

## The Zika Virus Infection in Pregnancy: Review and Implications for Research and Care of Women and Infants in Affected Areas

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The world has encountered a new and serious epidemic which has disproportionately affected fetuses and infants. What makes the Zika virus (ZIKV) epidemic such a threat in our times, is that a whole generation can be affected by birth defects caused by a seemingly innocuous maternal infection, which in most cases go unnoticed and undiagnosed. Spreading to over 80 countries and affecting millions, it is associated with severe birth defects known as congenital Zika syndrome (CZS), which include fetal brain development abnormalities (microcephaly and brain calcifications), retinal abnormalities, and contractures and hypertonia of the extremities. Testing strategies are challenging because of the lack of symptoms and cross-reactivity with other viral infections. Obstetrical complications include fetal loss and the need for an emergency cesarean delivery. The rate of CZS has been described as ranging from 5 to 6% among cohorts in the US, reaching 11% for 1st trimester exposure. Prolonged viremia during pregnancy has been documented in a few cases, reaching 89 days after the onset of symptoms in one case and 109 days after such onset in another. If the ZIKV can infect, multiply in, and persist in diverse placental cells, then movement across the placenta, the fetal brain, and the maternal peripheral blood is possible. There is a sense of urgency, and we need safe and effective vaccines and treatments, particularly for pregnant women. If we do not expand testing and develop methods for early diagnosis and treatment, thousands of infants will be exposed to a neurotropic virus that causes severe birth defects and that could also affect the lives of those who form the next generation. [*P R Health Sci J* 2018;37(Special Issue):S66-S72]

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The Zika virus (ZIKV) epidemic is unique and serious. What makes the ZIKV epidemic such a threat in our time, is the fact that a whole generation can be affected by birth defects caused by a seemingly innocuous infection, to the point that, in most cases, ZIKV infection is asymptomatic. The most severe manifestation of the now-termed congenital Zika syndrome (CZS) is microcephaly. This birth defect presents with stigmatizing characteristics and severe disabilities, forcing families to change their lives and to care for a child expected to have many special needs. This epidemic is an ongoing public health challenge. Pregnant women are the most vulnerable to the impact of this vector-transmitted infection (mosquito) which is also sexually transmitted. In fact, we have stated that the manifestations of CZS could just be the “tip of the iceberg” (1).

On February 1, 2016, the World Health Organization (WHO) declared the ZIKV outbreak a Public Health Emergency of International Concern (PHEIC), the reasons being the reported clusters of infants with microcephaly (more than 4,000, then) and the cases of adults with Guillain-Barré syndrome (GBS) related to the ZIKV infection (2). The concerns grew with the first reports of infants with microcephaly whose mothers had

had symptomatic ZIKV infection during pregnancy. This part of the story shows that a simple conversation can point towards scientific discoveries. Vanessa van der Linden, a neurologist in the Brazilian city of Pernambuco, saw (in August 2015) several babies with microcephaly whose mothers remembered having had a rash during their pregnancies. In addition, her mother, Ana, another doctor, who works in Recife, saw 7 babies with microcephaly in 1 day. All of these mothers remembered

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having had a rash early in their pregnancies. On October 2015, after a phone conversation in which the 2 doctors shared their experiences and concerns, Dr. Van der Linden alerted the Brazilian authorities of the increased number of cases of babies with microcephaly. It was then that the Brazil Ministry of Health reviewed the birth certificates and alerted the WHO. A series of evaluations and further documentation of the cases then led to the association of the ZIKV infection with the microcephaly cases (3–4). After examining the initial documentation, the WHO made its well-publicized statement declaring the PHEIC.

The vector transmission of ZIKV infection was reported in Brazil on May 2015, which supported the hypothesis that this virus could have been responsible for the unusually high rate of infant microcephaly cases that had been seen (5). According to the WHO, 84 countries have been categorized as areas with new introductions or re-introductions of ZIKV, with ongoing, interrupted, or past ZIKV transmissions during 2016 and 2017. By mid-2017, an additional group of 64 countries had established vectors with no ZIKV transmissions reported yet. Therefore, this is a global issue, particularly for pregnant women in those 84 countries, and potentially in many more (6).

In an editorial about ZIKV, Morens and Fauci refer to the secondary pandemic of ZIKV-associated microcephaly and other birth defects as one of the most disturbing aspects of the ZIKV epidemic. They furthermore continue to remind us that, due to the persistence of the vector and the historical re-appearances of prior epidemics (including dengue, the West Nile virus, and chikungunya) from past decades, this pandemic is not a 1-time crisis that will not be repeated (7).

### Historical background

A brief history of the ZIKV can be obtained from several sources, including the WHO website (8).

We are summarizing the WHO documentation of the ZIKV epidemic timeline as follows: The ZIKV was first identified in Uganda in 1947 in Rhesus monkeys in the Ziika Forest as part of a Rockefeller Foundation project to study yellow-fever vectors. Zika was later identified in humans in 1952. From 1969 to 1983, the virus was detected in mosquitoes found in equatorial Asia, including India, Indonesia, Malaysia, and Pakistan. The first large outbreak of ZIKV infection was reported on the island of Yap in the Federated States of Micronesia in 2007. Prior to this, only 14 cases of human ZIKV disease had been documented anywhere in the world. It was estimated that 73% of Yap's residents were infected with ZIKV during the outbreak. More outbreaks occurred in 3 groups of Pacific islands—French Polynesia, the Cook Islands, and New Caledonia—and on Easter Island, all occurring around 2013–4. In March 2015, Brazil notified the WHO of an illness characterized by skin rash that was appearing in their northeastern states. From February 2015 to 29 April 2015, nearly 7,000 mild cases were reported, with no deaths. Of 425 blood samples taken for differential diagnosis, 13% were positive for dengue. The tests for chikungunya, measles, rubella, parvovirus B19, and enterovirus were negative. No

tests for ZIKV were carried out at that point. By October 2015, Brazil was reporting an unusual number of microcephaly cases. On November 11, 2015, Brazil declared a national public health emergency due to the increase in the cases of suspected microcephaly, and by January 2016, a total of 3,893 suspected cases of microcephaly, including 49 deaths, had been reported. In February 2016, the WHO declared the ZIKV infection to be a Public Health Emergency of International Concern (PHEIC), as stated above (8).

This is a relatively new disease, presently without effective treatments or vaccines. Because it is mostly asymptomatic and laboratory testing can be difficult, it presents a challenge for science and for global health. We are going to summarize most of what has been published related to pregnancy and ZIKV infection in the past year, when the impact of the epidemic affected thousands of individuals and infants. We are not going to include the neurologic manifestations of GBS (covered elsewhere in this supplement).

### Scope of the problem in the Americas

A recent update (January 2018) from the Pan American Health Organization/World Health Organization (PAHO/WHO) regarding cumulative ZIKV numbers in the Americas informs us that there have been 583,451 suspected cases of ZIKV, of which 223,477 were later confirmed. In addition, there have been 20 deaths and 3,720 confirmed cases of CZS (9).

### Clinical manifestations of ZIKV in pregnancy

Zika is usually mild, with symptoms lasting for from several days to a week (10). The incubation period was calculated with data from 197 symptomatic travelers who had recently been infected with the ZIKV. The incubation period was calculated to be from 3 to 14 days. Of those 197 travelers, 50% became symptomatic within 1 week of having been infected, increasing to 99% within 2 weeks (11).

Driggers et al relate the story of a 33 y/o woman and her husband who traveled to Central America and who—upon returning home to Washington, DC—concomitantly began to experience symptoms of the ZIKV; from this report it can be inferred that the incubation period for the infection remains unchanged, even when the person infected is a pregnant woman (12).

The same mild symptoms of the ZIKV present themselves whether the infected individual is pregnant or not (2, 13–14). The symptoms are usually self-limited, lasting less than a week. The most common reported signs and symptoms are pruritic rash, arthralgia, conjunctivitis, and a low-grade fever (15). A published review of symptoms among pregnant women included the following, in decreasing order of frequency: maculopapular pruritic rash (44–93% of cases), conjunctivitis (35–58%), myalgia and arthralgia (39–64%), headache (53%), and adenopathy (40%) (16).

Only one case of GBS in pregnancy has thus far been reported, which suggests that the main target of this neurotropic virus

during pregnancy might be the fetus's and not the mother's central nervous system (CNS) (17).

### Testing issues and treatment guidelines

In order to document the epidemic, as well as to confirm diagnoses among symptomatic patients and most importantly among pregnant women who might be asymptomatic in the great majority of cases, accurate testing is essential. In areas with documented transmission, this testing is recommended during pregnancy, in all trimesters. The results should be used to counsel pregnant women and recommend additional imaging studies, to determine infant infection status (exposed infected vs. exposed uninfected), and as pre-conception counseling (18). In addition, tests are needed to distinguish febrile illnesses and neurologic conditions such as GBS. Because of the virus's general cross-reactivity with other flaviviruses, ZIKV serology (IgG or IgM) is challenging and might have less specificity, as virologic tests such as reverse transcription polymerase chain reaction (RT-PCR) have a limitation: a short timespan for diagnosis (18). In response to the pandemic, many organizations developed international, national, and country-specific guidelines and training materials and activities to prepare providers and communities to address the epidemic from diverse perspectives. Guidelines were developed by the WHO, the American College of Obstetrics and Gynecology (ACOG), the US Centers for Disease Control and Prevention (CDC), and other organizations and were posted on websites for easy access.

The CDC published specific guidelines for the evaluation and management of women of reproductive age with possible Zika exposure, pregnant women under the same circumstances, and potentially exposed infants. Guidelines for general prevention in potentially affected communities and for the prevention of sexual transmission were also developed (19–21). The WHO published guidelines for country-level surveillance, testing, and prevention and for the management of symptomatic individuals. Issues of screening were also addressed (22). The official reported number of pregnant women with laboratory evidence of possible ZIKV infection in Puerto Rico reached 3,300 by early 2017, the largest number of ZIKV-infected pregnant women in the USA. The CDC and the PR Department of Health carried out a survey (from August through December 2016) of 2,364 Puerto Rico residents having had a recent live birth (the Pregnancy Risk Assessment Monitoring System Zika Postpartum Emergency Response: PRAMS-ZPER). They (the CDC and the PR Department of Health) found high levels of concern about acquiring ZIKV infection during pregnancy, moderate reported use of repellent (45%), and much lower reported use of other prevention strategies. The authors recommended additional educational measures and increased ZIKV testing in pregnant women (23).

### Puerto Rico's response

Among the measures taken as part of the response to the ZIKV epidemic in PR, the Department of Health, the CDC, the United States Department of Health and Human Services (HHS), the

Health Resources and Services Administration (HRSA), and other groups collaborated on diverse aspects of a plan that included an awareness campaign, recommendations for vector control, guidance for the testing of pregnant women during prenatal care (modified according to evidence), recommending ZIKV testing of all pregnant women during each trimester and acute testing for all symptomatic patients, the recommendation that pregnant women be referred for ultrasound evaluation and care, the collection of infant blood and placental samples at delivery, a recommendation regarding the subspecialty evaluation of neonates, and recommending the longitudinal follow-up of the infants. In addition, the Ob-Gyn Department of the University of Puerto Rico School of Medicine established, in collaboration with the Carlos Albizu University (CAU), a multidisciplinary clinic for pregnant women with ZIKV for dedicated care within the model of group prenatal care. Funding for research in pregnancy provided by the National Institutes of Health (NIH), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Institute of Allergy and Infectious Diseases (NIAID) facilitated the implementation of the international Zika in Infants and Pregnancy (ZIP) study, which is ongoing in 11 sites located in 6 countries and territories (Brazil, Colombia, Costa Rica, Guatemala, Nicaragua, and Peru) and Puerto Rico. This large study, 2 sites of which are in Puerto Rico, will determine ZIKV seroincidence and maternal and infant complications in each country, will define the natural history and risks for transmission of the disease as well as the disease spectrum in infants, and will validate new testing protocols, among other scientific contributions, all of which will also help inform providers and patients about ZIKV risks (24).

The consequences of this epidemic are real and serious and have been documented not only by laboratory diagnoses but also with a recent population-based analysis of birth defects, which have increased substantially and have been linked to the ZIKV. A recent, population-based birth-defects analysis demonstrated an increase in the prevalence of birth defects potentially related to ZIKV. The prevalence increased 20-fold in territories with local transmission (PR and USVI) (25). This information adds to the accumulated reports of the seriousness and the impact of this epidemic among pregnant women and their infants.

### Complications during pregnancy

In a Brazilian cohort of 345 pregnant women, of which 182 (53%) were ZIKV positive, there was a 10-times higher frequency of emergency cesarean sections during labor, mostly due to suspected fetal hypoxia (fetal distress). There were similar rates of fetal losses between ZIKV positive and negative, but when adverse pregnancy outcomes (of all the women, with or without the virus) were combined, there were more adverse outcomes among the ZIKV-positive women ( $p < 0.001$ , in every trimester) (16). In Columbia, on the other hand, the epidemic has so far been linked to relatively few pregnancy complications. The rate of term deliveries for the 616 women with a ZIKV diagnosis was 82%, and the rate of preterm birth was 8%; 2% of the infants

were born at term with low birth weight and 1% died during the perinatal period. No microcephaly cases have been reported for the 1,850 pregnant women who contracted ZIKV in the third trimester (26). According to the Puerto Rico Zika Pregnancy Surveillance report (found on the PR Department of Health website), by the end of 2016, there had been 1,307 live births, and 1,203 women were still pregnant. The rate of pregnancy loss prior to 20 weeks was 2.8% (37/1307), and the number of pregnancy losses after 20 weeks was 13. These numbers seem to indicate a relatively low rate of pregnancy loss, but there might be a bias in reporting some of the outcomes (27).

### Evidence of causality, timing of infection, and CZS

ZIKV infection during pregnancy has been linked to fetal microcephaly and to other brain, ocular, and neurologic abnormalities among infants. Prior to the Zika epidemic, the reported rate of microcephaly varied from 1 to 6 cases per 10,000 births in the USA (28). In fact, the epidemic was identified by a peak in the number of infants born with microcephaly in Brazil. Initially, there were questions regarding the association of ZIKV and the CZS, with other factors considered being environmental contaminants, nutritional deficiencies, and genetic predisposition. In an elegant analysis of available epidemiologic and biologic data and using the criteria proposed for the assessment of potential teratogens, Rasmussen and colleagues concluded that “a causal relationship exists between prenatal Zika virus infection and microcephaly and other serious brain anomalies.” In support of that claim, they went on to observe the following: “. . . Zika virus infection at times during prenatal development that were consistent with the defects observed; a specific, rare phenotype involving microcephaly and associated brain anomalies in fetuses or infants with presumed or confirmed congenital Zika virus infection; and data that strongly support biologic plausibility, including the identification of Zika virus in the brain tissue of affected fetuses and infants” (29). Estimates of the rates of microcephaly linked to first-trimester exposure to ZIKV have run from as low as 1% (French Polynesian epidemic of 2013–14) to as high as 13% (Brazilian epidemic of 2015–16) (30–31). Two reports from ZIKV-infected pregnant women returning to the USA together with cases in the US territories have documented similar rates of the CZS: close to 6% overall, and up to 11% resulting from more than 400 pregnancies recorded in a registry of ZIKV-positive pregnant women and their infants in the USA and its territories. The incidence of infants with birth defects born to pregnant women with Zika was 6% for those women who presented with or without symptoms. In addition, the rate of birth defects in fetuses exposed during the first trimester (highest risk period for other defects) was 11% (32–33). In the US territories, the children born of mothers who acquired the ZIKV infection during the first, second, or third trimester had rates of Zika-associated birth defects of 8%, 5%, and 4%, respectively (33). The CZS has been characterized by Moore et al as having “5 features that are rarely seen with other congenital

infections or are unique to congenital Zika virus infection: (1) severe microcephaly with partially collapsed skull; (2) thin cerebral cortices with subcortical calcifications; (3) macular scarring and focal pigmentary retinal mottling; (4) congenital contractures; and (5) marked early hypertonia and symptoms of extrapyramidal involvement” (34). The postnatal development of microcephaly in infants born with normal-sized heads was documented for 13 infants born in Brazil without microcephaly, who later were diagnosed as such (microcephalic). These occurrences might have been caused by a late onset ZIKV infection which needed time for brain involution and necrosis. These manifestations were evidenced postnatally, during each infant’s first year of life. This raises the question of whether exposed (infected) infants that are born with normal-sized heads are still at risk for the development of yet undefined serious disability and/or brain dysfunction (35). Families (and in many settings, single mothers) of infants born with the CZS or any of the severe brain malformations associated with the ZIKV infection will have many challenges; these challenges are likely to include the need for specialized care at home, multiple appointments for sub-specialty evaluations and therapies, social stigma, and the expenses associated with having a special-needs child (weather covered by insurance or not), to mention just a few. The health care system needs to be aware and supportive of these challenges and planning for future care needs is essential.

### Ultrasound findings

Ultrasound (U/S) evaluations during pregnancy are an essential tool for providing the optimal care. They make it possible to determine gestational age (GA), the number of fetuses, cardiac activity (to determine viability), and placental localization and characteristics, and are critical in the evaluation of amniotic fluid volume and the identification of fetal anomalies. U/S evaluations are used regularly to determine fetal growth parameters and amniotic fluid and placental abnormalities.

The identification of congenital anomalies, particularly in the fetal CNS, can facilitate the diagnosis and management of ZIKV-exposed fetuses. Abnormalities of the CNS were detected at as early as 19 weeks in a pregnant woman who traveled to Colombia and had symptomatic ZIKV infection (fetus at 9 weeks, GA). Another report of intrauterine growth restriction (IUGR) at 18 weeks, GA, was made concerning a symptomatic pregnant woman whose fetus later developed CNS abnormalities and hydrops at 32 weeks GA (36). In that particular case, the U/S findings were not conclusive until much later in the pregnancy. These 2 cases demonstrated early and severe abnormalities related to the ZIKV infection. Because there is a tendency for the virus to induce fetal brain damage, most abnormalities are identified later in a given pregnancy. Some of the CNS abnormalities that might be detected by U/S include micro-calcifications, microcephaly, ventriculomegaly, reduced head circumference (HC) growth velocity, small/absent cavum septum pellucidum, asymmetrical cerebral hemispheres, partial or complete agenesis of the cerebellar vermis, hypoplastic

cerebellum, and prominent choroid plexus (37). Additional potential findings include cerebral calcifications, brain atrophy, stunted cerebral growth, absent corpus callosum, and ventriculomegaly (38). Access to U/S is not universal, and therefore, a fetus infected with ZIKV might not be diagnosed until delivery. A preliminary analysis of the US findings of the pregnant women diagnosed with ZIKV and followed at the University Hospital (in PR) shows a temporary decrease in head circumference (HC) associated with the Zika infection, with catch-up growth afterwards (personal communication, Alberto de la Vega, MD). These findings are presented elsewhere in this supplement. What are the implications of a temporary deceleration in fetal head growth with later catch-up? Severe CNS abnormalities are easier to identify than are neurodevelopmental abnormalities, which need long-term follow-up and close attention to a given infant's milestones.

### Transplacental infection and maternal viremia

For clinicians caring for pregnant women and for public health officials, there are many and serious difficulties with ZIKV diagnostic testing, even in the presence of acute illness.

Tests that rely on antibody detection are difficult to interpret because of potential cross-reactivity with other vector-transmitted diseases, such as dengue and chikungunya, which share the same vector (*Aedes aegypti*).

Recent modifications of the ZIKV testing recommendations will result in health care specialists relying more on RT-PCR testing of acute infection and less on the identification of IgM antibodies. The CDC's new guidelines state the following: "As the prevalence of Zika virus disease declines, the likelihood of false-positive test results increases. In addition, emerging epidemiologic and laboratory data indicate that, as is the case with other flaviviruses, Zika virus IgM antibodies can persist beyond 12 weeks after infection. Therefore, IgM test results cannot always reliably distinguish between an infection that occurred *during* the current pregnancy and one that occurred *before* the current pregnancy, particularly for women with possible Zika virus exposure before the current pregnancy" (39).

Accurate prenatal diagnosis of fetal infection is not yet available for ZIKV, and testing might be inconclusive. As an example, an amniotic fluid sample tested for ZIKV using RT-PCR could be reported as positive or negative. So far we don't have data to support the conclusion that a positive RT-PCR is predictive of fetal abnormalities or even the CZS. A negative test does not predict fetal health, either. An invasive procedure such as amniocentesis needs to be justified with additional benefits such as confirming other fetal diagnoses, and its results should be able to guide management and decision-making.

Because of the need to wait for fetal brain damage to occur after an infection (and before diagnosis), finding tests that will predict future damage might be difficult. Correlates of fetal damage need to be identified and characterized. Testing that would accomplish this remains an urgent need. Prolonged maternal viremia during pregnancy has been documented in a

few cases. Maternal viremia of up to 109 days after the onset of symptoms in serum samples of a pregnant Colombian woman in Spain were reported (13). Another case of prolonged viremia lasted for 70 days, until the pregnancy was terminated (14).

A study of 150 participants with confirmed ZIKV infection, the Zika Virus Persistence study (ZiPer), reported a persistence of viremia of more than 60 days in 4% (3/79) of the patients. There were 5 pregnant women in that study, of which 3 had viremia at 46 days after the onset of symptoms and 1 had viremia, 80 days after onset (12, 40–41).

Mysorekar and Diamond proposed, based on their study of mouse models and human cell and tissue samples, that ZIKV could replicate in trophoblasts, fetal endothelial cells, and Hofbauer placental macrophages (42). If the ZIKV can infect, multiply, and persist in diverse placental cells, then movement across the placenta and back and forth through the fetal brain, the placenta, and the maternal peripheral blood is possible.

In addition, they observed that: "ZIKV could cross the placental barrier without excessive damage and spread to the fetal brain, where it preferentially infects and injures neuronal progenitor cells. . . . Infection and death of neuroprogenitor cells could inhibit neuronal-cell differentiation, which would explain the cortical thinning, malformation of brain structures, and microcephaly that are observed during pregnancy in humans" (37, 42).

This hypothesis suggests the existence of a mechanism for fetal damage and also the increased chances of diagnosing active ZIKV infection in pregnancy because of the prolonged viral replication and persistence.

### Care needs

Health services need to incorporate prevention and testing for ZIKV, not just in pregnant women, who might be the most vulnerable at present, but also in men and children, who need to be able to be tested, particularly in areas where there is ongoing ZIKV transmission.

Because the infection is mostly asymptomatic, this presents the challenge of expanding testing and facilitating entry into care. Testing difficulties need to be addressed to find solutions to the (high) cost and complexity of laboratory assays, sensitivity of tests, and availability of resources. Testing strategies need to be developed to be able to identify acute infection and past exposure. Testing services need to incorporate patient-centered strategies, including access to quick results. Reproductive health care needs are to be covered so that the prevention of unwanted pregnancies is feasible and the attaining of desired pregnancies is a possibility as well. The care of pregnant women with a ZIKV diagnosis needs to include a multidisciplinary approach, with obstetricians, pediatricians, experts in maternal–fetal medicine (MFM) and imaging (US), mental health professionals, and family empowerment strategies.

### Research needs

The response of researchers and funding agencies to this pandemic has been immediate, coordinated, and

multidisciplinary, considering it an emerging disease. A relatively innocuous virus discovered in 1947 became a pathogenic threat associated with birth defects. This change in the panorama activated the research community, and we expect numerous findings and reports that will allow us to better (and sooner) understand, diagnose, and counsel pregnant women, who are the most vulnerable (43).

The numbers of cases reported by the PAHO and the WHO decreased in 2016 (compared to 2015), and most experts believe that the final numbers for 2017 will show that the prior epidemic proportions seen in those years will not have been sustained. Nevertheless, despite decreasing numbers, the threat still exists. Although vector transmission remained the main risk factor for the 2016 ZIKV epidemic, new data and an analyses of previous cases support the hypothesis that sexual transmission might have had an important role in sustaining the infections. An analysis of the cases reported in Brazil showed that even when considering the bias for the increased testing of pregnant women, there were 90% more registered cases per 100,000 women than men in the age groups of sexually active individuals (15–65 years), in contrast with those younger than 15 or older than 65 years of age (44). Abstract modeling of epidemics on sexual networks suggests that because the ZIKV persists much longer in semen than in cervico-vaginal secretions (180 vs. 20 days), assuming symmetric transmission risk, males would be 10 times more likely to transmit to a partner than females would. The authors postulate that under specific circumstances, populations of men who have sex with men (MSM) could sustain transmission on their own (45).

This work points towards the need for more research on the sexual transmission of the ZIKV as an adjuvant or an alternate pathway to sustaining an epidemic. Testing priorities need to consider not only pregnant women but men as well. The need for the testing of pregnant women in affected areas is supported by the fact that the CZS has been documented with similar frequency in both symptomatic and asymptomatic women and because 80% of all infections are asymptomatic.

Research is clearly needed in many fields of science for us to curtail the epidemic: 1. Vector control; 2. ZIKV diagnosis of acute illness, of prior immunity, and of correlates of immunity; 3. the development of safe and effective treatments for the initial infection and for its complications; 4. the development of safe and effective preventive vaccines; and 5. increasing knowledge and experience to be able to counsel women based on the trimester of exposure and risks. We need to understand the particularities of vulnerability for complications: Are they nutritional, immunologic, genetic, or related either to co-infections or to a specific viral strain?

Research is also needed to develop predictive prenatal screening and diagnostic tests such as the ones we use for genetic disorders like aneuploidy and neural tube defects. The development of vaccines and treatments will need to take pregnant women into account because even if a preventive vaccine were to be formulated, many pregnancies are unplanned and unanticipated. Vaccines and treatments need to be safe to

be administered during pregnancy. There is a sense of urgency because if we do not expand testing and develop treatments, early diagnosis, and preventive vaccines, thousands of infants will be exposed to a neurotropic virus that causes severe birth defects and that could also affect the lives of those who form the next generation.

## Resumen

El mundo se enfrenta a una nueva y seria epidemia que ha afectado desproporcionadamente a fetos e infantes. Lo que hace a la epidemia del virus de Zika (ZIKV) una amenaza en nuestros tiempos, es que una generación entera se puede ver afectada con defectos de nacimientos causados por una infección materna leve e inocua que muchas veces pasa desapercibida. Extendiéndose por más de 80 países y afectando a millones, se asocia a un síndrome de Zika congénito (CZS, por sus siglas en inglés), que incluye malformaciones del cerebro fetal (microcefalia y calcificaciones), anomalías en la retina y contracturas e hipertonia en las extremidades. Las pruebas diagnósticas son un reto por la falta de síntomas y la reactividad cruzada con otras infecciones virales. Las complicaciones obstétricas incluyen pérdidas fetales y cesáreas de emergencia en mayor proporción. El CZS se describe entre 5-6% de los embarazos reportados en EEUU y hasta un 11% en exposición del 1er trimestre. La viremia prolongada materna se ha reportado hasta 89 y 109 días. Si el virus puede infectar diversas células de la placenta, el movimiento de éste entre la placenta, el cerebro fetal y la sangre materna puede ser posible. Hay un sentido de urgencia y necesitamos tratamientos y vacunas seguras y eficaces particularmente para las embarazadas. Si no se expanden las pruebas diagnósticas, se desarrollan pruebas de diagnóstico temprano y tratamientos, miles de infantes se expondrán a un virus neurotrópico que podrá causar defectos congénitos y afectar la próxima generación.

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