartiles on growth charts, cerebroplacental ratio  $< 5$ th centile, or UA pulsatility index [PI]  $> 95$ th centile) were defined. For early-onset FGR ( $< 32$  weeks) 3 solitary parameters (AC  $< 3$ rd centile, EFW  $< 3$ rd centile, and absent end-diastolic velocity in the UA) and 4 contributory parameters (AC or EFW  $< 10$ th centile with a PI  $> 95$ th centile in either the UA or uterine artery) were agreed upon.<sup>6</sup> These definitions could be incorporated into existing and new SGA guidelines.

A recent publication has demonstrated that fetuses with a  $> 30\%$  reduction in EFW with a birthweight in the normal range are more likely to be acidotic at birth, have abnormal cerebroplacental ratio, and have lower percentage body fat.<sup>9</sup> This report provides further support for adding reduced growth velocity to definitions of FGR in future guidelines.

### Low-dose aspirin

Low-dose aspirin is recommended for women at increased risk of preeclampsia.<sup>36-38</sup> Recent publications on low-dose aspirin have demonstrated a marked reduction in risk of early-onset preeclampsia in women who are identified as high risk during first-trimester screening using combinations of maternal history, uterine artery Doppler, blood pressure, serum pregnancy-associated plasma protein (PAPP)-A, and placental growth factor and treated with low-dose aspirin 150 mg in the evening.<sup>39</sup> A reduction in SGA has also been demonstrated with low-dose aspirin treatment<sup>40</sup> especially in high-risk women.<sup>41</sup> A recent systematic review of low-dose aspirin trials concluded that aspirin was more effective in preventing preeclampsia and FGR when started at  $\leq 16$  weeks and in a dose of 100 mg compared with 60 mg.<sup>42</sup>

**TABLE 3**  
**Third-trimester ultrasound in low and high-risk women**

Country	United Kingdom	New Zealand	Canada	Ireland	United States	France
Screening with routine third-trimester ultrasound in low-risk women	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Recommended at 32 wk
Criteria for serial scanning	$\geq 1$ Major risk factor, unsuitable for fundal height monitoring, abnormal uterine artery Doppler (including notching); scans from 26–28 wk	Major risk factor(s) or unsuitable for fundal height monitoring; gestation to start scanning depends on severity of risk factors	Not specified	Women with risk factors from 26 wk	Previous SGA, other risk factors or unsuitable for fundal height monitoring	Not specified
Recommended biometry charts	EFW customized chart; no evidence to recommend 1 specific method of measuring AC nor which centile chart to use	EFW customized chart; AC on Australasian Society for Ultrasound in Medicine population charts	EFW or AC on population chart; charts not specified	EFW customized chart; biometry—chart not specified	EFW and biometry; charts not specified	EFW customized, biometry using French population ultrasound charts
Umbilical artery Doppler?	Yes—from 26–28 wk in high risk	If fetus small on biometry, or reduced growth velocity	If fetus small on biometry	Yes—criteria not specified	Yes—criteria not specified	Yes—criteria not specified
Interval between scans in suspected SGA/FGR	3 wk	2–3 wk	2 wk	2–4 wk	3–4 wk	3 wk

AC, abdominal circumference; EFW, estimated fetal weight; FGR, fetal growth restriction; SGA, small for gestational age.

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**TABLE 4**  
**Surveillance and timing of birth in late-onset small for gestational age/fetal growth restriction ( $\geq 32$  wk)**

Country	United Kingdom	New Zealand	Canada	Ireland	United States	France
UA Doppler frequency	Every 2 wk if UA Doppler normal, twice weekly if abnormal UA Doppler	Every 2 wk if UA Doppler normal, at least weekly if abnormal UA Doppler	Every 2 wk	Every 2 wk if UA Doppler normal, at least weekly if abnormal UA Doppler	From gestational age where delivery considered for fetal benefit; every 1–2 wk to assess for deterioration <sup>b</sup>	2–3 Weekly if Doppler studies normal, more frequent if severe FGR; weekly if UA Doppler abnormal
Cerebral Doppler studies	MCA Doppler $>32$ wk with normal UA Doppler	MCA Doppler and CPR every 2 wk $\geq 34$ wk; if Doppler(s) abnormal repeat at least weekly	MCA and DV Doppler studies but gestation not specified	MCA optional if UA Doppler abnormal—should not be used to indicate delivery	Insufficient evidence to support use of MCA Doppler in clinical practice	Cerebral artery Doppler every 2–3 wk if normal UA Doppler; increase frequency if UA Doppler abnormal
CTG	Not as only form of surveillance	Not as only form of surveillance; at least weekly if abnormal UA, MCA, CPR, uterine artery Doppler or EFW $<3$ rd centile	Not as only form of surveillance, consider if BPP abnormal	Not specified	Not as only form of surveillance; if abnormal UA Doppler, twice-weekly CTG and/or BPP <sup>b</sup>	“Essential element in assessment of SGA fetus,” frequency not specified
BPP	Do not use	Not as only form of surveillance	Weekly	Not standard	Not as only form of surveillance; if abnormal UA Doppler, twice-weekly CTG and/or BPP <sup>b</sup>	Not discussed
Timing of birth Abnormal Doppler <sup>a</sup>	Deliver by 37 wk if MCA PI $<5$ th centile or abnormal UA Doppler	Deliver by 38 wk if UA Doppler $>95$ th, MCA $<5$ th centile, CPR $<5$ th centile, uterine artery $>95$ th	Consider delivery $>34$ wk if Doppler studies (UA, MCA, DV) abnormal	Abnormal UA PI deliver at 37 wk or earlier if poor interval growth	Consider delivery $>37$ wk when decreased diastolic flow in UA	Birth from $\geq 37$ wk depending on EFW, amniotic fluid, and Doppler measurements
Timing of birth normal Doppler	If $>34$ wk deliver if static growth over 3 wk; offer delivery by 37 wk with involvement of senior obstetrician	If EFW $<3$ rd centile deliver by 38 wk; if EFW $>3$ rd and $<10$ th centile deliver at 40 wk unless other concern; if MCA and uterine Doppler studies not available, deliver at 38 wk	Discuss delivery vs ongoing monitoring $>37$ wk; if amniotic fluid volume or BPP abnormal, consider delivery	Isolated FGR (EFW $<10$ th centile, normal UA Doppler, and AFI), delay delivery until 37 wk, no later than 40 wk	FGR with no additional abnormal parameters, deliver at 38+0 to 39+6 wk	Birth from $\geq 37$ wk depending on EFW, amniotic fluid, and Doppler measurements
Mode of birth	If UA end-diastolic flow present, induction of labor with continuous CTG recommended	Individualize care; high risk of CS with abnormal CPR, MCA, or UA Doppler—continuous fetal monitoring from onset of labor	Not specified	Individualize care; consider CS $<34$ wk	FGR alone not indication for CS	Routine CS for FGR not recommended; CS recommended for very preterm FGR or severe UA Doppler abnormalities; continuous fetal monitoring in labor

AFI, amniotic fluid index; BPP, biophysical profile; CPR, cerebroplacental ratio; CS, cesarean delivery; CTG, cardiotocography; DV, ductus venosus; EFW, estimated fetal weight; FGR, fetal growth restriction; MCA, middle cerebral artery; PI, pulsatility index; SGA, small for gestational age; UA, umbilical artery.

<sup>a</sup> Pregnancies with absent or reversed end-diastolic volume are considered in Table 5; <sup>b</sup> Society for Maternal-Fetal Medicine guideline.

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Five of 6 guidelines (83%) recommend low-dose aspirin for prevention of SGA<sup>29-33</sup> with 3 specifying that low-dose aspirin should be started by 16 weeks<sup>29,32,33,41</sup> and the New Zealand Maternal Fetal Medicine Network guideline recommending that low-dose aspirin can be commenced up to 20 weeks.<sup>40</sup> The French guideline specifies that low-dose aspirin should be taken in the evening to maximize efficacy<sup>33</sup> and this advice, which is based on randomized controlled trial (RCT) evidence,<sup>43</sup> should also be incorporated into the other guidelines.

**The role of heparin to prevent SGA**

Consistent with an earlier meta-analysis,<sup>44</sup> the Canadian guideline recommends that heparin should be offered in selected women. The publication of an individual patient data meta-analysis,<sup>45</sup> along with findings from the Enoxaparin for the Prevention of Preeclampsia and Intrauterine Growth Restriction trial,<sup>46</sup> have demonstrated that enoxaparin is not effective in preventing FGR in women with previous severe or early-onset FGR, or in those with thrombophilia, and can therefore not be recommended for this purpose.

**Uterine artery Doppler velocimetry screening**

Second-trimester uterine artery Doppler velocimetry screening in the general population has a modest ability to predict later-onset FGR. A 2008 meta-analysis showed abnormal second-trimester uterine PI in low-risk/unspecified-risk women gave a positive likelihood ratio FGR of 3.4, increasing to 9.1 with uterine artery notching, with low negative likelihood ratios (0.87 and 0.89, respectively).<sup>47</sup> However, a recent randomized study failed to show any benefit on perinatal outcomes of universal second-trimester screening by uterine artery Doppler at the time of the anatomy scan for risk stratification in an unselected population.<sup>48</sup> Much of the benefit of uterine artery Doppler screening for FGR is identifying women at risk for early-onset preeclampsia.<sup>49</sup> Three of the guidelines (50%) recommend second-trimester uterine Doppler

**TABLE 5**  
**Management of early-onset small for gestational age/fetal growth restriction (<32 wk)**

Country	United Kingdom	New Zealand	Canada	Ireland	United States	France
Corticosteroids	Up to 35+6 wk	Up to 34+0 wk	Up to 34+0 wk	Up to 34+0 wk	Up to 34+0 wk	Up to 34+0 wk
Magnesium sulfate	Not specified	<30 wk <sup>b</sup>	Not specified	<32 wk	<32 wk	<32–33 wk
Recommended timing of delivery with AEDV and REDV	AEDV by 32 wk; REDV by 32 wk	AEDV by 34 wk; REDV by 32 wk	AEDV not specified; REDV not specified; “Requires intervention and possibly delivery”	AEDV no later than 34 wk; REDV no later than 30 wk	AEDV ≥34 wk <sup>a</sup> ; REDV ≥32 wk	AEDV ≥34 wk; REDV ≥34 wk
Indication for delivery	Abnormal computerized CTG or DV Doppler	Not applicable —NZMFMN guideline for SGA ≥34 wk	Abnormal BPP, CTG, or DV Doppler	Abnormal computerized CTG	Abnormal fetal surveillance (CTG, amniotic fluid, or BPP)	Abnormal computerized CTG or DV Doppler
Mode of delivery	CS for AEDV and REDV	CS for AEDV and REDV	Not specified	CS for AEDV and REDV	FGR alone not indication for CS	CS for AEDV and REDV

Includes surveillance for AEDV as this usually occurs <32 wk gestation, and >32 wk gestation delivery is usual practice. AEDV, absent end-diastolic volume; BPP, biophysical profile; CS, cesarean delivery; CTG, cardiogram; DV, ductus venosus; FGR, fetal growth restriction; NZMFMN, New Zealand Maternal Fetal Medicine Network; REDV, reversed end diastolic volume; SGA, small for gestational age.

<sup>a</sup> Society for Maternal-Fetal Medicine Doppler guideline<sup>40</sup>; <sup>b</sup> New Zealand magnesium sulfate guidelines.<sup>101</sup>

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**TABLE 6**  
**Recommendations from small-for-gestational-age guidelines where >50% consensus is achieved**

Country	United Kingdom	New Zealand	Canada	Ireland	United States	France
Definition of FGR on ultrasound	EFW <10th customized centile, or AC <10th population centile	EFW <10th customized centile or AC $\leq$ 5th population centile	EFW <10th or AC <10th population centiles	EFW <10th customized centile	EFW <10th population centile	EFW <10th customized centile
Risk assessment at booking?	Yes	Yes	Yes	Yes	Yes	Yes
Fundal height measurement	Serial fundal height on customized chart from 24 wk; ultrasound if <10th centile, slow or static growth	Serial fundal height on customized chart from 26 wk; ultrasound if reducing velocity or fundal height <10th centile	Serial fundal height—if less than gestation (wk) by >3 cm, ultrasound scan recommended	Serial fundal height on customized chart if available	Serial fundal height at every visit—ultrasound if >3 cm discrepancy with gestation	Serial fundal height screening from 22 wk leading to ultrasound if abnormal—reference chart not specified
Prevention: low-dose aspirin	Low-dose aspirin <16 wk in women with risk factors for preeclampsia	Women at high risk of growth restriction, consider low-dose aspirin 100 mg daily starting <20 wk	Low-dose aspirin for prior preeclampsia, growth restriction, or $\geq$ 2 SGA risk factors	Low-dose aspirin 75 mg daily for major SGA risk factors at <16 wk; consider heparin in individual cases	Insufficient evidence to recommend	Low-dose aspirin if previous: preeclampsia <34 wk or FGR <5th centile; 100–160 mg nocte start <16 wk
Prevention: smoking cessation and other interventions	Smoking cessation; no evidence for dietary measures	Smoking cessation in early pregnancy	Smoking cessation—any stage in pregnancy	Smoking cessation—any stage in pregnancy	Tobacco modifiable risk factor; no evidence for bed rest or dietary measures	Smoking cessation and support to become alcohol and drug free before pregnancy; limit multiple pregnancy in assisted reproductive technology; no evidence for bed rest
Screening with routine third-trimester ultrasound in low-risk women	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Recommended at 32 wk
UA Doppler?	Yes—from 26–28 wk in high risk	If fetus small on biometry, or reduced growth velocity	If fetus small on biometry	Yes—criteria not specified	Yes—criteria not specified	Yes—criteria not specified
UA Doppler frequency	Every 2 wk if UA Doppler normal, twice weekly if abnormal UA Doppler	Every 2 wk if UA Doppler normal, at least weekly if abnormal UA Doppler	Every 2 wk	Every 2 wk if UA Doppler normal, at least weekly if abnormal UA Doppler	From gestational age where delivery considered for fetal benefit; every 1–2 wk to assess for deterioration <sup>a</sup>	2–3 Weekly if Doppler studies normal, more frequent if severe FGR; weekly if UA Doppler abnormal

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(continued)

**TABLE 6**  
**Recommendations from small-for-gestational-age guidelines where >50% consensus is achieved (continued)**

Country	United Kingdom	New Zealand	Canada	Ireland	United States	France
Cerebral Doppler studies	MCA Doppler >32 wk with normal UA Doppler	MCA Doppler and CPR every 2 wk ≥34 wk; if Doppler(s) abnormal repeat at least weekly	MCA and DV Doppler studies but gestation not specified	MCA optional if UA Doppler abnormal—should not be used to indicate delivery	Insufficient evidence to support use of MCA Doppler in clinical practice	Cerebral artery Doppler every 2–3 wk if normal UA Doppler; increase frequency if UA Doppler abnormal
CTG	Not as only form of surveillance.	Not as only form of surveillance; at least weekly if abnormal UA, MCA, CPR, uterine artery Doppler, or EFW <3rd centile	Not as only form of surveillance, consider if biophysical profile abnormal	Not specified	Not as only form of surveillance; if abnormal UA Doppler, twice-weekly CTG and/or biophysical profile <sup>a</sup>	“Essential element in assessment of SGA fetus,” frequency not specified
Corticosteroids	Up to 35+6 wk	Up to 34+0 wk	Up to 34+0 wk	Up to 34+0 wk	Up to 34+0 wk	Up to 34+0 wk
Mode of delivery	CS for AEDV and REDV	CS for AEDV and REDV	Not specified	CS for AEDV and REDV	FGR alone not indication for CS	CS for AEDV and REDV

AC, abdominal circumference; AEDV, absent end-diastolic volume; CPR, cerebroplacental ratio; CS, cesarean delivery; CTG, cardiotocography; DV, ductus venosus; EFW, estimated fetal weight; FGR, fetal growth restriction; MCA, middle cerebral artery; REDV, reversed end-diastolic volume; SGA, small for gestational age; UA, umbilical artery.

<sup>a</sup> SMFM guideline.

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in high-risk women.<sup>29–31</sup> Although the predictive value of abnormal uterine Doppler is limited, a normal test may allow ruling out FGR in women with a baseline increase in risk.

### Measurement of fundal height

All guidelines recommend fundal height measurement with a tape measure, of which 3 (50%) recommend plotting on a customized chart<sup>29,31,32</sup> and 2 (33%) diagnose suboptimal fetal growth by McDonald rule, when fundal height measurement is >3 cm less than gestational age in weeks.<sup>27,30</sup> Given the increase in maternal weight since these charts were produced in the 1980s they may not be applicable in current practice.<sup>50,51</sup> A single randomized trial<sup>52</sup> did not show any difference in detection of SGA infants between palpation and fundal height measurement and plotting on a population chart.<sup>53</sup> Staff training in fundal height measurement is not discussed in this article.<sup>52</sup> Additionally, a meta-analysis of fundal height measurement to predict low birthweight and SGA found that fundal height when plotted on a population chart was not a good primary screening tool.<sup>53</sup> Four guidelines (67%) recommend that ultrasound scans should be considered in women with obesity and/or a fibroid uterus as fundal height measurements are not reliable.<sup>27,29,31</sup>

The Growth Assessment Protocol (GAP), a United Kingdom initiative that incorporates training in standardized measurement of fundal height and plotting this on customized growth charts, has been designed to improve detection of SGA infants before birth and to optimize management.<sup>54</sup> GAP is recommended by the National Health Service in the United Kingdom as part of a bundle of care designed to reduce stillbirth.<sup>55</sup> This program has been associated with increased detection of SGA babies and an associated reduction in stillbirth.<sup>56</sup> The Detection of Small for Gestational Age Fetus trial, a cluster RCT of implementation of GAP, will provide further evidence as to whether this initiative improves important clinical outcomes (ISRCTN67698474).

### Routine third-trimester ultrasound in low-risk women

Five of the 6 guidelines (83%) recommend that there is no role for a routine third-trimester scans in low-risk women.<sup>27,29-32,57</sup> Several of the randomized trials included in the Cochrane review of routine ultrasound >24 weeks in low-risk women (8 trials n = 27,024 women) performed the third-trimester scan too early for optimum detection of late onset of FGR.<sup>58,59</sup> A recent prospective cohort study, in 3977 nulliparous women from Cambridge, United Kingdom, demonstrated that a research scan at 36 weeks correctly identified 57% of women who delivered SGA babies, whereas selective use of scanning identified 20% of SGA.<sup>60</sup> As clinicians were blinded to the results of the 36-week scan it was not possible to evaluate the impact on clinical outcomes. Fetuses that were SGA, and had reduced growth velocity of the AC between the 20- and 36-week scans, had the highest morbidity. Consideration is now being given to whether a large RCT of late pregnancy ultrasound is feasible as the studies included in the Cochrane review to date are underpowered to demonstrate an effect on stillbirth.

### Timing of delivery in late-onset FGR

In FGR with abnormal Doppler studies (raised UA, uterine artery, or reduced cerebral Doppler indices) or EFW <3rd centile the majority of guidelines (5 of 6, 83%) recommend delivery at 37-38 weeks,<sup>28,29,31-33</sup> with some (3 of 6, 33%) recommending a more conservative approach when Doppler studies are normal and the FGR is not severe (ie, EFW not <3rd centile).<sup>27,28,31,32</sup> These recommendations are likely based on the findings of the Disproportionate Intrauterine Growth Intervention Trial at Term study<sup>26</sup> in which 650 women with suspected FGR >36 weeks were randomized to induction or expectant management with twice-weekly surveillance. There was no difference in the primary outcome of severe neonatal morbidity or in cesarean delivery. Women who were expectantly managed had a 2-fold increase in risk of developing preeclampsia (7.9% vs 3.7%,

$P < .05$ ) and were more likely to have a baby with birthweight <3rd centile (30% vs 13%,  $P < .001$ ). The recommendation was that “it is rational to choose induction to prevent possible neonatal morbidity and stillbirth.” A strength of Disproportionate Intrauterine Growth Intervention Trial at Term study is that additional data were published on outcomes in the children. There was no difference overall in neonatal morbidity between induction of labor and expectant management groups, but induction at <38 weeks was associated with increased neonatal unit admission.<sup>61</sup> It was recommended that, where possible, delivery should be delayed until 38 weeks with watchful monitoring. At 2 years an Ages and Stages questionnaire was administered. Severe FGR (birthweight <2.3 centile), more common with expectant management, was the most important predictor of abnormal Ages and Stages scores.<sup>62</sup> A health economics analysis demonstrated that costs were lower with induction at 38 weeks compared to earlier gestations.<sup>63</sup> These findings suggest that delivery at 38 weeks in the fetus with suspected FGR may be optimum, unless there are earlier concerns about fetal well-being, and are consistent with findings from population-based studies that show a marked increase in stillbirth from 38 weeks in the SGA baby.<sup>64</sup>

### Timing of delivery in early-onset FGR

The Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) of management of preterm FGR between 26-32 weeks has been published since these SGA guidelines were submitted or published.<sup>65</sup> TRUFFLE was a study of early FGR where mothers were allocated to 1 of 3 monitoring strategies to indicate timing of delivery: (1) reduced fetal heart rate short-term variability on CTG; (2) early changes in fetal ductus venosus (DV) waveform; or (3) late changes in fetal DV waveform. Many infants were delivered because of safety-net criteria for maternal or other fetal indications, or >32 weeks of gestation when the protocol was no longer applied. TRUFFLE now provides evidence that waiting until late changes occur in the DV or abnormal

CTG is associated with improved outcomes at 2 years of age. The recommendations from TRUFFLE should now be considered for incorporation into national SGA/FGR guidelines. As approximately 80% of cases in TRUFFLE delivered because of CTG abnormalities had late decelerations, this trial is unable to determine whether computerized CTG is superior to regular CTG for surveillance in FGR.

### Areas of controversy

*Customized or population birthweight centiles.* There is considerable controversy as to whether SGA at birth should be defined using customized, population, or ethnic-specific standards, and which population standard is better suited for international comparisons. Traditional population birthweight references are generated from regional/national databases and report average birthweight for gestational age, without accounting for maternal characteristics (or other factors) that contribute to infant birthweight.<sup>66,67</sup>

To overcome the limitations of multiple regional population standards, the INTERGROWTH-21st international standards for newborn size<sup>1</sup> proposed a universal birthweight standard compatible with the World Health Organization (WHO) child growth standards.<sup>2</sup> This was a prospective, multinational fetal growth and birthweight study that pooled data from 8 countries with diverse populations. While this approach is appealing in its simplicity, concerns over the appropriateness of combining data and the risks of overdiagnosing or underdiagnosing SGA in local populations have been raised.<sup>68-71</sup>

Within multiethnic populations, birthweight differences are observed between ethnic groups, even in low-risk populations.<sup>72-74</sup> Significant differences in fetal growth and birthweight have been reported in low-risk pregnancies between 4 ethnic groups in the United States by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) fetal growth studies,<sup>74</sup> which also illustrated the overdiagnosis of SGA in non-white populations using a white reference.

Recent publication of WHO fetal growth charts in low-risk pregnancies from 10 countries in Africa, Asia, Europe, and South America also showed considerable variation in both fetal ultrasound parameters and birthweight between countries,<sup>75</sup> and described these differences as “adaptive,” ie, physiological. Further, the application of ethnic-specific birthweight standards better assesses the risk of adverse neonatal and obstetric outcomes among SGA infants in multiethnic populations.<sup>76,77</sup> Evidence seems to be accumulating that ethnic-specific birthweight standards not only improve the detection of at-risk SGA infants, but also reduce the overdiagnosis of SGA among some ethnic groups.

Population birthweight references do not account for the well-established association between preterm birth and FGR, leading to potential underdiagnosis of preterm SGA.<sup>78-80</sup> Birthweight customization as described by Gardosi et al,<sup>81</sup> used in the United Kingdom, New Zealand, and Ireland, utilizes an ultrasound fetal weight reference<sup>82</sup> to overcome the systematic bias of preterm birth on birthweight, and also adjusts for maternal height, weight, parity, ethnicity, and infant sex. Infants classified as SGA by customized birthweight standards are at higher risk of perinatal morbidity and mortality than infants SGA by population birthweight standards.<sup>5,83</sup> Between 18-22% of infants SGA by population standards are reclassified as normally grown by customized standards and as the perinatal mortality of these reclassified babies is similar to those who are normally grown they can be considered to be “constitutionally small.”<sup>5,84,85</sup> Importantly, the inclusion of maternal characteristics in the customization model increases the detection of SGA infants at risk of perinatal death over and above use of the ultrasound reference alone.<sup>3,4</sup>

As there is currently no consensus on the appropriate birthweight standard to use (although accounting for ethnicity seems appropriate), it is important that local validation of the chosen standard is undertaken, to ensure its use is appropriate in a given setting.

### First-trimester biomarkers

While 3 of 6 guidelines (50%) recommend that PAPP-A should be considered a major risk factor for SGA,<sup>29,31,32</sup> no guidelines recommend PAPP-A as a stand-alone screening test for SGA. In the general population, low PAPP-A in the first trimester has a poor predictive ability (positive likelihood ratio of SGA 1.96; negative likelihood ratio 0.93), however the high specificity (0.96; multiples of the median <0.3) means that an abnormal value reported as part of first-trimester anomaly screening has value.<sup>86</sup>

While first-trimester screening for FGR has been the focus of much research, biomarkers have not performed well enough to date to be offered as stand-alone screening tests. Multiple biomarkers have been investigated, with commonly researched analytes including PAPP-A, human chorionic gonadotropin, placental growth factor, and soluble fms-like tyrosine kinase-1.<sup>49,87</sup> FGR biomarker prediction is improved by the addition of maternal characteristics and uterine artery Doppler studies at the 12-week scan, with detection rates for early and late FGR as high as 86% and 66%, respectively, for a 10% false-positive rate.<sup>49</sup> This increased detection, however, is mainly due to the increased prediction of FGR cases associated with preeclampsia.

### Research priorities

*Routine late third-trimester ultrasound?* A meta-analysis of randomized trials failed to demonstrate benefit from routine third-trimester scan<sup>57</sup> but is underpowered to detect and impact on stillbirth. Most included studies were relatively old. The most recent<sup>88</sup> published in 2003 reported a 30% reduction in SGA. Furthermore, most studies involved no change in management if SGA was diagnosed, which does not reflect current practice. Thus, the contemporary benefit of routine late third-trimester ultrasound on severe morbidity and mortality is unknown.

*When should late-onset SGA pregnancies with abnormal middle cerebral artery/cerebroplacental ratio Doppler indices be delivered?* Because of the association with adverse outcomes, 3 guidelines

recommend early delivery generally at 37 weeks in pregnancies with abnormal middle cerebral artery/cerebroplacental ratio. Although earlier birth may prevent stillbirth, it also has the potential to cause harm by adding the effects of premature birth to the existing problems of growth restriction. Randomized trials to address this question would need to be huge and may not be feasible.

*What ultrasound population charts should be used?* Population ultrasound references in common use tend to be older,<sup>89-93</sup> and are frequently limited by inaccurate or incomplete information on pregnancy dating.<sup>94</sup> Methodological limitations include the use of routine, hospital-based data and many studies do not account for pathological influences on fetal growth such as preeclampsia or gestational diabetes.<sup>94,95</sup> Rarely do ultrasound references account for maternal ethnicity, despite multiple studies showing variations in fetal biometric measurements between countries/ethnicities.<sup>71,74,96</sup> As fetal growth references are descriptive of whole populations, including pathology, they are specific to the population they are generated in and are not generalizable.

In contrast to references, fetal growth standards are developed under optimal conditions, excluding pathology, and are intended for general use. Customized fetal biometry standards accounting for individual maternal characteristics have been created,<sup>97-99</sup> but may have limited applicability in low-resource settings. Recent longitudinal studies in healthy pregnancies have been undertaken by the NICHD in the United States,<sup>74</sup> WHO,<sup>75</sup> and INTERGROWTH-21st,<sup>100</sup> with the aim of developing population fetal growth standards for international use. Prospective studies are required to assess the impact of using these new charts compared with existing local charts.

### Conclusions

This review has confirmed that where there is high-quality evidence from RCT and meta-analyses to guide management such as use of UA Doppler in SGA pregnancies and corticosteroids for

delivery <34 weeks, there is a high degree of consistency between national SGA guidelines. Recommendations from the limited existing RCTs of management of SGA pregnancies should also be incorporated into current and future SGA guidelines.<sup>26,65</sup> Currently, with a lack of RCT evidence to guide management of SGA pregnancies in many areas, existing guidelines incorporate evidence from observational studies and expert opinion. ■

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# Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease

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*Adapt yourself to the environment  
in which your lot has been cast,  
and show true love to the fellow-  
mortals with whom destiny has  
surrounded you.*

—Marcus Aurelius,  
*Meditations VI, 39*

## Fetal Programming of Adult Cardiovascular Disease

It is now accepted that the risk of cardiovascular disease (CVD), which is a leading cause of death in the twenty-first century, is influenced by the interaction between our genes and environment.

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In the modern world, cardiovascular disease is a leading cause of death for both men and women. Epidemiologic studies consistently have suggested an association between low birthweight and/or fetal growth restriction and increased rate of cardiovascular mortality in adulthood. Furthermore, experimental and clinical studies have demonstrated that sustained nutrient and oxygen restriction that are associated with fetal growth restriction activate adaptive cardiovascular changes that might explain this association. Fetal growth restriction results in metabolic programming that may increase the risk of metabolic syndrome and, consequently, of cardiovascular morbidity in the adult. In addition, fetal growth restriction is strongly associated with fetal cardiac and arterial remodeling and a subclinical state of cardiovascular dysfunction. The cardiovascular effects occurring in fetal life, includes cardiac morphology changes, subclinical myocardial dysfunction, arterial remodeling, and impaired endothelial function, persist into childhood and adolescence. Importantly, these changes have been described in all clinical presentations of fetal growth restriction, from severe early- to milder late-onset forms. In this review we summarize the current evidence on the cardiovascular effects of fetal growth restriction, from subcellular to organ structure and function as well as from fetal to early postnatal life. Future research needs to elucidate whether and how early life cardiovascular remodeling persists into adulthood and determines the increased cardiovascular mortality rate described in epidemiologic studies.

**Key words:** cardiovascular disease, echocardiography, epigenetics, fetal growth restriction and fetal programming

Subclinical CVD begins to evolve early in life, long before the clinical symptoms appear decades later and strong evidence supports that it may start before birth.<sup>1-3</sup> The best characterized prenatal risk factor for CVD is fetal growth restriction (FGR). Epidemiologic studies that have been published in the past four decades, first demonstrated that low birthweight was associated with an increased risk of death from coronary heart disease,<sup>4-12</sup> stroke,<sup>5,10</sup> hypertension,<sup>13-16</sup> impaired glucose tolerance, and non—insulin-dependent diabetes mellitus.<sup>15,17,18</sup> These associations have been described beyond disparities in life expectancy or healthcare system.<sup>10,19</sup> The phenomenon to explain this relationship was denominated *fetal programming*.<sup>20,21</sup> Structural, functional, and metabolic changes that occur in the fetus as an adaptive response to an adverse or

suboptimal environment persist into postnatal life, which leads to a greater risk of disease in adulthood.<sup>20,22</sup> In relation with CVDs, fetal programming is thought to occur through two main pathways: metabolic programming and cardiovascular remodeling.

Metabolic programming was the first hypothesis to explain the association of CVDs with low birthweight.<sup>23-25</sup> Nutrient restriction during a period of intense epigenetic programming, such as fetal life, would promote developmental pathways that best suit this environment, through the selection of “thrifty genes” (or molecular pathways).<sup>1,23,26,27</sup> Because in postnatal life nutrient availability will be normal, this programming will facilitate a higher incidence of metabolic disease, which includes obesity, diabetes mellitus, and metabolic syndrome, which secondarily may lead

**TABLE 1**  
**Glossary of terms**

Term	Explanation
2-Dimensional speckle tracking echocardiography	Imaging technique that analyzes the magnitude of myocardial deformation in different directions by the use of the naturally occurring speckle pattern in the myocardium.
Cardiomyocyte	Columnar-shaped cells 20 $\mu\text{m}$ in diameter and 60–140 $\mu\text{m}$ in length that make up the cardiac muscle.
Epigenetics	The study of the chemical modification of specific genes or gene-associated proteins of an organism.
Epigenome	Record of the chemical changes to the DNA and histone proteins of an organism.
Hypertrophy	The enlargement or overgrowth of an organ or part because of an increase in size of its constituent cells.
Intima-media thickness	Measurement of the thickness of tunica intima and tunica media, the innermost two layers of the wall of an artery.
M-mode echocardiography	One-dimensional analysis of the heart in motion. It provides both high spatial and temporal resolution and usually is used to measure the thickness of the ventricular walls and the volumes of the cardiac chambers.
Myocardial performance index (Tei index)	Doppler-derived index of combined systolic and diastolic function. Defined as the sum of isovolumic contraction time and isovolumic relaxation time divided by the ejection time.
Myocardial strain	Percentage of change in the length of a myocardial segment during a given period of time.
Sarcomere	Fundamental contractile unit within the cardiomyocyte, defined as the segment between 2 neighboring Z-lines (or Z-discs, or Z bodies).
Tissue Doppler imaging	Echocardiographic technique that uses Doppler effect principles to quantify the myocardial tissue motion.

Crispi. Long-term cardiovascular consequences of fetal growth restriction. *Am J Obstet Gynecol* 2018.

to CVDs.<sup>26,28</sup> Compelling experimental evidence supports the effects of nutrient restriction on epigenetic metabolic pathways in the offspring after FGR.<sup>29,30</sup> Likewise, postnatal follow-up studies of children with FGR have reported the influence of postnatal nutrition and catch-up in the risk of metabolic syndrome and obesity.<sup>31-33</sup> However, postnatal obesity, diabetes mellitus, or metabolic syndrome affect, in a highly heterogeneous manner, subjects who were born with a low birthweight and these conditions are actually uncommon in some reported cohorts.<sup>34,35</sup> Consequently, although metabolic programming must be a contributing factor, it cannot explain per se the epidemiologic association between FGR and CVDs.<sup>36</sup>

Over the last 10 years, a second important line of evidence has shown that FGR is also associated with direct changes in the cardiovascular system.<sup>37</sup> Because these changes persist into

childhood and early adulthood, primary *cardiovascular programming and remodeling* can also be an important link to explain the association between FGR and adult CVDs.<sup>38</sup> However, cardiovascular remodeling leads to subclinical changes in cardiac and vascular structure and function. Therefore, as with metabolic programming, it remains to be established how these changes combine with other prenatal or postnatal factors to lead to clinical CVD in adulthood. In this review, we will focus on the evidence that supports fetal cardiovascular remodeling in FGR; we will discuss potential pathways for its association with clinical CVDs in adults, and the potential implications for preventive public health strategies and treatments that could have a strong impact in the reduction of CVDs. **Table 1** is a glossary containing terms used in this review that might be new or uncommon for obstetricians and gynecologists.

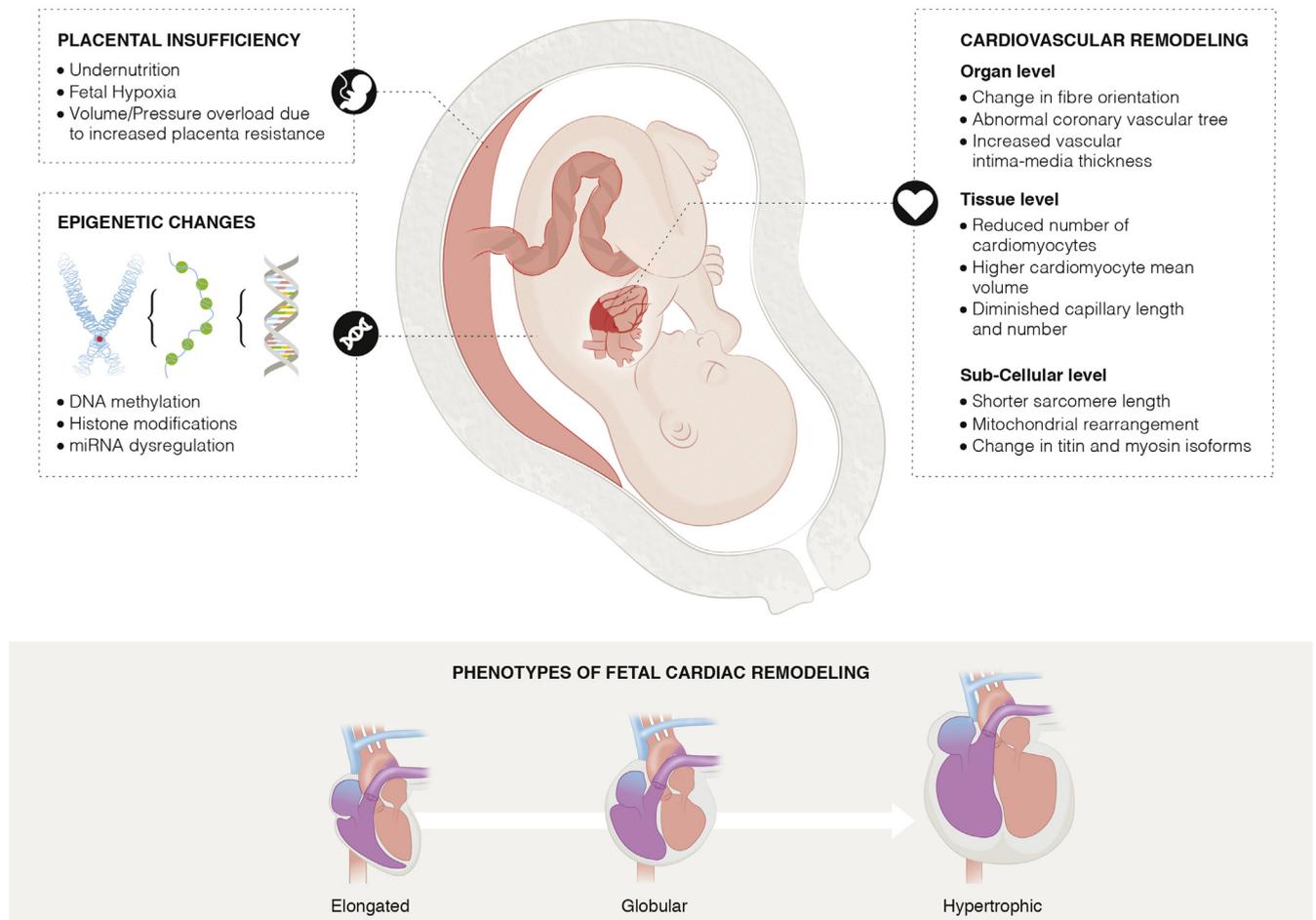
## Cardiovascular Remodeling and Dysfunction in FGR

### Fetal cardiovascular adaptations to FGR

FGR, defined as a failure to achieve the genetic growth potential, affects 7–10% of pregnancies.<sup>39</sup> In the majority of cases, fetal smallness is the consequence of placental insufficiency. FGR has two main clinical presentations according to the gestational age of appearance, early and late onset, which are discussed in detail elsewhere.<sup>40-43</sup> By arbitrary convention, late-onset small fetuses are usually subclassified into late-onset FGR (birthweight <3rd percentile or abnormal fetoplacental and uterine Doppler findings) or small for gestational age (SGA; birthweight 3rd - 9th percentile and normal Doppler findings).<sup>44-47</sup> Although they differ in severity, clinical features,<sup>48-52</sup> and perinatal outcomes,<sup>40,52-54</sup> all the aforementioned clinical forms (early or late

FIGURE 1

## Fetal cardiovascular programming and remodeling associated to fetal growth restriction



Sustained restriction of nutrients and oxygen is associated with cardiovascular remodeling at organ, tissue, and subcellular levels (**right upper panel**) and with epigenetic changes (**mid left panel**). Different fetal cardiac phenotypes—elongated, globular and hypertrophic (**lower panel**)—may be observed by cardiac imaging, depending on the severity/duration of the insult. Other abnormalities not included in this figure (such as hypertension, endothelial dysfunction, and insulin resistance) can operate simultaneously.

*miRNAs*, microRNAs.

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FGR or SGA) have been reported to be associated with cardiovascular programming and remodeling.<sup>55-58</sup>

Placental insufficiency has two direct effects on fetal cardiovascular development. First, reduced oxygen and nutrients supply may disrupt cardiomyocyte growth and fiber architecture; and second, villous hypoplasia/thrombosis leads to increased placental resistance and chronic cardiac afterload. Consequently, the developing myocardium develops a variety of changes in cardiac macro and microstructure and function, which is defined as *cardiac remodeling*, to

maintain ventricular output (**Figure 1**). Initially, the heart develops a more spherical shape that allows maintaining stroke volume with less contraction force, while also reducing wall stress to better tolerate pressure overload.<sup>59,60</sup> This may happen in one ventricle (“elongated” phenotype, where a globular right ventricle pushes the septum and elongates the left ventricle) or both ventricles (“globular” phenotype). In more severe and/or prolonged cases, increased sphericity may not be enough, then hypertrophy develops to increase contractility and decrease local wall

stress. Thus, cardiomegaly is a characteristic change, with three different phenotypes (elongated, globular, and hypertrophic) suggesting a progression of severity.<sup>60</sup> Early-onset FGR is more associated with a hypertrophic response, whereas cardiac phenotypes late-onset FGR usually develops globular or elongated.<sup>60</sup> Evaluation of cardiac morphometric parameters, such as the sphericity index, might be more stable and reproducible compared with functional parameters (eg, more susceptible of being affected by heart rate or fetal movements).

Alterations in cardiac shape are accompanied by subclinical cardiac dysfunction.<sup>59</sup> Both can be demonstrated with fetal echocardiography.<sup>61,62</sup> M-mode and tissue Doppler imaging show reduced longitudinal myocardial motion (reduced tricuspid and mitral annular excursion [tricuspid annular plane systolic excursion/mitral annular plane systolic excursion] and annular peak velocities), which reflects subclinical systolic dysfunction.<sup>58-60</sup> Likewise, diastolic dysfunction appears from early stages<sup>63-67</sup> as increased pulsatility in ductus venosus,<sup>49,68,69</sup> abnormal transmitral E/A ratios (a marker of left ventricular function that reflects early ventricular filling [the E wave] and late diastolic filling caused by atrial contraction [the A wave]),<sup>49,66,69</sup> prolonged isovolumic relaxation time and myocardial performance index (Tei index),<sup>66</sup> and decreased diastolic annular peak velocities (E' and A').<sup>63,65,66,69-73</sup> Additionally, 2-dimensional speckle tracking techniques demonstrate the postsystolic shortening that suggests abnormal myocardial regional deformation as a response of chronic pressure overload in early-onset FGR.<sup>74</sup> Taking all together, we believe that fetal echocardiography identifies a high-risk group within the FGR fetuses who could be targeted for early screening of blood pressure and other cardiovascular risk factors later in life and for promoting healthy diet and physical exercise.<sup>58</sup> Finally, biomarkers of cardiac dysfunction like B-type natriuretic peptide<sup>66,71</sup> and markers that reflect cardiac injury, such as troponin,<sup>69,75</sup> are increased in the cord blood of growth-restricted fetuses in both early and late-onset FGR in a severity-dependent manner.<sup>63,67</sup>

### Postnatal persistence of cardiovascular remodeling associated to FGR

Echocardiography in FGR neonates reveals similar changes to those in fetuses that include cardiac morphometry (eg, dilated left atria and interventricular septal hypertrophy), diastolic (reduced absolute E and A wave velocities, higher E/A ratio, and prolonged isovolumic relaxation time), and systolic function

(reduced contractility and cardiac output).<sup>69-71</sup> Likewise, other studies reported impaired global longitudinal strain and regional asynchrony at 2–5 days of life,<sup>76</sup> systolic and diastolic cardiac dysfunction<sup>77</sup>, and increased cord blood serum concentrations of B-type natriuretic peptide.<sup>78</sup> Regarding vascular changes, FGR neonates have increased blood pressure,<sup>79</sup> arterial stiffness,<sup>79-81</sup> and aortic intima–media thickness (IMT), which is a marker of preclinical atherosclerosis.<sup>82,83</sup>

Cardiovascular changes associated to FGR persist also into childhood (Figure 2). Remarkably, both early- and late-onset forms of FGR and SGA are associated with cardiac remodeling. Children with both, early and late-onset FGR, have more globular hearts, reduced longitudinal motion, and impaired relaxation in early and late childhood.<sup>57</sup> Children with milder late-onset FGR show reduced longitudinal motion, apparently compensated by increased radial function, although early-severe FGR cases fail to show the compensatory increase in radial motion, which leads to reduced stroke volume accompanied by a compensatory increase in heart rate to maintain cardiac output.<sup>56,57</sup> Significant vascular changes have also been reported that include microvascular endothelial dysfunction and increased blood pressure and IMT.<sup>56,57,84</sup> Furthermore, autopsy studies of children 1–13 years old demonstrated atherosclerotic lesions in the aorta, which is associated inversely with birthweight.<sup>85</sup>

A recent study reported persistence of FGR-associated cardiac remodeling until preadolescence (8–12 years old), with more spherical ventricles, reduced longitudinal motion, and impaired relaxation.<sup>86</sup> Literature on vascular structure and function in adolescents and young adults with FGR is controversial. A Swedish cohort showed smaller aortic dimensions in young adults born with severe FGR.<sup>87,88</sup> Two large cohorts recently have found no association with arterial wall thickening (IMT) at 11–19 years old.<sup>89,90</sup> Large population studies seem to confirm a significant inverse correlation between low birthweight and

blood pressure in people of all ages.<sup>91</sup> However, this association is of little magnitude (an increase of 1–4 mm Hg), which could explain the absence of significant differences in small sample sizes.

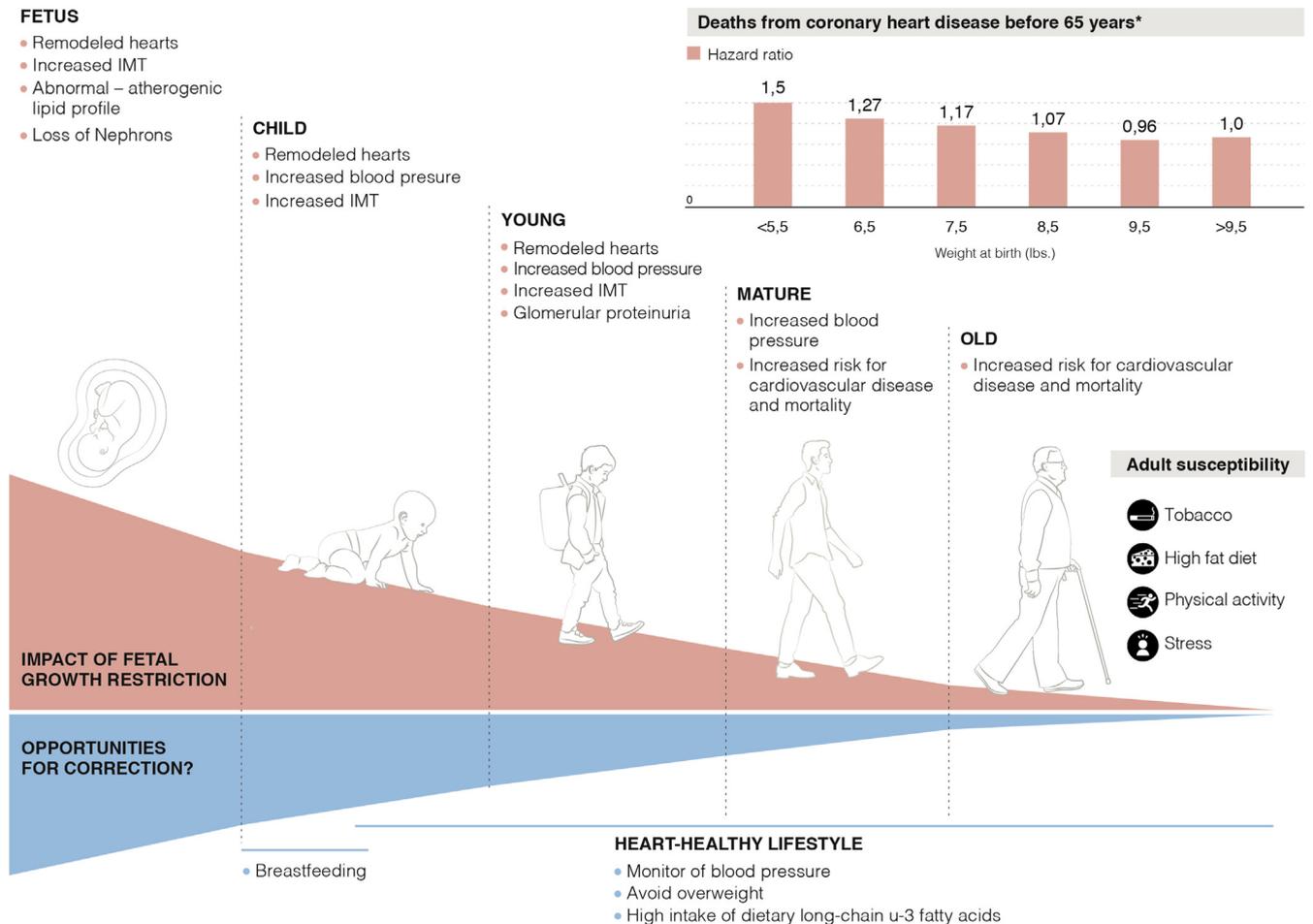
### CVD in adults born with FGR

Aside from retrospective epidemiologic evidence, there are very few prospective studies in former low birthweight adults. The Cardiovascular Risk in Young Finns study was initiated in 1980 and enrolled 3596 children and adolescents aged 3–18 years.<sup>92</sup> At an average of 31 years old, those children born SGA (<10th percentile) had markedly greater triglycerides, low density lipoprotein cholesterol, systolic blood pressure, and IMT compared with controls.<sup>93</sup> In the most recent follow-up evaluation (34–49 years), there were subtle differences in heart size and lower left ventricular stroke volume, with normal ventricular sphericity indices, diastolic function, and blood pressure in SGA at term.<sup>94</sup> The Enigma study, a long-term follow-up study of 882 young individuals from the United Kingdom, reported a small increase in systolic blood pressure and central pulse pressure in young adults (mean age, 21 years) born SGA (<9th percentile).<sup>95</sup> However, this association disappeared after adjustment for body size.<sup>95</sup> Similar findings have been reported in a longitudinal follow-up study from the United States that described 20-year-old young adults born with very low birthweight (<1500 g) between 1977 and 1979.<sup>96</sup>

Interpretation of these studies is challenging, taking into account the multiple influences that occur during the life of these individuals and the inherent limitations in the accuracy of obstetric information. In any event, available data suggest that, as life progresses, multiple factors seem to intervene, which as a whole attenuate the differences observed in FGR both in utero and during early life. Whether there are specific subgroups where cardiovascular differences persist or worsen remain open questions for future research, as briefly discussed later on this review.

FIGURE 2

## Hypotheses on the potential influence of prenatal environment on the risk of cardiovascular disease



Epidemiologic evidence that supports the association between fetal growth and cardiovascular risk (**upper panel**). A hypothesis on the potential combination of the prenatal effects of fetal growth restriction with cardiovascular health and risk factors during lifetime and the potential influence of preventive strategies. \*Calculated from<sup>4</sup>.

IMT, intima media thickness.

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### Other factors that influence the developmental origins of CVD

Besides FGR, prematurity is a common cause of low birthweight. Preterm birth is also linked to cardiac remodeling (shorter and smaller ventricles with increased mass),<sup>97</sup> higher blood pressure later in life<sup>98</sup> and insulin resistance.<sup>99,100</sup> Furthermore, in a nationwide Swedish cohort study that included >2.6 million live births, Carr et al<sup>101</sup> have provided the first evidence that preterm birth increases the risk of clinical heart failure during childhood and adolescence. A relevant finding of The Cardiovascular Risk in

Young Finns study is the discrimination between birthweight and prematurity in the susceptibility to CVDs.<sup>92</sup> Reduced fetal growth and preterm birth increased independently the severity of subclinical carotid atherosclerosis and reduced arterial endothelial function in early adulthood.<sup>93</sup> However, this association was most pronounced in those born preterm with FGR; for those born preterm without FGR, vascular markers did not differ from controls, which indicated that impaired fetal growth drives the association of preterm birth with poor vascular health, as opposed to

prematurity per se.<sup>93</sup> In addition, a recent study that included only preterm gestations (delivered at 30 weeks gestation) has shown that, 10 days after birth, infants with FGR have higher systolic blood pressure and maximum aorta intima-media thickness compared with preterm AGA infants.<sup>102</sup> These studies suggest that the mechanisms that program increased cardiovascular risk after preterm birth differ from those that contribute to increased risk in those born low birthweight but at full term.

Preeclampsia is often associated to FGR and prematurity. Interestingly,

offspring of preeclamptic pregnancies have increased blood pressure during childhood<sup>103,104</sup> and higher risk of stroke later in life.<sup>105</sup> A 20-year follow-up study found that preterm offspring of hypertensive pregnancies have evidence of endothelial dysfunction and greater subclinical atherosclerosis. The authors postulated that abnormal vascular development in the fetus in response to the same placenta-related factors that affect the mother might represent the underlying mechanism.<sup>106</sup> Other factors such as maternal obesity<sup>107</sup> and diabetes mellitus<sup>108</sup> have been also postulated as potential factors that influence fetal metabolic programming and cardiovascular remodeling. However, the experimental evidence that supports its role in CVD programming is limited compared with that with FGR, and long-term follow-up studies have discredited the role of some such as maternal diabetes mellitus.<sup>109,110</sup> The extent of the influence of these other perinatal factors in the individual susceptibility to CVD may be established in response to the intrauterine milieu or because of genetic variation that determines both general and vascular development of the fetus.

### Biologic Basis for Fetal Cardiovascular Programming

#### FGR and cardiac remodeling at organ, cellular, and subcellular level

The biologic basis for fetal programming derives from copious evidence from animal experimentation, with the use of animal models of ligature of the uteroplacental vessels, maternal hypoxia, reduction in maternal food intake or protein restriction, and finally, glucocorticoid exposure. Adult offspring of pregnant rats that were subjected to undernutrition develop obesity, hyperinsulinemia, and hyperleptinemia,<sup>111</sup> specifically in the presence of inactivity and a high-fat diet.<sup>112</sup> Animal models of maternal nutrient deprivation reported reduced number of cardiomyocytes at birth,<sup>113</sup> increased myocardial interstitial fibrosis,<sup>114</sup> expression changes of profibrotic genes and structural cardiovascular abnormalities,<sup>115</sup> and, importantly, impairment of recovery after myocardial

ischemia in the offspring.<sup>116</sup> Cardiac hypertrophy and coronary artery vascular reactivity is also evident in lambs born to ewes undernourished during early gestation.<sup>117</sup> Maternal food restriction also induces reduced glomerular number<sup>118</sup> and structural changes (remodeling) in smooth muscle content of small and large vessels in neonatal and young adult rat offspring.<sup>119</sup> Studies that mimic placental insufficiency by reduction of uteroplacental vasculature have reproduced biometric and cardiovascular changes of human FGR, such as increased ductus venous pulsatility, more spherical ventricles, reduced longitudinal motion, and presence of postsystolic shortening.<sup>120,121</sup>

Experimental FGR models have shown the extensive variety of cellular and subcellular changes induced by this condition, which include reduced number of cardiomyocytes, increased cardiomyocyte volume, reduction in myocardium microvascularization,<sup>122</sup> shorter sarcomeres, mitochondrial rearrangement, and altered gene expression related to energy and oxygen homeostasis.<sup>123,124</sup> Reduced sarcomere length have also been reported in human fetuses.<sup>125</sup> Other studies that focused on chronic hypoxia showed changes in fetal cardiac structure and function,<sup>126,127</sup> increased collagen content,<sup>128</sup> changes in cardiomyocyte proliferation and apoptosis,<sup>129</sup> postnatal changes in the isoforms of proteins that are important for the sarcomeric structure, including titin and myosin,<sup>130,131</sup> and increased cardiac susceptibility to ischemia reperfusion.<sup>132,133</sup>

#### Molecular mechanisms of fetal programming: epigenetics

Epigenetic changes have been postulated as the most important mechanism driving fetal programming.<sup>134</sup> Individuals prenatally exposed to the Dutch famine of 1944-45 had, six decades later, less DNA methylation of the imprinted insulin growth factor-2 gene compared with their unexposed, same-sex siblings.<sup>135</sup> Clinical studies have reported that the DNA methylation pattern in cells from cord blood<sup>136,137</sup> and placenta<sup>138</sup> between FGR human

pregnancies and controls is different, affecting genes involved in metabolism and adipose tissue differentiation. Importantly, the phenotypic effects of epigenetic modifications during development may not manifest until later in life, especially if they affect pathways of genes that modulate responses to environmental challenges, such as a high-fat diet.<sup>139</sup>

The influence of the prenatal environment in the epigenome has also been shown in experimental studies. A caloric-dense maternal diet has the ability to generate epigenetic effects on the offspring, altering fetal chromatin structure in primates.<sup>140</sup> Moreover, maternal undernutrition leads to long-term cholesterol dysregulation in the offspring via epigenetic mechanisms,<sup>141</sup> modifies gene expression of fetal renal transcription and growth factors,<sup>47</sup> and can alter permanently the expression of miRNAs in the aortas of newborn and aging rat offspring.<sup>142</sup> These epigenetic marks may also be transmitted to future generations.<sup>134,143</sup> This effect has also been demonstrated in animal models, showing that fetal adaptations such as endothelial dysfunction, hypertension, and insulin resistance are passed to the second and third generation of undernourished pregnant rats.<sup>144</sup>

The relevance of epigenetics in the adaptation to chronic cardiac failure has been highlighted in human adults, with distinct reported signatures of DNA methylation in cardiac tissue.<sup>145,146</sup> A recent analysis of the DNA methylome from cardiomyocytes of neonatal healthy, adult, and adult with failing heart revealed a dominant role for DNA methylation as a highly dynamic and reversible process during cardiomyocyte development, postnatal maturation, and disease.<sup>147</sup> In fetal life, treatment of pregnant rats with hypoxia leads to DNA hypermethylation that has been associated with early transition from mono- to binucleate cardiomyocyte, which reduces the number of cardiomyocytes in the developing heart,<sup>148</sup> and an increase in the susceptibility to ischemic injury in the offspring.<sup>149</sup> These considerations point to epigenetic processes

that play a key role in the developmental origins of CVD.

### Clinical Implications, Open Questions, and Opportunities for Research

The evidence summarized herein supports that FGR induces cardiovascular programming and remodeling, and that it is plausible that these changes pose an increased risk for CVD later in life. However, whether and how other factors that appear later in life interact with this predisposition to evolve to clinical CVD remains a subject of research. The “second hit” hypothesis, which is well accepted in fields such as human oncology, postulates that a genetic/epigenetic predisposition requires a second insult to manifest as clinical disease. Therefore, it is not unreasonable to postulate that cardiovascular sub-clinical remodeling in growth-restricted fetuses entails a higher predisposition, which needs to be combined with other factors to evolve to clinically relevant disease. And hence, some of the structural and functional changes that result from fetal programming could be corrected or further deviated, depending on other events or exposures during life.

In combination with this idea, a second important aspect that needs to be addressed by future research is the existence of windows of opportunity (Figure 2). As shown in animal models, changes in metabolism or epigenetic patterns that are determined by prenatal exposure are correctable if the intervention is introduced very early in life, but not later.<sup>150-153</sup> Regardless of whether there is a well-defined period, a “window of opportunity” that “closes” later in life, or just a steady decline of the opportunity for correction as the individual matures, evidence suggests that early life interventions can have strong effects on the cardiovascular changes that are associated with FGR. Key putative early life intervention strategies that may improve or restore vascular and cardiac health in a childhood that was affected by FGR include maintenance of healthy weight, promotion of breastfeeding,<sup>154</sup> and dietary

interventions.<sup>155,156</sup> Observational and in-vivo studies indicate that breastfeeding and consumption of a diet with a high polyunsaturated:saturated fat ratio in early childhood improves cardiovascular remodeling in individuals born with FGR.<sup>37,154</sup> Similarly, dietary consumption of either marine (eicosapentaenoic acid) and docosahexaenoic acid or plant-derived ( $\alpha$ -linolenic acid) omega-3 fatty acids appear to have specific hemodynamic and vascular benefits in children and adolescents who were born SGA, but not in children who were born with normal birthweight.<sup>90,156,157</sup>

Therefore, important challenges for future research are to ascertain the mechanistic pathways whereby fetal cardiovascular programming might lead to CVD in adulthood. Although it is likely that, as a whole, the effects of FGR on adult cardiovascular mortality rate are not huge, the identification of specific subgroups at higher risk, and especially the characterization of lifestyle factors that promote accelerated progression to CVD disease in subjects who experienced FGR, could have a strong influence on their quality of life. Considering that FGR affects a large share of the population, the possibility of reducing morbidity in only a fraction of these patients could be remarkable.

In summary, FGR has a strong influence in cardiovascular health, opening opportunities to improve public health by the identification of perinatal factors that can determine strongly the individual's health and potentially accelerate the implementation of preventive strategies starting from fetal or early postnatal life. ■

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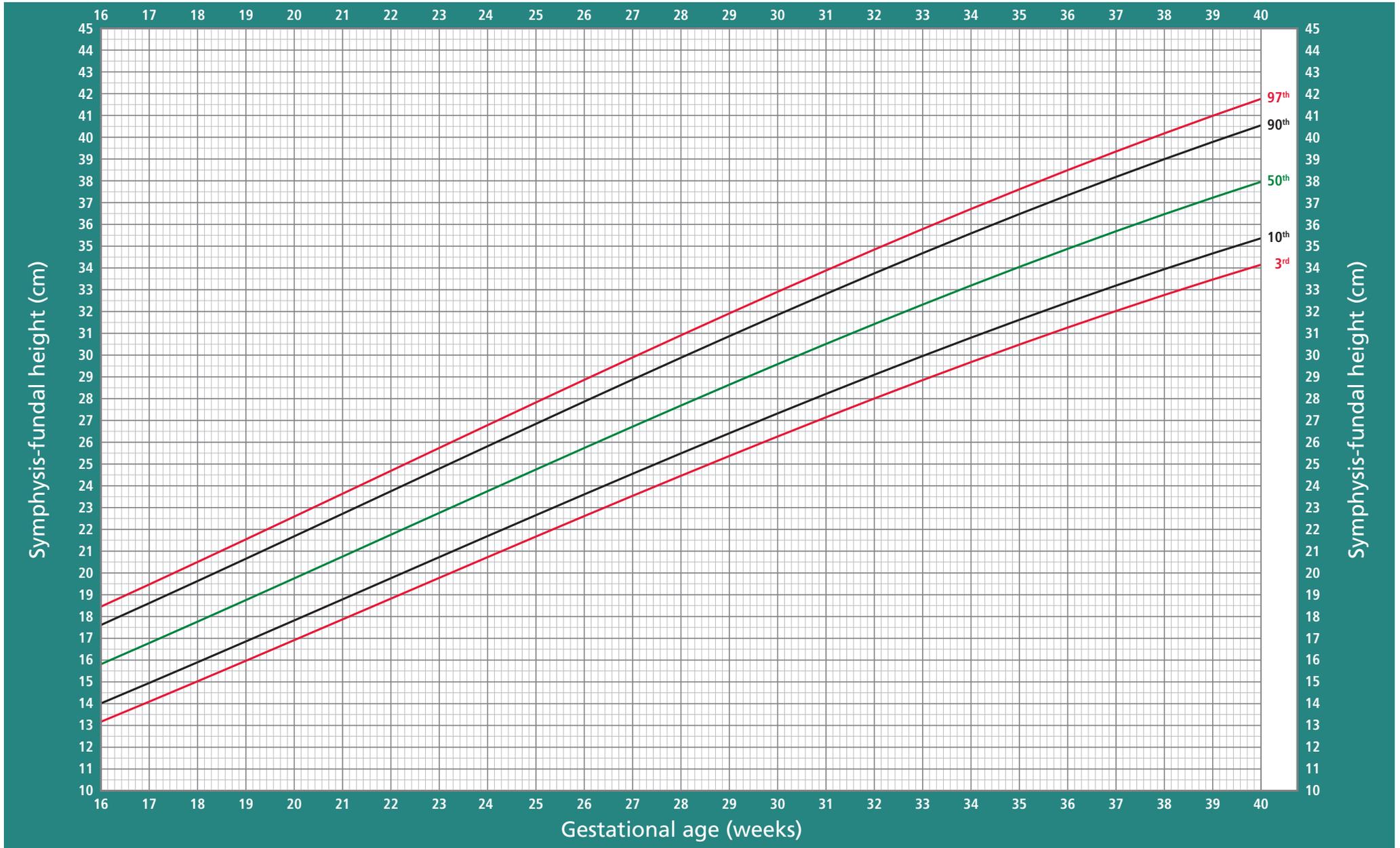
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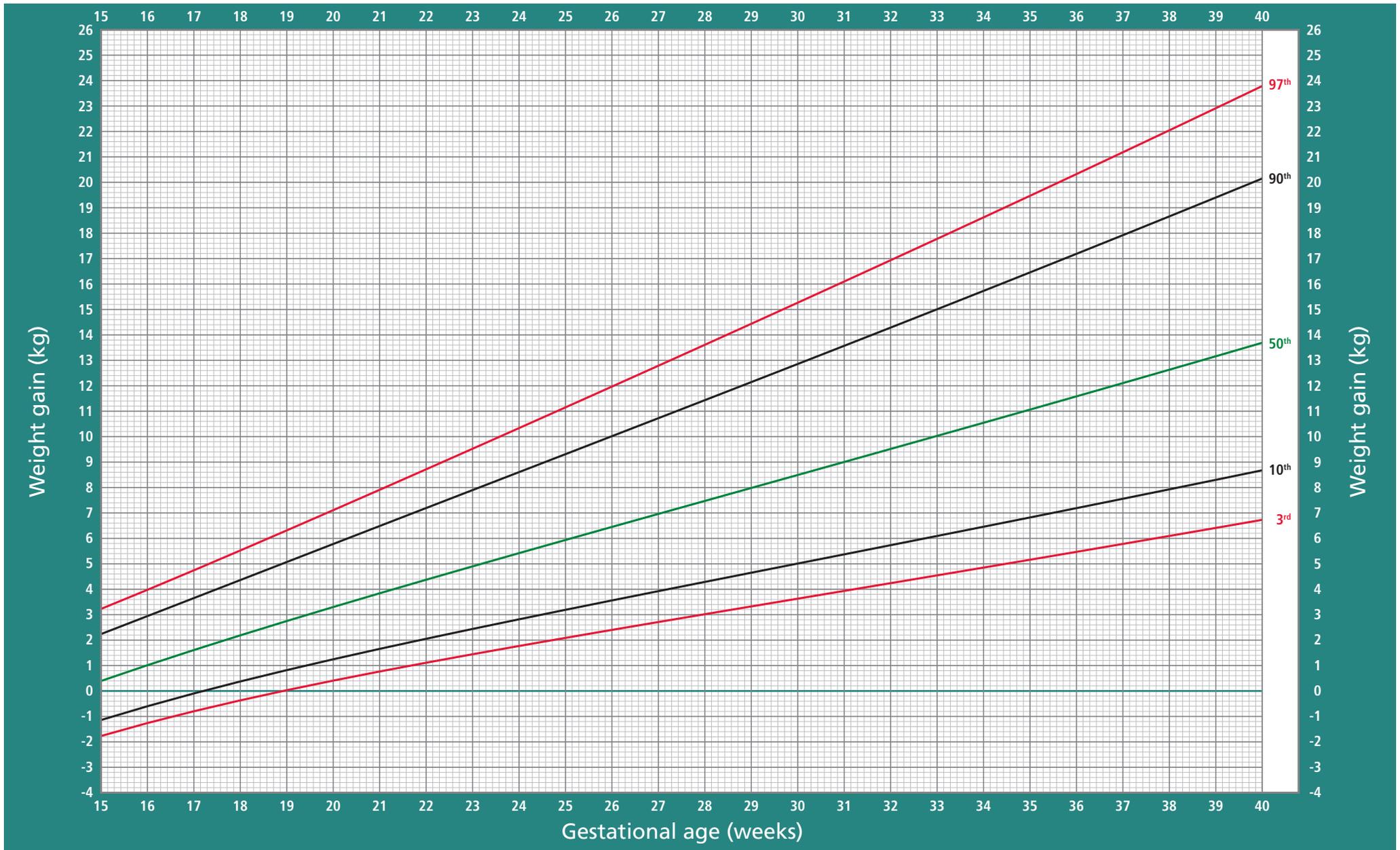
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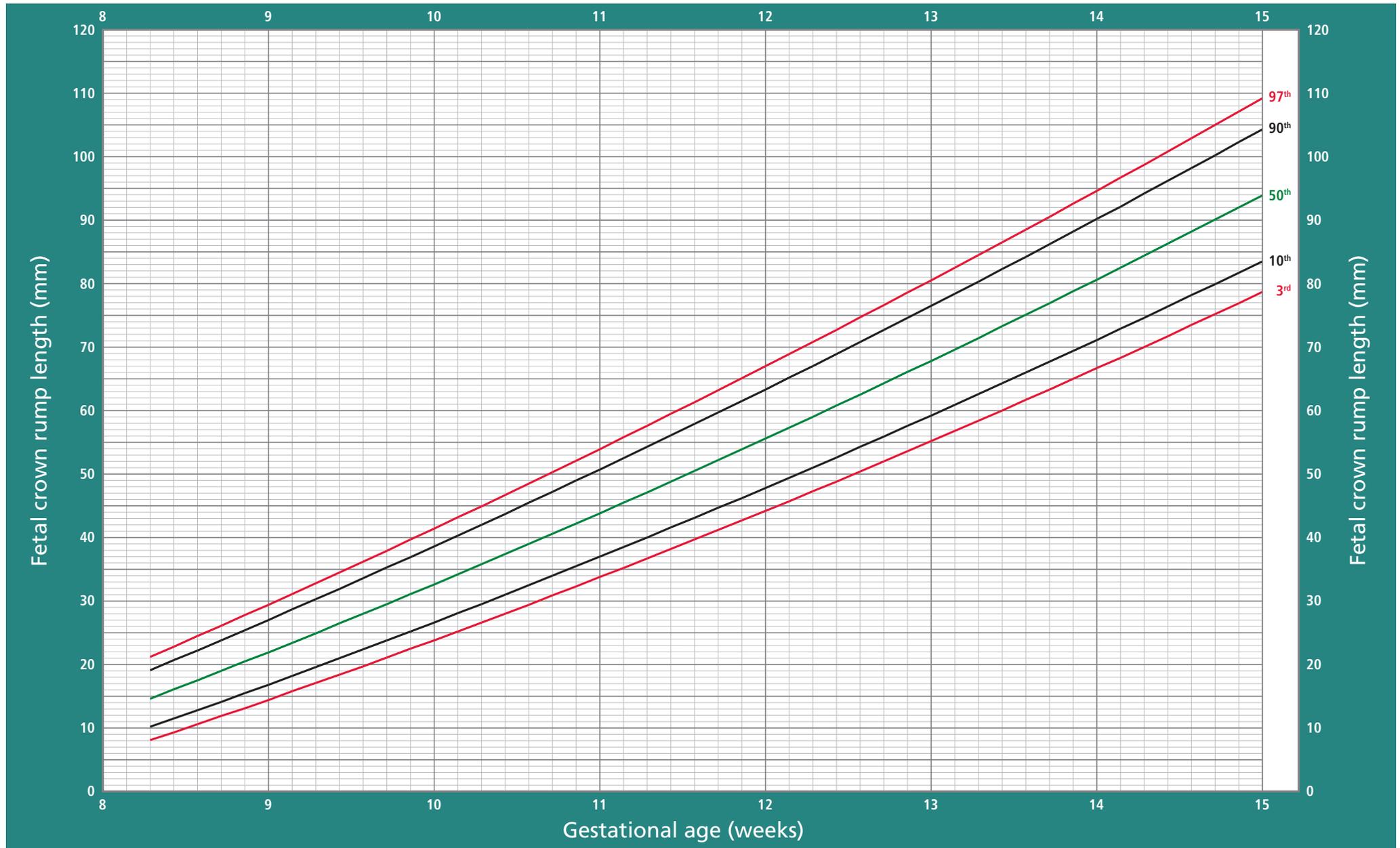
# International Symphysis-Fundal Height Standards



# International Gestational Weight Gain Standards



# International Standards for Fetal Crown Rump Length by Gestational Age

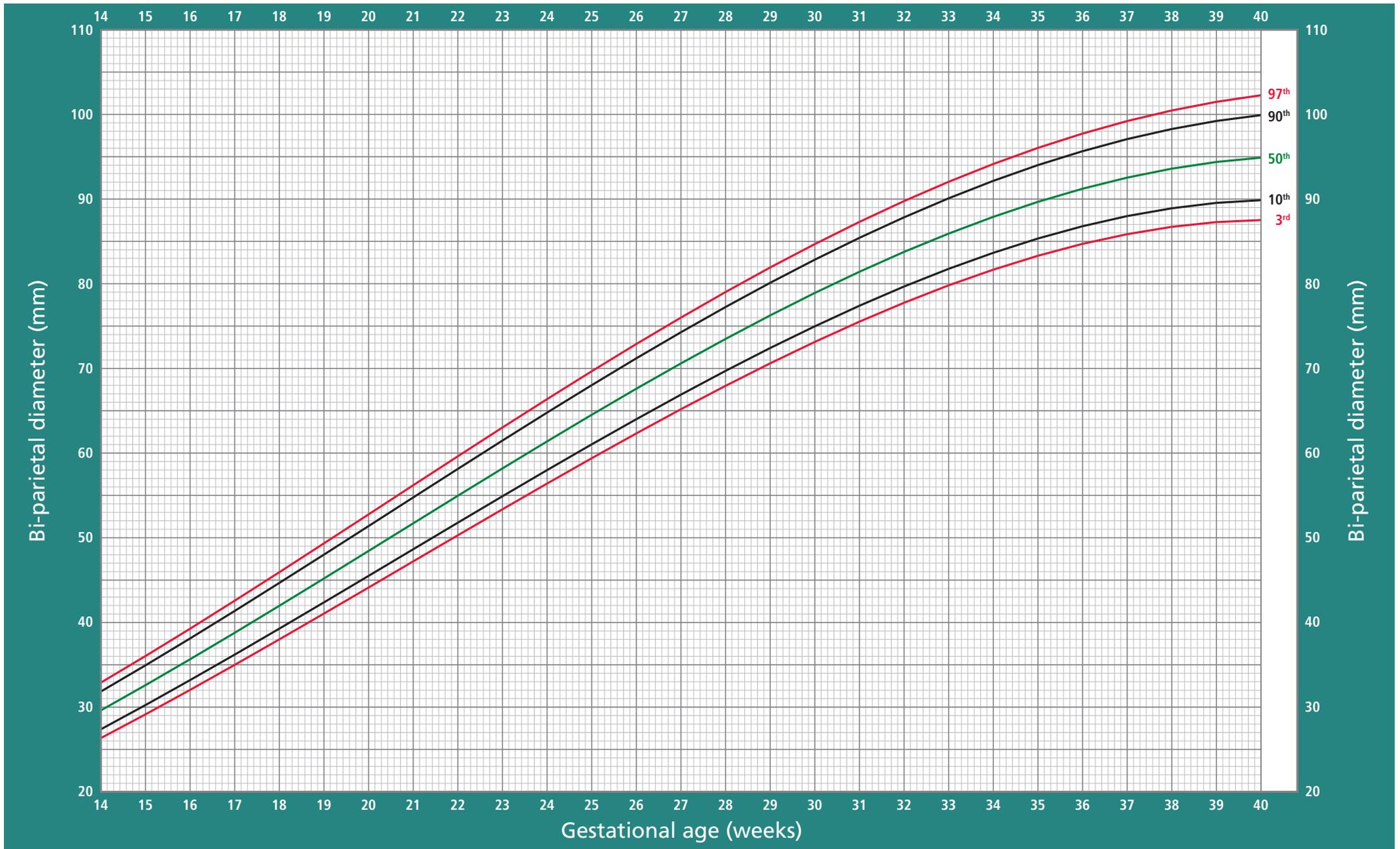


# International Standards for Pregnancy Dating based on INTERGROWTH-21st Measurements of Crown-Rump Length (CRL)

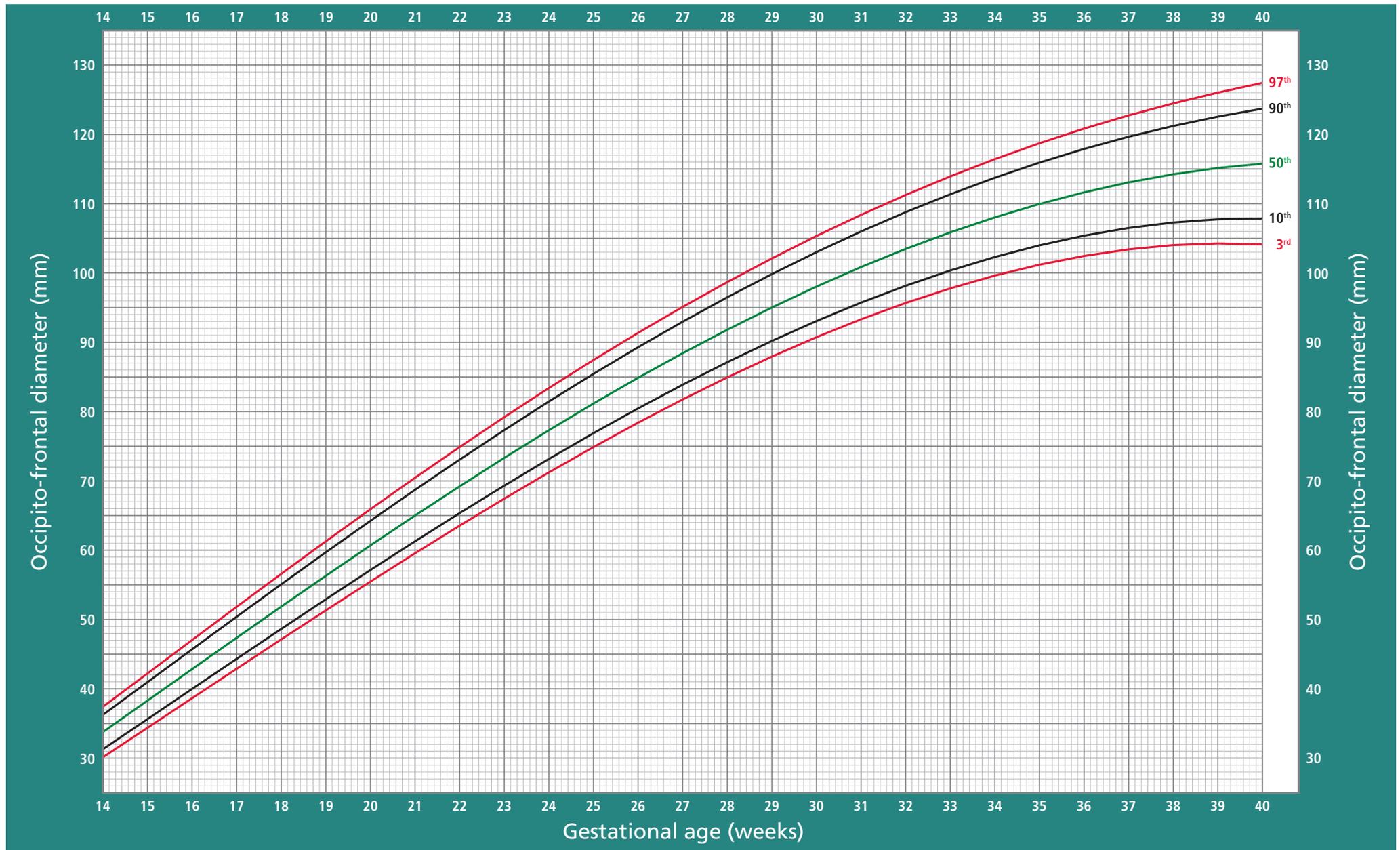


CRL (mm)	Gestational age (weeks)					CRL (mm)	Gestational age (weeks)				
	3 <sup>rd</sup>	10 <sup>th</sup>	Centiles				3 <sup>rd</sup>	10 <sup>th</sup>	Centiles		
			50 <sup>th</sup>	90 <sup>th</sup>	97 <sup>th</sup>				50 <sup>th</sup>	90 <sup>th</sup>	97 <sup>th</sup>
15	7+5	7+6	8+3	8+6	9+1	56	11+1	11+3	12+1	12+5	13+0
16	7+5	8+0	8+3	9+0	9+1	57	11+2	11+4	12+1	12+6	13+1
17	7+6	8+1	8+4	9+1	9+2	58	11+2	11+4	12+2	12+6	13+1
18	8+0	8+1	8+5	9+1	9+3	59	11+3	11+5	12+2	13+0	13+2
19	8+0	8+2	8+6	9+2	9+4	60	11+3	11+5	12+3	13+0	13+2
20	8+1	8+3	8+6	9+3	9+4	61	11+4	11+6	12+3	13+1	13+3
21	8+2	8+3	9+0	9+4	9+5	62	11+4	11+6	12+4	13+1	13+4
22	8+2	8+4	9+1	9+4	9+6	63	11+5	12+0	12+4	13+2	13+4
23	8+3	8+5	9+1	9+5	10+0	64	11+5	12+0	12+5	13+3	13+5
24	8+4	8+5	9+2	9+6	10+0	65	11+6	12+1	12+6	13+3	13+5
25	8+4	8+6	9+3	9+6	10+1	66	11+6	12+1	12+6	13+4	13+6
26	8+5	9+0	9+3	10+0	10+2	67	12+0	12+2	13+0	13+4	14+0
27	8+6	9+0	9+4	10+1	10+3	68	12+0	12+2	13+0	13+5	14+0
28	8+6	9+1	9+5	10+1	10+3	69	12+1	12+3	13+1	13+5	14+1
29	9+0	9+2	9+5	10+2	10+4	70	12+1	12+3	13+1	13+6	14+1
30	9+0	9+2	9+6	10+3	10+5	71	12+2	12+4	13+2	14+0	14+2
31	9+1	9+3	10+0	10+3	10+5	72	12+2	12+4	13+2	14+0	14+2
32	9+2	9+3	10+0	10+4	10+6	73	12+3	12+5	13+3	14+1	14+3
33	9+2	9+4	10+1	10+5	11+0	74	12+3	12+5	13+3	14+1	14+4
34	9+3	9+5	10+2	10+5	11+0	75	12+4	12+6	13+4	14+2	14+4
35	9+3	9+5	10+2	10+6	11+1	76	12+4	13+0	13+4	14+2	14+5
36	9+4	9+6	10+3	11+0	11+2	77	12+5	13+0	13+5	14+3	14+5
37	9+5	9+6	10+3	11+0	11+2	78	12+5	13+1	13+6	14+4	14+6
38	9+5	10+0	10+4	11+1	11+3	79	12+6	13+1	13+6	14+4	14+6
39	9+6	10+1	10+5	11+2	11+4	80	12+6	13+2	14+0	14+5	15+0
40	9+6	10+1	10+5	11+2	11+4	81	13+0	13+2	14+0	14+5	15+1
41	10+0	10+2	10+6	11+3	11+5	82	13+0	13+3	14+1	14+6	15+1
42	10+0	10+2	10+6	11+4	11+5	83	13+1	13+3	14+1	14+6	15+2
43	10+1	10+3	11+0	11+4	11+6	84	13+1	13+4	14+2	15+0	15+2
44	10+1	10+3	11+1	11+5	12+0	85	13+2	13+4	14+2	15+0	15+3
45	10+2	10+4	11+1	11+5	12+0	86	13+2	13+5	14+3	15+1	15+3
46	10+3	10+5	11+2	11+6	12+1	87	13+3	13+5	14+3	15+1	15+4
47	10+3	10+5	11+2	12+0	12+2	88	13+3	13+6	14+4	15+2	15+4
48	10+4	10+6	11+3	12+0	12+2	89	13+4	13+6	14+4	15+3	15+5
49	10+4	10+6	11+4	12+1	12+3	90	13+4	14+0	14+5	15+3	15+6
50	10+5	11+0	11+4	12+1	12+3	91	13+5	14+0	14+5	15+4	15+6
51	10+5	11+0	11+5	12+2	12+4	92	13+5	14+1	14+6	15+4	16+0
52	10+6	11+1	11+5	12+3	12+5	93	13+5	14+1	14+6	15+5	16+0
53	10+6	11+1	11+6	12+3	12+5	94	13+6	14+1	15+0	15+5	16+1
54	11+0	11+2	11+6	12+4	12+6	95	13+6	14+2	15+0	15+6	16+1
55	11+0	11+3	12+0	12+4	12+6						

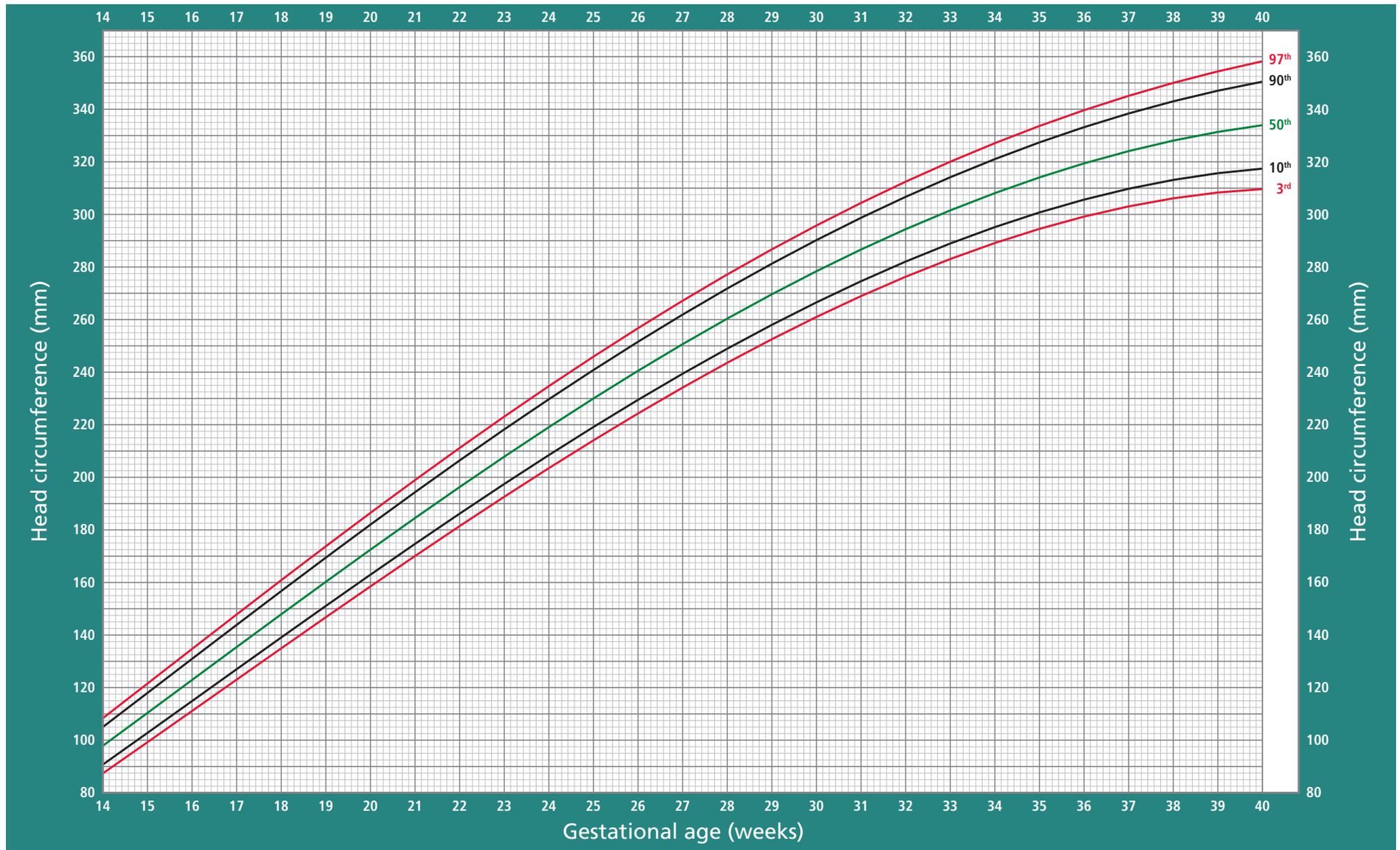
# International Fetal Growth Standards Bi-Parietal Diameter



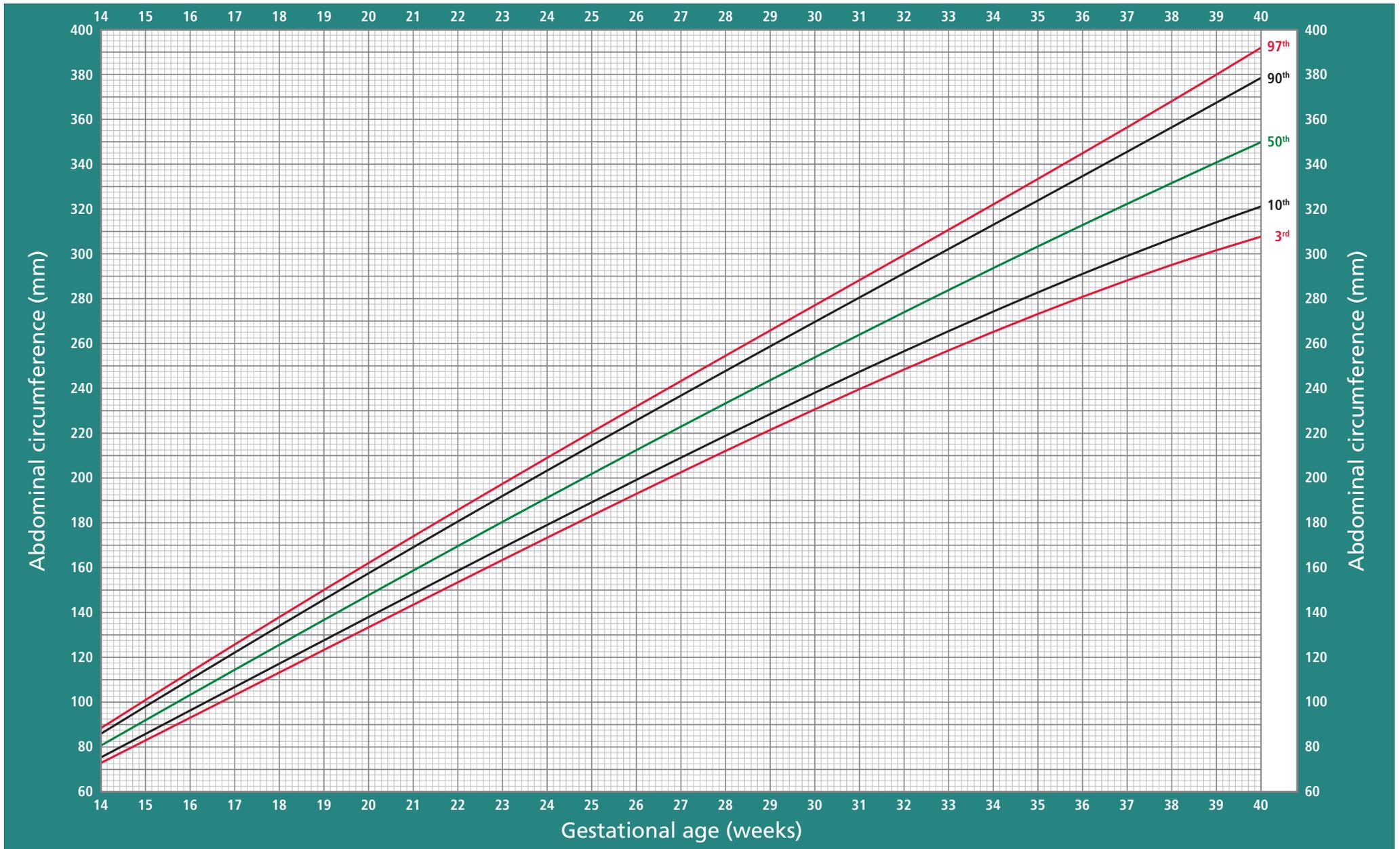
# International Fetal Growth Standards Occipito-Frontal Diameter



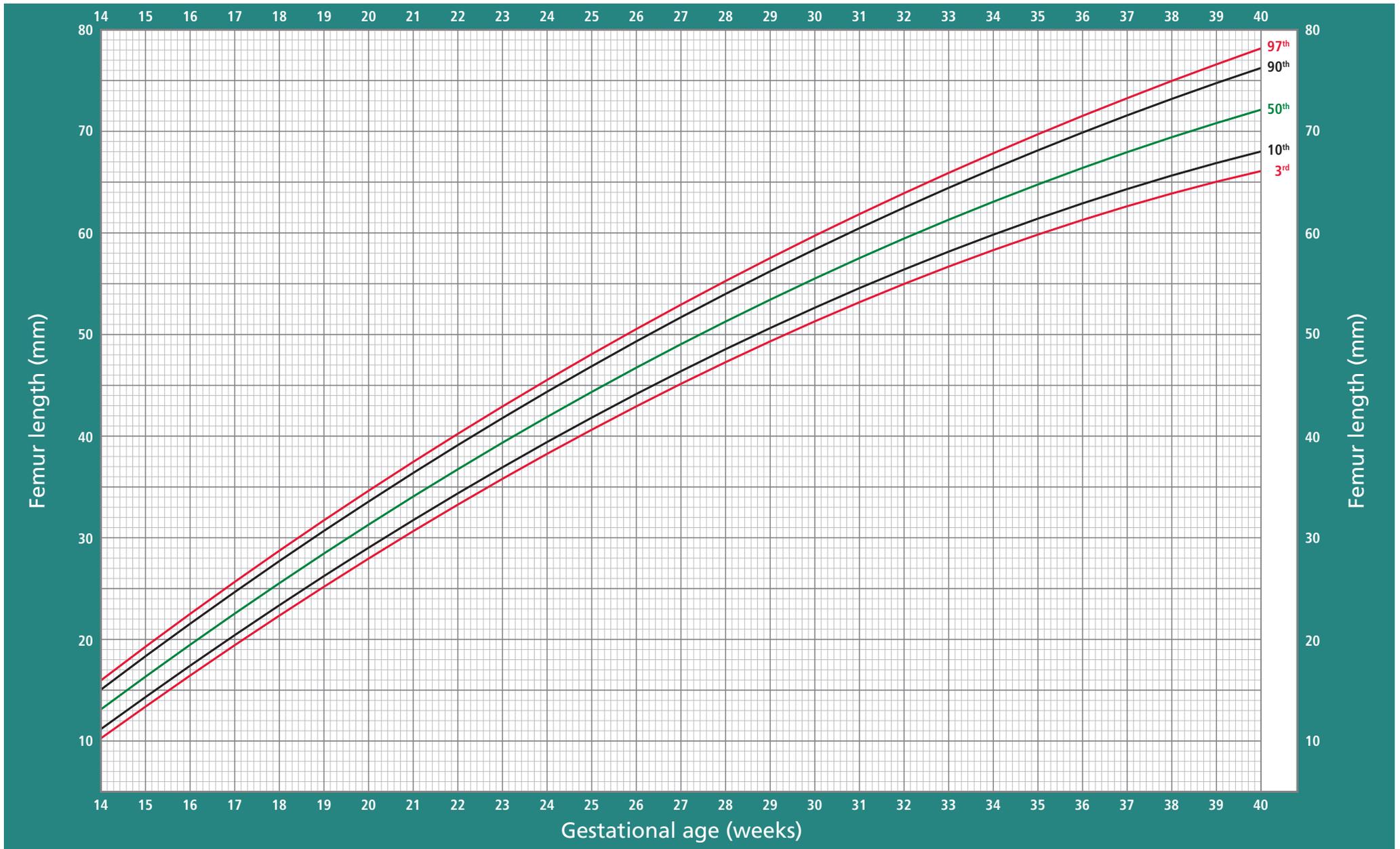
# International Fetal Growth Standards Head Circumference



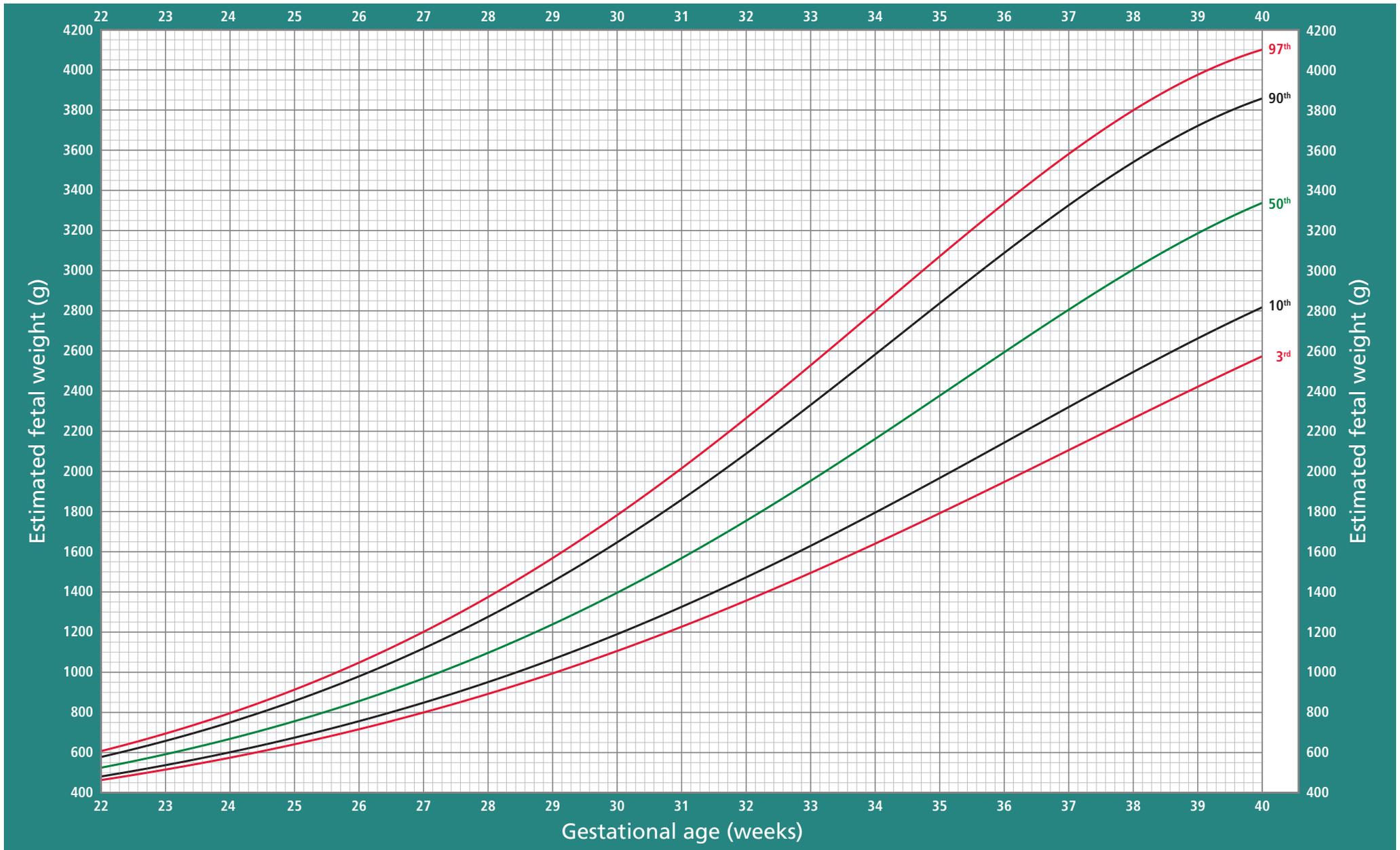
# International Fetal Growth Standards Abdominal Circumference



# International Fetal Growth Standards Femur Length



# International Fetal Growth Standards Estimated Fetal Weight





## Bi-Parietal Diameter (mm)

Gestational age (exact weeks)	Centiles						
	3 <sup>rd</sup>	5 <sup>th</sup>	10 <sup>th</sup>	50 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	97 <sup>th</sup>
14	26.3	26.7	27.4	29.6	31.8	32.5	32.9
15	29.1	29.6	30.2	32.6	34.9	35.6	36.0
16	32.0	32.5	33.2	35.7	38.1	38.8	39.3
17	35.0	35.5	36.2	38.8	41.4	42.1	42.6
18	38.0	38.5	39.3	42.0	44.7	45.4	45.9
19	41.1	41.6	42.4	45.2	48.0	48.8	49.3
20	44.1	44.7	45.5	48.4	51.4	52.2	52.8
21	47.2	47.8	48.6	51.7	54.8	55.6	56.2
22	50.3	50.9	51.8	55.0	58.1	59.0	59.6
23	53.4	54.0	54.9	58.2	61.5	62.4	63.0
24	56.4	57.0	58.0	61.4	64.8	65.7	66.4
25	59.4	60.0	61.0	64.5	68.0	69.0	69.7
26	62.3	63.0	64.0	67.6	71.2	72.2	72.9
27	65.2	65.9	66.9	70.6	74.3	75.3	76.0
28	67.9	68.6	69.7	73.5	77.3	78.3	79.0
29	70.6	71.3	72.4	76.3	80.1	81.2	81.9
30	73.1	73.9	75.0	78.9	82.8	84.0	84.7
31	75.5	76.3	77.4	81.4	85.4	86.6	87.3
32	77.8	78.5	79.7	83.8	87.8	89.0	89.8
33	79.8	80.6	81.8	85.9	90.1	91.3	92.0
34	81.7	82.4	83.7	87.9	92.2	93.4	94.1
35	83.3	84.1	85.3	89.7	94.0	95.2	96.0
36	84.7	85.5	86.8	91.2	95.7	96.9	97.7
37	85.9	86.7	88.0	92.5	97.1	98.4	99.2
38	86.7	87.6	88.9	93.6	98.3	99.6	100.5
39	87.3	88.2	89.6	94.4	99.2	100.6	101.5
40	87.5	88.4	89.9	94.9	99.9	101.3	102.3

## Occipito-Frontal Diameter (mm)

Gestational age (exact weeks)	Centiles						
	3 <sup>rd</sup>	5 <sup>th</sup>	10 <sup>th</sup>	50 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	97 <sup>th</sup>
14	30.1	30.6	31.3	33.8	36.2	36.9	37.4
15	34.4	34.9	35.6	38.3	41.0	41.7	42.2
16	38.6	39.2	40.0	42.8	45.7	46.5	47.0
17	42.9	43.5	44.3	47.4	50.4	51.3	51.8
18	47.1	47.7	48.6	51.9	55.1	56.0	56.6
19	51.3	51.9	52.9	56.3	59.7	60.7	61.3
20	55.5	56.1	57.1	60.7	64.2	65.3	65.9
21	59.6	60.2	61.3	65.0	68.7	69.8	70.5
22	63.5	64.2	65.4	69.2	73.1	74.2	74.9
23	67.4	68.2	69.3	73.3	77.3	78.5	79.2
24	71.2	72.0	73.2	77.3	81.5	82.6	83.4
25	74.9	75.7	76.9	81.2	85.4	86.7	87.4
26	78.4	79.2	80.5	84.9	89.3	90.5	91.4
27	81.7	82.6	83.9	88.4	93.0	94.3	95.1
28	84.9	85.8	87.1	91.8	96.5	97.8	98.7
29	87.9	88.8	90.2	95.0	99.8	101.2	102.1
30	90.7	91.6	93.1	98.0	103.0	104.4	105.3
31	93.3	94.3	95.7	100.9	106.0	107.4	108.4
32	95.7	96.6	98.2	103.5	108.8	110.3	111.3
33	97.8	98.8	100.4	105.9	111.4	112.9	113.9
34	99.6	100.7	102.3	108.0	113.7	115.4	116.4
35	101.2	102.3	104.0	110.0	115.9	117.6	118.7
36	102.5	103.6	105.4	111.6	117.9	119.7	120.8
37	103.4	104.6	106.5	113.1	119.7	121.5	122.7
38	104.0	105.3	107.3	114.2	121.2	123.2	124.5
39	104.3	105.6	107.7	115.1	122.6	124.7	126.0
40	104.1	105.6	107.8	115.8	123.7	126.0	127.4



## Head Circumference (mm)

Gestational age (exact weeks)	Centiles						
	3 <sup>rd</sup>	5 <sup>th</sup>	10 <sup>th</sup>	50 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	97 <sup>th</sup>
14	87.4	88.7	90.7	97.9	105.0	107.1	108.4
15	99.2	100.6	102.8	110.4	118.0	120.1	121.5
16	111.1	112.6	114.9	122.9	130.9	133.2	134.7
17	123.0	124.6	127.0	135.4	143.9	146.3	147.8
18	134.9	136.6	139.1	147.9	156.7	159.2	160.9
19	146.8	148.5	151.1	160.3	169.5	172.1	173.8
20	158.5	160.2	163.0	172.5	182.0	184.7	186.5
21	170.1	171.9	174.7	184.5	194.3	197.1	199.0
22	181.4	183.3	186.2	196.3	206.4	209.3	211.2
23	192.6	194.5	197.5	207.8	218.2	221.2	223.1
24	203.5	205.4	208.5	219.1	229.7	232.7	234.7
25	214.1	216.0	219.1	230.0	240.8	243.9	245.9
26	224.3	226.3	229.5	240.5	251.6	254.7	256.7
27	234.1	236.2	239.4	250.7	261.9	265.1	267.2
28	243.6	245.7	248.9	260.4	271.8	275.1	277.2
29	252.5	254.7	258.0	269.6	281.3	284.6	286.7
30	261.0	263.2	266.5	278.4	290.2	293.6	295.8
31	268.9	271.1	274.6	286.6	298.7	302.1	304.4
32	276.3	278.5	282.1	294.4	306.7	310.2	312.5
33	283.0	285.3	288.9	301.5	314.1	317.7	320.0
34	289.1	291.5	295.2	308.1	321.0	324.7	327.1
35	294.5	296.9	300.8	314.1	327.4	331.2	333.6
36	299.2	301.7	305.6	319.4	333.2	337.1	339.6
37	303.1	305.7	309.8	324.1	338.4	342.5	345.1
38	306.1	308.9	313.1	328.1	343.0	347.3	350.0
39	308.3	311.2	315.7	331.4	347.1	351.5	354.4
40	309.6	312.7	317.4	333.9	350.5	355.2	358.3

## Abdominal Circumference (mm)

Gestational age (exact weeks)	Centiles						
	3 <sup>rd</sup>	5 <sup>th</sup>	10 <sup>th</sup>	50 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	97 <sup>th</sup>
14	72.9	73.8	75.3	80.6	85.9	87.4	88.4
15	82.9	84.1	85.8	91.9	98.1	99.8	100.9
16	93.0	94.3	96.3	103.2	110.1	112.1	113.4
17	103.1	104.5	106.7	114.4	122.1	124.3	125.7
18	113.2	114.8	117.2	125.6	134.0	136.4	138.0
19	123.3	125.0	127.6	136.7	145.8	148.4	150.1
20	133.4	135.2	138.0	147.7	157.5	160.3	162.1
21	143.4	145.3	148.3	158.7	169.1	172.0	174.0
22	153.5	155.5	158.6	169.6	180.6	183.7	185.7
23	163.4	165.6	168.9	180.4	192.0	195.3	197.4
24	173.3	175.6	179.0	191.2	203.3	206.8	209.0
25	183.2	185.5	189.1	201.8	214.5	218.1	220.5
26	192.9	195.4	199.1	212.4	225.7	229.5	231.9
27	202.6	205.1	209.1	222.9	236.8	240.7	243.2
28	212.1	214.7	218.8	233.3	247.8	251.9	254.5
29	221.4	224.2	228.5	243.6	258.7	263.0	265.8
30	230.6	233.5	238.0	253.8	269.6	274.1	277.0
31	239.6	242.6	247.4	263.9	280.5	285.2	288.3
32	248.4	251.6	256.5	273.9	291.3	296.3	299.5
33	256.9	260.3	265.5	283.8	302.2	307.4	310.7
34	265.2	268.7	274.3	293.6	313.0	318.5	322.0
35	273.2	276.9	282.8	303.3	323.8	329.6	333.4
36	280.8	284.8	291.0	312.8	334.6	340.9	344.9
37	288.1	292.4	299.0	322.3	345.5	352.1	356.4
38	295.1	299.6	306.7	331.6	356.4	363.5	368.1
39	301.6	306.5	314.1	340.8	367.4	375.0	379.9
40	307.7	312.9	321.1	349.8	378.5	386.7	392.0

# International Fetal Growth Standards



## Femur Length (mm)

Gestational age (exact weeks)	Centiles						
	3 <sup>rd</sup>	5 <sup>th</sup>	10 <sup>th</sup>	50 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	97 <sup>th</sup>
14	10.3	10.6	11.2	13.1	15.1	15.6	16.0
15	13.4	13.7	14.3	16.3	18.3	18.9	19.3
16	16.4	16.8	17.4	19.5	21.5	22.1	22.5
17	19.4	19.8	20.4	22.5	24.7	25.3	25.7
18	22.3	22.7	23.4	25.5	27.7	28.3	28.7
19	25.2	25.6	26.2	28.5	30.7	31.3	31.7
20	28.0	28.4	29.0	31.3	33.6	34.2	34.6
21	30.6	31.1	31.7	34.1	36.4	37.0	37.5
22	33.3	33.7	34.4	36.7	39.1	39.8	40.2
23	35.8	36.2	36.9	39.4	41.8	42.5	42.9
24	38.3	38.7	39.4	41.9	44.4	45.1	45.5
25	40.6	41.1	41.8	44.4	46.9	47.6	48.1
26	42.9	43.4	44.1	46.7	49.3	50.1	50.5
27	45.1	45.6	46.4	49.0	51.7	52.5	52.9
28	47.3	47.8	48.6	51.3	54.0	54.8	55.3
29	49.3	49.8	50.6	53.4	56.2	57.0	57.5
30	51.3	51.8	52.6	55.5	58.4	59.2	59.7
31	53.2	53.7	54.6	57.5	60.5	61.3	61.9
32	55.0	55.5	56.4	59.4	62.5	63.4	63.9
33	56.7	57.3	58.2	61.3	64.4	65.3	65.9
34	58.3	58.9	59.8	63.1	66.3	67.2	67.8
35	59.8	60.5	61.4	64.8	68.1	69.1	69.7
36	61.3	61.9	62.9	66.4	69.9	70.9	71.5
37	62.6	63.3	64.3	67.9	71.6	72.6	73.3
38	63.9	64.6	65.6	69.4	73.2	74.3	75.0
39	65.0	65.8	66.9	70.8	74.7	75.9	76.6
40	66.1	66.8	68.0	72.1	76.2	77.4	78.2

## Estimated Fetal Weight (g)

Gestational age (exact weeks)	Centiles						
	3 <sup>rd</sup>	5 <sup>th</sup>	10 <sup>th</sup>	50 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	97 <sup>th</sup>
22	463	470	481	525	578	596	607
23	516	524	538	592	658	680	695
24	575	585	602	669	751	778	796
25	641	654	674	756	858	891	913
26	716	732	757	856	980	1020	1048
27	800	818	849	969	1119	1168	1202
28	892	915	951	1097	1276	1335	1375
29	994	1021	1065	1239	1452	1521	1569
30	1106	1138	1190	1396	1647	1728	1783
31	1227	1265	1326	1568	1860	1953	2016
32	1357	1401	1473	1755	2089	2195	2266
33	1495	1547	1630	1954	2332	2450	2529
34	1641	1700	1795	2162	2583	2713	2800
35	1792	1860	1967	2378	2838	2978	3071
36	1948	2024	2144	2594	3089	3237	3335
37	2106	2190	2321	2806	3326	3480	3582
38	2265	2355	2495	3006	3541	3697	3799
39	2422	2516	2663	3186	3722	3876	3976
40	2574	2670	2818	3338	3858	4006	4101

Fetal Weight Estimation was undertaken using the INTERGROWTH-21st formula by Stirnemann et al. *Ultrasound Obstet Gynecol* 2016