Update: Zika virus infection in pregnancy

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Declaration of Interest

NONE
Objectives

- briefly review the epidemiology; clinical presentation, and damage-response of humans to Zika virus (ZIKV) fever or disease

- review current guidelines from the US Centers for Disease Control (CDC) for testing, management, and prevention of ZIKV disease

(Nice To Meet Ya, Zika; http://www.popsci.com/pluto-in-3-d-complete-structure-zika-and-other-amazing-images-weve-encountered)
Brief epidemiology of ZIKV

- ZIKV named after Zika "overgrown" Forest
  - isolated from a caged rhesus macaque @ Yellow Fever Virus Research Centre (Uganda in 1947)

- single-stranded RNA Flavivirus

- documented modes of ZIKV transmission
  - primary
    - infected mosquito biting human
  - secondary
    - vertical transmission from mother to foetus
    - transfusion of infected blood to human
    - various modes of sexual intercourse
      - vaginal
      - anal
      - oral
Brief epidemiology of ZIKV (cont’d)

• documented modes of ZIKV transmission (cont’d)
  o transplantation of infected organ to ZIKV-naïve recipient
  o exposure of laboratory workers to ZIKV

Brief epidemiology of ZIKV cont’d

ZIKV vectors

• **Aedes aegypti**
  - most common ZIKV vector
  - aggressively bites during day-time and also carries
    • yellow fever virus
    • dengue virus
    • chikungunya virus
    • West Nile virus (discovered in Uganda in 1937)
    • Japanese encephalitis virus (JEV)

• **Aedes albopictus**

• **Aedes africanus**

• **Aedes luteocephalus**
Countries and territories reporting mosquito-borne transmission of Zika virus

Data as of 14 December 2016

Clinical presentation of ZIKV disease

- Major symptoms include ≥2 of the following:
  - Pruritic maculopapular rash
  - Abrupt onset of low-grade fever
    - 37.8 to 38.5°C
  - Arthralgia
    - Small joints of feet and hands
  - Conjunctivitis
    - Red eyes without purulent discharge
Clinical presentation of ZIKV disease cont’d

- common symptoms include
  - headache
  - myalgia
  - retro-orbital pain
  - asthaenia
    - abnormal physical weakness or lack of energy

Source:
- Chen LH; Zika Virus Infection in a Massachusetts Resident After Travel to Costa Rica: A Case Report; Ann Intern Med. 2016;164(8):574
Clinical presentation of ZIKV disease cont’d

ZIKV Incubation and viraemia

- **incubation period**
  - 3–14 days

- **Zika viremia**
  - few to 7 days
  - may persist longer in pregnant women

- **ZKV remains in semen longer than in blood**
Hypothesized pathogenesis of Zika Virus

- primary vertebrate hosts
  - monkeys
  - humans

1. ZIKV incubates in mosquitoes for ~ 10 days

2. ZIKV infects dendritic cells near site of inoculation

3. ZIKV spreads to lymph nodes and the bloodstream

4. ZIKV replicates in both cytoplasm and nucleus of cells
   - Flaviviruses generally replicate only in the cytoplasm
Diagnostic tests for ZIKV

molecular test for ZIKV

- RNA NAT nucleic acid testing (RNA NAT)
  - serum - first two weeks after symptom onset
  - urine
    - <14 days after onset of symptoms
    - collect with a patient-matched serum specimen
  - positive RNA NAT result on any sample
    - ZIKV infection CONFIRMED
      - no additional testing indicated
**Diagnostic tests for ZIKV (cont’d)**

### Molecular test for ZIKV cont’d

- **Negative RNA NAT result**
  - ZIKV infection **not excluded**
  - do IgM antibody (serological) test

- **Asymptomatic pregnant women s/p travel to active ZIKV areas**
  - RNA NAT serum and urine
    - within 2 weeks of date of last possible exposure

- **IgM positive pregnant women presenting for care ≥ 2 weeks s/p exposure**
  - Asymptomatic pregnant women
    - IgM test as part of routine obstetric care in the 1st and 2nd trimester
      - reflex RNA NAT if IgM positive

Diagnostic tests for ZIKV (cont’d)

**Triplex Real-time RT-PCR Assay**
- detects RNA from
  - Zika virus
  - dengue virus
  - chikungunya virus

- not yet approved by FDA
  - under US FDA “Emergency Use Authorization (EUA)”

**Serological test for Zika Virus**
- Zika virus-specific IgM and neutralizing antibodies
  - variable IgM levels ~4 days s/p onset of symptoms to 12 weeks

- if RNA NAT is negative on serum and urine do serum IgM for
  - Zika virus
  - dengue virus
  - chikungunya virus

Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay
- Zika MAC-ELISA
  - qualitative detection of Zika virus IgM antibodies in serum or CSF
  - challenging to interpret
    - cross-reaction with other flaviviruses
    - possible non-specific reactivity
    - requires confirmation by plaque-reduction neutralization testing (PRNT)


- plaque-reduction neutralization testing (PRNT) performed by
  - CDC or a CDC-designated confirmatory testing laboratory
  - confirms Zika MAC-ELISA
    - presumed positive
    - equivocal
    - inconclusive

ZIKV-associated GBS

- **WHO recommendations for testing**
- **DO NOT DELAY TREATMENT WHILE TESTING FOR TRIGGERS OF GBS**
  - DRAW BLOOD FOR ZIKA AND OTHER FLAVIVIRUSES BEFORE IMMUNOTHERAPY
  - reverse-transcription polymerase chain reaction (RT-PCR) of blood and urine samples
  - flavivirus IgM tests
  - may consider
    - CSF analysis with RT-PCR
    - serological testing (e.g. IgM, IgG, neutralizing antibodies or antibody index)
Assess for Possible Exposure to Zika Virus Infection
(See references on back for more information.)

Do you live in or do you frequently travel (daily or weekly) to an area with active Zika virus transmission?

YES | NO

Have you traveled to an area with Zika during pregnancy or just before you became pregnant [8 weeks before conception or 6 weeks before your last menstrual period]?

YES | NO

Have you had sex (vaginal, anal, or oral sex) without a condom or shared sex toys with a partner who lives in or has traveled to an area with Zika?

YES | NO

If your pregnant patient answered “NO” to ALL questions, she is at low risk for exposure to Zika.

References:
1. Possible exposure to Zika virus that warrants testing includes one or more of the following:
   a. Living in an area with active transmission
   b. Travel to an area with active transmission
   c. Sex (vaginal, anal, and oral sex) without a condom or the sharing of sex toys with a person who traveled to or lives in an area with active transmission
2. Visit CDC’s website to see areas with active Zika transmission: http://www.cdc.gov/zika/geo/index.html
3. Please see the algorithm on the back from CDC’s Updated Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure to guide testing and interpretation of results. (http://www.cdc.gov/mmwr/volumes/65/wr/mm6529e1.htm?s_cid=mm6529e1_e)
US CDC’s Response to Zika

Testing and interpretation recommendations* † ‡ § ¶ for a pregnant woman with possible exposure to Zika virus** — United States (including U.S. territories)

PREGNANT WOMAN

Assess for possible Zika virus exposure
Evaluate for signs and symptoms of Zika virus disease

• Symptomatic: <2 weeks after symptom onset, or
• Asymptomatic and NOT living in an area with active Zika virus transmission: <2 weeks after possible exposure

Zika virus rRT-PCR on serum and urine

Positive Zika virus rRT-PCR on serum or urine:
Recent Zika virus infection

• Symptomatic: Zika virus IgM and dengue virus IgM
• Asymptomatic and NOT living in an area with active Zika virus transmission: Zika virus IgM 2–12 weeks after exposure

Zika virus IgM and dengue virus IgM negative:
No recent Zika virus infection

Zika virus PRNT ≥10 and dengue virus PRNT <10:
Recent Zika virus infection

Abbreviations: IgM = immunoglobulin M; PRNT = plaque reduction neutralization test; rRT-PCR = real-time reverse transcription–polymerase chain reaction.

* A pregnant woman is considered symptomatic if one or more signs or symptoms (fever, rash, arthralgia, or conjunctivitis) consistent with Zika virus disease is reported whereas a pregnant woman is considered asymptomatic if symptoms are NOT reported.

† Testing includes Zika virus rRT-PCR on serum and urine samples, Zika virus and dengue virus Immunoglobulin M (IgM), and plaque reduction neutralization test (PRNT) on serum samples. PRNT results that indicate recent flavivirus infection should be interpreted in the context of the currently circulating flaviviruses. Refer to the laboratory guidance for updated testing recommendations (http://www.cdc.gov/zika/laboratories/lab-guidance.html). Because of the overlap of symptoms in areas where other viral illness are endemic, evaluate for possible dengue or chikungunya virus infection.

‡ Dengue IgM antibody testing is recommended only for symptomatic pregnant women.

§ If Zika virus rRT-PCR testing is requested from laboratories without IgM antibody testing capacity or a process to forward specimens to another testing laboratory, storing of additional serum samples is recommended for IgM antibody testing in the event of a rRT-PCR negative result.

¶ For the United States (including U.S. territories), possible exposure to Zika virus includes travel to or residence in an area with active Zika virus transmission (http://wwwnc.cdc.gov/travel/notices/), or sex (vaginal sex (penis-to-vagina sex), anal sex (penis-to-anus sex), and oral sex (mouth-to-penis sex or mouth-to-vagina sex), and the sharing of sex toys) without a barrier method to prevent infection (male or female condoms for vaginal or anal sex, male condoms for oral sex (mouth-to-penis), and male condoms cut to create a flat barrier or dental dams for oral sex (mouth-to-vagina) with a partner who traveled to, or lives in an area with active Zika virus transmission.

** Possible exposure to Zika virus includes travel to or residence in an area with active Zika virus transmission (http://wwwnc.cdc.gov/travel/notices/), or sex (vaginal sex (penis-to-vagina sex), anal sex (penis-to-anus sex), oral sex (mouth-to-penis sex or mouth-to-vagina sex), and the sharing of sex toys) without a barrier method to prevent infection (male or female condoms for vaginal or anal sex, male condoms for oral sex (mouth-to-penis), and male condoms cut to create a flat barrier or dental dams for oral sex (mouth-to-vagina) with a partner who traveled to, or lives in an area with active Zika virus transmission.

†† If Zika virus rRT-PCR testing is requested from laboratories without IgM antibody testing capacity or a process to forward specimens to another testing laboratory, storing of additional serum samples is recommended for IgM antibody testing in the event of a rRT-PCR negative result.
**Management of ZIKV**

**General supportive care**

- **Treat symptoms**
  - acetaminophen to reduce fever and pain
- **Rest adequately**

- **Drink fluids to prevent dehydration**

- **Avoid aspirin and other NSAIDs**
  - NSAIDs can exacerbate bleeding if undiagnosed dengue

- **Review current medications to avoid drug-drug interactions**

[www.cdc.gov/Zika](http://www.cdc.gov/Zika)
confirmed/presumptive recent ZIKV/Flavivirus infection

• prenatal management
  o serial ultrasounds q3-4 weeks foetal anatomy and growth assessment
  o amniocentesis

• individualize according to woman’s preference

(www.cdc.gov/Zika)
Management of ZIKV (cont’d)

Post-natal management

- Live birth - test serum (and CSF if collected for other reasons)
  - RNA NAT
  - Zika-specific and dengue-specific IgM
  - Zika rRT-PCR with/without immunohistochmepical staining
    - Umbilical cord
    - Placenta

(www.cdc.gov/Zika)
Management of ZIKV (cont’d)

- post-natal management cont’d
  - foetal loss
    - Zika rRT-PCR with/without immunohistochchemical staining
      - foetal tissue

No evidence of ZIKV or dengue fever
- prenatal ultrasound to exclude congenital ZIKV infection
  - normal ultrasound
    - base care upon ongoing risk of woman for ZIKV infection
  - abnormal ultrasound
    - repeat Zika rRT-PCR and IgM test

(www.cdc.gov/Zika)
# Clinical management of a pregnant woman with suspected Zika virus infection

<table>
<thead>
<tr>
<th>Interpretation of Laboratory Results*</th>
<th>Prenatal Management</th>
<th>Postnatal Management</th>
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<tbody>
<tr>
<td>Recent Zika virus infection</td>
<td></td>
<td>LIVE BIRTHS:</td>
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<tr>
<td></td>
<td>• Consider serial ultrasounds every 3–4 weeks to assess fetal anatomy and growth†</td>
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<td></td>
<td>• Decisions regarding amniocentesis should be individualized for each clinical circumstance§</td>
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<tr>
<td>Recent flavivirus infection; specific virus cannot be identified</td>
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<td>FETAL LOSSES:</td>
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<td>• Zika virus rRT-PCR and IHC staining of umbilical cord and placenta is recommended.‖</td>
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<tr>
<td>Presumptive recent Zika virus infection**</td>
<td>• Consider serial ultrasounds every 3–4 weeks to assess fetal anatomy and growth.</td>
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<td>• Cord blood and infant serum should be tested for Zika virus rRT-PCR, Zika IgM, and dengue virus IgM antibodies. If CSF is obtained for other reasons, it can also be tested.</td>
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<td>Recent dengue virus infection</td>
<td>Clinical management in accordance with existing guidelines (<a href="http://apps.who.int/iris/bitstream/10665/44188/1/9789241547871_eng.pdf">http://apps.who.int/iris/bitstream/10665/44188/1/9789241547871_eng.pdf</a>)</td>
<td></td>
</tr>
</tbody>
</table>
| No evidence of Zika virus or dengue virus infection | • Prenatal ultrasound to evaluate for fetal abnormalities consistent with congenital Zika virus syndrome.† |...
Prevention of ZIKV and adverse pregnancy outcomes

• **Recommend and long-acting reversible contraception (LARC) during Zika outbreaks**

  • safe and most effective reversible birth control
  
  • effortless after correct insertion
    - remains effective 3-10 years

  • highest adherence and satisfaction rates

• previous users recover immediate fertility

Prevention of ZIKV fever

- Pregnant women should avoid travel to areas with an active infestation.

- Travelers should take the basic precautions to protect themselves from mosquito bites.

- During outbreaks, health authorities may advise that spraying of insecticides be carried out.

- Reducing mosquito populations and avoiding bites, which occur mainly during the day.

- Eliminating and controlling Aedes aegypti mosquito breeding sites reduces the chances that Zika will be transmitted.

- DEET
  - N,N-Diethyl-meta-toluamide
**How GM mosquitoes work**

1. GM male with sterile gene and wild female mate
2. Female lays eggs that contain sterile gene
3. Eggs hatch into larva and treated with tetracycline so it can grow into a pupa (4)
4. Larva develops into pupa
5. Pupa grows into adult, researchers have more supplies of GM males to release into the wild

**Life cycle of wild male and female mosquitoes produces blood-sucking females**

1. Male and female male
2. Female lays eggs
3. Eggs hatch into larva
4. Larva develops into pupa
5. Pupa grows into adult

Introduction of GM males breaks this cycle as faulty gene causes offspring to prematurely die.

More GM males are created in the lab by adding tetracycline to larvae to allow development.
Significant ZIKV-associated neurological complications

**Acute transverse myelitis**
- partial or complete loss of voluntary motor function in the pelvic limbs >/< T2
  - dermatome-specific sensory loss
- commonly involves early bladder and bowel incontinence
- essentially spares cranial nerves
- MRI of spine +/- gadolinium enhancement usually locates focal areas of involvement
- CSF shows pleocytosis and/or increased IgG index
- equivocal EMG/NCV findings
- Rx: high-dose steroids

**Acute inflammatory demyelinating polyneuropathy (AIDP) or GBS**
- weakness and sensory loss move upward from legs to arms
- commonly involves cardiovascular instability (autonomic dysfunction)
  - rarely causes bladder/bowel incontinence
- commonly affects cranial nerves
  - weak facial muscles (CN 3,4,6)
  - palsy of extra-ocular muscles (CN 7)
- MRI of spine is normal
- specific pattern of EMG/NCV findings
- CSF shows elevated protein without pleocytosis
- specific pattern of EMG/NCV findings
- Rx: IVIG or therapeutic plasma exchange (avoid steroids)
Congenital Zika syndrome

- Features include
  - Severe microcephaly with partially collapsed skull
  - Thin cerebral cortices with subcortical calcifications
  - Macular scarring and focal pigmentary retinal mottling
  - Marked early hypertonia
  - Congenital joint contractures (arthrogryposis)
    - "Curving of joints"

(Moore, CA, et. al.; Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians; JAMA Pediatr. 2016 Nov)
Newborn infant congenitally infected with Zika virus. Clinical features of congenital Zika syndrome include microcephaly, facial disproportion, hypertonia/spasticity, hyperreflexia, seizures, irritability, arthrogryposis, club feet, retinal abnormalities, and hearing loss.