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### Etiological agents of microcephaly: implications for diagnosis during the current Zika virus epidemic

We read with interest the Physician Alert by Oliveira Melo *et al.*<sup>1</sup>, and believe it is necessary to discuss certain aspects related to the search for better links between Zika virus infection and microcephaly. In the current context, it is of the utmost importance to acquire the best possible evidence of this association, particularly considering the epidemiological, clinical and even ethical implications, such as suggestion of terminating infected pregnancies.

In the cases presented, it would be interesting to know at what point maternal real-time polymerase chain reaction was performed; the negative results in both patients might be explained by samples not being taken within the first 5 days of infection. The growing Zika virus pandemic in Latin America and the Caribbean region and its association with potential fetal neurological damage, particularly microcephaly, demands an exhaustive, rational assessment of other causes of this congenital defect. In the report<sup>1</sup>, there are no data on serological or molecular testing of other potential causes, such as those included in the STORCH (syphilis, toxoplasmosis, other infections, rubella, cytomegalovirus (CMV) and herpes simplex)

infection group. CMV and *Toxoplasma* in particular have been associated with brain calcifications that can be detected by ultrasound examination. Microcephaly is often a multifactorial condition which may be present at birth or develop later<sup>2</sup>. There are clear associations with both genetic and environmental factors<sup>2</sup>, so it is important in all suspected cases to assess other potential contributing factors, including chromosomal abnormalities and prenatal factors such as exposure to alcohol and other drugs of abuse, irradiation and intrauterine infection, which can affect growth and development of the brain.

It is important to remember that there are many cases reported worldwide sharing the same presentation but labeled as autosomal recessive congenital infection-like syndrome or pseudo-STORCH syndrome. These patients have the association of intrauterine growth restriction, microcephaly, intracranial calcifications, white-matter abnormalities, microphthalmia, bilateral cataracts and hearing loss<sup>3</sup>. While Zika virus was described more than 60 years ago, its real impact on the prenatal period is still a matter of extensive research, in particular to demonstrate a causal link. It is known that the virus can invade the brain and may be capable of causing damage. Some of its possible effects which are being investigated include alterations of centrosomes and a process called autophagy, resulting in neurological alterations, including microcephaly<sup>4</sup>. There is a need for more evidence to confirm or refute this link.

The epidemic is spreading, Brazil and Colombia being the countries most affected by this emerging arbovirus in the region. Hence, there is an urgent need for full evaluation of suspected cases, particularly in other

countries in order to confirm similar findings to those reported in Brazil. This will require interdisciplinary management, in order to clarify the true burden of this infection on pregnant women in the immediate future<sup>5</sup>.

J. L. Alvarado-Socarras†‡ and  
A. J. Rodríguez-Morales\*‡§

†Neonatal Unit, Department of Pediatrics, Fundación  
Cardiovascular de Colombia, Floridablanca, Santander,  
Colombia;

‡Organización Latinoamericana para el Fomento de la  
Investigación en Salud (OLFIS), Bucaramanga,  
Santander, Colombia;

§Public Health and Infection Research Group, Faculty  
of Health Sciences, Universidad Tecnológica de Pereira,  
Pereira, Risaralda, Colombia  
\*Correspondence.

(e-mail: arodriguez@utp.edu.co)

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