Practice Advisory: Interim Guidance for Care of Obstetric Patients During a Zika Virus Outbreak

This is an area of evolving care and practice. Fellows should check periodically for revisions and updates on ACOG's Practice Advisories webpage (http://www.acog.org/About-ACOG/News-Room/Practice-Advisories), CDC's website (http://www.cdc.gov/zika/) and SMFM's website (https://www.smfm.org/). ACOG and SMFM will communicate important changes and updates to this guidance.

The Centers of Disease Control and Prevention (CDC) issued a health advisory, travel advisory and an early release MMWR concerning Zika virus (Zika) and its potential impact on pregnant women and their fetuses. This Practice Advisory reiterates the prevention strategies to minimize exposure to Zika and summarizes the current guidance for management of pregnant women who have been exposed.

Background:

Zika was reported in May 2015 in South America and since then has spread throughout the Americas. The CDC and Pan American Health Organization (PAHO) websites maintain and update the list of areas where Zika virus transmission has been identified.

The virus spreads to humans primarily through infected *Aedes aegyti* mosquitoes. Once a person is infected, the incubation period for the virus is approximately 3-12 days. Symptoms of the disease are non-specific but may include fever, rash, arthralgias, and conjunctivitis. It appears that only about 1 in 5 infected individuals will exhibit these symptoms and most of these will have mild symptoms. It is not known if pregnant women are at greater risk of infection than non-pregnant individuals.

Zika during pregnancy has been associated with birth defects, specifically significant microcephaly. Transmission of Zika to the fetus has been documented in all trimesters; Zika virus RNA has been detected in fetal tissue from early missed abortions, amniotic fluid, term neonates and the placenta. However, much is not yet known about Zika virus in pregnancy. Uncertainties include the incidence of Zika virus infection among pregnant women in areas of Zika virus transmission, the rate of vertical transmission and the rate with which infected fetuses manifest complications such as microcephaly or demise. The absence of this important information makes management and decision making in the setting of potential Zika virus exposure (i.e. travel to endemic areas) or maternal infection, difficult. Currently, there is no vaccine or treatment for this infection.

Prevention Guidance:

- Avoiding exposure is best. Pregnant women should delay travel to areas where Zika outbreaks are ongoing when possible. Women considering pregnancy should discuss the advisability of travel with their obstetric providers. See the CDC and PAHO websites for updated lists of affected countries.
- When traveling to areas where Zika has been reported, take all precautions to avoid mosquito bites including the use of EPA-approved bug spray with DEET, covering exposed skin, staying in air-conditioned or screened-in areas, and treating clothing with permethrin.
    - Providers should specifically communicate to pregnant women that when used as directed on the product label, EPA-registered insect repellents including those with DEET and permethrin can be used safely during pregnancy.
    - These protective measures should be followed both day and night as the *Aedes aegyti* mosquito (which carries Zika virus) bites primarily during the day as well as at dusk and dawn. Reapplication of insect repellant should be practiced as directed on the product label.

Management of women with history of travel to an area with ongoing Zika virus transmission:

Management of women exposed to Zika virus including those with suspected infection or evidence of fetal effects is evolving. Recommendations for management will be updated periodically to reflect changing evidence and emerging consensus.

Obstetrician-gynecologists and other health care providers should ask all pregnant women about recent travel. Women who traveled during pregnancy to an area with ongoing Zika virus transmission should be evaluated. Because perinatal transmission of Zika has been documented and may be associated with poor fetal outcomes, it is important to diagnose and identify affected fetuses to allow appropriate counseling of patients. Consideration of pregnancy termination or delivery at a center with appropriate neonatal expertise may be warranted in the context of test results, gestational age, and severity of ultrasonographic findings.

Evaluation of women with Zika virus exposure will vary based on whether or not they manifest symptoms and the timing of such. Evaluation of the fetus for potential infection, however, should be undertaken based on exposure alone regardless of maternal symptoms or testing results.

Evaluation of Women with Clinical Illness During or Within Two Weeks of Travel

- These women should be tested for evidence of Zika virus infection. Testing begins with evaluation of maternal blood using serum reverse transcriptase-polymerase chain reaction (RT-PCR). A positive PCR in these patients is considered diagnostic of maternal Zika virus infection. Because Zika virus RT-PCR is not available widely, providers should contact their state health departments' vector-borne or infectious disease programs to determine where to send samples. RT-PCR testing of maternal serum is positive only for a brief window when the infected person has viremia, a period that is estimated at 3-7 days from the onset of symptoms. Immunoglobulin M (IgM) and neutralizing antibody testing can also performed to diagnose Zika virus infection on specimens collected ?4 days after onset of illness. Unfortunately these tests are difficult to interpret and false-positive results can occur; cross-reaction with other related infections such as dengue and yellow fever are common with antibody testing. Zika virus testing is performed at the CDC Arbovirus Diagnostic Laboratory and a few state health departments. Contact your state health department to facilitate testing. For more information on testing protocol see CDC's Memorandum on Updated diagnostic testing for Zika, chikungunya, and dengue viruses in US Public Health Laboratories.

- Fetal evaluation as described below should be undertaken in all exposed women with symptoms regardless of maternal testing results. Given the apparent limited window for viremia, negative testing cannot exclude maternal or fetal infection.

Evaluation of Women without Symptoms During or within Two weeks of Travel

- Universal testing for maternal infection is not recommended in this group.
- Consider fetal evaluation as described below.
- Testing for maternal infection is only recommended for those with ultrasound abnormalities. Because timing of infection in women without symptoms cannot be known, such testing will involve Immunoglobulin M (IgM) and neutralizing antibody testing as discussed above.

Fetal Evaluation

- Serial ultrasounds that are recommended (evidence of maternal infection) or undertaken (no evidence of maternal infection) to evaluate and monitor fetal anatomy and well-being can be done every 3-4 weeks.
    - Ultrasound examinations should focus on development of findings such as intracranial calcifications and microcephaly, as those abnormalities have been most frequently reported in affected pregnancies.
    - Serial ultrasounds are recommended in the setting of maternal infection and should be considered even among those with exposure alone because the natural history of Zika virus in utero infection is not known, and the time from exposure and infection to clinical manifestations is uncertain. Therefore one reassuring ultrasound, particularly if obtained close to the time of infection, may not preclude later concern, and cases with delayed findings have been reported.
- When imaging raises suspicion for fetal infection, amniocentesis for Zika virus testing of amniotic fluid may be considered. The CDC algorithm also suggests that amniocentesis be offered in cases in which there is demonstrated maternal Zika virus infection, even if sonographic findings are not present. While it is assumed that assay performance on amniotic fluid is similar to that with maternal serum, this is not certain. Nor is it known how long after a pregnant woman becomes infected she can transmit the virus to the fetus or for what duration amniotic fluid will be PCR positive.

The many uncertainties about Zika virus biology highlight the challenges of managing and counseling about exposures and infection in pregnancy. Referral to a maternal-fetal medicine or infectious disease specialist with expertise in pregnancy management is recommended (Peterson, 2016) and may be useful particularly for those pregnancies with demonstrated maternal infection or concerning fetal findings.

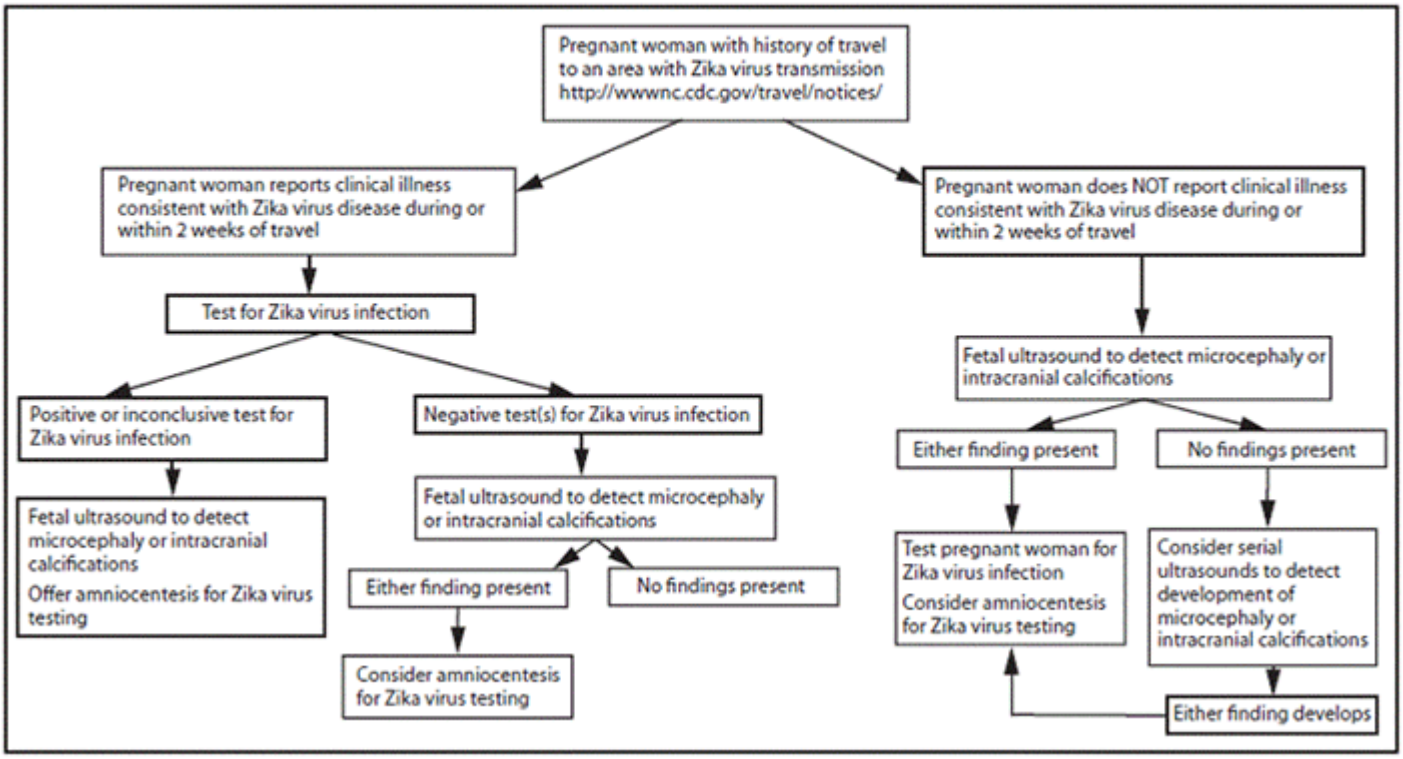
Another important feature of the CDC algorithm is the recommendation that specimens obtained after Zika virus infection is suspected or diagnosed, should be sent to pathology for further evaluation. This includes fetal remains and placental tissue which can be examined using Zika virus RT-PCR, histopathologic examination and immunohistochemical staining. This testing is recommended to advance the understanding of Zika infection in pregnancy and provide insight to patient counseling in the setting of fetal loss.

Other Management Considerations:

Although the presence of Zika in breast milk has been reported, it is in very small amounts and unlikely to be harmful for the neonate. Infection through oral intake is not known and any effects of neonatal

infection, as with adults, are likely to be mild and of short term consequence. The benefits of breastfeeding likely outweigh the potential neonatal risks. Therefore, the recommendation is that women should continue to breastfeed.

Interim guidance: testing algorithm*,†, for a pregnant woman with history of travel to an area¶ with Zika virus transmission, with or without clinical illness** consistent with Zika virus disease



*Availability of Zika virus testing is limited; consult your state or local health department to facilitate testing. Tests include Zika virus reverse transcription–polymerase chain reaction (RT-PCR) and Zika virus immunoglobulin M (IgM) and neutralizing antibodies on serum specimens. Given the overlap of symptoms and endemic areas with other viral illnesses, evaluate for possible dengue or chikungunya virus infection.
† Laboratory evidence of maternal Zika virus infection: 1) Zika virus RNA detected by RT-PCR in any clinical specimen; or 2) positive Zika virus IgM with confirmatory neutralizing antibody titers that are ?4-fold higher than dengue virus neutralizing antibody titers in serum. Testing would be considered inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titers.
§ Amniocentesis is not recommended until after 15 weeks of gestation. Amniotic fluid should be tested for Zika virus RNA by RT-PCR.>
¶ Updates on areas with ongoing Zika virus transmission are available online (http://wwwnc.cdc.gov/travel/notices/).
** Clinical illness is consistent with Zika virus disease if two or more symptoms (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) are present.
Source: Petersen EE, Staples JE, Meaney-Delman, D, et al. Interim Guidelines for Pregnant Women During a

Zika Virus Outbreak - United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65(Early Release):1-4. DOI: http://dx.doi.org/10.15585/mmwr.mm6502e1er

References and Resources:

American College of Obstetricians and Gynecologists. Immunization for women. Available at: http://www.immunizationforwomen.org. Retrieved January 20, 2016.

- Specific Zika virus information is available at:
  - American College of Obstetricians and Gynecologists. Zika virus updates. Available at: http://immunizationforwomen.org/providers/Zika-Virus-Updates. Retrieved January 20, 2016.

Centers for Disease Control and Prevention. Recognizing, managing, and reporting Zika virus infections in travelers returning from Central America, South America, the Caribbean, and Mexico. CDC Health Advisory. Atlanta (GA): CDC; 2016. Available at: http://emergency.cdc.gov/han/han00385.asp. Retrieved January 20, 2016.

Centers for Disease Control and Prevention. Updated diagnostic testing for Zika, chikungunya, and dengue viruses in US Public Health Laboratories. Memorandum. Atlanta (GA): CDC; 2016. Available at: http://www.aphl.org/Materials/CDCMemo_Zika_Chik_Deng_Testing_011916.pdf#search=zika. Retrieved January 20, 2016.

Centers for Disease Control and Prevention. Effects of disasters on pregnant women: environmental exposures. Available at: http://www.cdc.gov/ncbddd/disasters/environmental.html. Retrieved January 20, 2016.

Centers for Disease Control and Prevention. Insect repellent use and safety. Available at: http://www.cdc.gov/westnile/faq/repellent.html. Retrieved January 20, 2016.

Centers for Disease Control and Prevention. Travel health notices. Available at: http://wwwnc.cdc.gov/travel/notices. Retrieved January 20, 2016.

Centers for Disease Control and Prevention. Zika virus. Available at: http://www.cdc.gov/zika. Retrieved January 20, 2016.

Centers for Disease Control and Prevention. Zika virus: transmission. Available at: http://www.cdc.gov/zika/transmission/index.html. Retrieved January 20, 2016.

Nasci RS, Wirtz RA, Brogdon WG. Protection against mosquitoes, ticks, and other arthropods. In: Centers for Disease Control and Prevention. CDC health information for international travel 2016. New York (NY): Oxford University Press; 2016. Available at: http://wwwnc.cdc.gov/travel/yellowbook/2016/the-pre-travel-consultation/protection-against-mosquitoes-ticks-other-arthropods. Retrieved January 20, 2016.

Pan American Health Organization. Zika virus infection. Available at: http://www.paho.org/hq/index.php?option=com_topics&view=article&id=427&Itemid=41484. Retrieved January 20, 2016.

Petersen EE, Staples JE, Meaney-Delman D, Fischer M, Ellington SR, Callaghan WM, et al. Interim guidelines for pregnant women during a Zika virus outbreak - United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65(Early Release):1-4. Available at: http://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6502e1er.pdf. Retrieved January 20, 2016.

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