Optimizing Natural Fertility
The Role of Lifestyle Modification

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KEYWORDS

- Natural fertility
- Preconception counseling
- Obesity
- Lifestyle modifications

KEY POINTS

- Preconception counseling allows health care providers to optimize maternal and neonatal outcomes before conception.
- Preconception counseling also provides a unique opportunity for health care providers to recommend, often simple, interventions to optimize natural fertility.
- Maternal obesity must be addressed during preconception counseling and include both patient education and recommendations regarding weight loss.
- The current body of literature examining lifestyle modifications and fertility is comprised of small cohort studies, most focus on polycystic ovarian syndrome, and use surrogate markers of fertility.
- Although the literature does support the improvement in ovulation and pregnancy rates with modest weight loss, the impact on live birth rates is not clear.
- Calorie restriction and exercise both seem to be beneficial in improving fertility; the optimal macronutrient content of a diet is not known.

INTRODUCTION

Human reproduction is notoriously inefficient, with average cycle fecundity averaging around 20%\textsuperscript{,1} Preconception counseling allows physicians to help patients frame expectations for conception by reviewing baseline fecundity rates. Additionally, physicians can help educate patients on methods to optimize their natural fertility (Box 1), in the absence of, or concern for, pathologic conditions, before recommending aggressive interventions.

Perhaps more importantly, patients presenting for preconception counseling allow their physician to have a powerful platform to recommend interventions to improve.

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overall health, in addition to improving maternal and neonatal outcomes before conception. The American Congress of Obstetrics and Gynecology (ACOG) has established clear recommendations for considerations during preconception counseling:

ACOG Preconception Guidelines 2005
1. Evaluate preexisting, uncontrolled, or undiagnosed maternal diseases
2. Review prior obstetric history

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**Box 1**

- Fertility declines with age
  - Women: 35 Men: 50
- Frequency of Intercourse
  - Intercourse every day to every other day yields highest cycle fecundability
- ‘Fertile Window’
  - 6 day interval ending on the day of ovulation
  - Peak fecundability when intercourse occurs within 2 days of ovulation
    - Declines dramatically on the day of presumed ovulation
- Monitoring Ovulation
  - Cervical mucus functioned as well or better than basal body temperature or urinary LH monitoring
  - Some evidence that LH detection kits decrease time to conception
- Coital Practices
  - No evidence that fecundability is affected by coital position
  - Mineral oil, canola oil, hydroxyethylcellulose based lubricants do not adversely affect sperm motility
    - Avoid water based lubricants (Astroglide®, KY Jelly®) due to affect on sperm motility
- Smoking
  - Increased risk of infertility, miscarriage
  - Reduced time to menopause (1–4 years)
  - Male fertility: smoking may decrease parameters in semen analysis
- Alcohol
  - No evidence that moderate consumption negatively impacts fertility
  - Can affect fetal development, thus consumption should cease at first signs of pregnancy
- Caffeine
  - Moderate consumption (1–2 cups of coffee/day) has no adverse effects on fertility or pregnancy outcomes
- Weight
  - Over and underweight at risk for infertility and increased time to conception

3. Review vaccination history  
4. Review medications, radiation exposure, and environmental hazards  
5. Review mental health issues  
6. Recommend folic acid 400 mcg/d or higher (4 mg/d) depending on risk factors  
7. Evaluate family history and genetic risk.

In the setting of the obesity epidemic, physicians will be faced with an obese patient desiring conception. Although most patients and physicians are aware of the above recommendations for those seeking pregnancy, as well as the effect of weight on fertility, many physicians struggle when recommending a “prescription for weight loss.”

The remainder of the article focuses on the available evidence regarding lifestyle modification (LSM) and fertility, and includes the aims listed in Box 2.

LSM improves fertility because it3–11

1. Decreases adipose tissue  
   a. Improves insulin sensitivity  
   b. Increases sex hormone–binding globulin (SHBG)  
   c. Increases ovulatory cycles  
   d. Improves pharmacodynamics of medications  
   e. Improves hypothalamic function

2. Improves metabolic function of remaining adipose tissue

3. Reduces inflammation.

Although there is biologic plausibility for LSM improving fertility, there has not yet been confirmation in the literature. There are few well-controlled, randomized studies to date that have evaluated the effects of LSM specifically on fertility. Many of the studies that address reproductive function are small cohort studies or observational trials with no placebo group, high dropout rates, and surrogate markers for fertility.

**OVULATION INDUCTION**

*Modest Weight Loss*

Several studies have documented the resumption of ovulation after only modest weight loss of 5% to 10% of total body weight.  

Crosignani and colleagues12 found resumption in spontaneous ovulation with small reductions in overall body weight. These investigators placed 33 women with obesity, chronic anovulation, infertility, and polycystic ovaries on a 1200 kcal diet and recommended regular exercise. The women were evaluated once they reached 5% and

<table>
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<th>Box 2</th>
<th>Aims of article</th>
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<tr>
<td>1. Investigate the effects of LSM in obese women, including those with PCOS on the following reproductive outcomes:</td>
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<td>a. Ovulation rates</td>
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<td>b. Pregnancy rates</td>
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<td>c. Live birth rates</td>
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<td>d. ART success</td>
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<td>2. Describe the available literature on the most effective diet and exercise regimens for improving fertility</td>
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10% total body weight loss. Twenty-five women lost at least 5% of their starting body weight and 11 women achieved 10% weight loss. Of the women who lost weight, 15 had resumption of ovulation. Among those women who did not lose the recommended weight, none experienced improvements in their menstrual cycles or conceived.

Only one study to date has studied obese, non-PCOS women. Clark and colleagues\textsuperscript{13} completed an observational cohort study with 13 obese, clomiphene citrate (CC)-resistant women, including five with PCOS, with at least a 2-year history of infertility. PCOS and CC resistance were not clearly defined. All participants delayed conventional fertility treatments to participate in a 6-month diet and exercise program. After 4 months, the cohort had a mean weight loss of 4.3 kg and 92% of the group had achieved ovulation at that time, as demonstrated by urinary pregnanediol results.

**Reduction in Centripetal Adipose Tissue**

Centripetal adipose tissue is more metabolically active than subcutaneous adipose tissue and contributes more to insulin resistance.\textsuperscript{14} Reductions in centripetal adipose tissue have been shown to (1) lower insulin resistance, (2) increase SHBG, and (3) potentially improve ovulation. Several studies have documented improved ovulation after reduction in centripetal adipose tissue (Table 1).

**LSM and Response to CC**

The traditional medication used to induce ovulation in women with eugonadotropic anovulatory infertility is CC. Success rates are as high as 80% but are lower for obese women.\textsuperscript{15} Palomba and colleagues\textsuperscript{16} hypothesized that short LSM would improve response to medication. They conducted a randomized, controlled, single-blinded cohort study that involved 96 overweight or obese women with PCOS who were CC-resistant. Resistance was defined as failure to ovulate after a maximum dose of 150 mg of CC. The women were randomized to one of three groups for 6 weeks: (1) hypocaloric diet with structured exercise training (SET), (2) observation with CC, and (3) hypocaloric diet with SET and CC (combination). The primary outcome was rate of ovulation. The diet was high protein (35% protein, 45% carbohydrate, 20% fat) and adjusted to create a 1000 kcal deficit per day. The exercise training was three sessions per week, in 30-minute increments, on a bicycle ergometer, with the workload adjusted to 60% and 70% of maximal oxygen consumption. The combination group had the highest rate of ovulation at 37.5% compared with the hypocaloric diet and SET group at 12.5% and the CC alone group at 9.4%.

**PREGNANCY RATES**

Even obese women who are ovulatory demonstrate increased time-to-conception, which suggests detrimental effects of obesity on fertilization or implantation.\textsuperscript{17}

**Modest Weight Loss**

Just as modest weight loss is beneficial for ovulation rates, a similar improvement is seen in pregnancy rates. In the hallmark study that evaluated LSM and fertility, Kiddy and colleagues\textsuperscript{18} demonstrated improved fertility after modest weight loss. They evaluated 24 obese patients with PCOS and placed them on a 1000 kcal, low-fat diet for 6 to 7 months. Five of the 11 women who had ovulatory dysfunction at baseline conceived after losing more than 5% of their total body weight.
<table>
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<tr>
<th>Author</th>
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<th>Intervention</th>
<th>Primary Outcome</th>
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<tr>
<td>Palomba et al,21 2008</td>
<td>Observational cohort</td>
<td>40 obese, infertile women with PCOS</td>
<td>24 wk structured exercise program (SET) vs diet SET = 3 times weekly exercise sessions on a bicycle ergometer for 30 min. with target VO2 60%–70% Diet = high protein (35% protein, 45% carbohydrate, 20% fat) and an 800 kcal total deficit per day</td>
<td>Pregnancy rate</td>
<td>No difference in PR When stratifying by intervention and by outcome: Ovulatory patients ↓ waist circumference &gt; non-ovulatory patients SET: −9.6 cm vs −2.5 cm *P &lt; .05; diet group: −9.4 cm vs −2.8 cm *P &lt; .05&lt;sup&gt;18&lt;/sup&gt;</td>
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<td>Thomson et al RCT</td>
<td>94 obese women with PCOS</td>
<td>20 wk of one of the following: 1. Hypocaloric, high protein diet (DO) 2. Diet and aerobic exercise (DA) 3. Diet and aerobic/resistance training (DC)</td>
<td>Weight loss Regardless of intervention, those who ovulated were more likely to have greater reductions in waist circumference and abdominal fat mass as determined by dual energy X-ray absorptiometry WC 13.4 vs 10.0 cm *P &lt; .02 and AbFM 0.5 vs 0.3 cm *P &lt; .05&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Huber-Buchholz et al,8 1999</td>
<td>Cohort</td>
<td>46 women with irregular menses</td>
<td>28 women received Group or individual diet and exercise counseling * 6 mo vs 18 controls</td>
<td>Ovulation</td>
<td>Women who ovulated after LSM were more likely to have reduced waist circumference and central abdominal fat than those that did not resume ovulation&lt;sup&gt;11&lt;/sup&gt;</td>
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<td>Kuchenbecker et al Cohort</td>
<td>22 anovulatory, infertile women with PCOS</td>
<td>LSM program * 6 mo: Individualized exercise Hypocaloric diet (500 kcal/day deficit)</td>
<td>Ovulation</td>
<td>At three months, the ovulatory women were more likely to have lost more intra-abdominal fat by CT scan (12% vs 5% *P = .002) These differences became even more pronounced when analyzed at 6 months. (18.5% vs 8.6% *P = .005)&lt;sup&gt;19&lt;/sup&gt;</td>
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Similarly, Crosignani and colleagues\(^\text{12}\) found improved pregnancy rates in a group of anovulatory, infertile, obese women with weight loss of only 5% of their total body weight.

Galletly and colleagues\(^\text{19}\) found similar improvements in pregnancy rates during fertility treatment after LSM in women who had modest weight loss (mean 6.2 kg \(\pm\) 4.5 kg).

A reduction in serum insulin with an associated increase in SHBG is the proposed mechanism behind the improvement in pregnancy rates after modest weight loss. Hollmann and colleagues\(^\text{20}\) demonstrated a pregnancy rate of nearly 30% after a 32-week LSM program in a cohort of obese, anovulatory patients after only modest weight loss. They related the improved pregnancy rates to improved glucose tolerance. Before the intervention, nearly 50% had impaired glucose tolerance; after LSM, only 4% had impaired glucose tolerance.

Palomba and colleagues\(^\text{21}\) demonstrated improved glucose metabolism in their group of obese, infertile women with PCOS after 24 weeks of LSM. As described previously, the women were randomized to a SET program or to dietary intervention. The SET group had greater reduction in fasting insulin and SHBG than the dietary group did. Although no improvement in pregnancy rate was seen, due to high dropout rate of 25%, they were unable to detect a significant difference between groups. However, the SET group did trend toward a higher pregnancy rate than the diet group did; 35% versus 10% \((P = .058)\). Researchers hypothesized that the benefits of exercise in inducing skeletal muscle glucose metabolism resulted in these differences in insulin levels and, subsequently, the projected improvement in fertility.

**LIVE BIRTH RATES**

Obese women have lower live birth rates than age-matched normal weight controls owing to several factors, including increased risk of miscarriage.\(^\text{22–24}\)

Also contributing to the reduced live birth rate is the association between obesity and aneuploidy and fetal anomalies.\(^\text{25,26}\) Obese women are also more likely to develop pregnancy complications and are more likely to experience intrauterine fetal demise and early neonatal death, which also impact the live birth rate.\(^\text{27,28}\) Discussion of these factors is beyond the scope of this article.

To date, only one study has evaluated the impact of LSM on live birth rates (Box 3).

**ASSISTED REPRODUCTIVE TECHNOLOGIES**

Most studies have not found that obesity impacts clinical pregnancy rates in assisted reproductive technology (ART) cycles. However, the largest study to date, from the SART CORS (Society for Assisted Reproductive Technology Clinic Outcomes Reporting System) database, demonstrated a significant impact of obesity. This retrospective cohort study of more than 45,000 embryo transfers found that increasing BMI was associated with higher odds of clinical pregnancy failure in women younger than 35-years-old, although BMI did not seem to affect donor oocyte cycles.\(^\text{29}\) Other studies have found that increasing BMI is associated with poorer response to stimulation, as well as increased risk of cycle cancellation and treatment failure.\(^\text{30,31}\)

Only one study to date has examined the effects of LSM and ART outcomes in a randomized fashion (Box 4).

**CLINICAL RECOMMENDATIONS**

Among the studies on fertility outcomes, a small number have compared interventions to determine the optimal diet and exercise regimen, few have compared diet to
exercise, and even fewer have used clinically relevant reproductive outcomes to assess the efficacy of lifestyle modifications. National organizations have attempted to raise awareness among clinicians but guidelines are limited. The ACOG and the American Dietetic Association recognize the importance of prepregnancy weight loss for obese patients, but neither make specific recommendations about how to go about achieving this goal.\(^ {32,33}\)

**Box 3**

**LSM and LBR**

*Clark and colleagues*

- Expanded upon previous study
- Cohort of 87 women who had undergone the same lifestyle modification program for 6 mo
- 20 women dropped out
- Pre-program data is reported for comparison
- Average weight loss was 10.2 kg ± 4.3 kg
- After the program, the women went back to attempting conception
  - Spontaneously or with assistance via techniques ranging from ovulation induction to IVF/ICSI
- Regardless of the method of conception, those who remained in the program had higher pregnancy rates than those who dropped out
- Live birth rate = 67% after the program
- Miscarriage rate after the intervention dropped to 18% from 75% prior to starting the LSM. (\(P<.01\))\(^ {4}\)

**Box 4**

**LSM and ART success**

*Moran and colleagues*

- Pilot study on short term weight loss and IVF in an obese cohort with a BMI 28–45
- Randomized to active dietary intervention and exercise for 5–9 weeks or standard treatment prior to oocyte retrieval
  - Diet = hypocaloric and high protein
  - Exercise = home based conditioning with walking
- 46 women were randomized
  - 18 completed the active intervention, 20 completed the standard therapy
- Both groups had reductions in waist circumference
  - Intervention group had reduced weight and BMI
- No difference in pregnancy rate or live birth rate
  - Only powered to 38%
  - However, those who had reduction in waist circumference had a higher odds ratio of becoming pregnant. (OR 1.286 \(P = .042\))\(^ {4}\)
DIET

Energy Restriction

The literature supports energy restriction as a method of improving metabolism and fertility. As noted above, Crosignani and colleagues\textsuperscript{12} demonstrated improved ovulation rates and pregnancy rates with an energy-restricted diet. These investigators restricted calories per day by 800 to 1000.\textsuperscript{18,20} However, there is no data regarding the optimal amount of caloric restriction and fertility.\textsuperscript{34}

Macronutrient Content

There are few studies that evaluate fertility and diets using different macronutrients. In theory, diets with a low glycemic index or high in protein, which would improve insulin resistance, may be more effective in women with PCOS; however, this has not been supported by data.\textsuperscript{34} Similarly, low carbohydrate diets would seem to be beneficial in obese women, but this diet has also not been shown to improve reproductive outcomes.

Moran and colleagues\textsuperscript{35} randomized 45 obese women with PCOS to a high-protein diet (30% protein, 40% carbohydrate, 30% fat) or a low-protein diet (55% carbohydrate, 15% protein, 30% fat) and followed them for 16 weeks. There was no difference in weight loss or changes in body composition between diets. Additionally, there was no difference between the two diets in resumption of ovulation. However, due to a high dropout rate of 37%, the study was underpowered to detect a difference.

EXERCISE

The type, amount, and duration of exercise needed to improve reproductive outcomes are not known. The types of exercise programs included in LSM are widely varied in the literature regarding fertility, ranging from recommendations to increase physical activity to structured treadmill training with targeted oxygen consumption. However, the data from Clark and colleagues\textsuperscript{13,36} underscores the potential significance of a SET intervention, including

- Improved ovulation rates, pregnancy rates, and live birth rates
- 1 hour of structured aerobic exercise per week, plus group therapy.

Only one study to date attempts to determine what method of exercise is the most beneficial in improving fertility (Box 5).

Diet Versus Exercise

Only two studies have examined the impact of diet versus exercise on defined reproductive outcomes.

Palomba and colleagues,\textsuperscript{21} as described previously, randomized women to 24 weeks of either a SET program or a high-protein, hypocaloric diet. The SET group had higher ovulation rates, 24.8%, versus the diet group, 15.1% ($P = .032$), and no difference in pregnancy rates for the SET group, 6.2%, versus the diet group, 1.7% ($P = .075$); however, the study was underpowered. The ovulatory patients who were in the diet group lost more weight than the ovulatory SET patients, ($-10.5$ kg vs $-5.6$ kg, $P<.05$). To explain this finding, the investigators hypothesized that the exercise in the SET group enhanced skeletal muscle metabolism and, thus, improved glucose metabolism, as evidenced by the lower fasting insulin levels compared with the diet group ($-23.4$ vs $-13.1$, $P = <.05$). The improved insulin sensitivity would then increase ovulation and, thereby, improve pregnancy rates, despite less weight loss in the SET group. Although this study suggests the importance of exercise in an LSM program, it was not randomized, had no control group, and was underpowered.
A recently published randomized controlled trial, examined the effects of diet versus exercise on anthropometric indices and endocrine parameters. A secondary outcome was ovulation rate. Fifty-seven women with all three Rotterdam criteria for PCOS and a BMI greater than 27 were randomized to diet, exercise, or a diet and exercise group for 4 months. Fourteen patients dropped out, leaving 43 for analysis. Weight loss was more pronounced in the diet (6%) and combination groups (5%) than in the exercise group (3%, \( P < .05 \)). Ovulation was detected by midluteal progesterone in 15 out of 43 women. There was no significant difference between groups.37

**Expert Opinion**

Because the literature fails to provide clinicians with concrete, evidence-based recommendations; expert panels have attempted to fill in the gaps. The Androgen Excess and Polycystic Ovarian Syndrome Society (AEPCOS) focuses on obese women with PCOS and, in their position statement, notes the current paucity of data regarding clinical recommendations (Box 6).38

For obese women without PCOS, there are no specific recommendations, other than weight loss. Thus, the authors must extrapolate from the general population, and rely on the National Institute of Health recommendations for obese adults:

- Hypocaloric diet, 500 to 1000 calorie deficit per day
- Macronutrient composition: 50% to 60% carbohydrate, 26% fat, and 19% protein
- Moderate to vigorous physical activity for 60 minutes most days of the week.

Although the optimal diet and exercise regimen remains uncertain, what can be gathered from the literature is that the institution of a hypocaloric diet resulting in a reduction in weight of at least 5% to 10%, impacts fertility. Exercise seems to help reduce visceral adipose tissue.
Patients seeking conception are often a highly motivated group and physicians are in a unique situation to make recommendations that may improve, not only maternal and neonatal outcomes, but, potentially, a woman’s overall health and long-term morbidity and mortality.

ACOG and the American Society for Reproductive Medicine very clearly state the recommendations in terms of preconception counseling and the optimization of natural fertility; however, to date, no group has given a definitive endorsement of a specific LSM to improve fertility in the general population.

Certainly the silence from professional organizations is due to the current state of the literature regarding LSM and fertility. The studies that exist are small, without placebo groups, possess high drop-out rates, are often underpowered, and frequently do not include women with the highest BMIs. Minorities are also largely understudied in the area of LSM. Lifestyle modifications in women without PCOS is also absent from the literature.

Current literature supports the improvement of ovulation rates and pregnancy rates with only modest weight reduction and, specifically, interventions that target centripetal adiposity.

What is less clear is the relationship of LSM on live birth rates and ART cycles.

Preconception counseling should include a discussion of the negative impact of weight on maternal and neonatal outcomes; however, again, the magnitude of benefit from LSM on mitigating these conditions is not known. Research is needed on the most effective intervention for weight loss as well as the amount of weight loss necessary to impact reproductive outcomes.

The role of LSM on long-term, overall health is, perhaps, the real question. Does LSM limit weight gain over a person’s life? Does LSM diminish the negative effects of obesity?

**Box 6**

**LSM principles suggested for obesity management in PCOS**

1. Lifestyle modification is the first form of therapy, combining behavioral (reduction of psychosocial stressors), dietary, and exercise management.

2. Reduced-energy diets (500–1000 kcal/day reduction) are effective options for weight loss and can reduce body weight by 7% to 10% over a period of 6 to 12 months.

3. Dietary pattern should be nutritionally complete and appropriate for life stage and should aim for <30% of calories from fat, <10% of calories from saturated fat, with increased consumption of fiber, fibre, whole-grain breads and cereals, and fruit and vegetables.

4. Alternative dietary options (increasing dietary protein, reducing glycemic index, reducing carbohydrate) may be successful for achieving and sustaining a reduced weight but more research is needed in PCOS.

5. The structure and support within a weight-management program is crucial and may be more important than the dietary composition. Individualization of the program, intensive follow-up and monitoring by a physician, and support from the physician, family, spouse, and peers will improve retention.

6. Structured exercise is an important component of a weight-loss regime; aim for >30 minutes per/day.

of weight on cardiovascular health and development of metabolic syndrome? Does LSM reduce mortality? If so, it is our duty as physicians to recommend these modifications to our young, otherwise healthy patients. Catching a captive audience, who desire fertility, and recommending modifications in lifestyle that could potentially impact reproductive success, as well as overall morbidity, mortality, and quality of life, is our obligation.

REFERENCES


