HHS Public Access

Author manuscript

JAMA Pediatr. Author manuscript; available in PMC 2020 September 28.

Published in final edited form as:

JAMA Pediatr. 2019 January 01; 173(1): 16–18. doi:10.1001/jamapediatrics.2018.4164.

Revealing the Effects of Zika—Detection of Brain Abnormalities and Other Disabilities Associated With Congenital Infection

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Although Zika has faded from the media headlines, it remains an important clinical and public health risk for many women and their families. Zika virus infection during pregnancy can cause serious defects of the brain and eye in the offspring, and it has been linked to other neurodevelopmental disabilities, such as seizures, joint contractures, swallowing difficulties, vision impairment, and hearing loss.[1–3] Women who are pregnant, attempting conception, or at risk for unintended pregnancy may be at risk for the devastating consequences of congenital Zika virus infection if they or their partners live in or travel to affected areas. Although Zika virus transmission is much lower now than it was in 2016, there remain nearly 100 countries and territories with some risk of Zika infection (https://www.cdc.gov/zika/geo/index.html). Although the magnitude of risk to pregnant travelers, pregnant partners of travelers, or residents of areas with risk of Zika is unclear, potential risks might be of greatest concern for travelers who are likely to lack immunity to Zika. Travelers to and residents of these areas should remain vigilant about these risks and consult with a health care professional regarding ongoing risks in affected areas.

After Zika virus exposure in pregnancy from either mosquitoes or sex with Zika-infected individuals, there are recommendations for care and evaluation during pregnancy but limited information on the effectiveness of these strategies for identifying fetal abnormalities.[4] The study in this issue of *JAMA Pediatrics* from Mulkey et al[5] highlights the limitations of prenatal identification of fetal abnormalities and the unfulfilled promise of fetal brain magnetic resonance imaging (MRI). Early in the 2016 Zika outbreak, investigators expressed optimism about the potential benefits of fetal brain MRI, remarking that “the superior soft-tissue resolution of fetal brain MRI might be more sensitive to developmental and encephaloclastic changes, thereby expediting the detection of evolving brain anomalies.”[6(p2149)] Unfortunately, this optimism was short lived, and Mulkey et al[5] conclude that “for most of our cases, fetal MRI did not add value beyond” ultrasonography. There

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflict of Interest Disclosures: None reported.

have been few comparative data on the relative sensitivity of prenatal ultrasonography and magnetic resonance imaging (MRI) in detecting brain abnormalities associated with Zika to inform clinical decision-making. Mulkey et al[5] report that MRI detected abnormalities in 3 fetuses (4%), while prenatal ultrasonography detected 2 of these abnormalities. In the case where ultrasonographic examination failed to detect an abnormality, there was a falloff in head circumference growth between 18 and 22 weeks.

Current US Centers for Disease Control and Prevention (CDC) guidance for pregnant women with possible Zika virus infection in pregnancy is to consider serial ultrasonography every 3 to 4 weeks to monitor fetal growth and neuroanatomy.[4] Given that 2 of 3 fetuses with brain abnormalities in the study by Mulkey et al[5] were identified by prenatal ultrasonography, the additional cost, stress, time, and discomfort for the patient, as well as limited accessibility of MRI for patients who are pregnant, should be considered in making individualized decisions about how to monitor fetal growth and neuroanatomy during pregnancy.

The CDC recommends that all infants with laboratory evidence of a possible maternal Zika virus infection in pregnancy receive a head ultrasonographic examination and ophthalmological examination by age 1 month, as well as an automated auditory brainstem response by the same point if newborn hearing screen used only otoacoustic emissions methods. In addition, consistent with recommendations for all infants, growth parameters should be assessed at each well-child visit, and infants and children should receive age-appropriate vision screening and developmental monitoring and screening using validated tools.[7]

The destructive effect of Zika infection can be missed if infants do not receive all recommended evaluations in a timely manner. For example, the need for neuroimaging soon after birth has been supported by a longitudinal study showing that calcifications might be diminished or not detected on images at 1 year of age.[8] Posterior eye defects that can be associated with Zika infection will likely only be detected during an ophthalmological examination, but many infants are not receiving this care from a specialist. In a recent CDC report of 1450 infants in the US territories who were at least 1 year old and had laboratory evidence of possible Zika virus infection during pregnancy, only 36% of the infants had an ophthalmological evaluation reported to the surveillance network.[3] Interventions for vision impairment cannot only improve vision but also potentially affect brain development in young children by increasing their interaction with the environment.[9,10] Similarly, while severe microcephaly and serious brain abnormalities might be detected soon after birth, if not prenatally, neurodevelopmental disabilities might not be identified early or at all without developmental screening or evaluation with a validated tool. While this is recommended for all children regardless of Zika exposure, uptake varies tremendously, with only about one-third of US children receiving this recommended evaluation.[11] It is not clear how many children born to infected mothers in the case series by Mulkey et al[5] were completely evaluated according to CDC recommendations or how many have clinical effects associated with congenital infection, including eye defects and neurodevelopmental disabilities. While the study by Mulkey et al[5] assessed risk of brain anomalies, the CDC has reported[3] that 14% of children at least 1 year old with laboratory evidence of Zika virus infection during

pregnancy had a diagnosis of a Zika-associated birth defect of the brain or eye, a neurodevelopmental disability possibly linked to Zika, or both. Additionally, at present, we can only assess the proportion with birth defects and/or neurodevelopmental disabilities among infants from all pregnancies with laboratory evidence of Zika infection, because we do not have a reliable method for determining which fetuses or infants acquired Zika virus infection via vertical transmission.

Zika has been a difficult virus to contend with, and many diagnostic and clinical challenges remain. Although the current study[5] adds to the growing body of evidence regarding prenatal and postnatal identification of brain abnormalities, there are still many unanswered questions. For example, we need better diagnostic testing to identify those who are currently infected, as well as testing to document prior infection and current immunity. Longitudinal surveillance and research are essential to fully understand the effects of Zika virus and ensure that we are prepared for the next Zika outbreak, including continually updating and improving the clinical guidance for the care of pregnant women and infants. Most importantly, we need a safe and effective vaccine to eliminate congenital Zika infection.

Sadly, the Zika story is not over for children and families who have been affected by Zika virus infection during pregnancy. Zika was affecting pregnant women and their infants years before its teratogenic effect was recognized,[1,2] and Zika will remain a serious risk to pregnant women and their infants until we have a safe vaccine that can fully prevent Zika virus infection during pregnancy. Until then, ongoing public health efforts are essential to protect mothers and babies from this threat and ensure all disabilities associated with Zika virus infection are promptly identified, so that timely interventions can be provided.

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