ZIKA VIRUS AND PREGNANCY

Current as of September 5, 2017
Background
Zika belongs to the flavivirus family of viruses and is closely related to a number of other human pathogenic viruses, including the viruses that cause yellow fever, dengue fever, and chikungunya. These infections are spread via the bite of the Aedes species mosquito, which is found in many tropical and subtropical locations, including parts of the United States. Many people infected with the Zika virus will not exhibit any symptoms. Of those who do, most develop an acute febrile illness that lasts several days to a week and then resolves completely. Hospitalization is rare. The most common symptoms of Zika are fever, rash, joint pain, and conjunctivitis (red eyes).

To date, the most critical clinical issue is the strong association between Zika infection in pregnancy and the development by the fetus of congenital abnormalities. The most concerning of these is microcephaly, in which an infant’s head is significantly smaller than children of the same age and gender. This condition is often associated with developmental delay and other neurological issues. Much is still unknown about the precise relationship between development of this condition and the preceding Zika infection. Additionally, in areas affected by Zika, the reports of Guillain-Barré syndrome (uncommon sickness of the nervous system) have increased. Researchers continue to work to understand more about the spread of the virus, as well as the impact to pregnant women and unborn fetuses.

Current Concern
Prior to 2015, there had been no outbreaks of Zika outside of Africa, Southeast Asia, and the Pacific Islands. In May 2015, the first confirmed case of infection was reported in Brazil, and cases have now been reported in numerous countries in Central and South America. On July 29, 2016, the Centers for Disease Control and Prevention (CDC) reported the first cases of local mosquito-borne Zika virus transmission in the continental US (Florida). However, since early 2017, the reported incidence of Zika virus disease in the region has declined. The CDC is actively involved in monitoring the situation and developing improved case definitions and diagnostic test options. In addition, the CDC has issued a travel advisory recommending that pregnant women defer travel to areas of the world where Zika transmission is ongoing.

Zika Infection and Diagnosis
The diagnosis of Zika virus infection is made through molecular and serologic testing. Test methods include (1) nucleic acid amplification (NAA), (2) immunoglobulin M (IgM) detection, and (3) plaque reduction neutralization test (PRNT) for Zika virus antibodies.

Zika and Pregnancy
On July 24, 2017, the CDC updated its interim guidance for US health care providers who are caring for pregnant patients with possible exposure to Zika virus. The CDC noted that “All pregnant women in the United States and U.S. territories should be asked about possible Zika virus exposure before and during the current pregnancy at every prenatal care visit.” Possible exposures to Zika virus include travel to or residence in an area with active Zika virus transmission, or sex with a partner who has traveled to or resides in an area with active Zika virus transmission without using condoms or other barrier methods to prevent infection.

The clinical guidance also focuses on key points related to testing for symptomatic and asymptomatic pregnant women with exposure to Zika. Please see Figure 1 and Figure 2 for “updated interim guidance: testing and interpretation recommendations” from the CDC for pregnant women with possible exposure to Zika virus.

What can health care providers do for pregnant patients?

- Know the symptoms of Zika and ask patients about their travel history. The most common symptoms of Zika are fever, rash, joint pain, and conjunctivitis.
- Contact their state and local health departments for laboratory testing.
- Educate a pregnant woman and her partner about how to prevent Zika transmission.
- Call CDC and the state or local health department for clinical consultation. Notify state and local health departments when they have cases of Zika.
- Offer testing to pregnant women and others with symptoms of Zika who have traveled to areas with Zika. The CDC has made available testing algorithms and additional clinical guidance on their website for health care providers. Please visit www.cdc.gov for more information.
Testing for Zika infection: CDC Testing Algorithm

Figure 1. Updated interim testing recommendations and interpretation of results for symptomatic pregnant women with possible Zika virus exposure**.††† — United States (including U.S. territories), July 2017.

ASK pregnant women about
Travel to or residence in areas with risk for Zika virus transmission before and during current pregnancy
Possible sexual exposure before and during current pregnancy
A diagnosis of laboratory-confirmed Zika virus infection before current pregnancy
Symptoms of Zika virus disease during current pregnancy (e.g., fever, rash, conjunctivitis, and arthralgia)
If no symptoms reported, refer to asymptomatic algorithm

Before testing, discuss testing limitations and potential risks for misinterpretation of test results

WHOM to test?
Pregnant women reporting possible exposure during current pregnancy and symptoms of Zika virus disease

WHEN to test?
As soon as possible, through 12 weeks after symptom onset

WHICH tests?
Zika virus NAT (serum and urine) AND Zika virus IgM serology (serum)

RESULTS and ADDITIONAL tests
Positive Zika virus NAT
Positive Zika virus IgM
Further testing may be warranted
Negative Zika virus NAT AND negative Zika virus IgM
Plaque reduction neutralization test (PRNT)
Negative Zika virus NAT AND positive Zika virus IgM

Interpretation
Acute Zika virus infection
Zika virus infection: timing of infection cannot be determined
For pregnant women without Zika virus exposure before the current pregnancy, positive IgM represents recent Zika virus infection
Zika virus PRNT ≥10 AND dengue virus PRNT <10
Zika virus PRNT ≥10 AND dengue virus PRNT <10
Zika virus PRNT <10
Flavivirus infection: specific virus and timing of infection cannot be determined
For pregnant women with possible Zika virus exposure before the current pregnancy, positive IgM represents recent unspecified flavivirus infection

Abbreviations: IgM = immunoglobulin M; NAT = nucleic acid test; PRNT = plaque reduction neutralization test.
** Ask type and duration of Zika virus exposure before and during current pregnancy. Exposure before the current pregnancy might limit interpretation of Zika virus IgM results; pretest counseling can help inform testing decisions.
††† Some patients may choose not to receive Zika virus IgM testing.
** Zika virus testing is not routinely recommended for pregnant women with a previous diagnosis of laboratory-confirmed Zika virus infection by either NAT or serology (positive IgM or dengue virus IgM and Zika virus PRNT ≥10 AND dengue virus PRNT <10 results).
§§ This algorithm also applies to women with possible Zika virus exposure who have a fetus with prenatal ultrasound findings consistent with congenital Zika virus syndrome.
**§ The duration of detectable Zika virus RNA in pregnant women following infection is not known. Preliminary data suggest that NAT may retain positive for several weeks after symptom onset in some pregnant women. Zika virus IgM antibodies are most likely to be detected within 12 weeks after infection; however, IgM antibodies might be detected for months after infection, limiting the ability to determine whether infection occurred before or during the current pregnancy.
**§ § Positive Zika virus IgM antibody testing is recommended for asymptomatic pregnant women. For laboratory interpretation in the presence of dengue virus IgM results, refer to https://www.cdc.gov/dengue/clinicallab/ laboratory.html.
** Nonnegative results include “positive,” “equivocal,” presumptive positive, or “possible positive.” These are examples of assay interpretation that might accompany test results; nonnegative serology terminology varies by assay.
**§§ Persons with ongoing possible Zika virus exposure include those who reside in or frequently travel (e.g., daily or weekly) to an area with risk for Zika virus transmission.
**§§§ For the purposes of this guidance, recent possible Zika virus exposure or Zika virus/flavivirus infection is defined as a possible exposure or infection during the current pregnancy or periconceptional period.

Figure 2. Updated interim testing recommendations and interpretation of results for asymptomatic pregnant women with possible Zika virus exposure**.††† — United States (including U.S. territories), July 2017.

ASK pregnant women about
Travel to or residence in areas with risk for Zika virus transmission before and during current pregnancy
Possible sexual exposure before and during current pregnancy
A diagnosis of laboratory-confirmed Zika virus infection before current pregnancy
Symptoms of Zika virus disease during current pregnancy (e.g., fever, rash, conjunctivitis, and arthralgia)
If no symptoms reported, refer to asymptomatic algorithm

Before testing, discuss testing limitations and potential risks for misinterpretation of test results

WHOM to test?
Asymptomatic pregnant women with ongoing possible Zika virus exposure

WHEN to test?
Three times during pregnancy. First test at initiation of prenatal care

WHICH tests?
Zika virus NAT (serum and urine)

RESULTS
Positive Zika virus NAT
Negative Zika virus NAT
No Zika virus RNA detected (Zika virus infection during pregnancy cannot be ruled out)

Interpretation
Acute Zika Virus Infection
No Zika virus RNA detected (Zika virus infection during pregnancy cannot be ruled out)

Abbreviations: IgM = immunoglobulin M; NAT = nucleic acid test; PRNT = plaque reduction neutralization test.
* Ask type and duration of Zika virus exposure before and during current pregnancy. Exposure before the current pregnancy might limit interpretation of Zika virus IgM results; pretest counseling can help inform testing decisions.
† Zika virus testing is not routinely recommended for pregnant women with a previous diagnosis of laboratory-confirmed Zika virus infection by either NAT or serology (positive IgM or dengue virus IgM and Zika virus PRNT ≥10 AND dengue virus PRNT <10 results).
§ The interval for Zika virus NAT testing during pregnancy is unknown. Preliminary data suggest that NAT may remain positive for several weeks after infection in some pregnant women. For women without a prior laboratory-confirmed diagnosis of Zika virus infection, NAT testing should be offered at the initiation of prenatal care, and Zika virus RNA is not detected on clinical specimens, two additional tests should be offered during the course of the pregnancy coinciding with prenatal visits. The proportion of fetuses and infants with Zika virus–associated birth defects is highest among women with first and early second trimester infections; therefore, all NAT testing during the first and second trimesters might be considered to help identify infections early in pregnancy. However, adverse outcomes have been associated with infection diagnosed in the third trimester, therefore, testing every trimester might be considered.
$ Despite the high specificity of NAT, false positive IgM results have been reported. If both serum and urine specimens are NAT positive, interpret as acute Zika virus infection. If NAT is only positive on serum or urine, testing should be repeated on the original NAT-positive specimen. If repeat NAT is positive, results should be interpreted as evidence of acute Zika virus infection. If repeat NAT testing is negative, results are indeterminate and health care providers should repeat Zika virus IgM antibody testing on a serum specimen collected ≥2 weeks after symptom onset. If subsequent IgM antibody test is positive, interpret as evidence of acute Zika virus infection, but if negative, interpret as no evidence of Zika virus infection.
** Possible Zika virus exposure includes travel to or residence in an area with risk for Zika virus transmission (https://www.cdc.gov/travel/page/zika-travel-information) during pregnancy or the periconceptional period (8 weeks before conception [6 weeks before the last menstrual period], or sex without a condom during pregnancy or the periconceptional period, with a partner who traveled to, or resides in an area with risk for Zika virus transmission.
†† For the purposes of this guidance, recent possible Zika virus exposure or Zika virus/flavivirus infection is defined as a possible exposure or infection during the current pregnancy or periconceptional period.

Note from LabCorp: Please contact your LabCorp representative about the dengue virus IgM test. Per the CDC, dengue virus IgM antibody testing is recommended only for symptomatic pregnant women.
Testing for Zika infection: CDC Clinical Management*

Table 1. Interim guidance for Zika virus testing* of formalin-fixed, paraffin-embedded placental, fetal, or infant autopsy tissues† for completed pregnancies with possible Zika virus exposure during pregnancy — United States (including U.S. territories), July 2017

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>Testing of placental tissues</th>
<th>Testing of placental and fetal tissues</th>
<th>Testing of placental and infant autopsy tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth, possible Zika virus–associated</td>
<td>Should be considered to aid in maternal diagnosis</td>
<td>Should be considered to aid in maternal diagnosis</td>
<td>Should be considered to aid in infant and maternal diagnosis</td>
</tr>
<tr>
<td>birth defects***</td>
<td>Not indicated†††</td>
<td>May be considered to aid in fetal diagnosis</td>
<td>Should be considered to aid in infant and maternal diagnosis</td>
</tr>
<tr>
<td>Live birth, no obvious Zika virus–associated</td>
<td></td>
<td>May be considered to aid in fetal diagnosis</td>
<td></td>
</tr>
<tr>
<td>birth defects at birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy loss, possible Zika virus–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>associated birth defects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy loss, no obvious Zika virus–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>associated birth defects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant death following live birth</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IHC = immunohistochemistry; NAT = nucleic acid test; RT-PCR = reverse-transcription polymerase chain reaction.

* Zika virus testing on formalin-fixed, paraffin-embedded tissue specimens is conducted at CDC’s Infectious Diseases Pathology Branch (IDPB) and includes Zika virus RT-PCR on placental and fetal/infant tissues. Zika virus IHC may be performed on placental tissues into the second trimester, fetal tissues from any gestational age, and infant autopsy tissues.

† Placental tissues include placental disc, umbilical cord, and fetal membranes. Zika virus RNA can be focal within placental tissues, and testing of three sections of placenta, one section of umbilical cord, and one section of fetal membrane is recommended (https://www.cdc.gov/zika/laboratories/test-specimens-tissues.html). For pregnancy losses and infant deaths, submission of placental tissues in addition to fetal or infant autopsy tissues, if available, is preferred, but if not available will not preclude placental testing.

‡ Possible Zika virus exposure includes travel to or residence in an area with risk for Zika virus transmission (https://www.cdc.gov/zika/geo/index.html) during pregnancy or the periconceptional period (8 weeks before conception to 6 weeks before the last menstrual period), or sex without a condom, during pregnancy or the periconceptional period, with a partner who traveled to, or resides in an area with risk for Zika virus transmission.

§ Possible Zika virus–associated birth defects that meet the CDC surveillance case definition include the following: brain abnormalities and/or microcephaly, intracranial calcifications, ventriculomegaly, neural tube defects and other early brain malformations, eye abnormalities, or other consequences of central nervous system dysfunction including arthrogryposis (joint contractures), congenital hip dysplasia, and congenital deafness (https://www.cdc.gov/zika/geo/index.html). In all cases, infants or fetuses with possible Zika virus–associated birth defects should also be evaluated for other etiologies of congenital anomalies.

¶¶ Includes pregnant women with negative Zika virus NAT and negative Zika virus IgM ≤12 weeks after symptom onset or exposure.

§§ All or part of possible maternal Zika virus exposure, or symptom onset occurred >12 weeks before maternal serum specimen was collected.


LabCorp now offers a Zika virus NAA test (Aptima® Zika Virus Assay) and a Zika virus IgM test (ZIKV Detect™ IgM Capture ELISA) authorized by the FDA for emergency use.

For more information about specimen collection, please refer to the online Test Menu at www.LabCorp.com.

References