Editorial

Challenges of Zika Virus Infection in Pregnant Women

Desafios da infecção pelo vírus Zika em gestantes

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The zika virus (ZIKV) is an arbovirus belonging to the genus *Flavivirus* of the *Flaviviridae* family that is transmitted by mosquitoes of the genus *Aedes*. It has a transmission mechanism similar to dengue, yellow fever, and chikungunya viruses.[1]

The first description of ZIKV occurred in 1947 when it was isolated in *Rhesus* monkeys used as sentinels for yellow fever. This discovery occurred in the Zika forest in southern Uganda, hence the name of the virus. The description of the first infection in humans occurred in Nigeria in 1954, and its dispersion within the African continent can be considered slow. Until 2007, documented reports indicated that the number of people affected by this viral infection did not exceed 50 in sporadic occurrences in Africa and in some countries of Southeast Asia. After this apparent decrease in its dispersion, the first epidemic of ZIKV was observed in 2007 on the Pacific island of Yap in the Federated States of Micronesia in the Pacific Ocean.[2] In 2013, there were other epidemic outbreaks in French Polynesia and Easter Island before it finally reached Brazil between 2013 and 2014.

Along this course, the virus underwent genomic recombinations. Currently, two strains are recognized, one African and another one Asian, the latter being responsible for the epidemic in Brazil.[3,4] These mutations appear to be responsible for the appearance of this pathogenic profile that directly or indirectly associates ZIKV with the occurrence of lesions in the central nervous system of human fetuses. In this context, one should also recall the significant increase in the number of cases of Guillain-Barré syndrome and encephalitis in people affected by that infection. Several other changes occurred in the virus, including a greater adaptation to mosquitoes of the genus *Aedes*.[5] Considering this vector evidence, it seems that the spectrum of difficulties in this area has the potential to increase.

The epidemiological evidence indicating the possibility of an association between ZIKV infection and the occurrence of microcephaly in fetuses of affected mothers is a sufficiently alarming challenge that requires an urgent joint effort from all areas of healthcare directly or indirectly linked to the diagnosis and care of pregnant women and newborns affected by this infection. Considering the effects it could have on the intrauterine development of the fetal central nervous system, one could safely say that the reproductive process in humans has not been impacted so forcefully by a microorganism in many years.[6]

The observation that maternal ZIKV infection was associated with the occurrence of microcephaly was the motivation for the demand of differentiated care for pregnant women with this infection.[7] However, there is no consensus yet on whether the dual diagnosis of ZIKV and microcephaly is derived from a pure, accidental, or incidental causal association.[8] Undoubtedly, this insecurity led to a considerable number of studies pursuing an answer. Additionally, according to Oliveira Melo et al,[9] the microcephaly associated with ZIKV would be just the tip of the iceberg, indicating the imperative need for an urgent production of data regarding the vertical transmission of this virus. In fact, with the advances in knowledge on the subject, it was possible to confirm to date a series of additional harmful effects on the perinatal health of these infants, such as diffuse lesions in the central nervous system, serious ocular involvement, and arthrogryposis.[10–12] The results obtained by Mlakar et al[13] demonstrated unequivocally the presence of the virus in various organs of a fetus whose mother was affected by infection in the first trimester of pregnancy; they also support the view of Vogel[14] that it is very likely that the ZIKV is directly responsible for the genesis of these lesions. However, to date, more questions than answers exist on this particular topic.

The results of the ZIKV epidemic in French Polynesia in 2013 indicate that the infection affected 10.4% of the

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population of that community.[2] By extrapolating these data to Brazil and considering our sanitation conditions, there is no room for optimism. The trends of what is already occurring in some Brazilian cities have been confirmed; one can expect the occurrence of more than 60 thousand cases of infection by this virus in pregnant women in the next year, unless effective control measures are urgently adopted.

Regarding the viral transmission of ZIKV by mosquitoes of the genus *Aedes*, an additional concern arose from the confirmation of the sexual transmission of the virus.[15] This has brought objective difficulties and limitations for couples with planned pregnancies. At least three factors lead the uncertainties and are increasing the family planning dropout rate. The first one is related to the possibility that up to 80% of ZIKV infections are asymptomatic. These percentages have not yet been confirmed in Brazil, but this is the existing information to date.[16] The second factor refers to the nonexistence of a serological examination that will allow healthcare professionals to state with certainty that the couple is not in a post-infection period. Certainly, this situation generates great uncertainty. The third factor refers to the RNA reverse-transcriptase polymerase chain reaction (RNA RT-PCR of ZIKV), which is not available in public health facilities with the ease and speed that these reproductive procedures require. The infection timing is critical for diagnosis because the effectiveness of this technique for the diagnosis using plasma or serum is objectively reduced after the fifth day following the onset of clinical symptoms.

Given these difficulties and diagnostic limitations, a first strategy to provide proper care for patients who plan on becoming pregnant is to tell them they should reconsider their decision. If postponing the pregnancy is possible, that should be the strategy for the moment. If there are limitations to postponement (age limit, remission period of some diseases), one should resort to seminal evaluation with RT-PCR of viral DNA and serological tests to detect any asymptomatic infections. Nonetheless, it should be noted that serologic tests have limited availability across the developing world, including Brazil. Women who opt for pregnancy must be reminded of the prophylactic strategies to avoid mosquitoes, like the creation of a mechanical barrier by placing screens on windows and doors. Another strategy is the use of clothing that reduces skin exposure, as well as the use of insect repellents. Unfortunately, these measures require changes in behavior and a clear understanding of maternal vulnerability. Without systematic adherence, prophylactic failure will become the epilogue of this story!

It seems unthinkable that modern science has not yet managed to overcome the difficulty of developing a sensitive and specific technique to detect the acute phase of ZIKV infection without the limitation of cross-reactions with infections caused by other arboviruses (like dengue, chikungunya, and yellow fever). Besides dramatically increasing the costs, this forces the diagnosis of ZIKV infection to be performed by exclusion. At the moment, the method used to measure antibodies in large scale recommended by the Brazilian Ministry of Health is based on the enzyme-linked immunosorbent assay (ELISA) in-house technique, a protocol established by the Centers for Disease Control and Prevention (CDC).[17] This method has already been standardized in some reference laboratories in Brazil, but with limited availability. These laboratories are indicated to serve primarily pregnant women with a history of exanthematous disease who are outside the ideal period of collection for the RT-PCR test for ZIKV, or pregnant women that present a diagnosis of fetal microcephaly during pregnancy without a prior diagnosis of ZIKV infection. But we are all still waiting with anxiety for a serological examination that minimally meets this demand for the diagnosis of ZIKV infection.

Conceptually, microcephaly represents a disruption of the neurological development, causing the measure of the fetal or newborn head circumference (HC) to be 2 standard deviations (SD) below the normal limit by gestational age and sex.[18] In general, the neurological prognosis of a child with microcephaly confirms the obvious; the more serious and accentuated the microcephaly, the more compromised the prognosis. Mild microcephaly is identified when the measure of the HC is 2–3 SD below the mean, while severe microcephaly is considered when the measure of the HC is below 3 SD. In severe microcephaly, it is rare for neuropsychomotor development to fall outside the norm. However, it is very difficult to predict prognosis in cases of mild microcephaly.[19]

Parents and obstetricians rely on ultrasonography for the diagnosis of fetal microcephaly. This situation of high anxiety for parents, linked to the severity of the disease, makes the sonographer seek the most reliable parameters in order for the examination results to reflect biological reality. In addition to the technical ability to proper assess the measures, the search for standards has recently become a great concern among the scientific community. Various reference curves to qualify HC growth have been suggested and used over the past few months, in particular Fenton's curve,[20] the curve of Chervenak et al (1984, 1987)[21,22] and the curve of Papageorghiou et al.[23,24] All of these curves have pros and cons that limit or stimulate their systematic adoption as protocol. After a discussion with various healthcare collegiate bodies in Brazil[16] and abroad,[7] it was agreed that the curve of Oxford, called *Intergrowth 21*, should be used to evaluate fetal growth.[23] This reference curve for the growth of the cranial circumference is easy to use, and it has been designed with samples from several countries, including those of Brazilian children; the curve also contemplates the evaluation of preterm fetuses. For full-term children, a good option is the curve of the World Health Organization (WHO).[25] These same principles have guided the choice for the reference standards for the diagnosis of microcephaly after birth: *Intergrowth 21*[26] curves were chosen to assess preterm children in the postnatal period, and the curve of the WHO[25] was chosen in the case of full-term children.

In the routine care of pregnant women infected by ZIKV, one can observe a dramatic increase in psychological vulnerability that clearly indicates the need for specific institutional efforts to direct the provision of psychotherapy support for these mothers and their families.[27] In addition to the psychological vulnerability, there is also

social vulnerability, and support for that must be provided as well.

In general, based on the available epidemiological data, ZIKV infection in pregnant women will have an enormous impact on the health of the affected Latin American countries, mainly in terms of caring for these children after birth. This conclusion is derived from the high prevalence of infection already observed both in the general population and in pregnant women in these countries. Certainly, these facts will require the adoption of strategies that involve financial costs; and the adoption of these strategies will now compete for funding that was already precarious considering the health problems previously existing in these countries.

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