Zika Virus and the Pregnant Woman

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History of Zika Virus

• Initially identified in 1947 in a rhesus monkey in the Zika Valley in Uganda through a yellow fever surveillance program
• First human case reported in Uganda in the 1950s
• Spread from Northern Africa to South East Asia
  – Limited to small-scale epidemics until 2007 when it hit the Yap Islands

History of Zika Virus

• 2007 Yap Island, Micronesia
  – 73% of the population became infected
• Since then rapid spread into the Pacific and then the Americas
• Rare reports of fetal effects until Brazil
Initial reports of possible congenital infection associated with ZIKV infection

• 2013-2014 French Polynesia
  - ZIKV seropositivity before outbreak 0-1.7%  
  - Estimated 10% of the population were infected (~28,000 persons)  
  - GBS 40 cases, 8 cases fetal and neonatal microcephaly  
    • 1% women infected in the first trimester

Brazil 2015

• Northeastern Brazil May 2015 first reported at the same time Dengue was circulating  
• September, 2015 an increase in microcephaly cases reported in the same areas as the Zika epidemic (20 cases per 10,000 live births – 20 fold increase)
At a Glance – Zika in the US
February 8th, 2017

• US States
  – Travel-associated cases reported: 4,780
  – Locally acquired vector-borne cases reported: 220
  – Total: 5,001
    • Sexually transmitted: 41
    • Guillain-Barre syndrome: 13

• US Territories
  – Travel-associated cases reported: 140
  – Locally acquired cases reported: 36,498
  – Total: 36,638

At a Glance – Zika in the US
February 8th, 2017

• Maryland
  – Local cases 0
  – Travel Associated Cases 130 (3)

• Alabama
  – Local Cases 0
  – Travel Associated Cases 38 (1)
**Affected Pregnant Women**
**January 24th, 2017**

- 4,465 Laboratory Evidence Zika infections in pregnant women
  - 1,394 in the United States
  - 3,071 in the U.S. territories
- ~55% had clinical symptoms
- Outcomes (999 completed pregnancies)
  - 38 liveborn infants with birth defects
  - 5 pregnancy losses with birth defects

**Zika Virus Infection**

- Incubation ~3-14 days
- Viremia 11-13 days
  - > 10 weeks in pregnancy
  - >60 days GBS cases
  - May last in semen and cervical mucous
- Presence of viral RNA may not equal transmission risk if antibodies have formed

**Zika Virus Infection**

- Only 20% of infected individuals develop symptoms
  - Acute onset fever, maculapapular rash, arthralgias (joint pain) and conjunctivitis are the big 4
  - Myalgias, headache, retro-orbital pain, pruritis and vomiting
ZIKV Transmission

- **Aedes** genus of mosquito is the common vector (Aedes aegypti and Aedes albopictus)
- **Vertical transmission**
  - Antepartum
  - Intrapartum
  - Breastfeeding – no cases but ZIKV RNA is found in breast milk. Official recommendation is to allow breastfeeding
- **Sexual transmission** (male to female, male to male and female to male)
- Blood bank
- Laboratory exposure

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Sexual Transmission of Zika Virus

- Zika virus can be transmitted via sex without a condom though the actual risk is low
- Most reported cases have been from symptomatic persons (male to female, male to male and female to male)
- 2 cases of asymptomatic male to female transmission

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Sexual transmission of Zika virus confirmed.
Zika and Blood Transfusion

- No confirmed blood transfusion transmission cases in the US
  - One suspected case in Brazil
- FDA recommendations
  - Screen all donated WB or blood components

Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?

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3. R. Ximenes3,
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February 2016

2 Pregnant women diagnosed with fetal microcephaly
- Blood test for Zika negative
- RT-PCR of the amniotic fluid positive
Case 1 at 30 weeks gestation
Case 2 at 29 weeks gestation

Ultrasound in Obstetrics & Gynecology
Volume 47, Issue 1, pages 6-7, 5 JAN 2016 DOI: 10.1002/uog.15831

Intracranial calcifications
Absent normal vermis
Dysgenesis of the corpus callosum
Brain atrophy
Brazilian Ministry of Health Task Force Findings

- The initial 35 infant cohort (≤ 2 SD)
  - All mothers lived in or traveled to endemic areas
    - 74% had a rash in first or second trimester
  - 71% severe microcephaly ≥ 3 SD
  - 49% had at least one neurologic abnormality
  - 27/35 infants had neuroimaging and 100% were abnormal
    - Brain calcifications, cell migration abnormalities, cortical/subcortical atrophy

CDC MMWR 1/22/2016

What is Microcephaly….

- Head significantly smaller than would be expected at a specific gestational age and sex
- Associated with
  - Genetic disorders (Chromosomal and single gene disorders)
  - Environmental
    - Perinatal infections
    - Prenatal exposure to drugs or chemicals
    - Perinatal hypoxia or trauma

Biologic Link between Zika and Microcephaly

- Ming, G et al Johns Hopkins March 2016
  - The Zika virus selectively infects cells from the brain cortex resulting in cell destruction or at least disrupted growth by cell cycle dysregulation
    - Cortical neural progenitor cells

Cell Stem Cell
Fetal effects

• Microcephaly and intracranial calcifications
  – Vertical transmission – symptoms at 13 weeks gestation
  – Ultrasound at 14 and 20 weeks normal anatomy and growth
  – 29 weeks gestation “abnormal”
  – 32 weeks: IUGR <3%, normal AFI, placental calcifications, HC <2%, moderate ventriculomegaly, numerous intracranial calcifications and “blurred anatomy” Dopplers all normal

NEJM Brief Report 2/12/2016

Fetal effects

• Pregnancy termination : 5%, prominent microcephaly at the 1%, whole brain weight 4SD below average. Small cerebellum and brain stem, complete agyria and internal hydrocephalus, numerous calcifications. Virus particles identified with EM, RT-PCR positive in brain only, negative for other flaviviruses

NEJM Brief Report 2/12/2016
Fetal/Neonatal effects

- Eye abnormalities
  - 29 infants with microcephaly in Brazil
  - 35% had ocular abnormalities (chorioretinal atrophy and focal pigment motting)
Congenital ZIKV Infection

- Microcephaly
- Brain atrophy
- Ventricular enlargement
- Intracranial calcifications
- Ocular defects
- Joint contractures
- Hydrops fetalis
- Absence of the corpus callosum
- Vermian agenesis
- Agenesis of the thalami
- Cataracts
- Vermian agenesis
- Intracranial calcifications
- Ocular defects
- Joint contractures
- ……………..

Pregnancy Effects

- Unknown if pregnant women are more susceptible
- Disease does not appear to be any worse in pregnancy
- Transmission to the fetus has been documented in all trimesters though first and second trimester probably highest risk for miscarriage and congenital microcephaly
Week of Gestation at the Time of ZIKV Infection and Abnormal Ultrasonographic and Doppler Findings.

Third Trimester Maternal ZIKV Infection

- 2 cases of maternal ZIKV in the 36th week of gestation confirmed by qPCR maternal urine
  - Normal HC at birth
  - Superependymal cysts and lenticulostriate vasculopathy in postnatal imaging

ZIKV Testing (11/25/2016 MMWR)

- RT-PCR validated
  - Serum, amniotic fluid, urine, placenta, fetal tissues, semen
  - Good about 7-14 days of symptom onset (urine up to 14 days)
- Serologic testing
  - IgM (ELISA) turns positive ~ 4-7 days
    - Cross-reaction with other flaviviruses, including vaccination and infections
  - Plaque reducing neutralization test (PRNT)
- Immunohistochemical staining
Interim Guidance for Interpretation of Zika Virus Antibody Test Results
MMWR June 3, 2016

• A positive ZIKV PCR confirms infection but a negative test does not rule out infection
• If IgM is positive, equivocal or inconclusive, do a PRNT
  – Interpretation has been recently updated – more conservative to reduce the possibility of missing Zika (or dengue)

Preconception counseling

• Couples planning to conceive who do not live in areas of active Zika virus transmission
  – Avoid travel to areas of active Zika virus transmission
• Men with Zika virus disease or who have a possible Zika virus exposure, regardless of symptoms, should wait 6 months to conceive
• Women who travel, regardless of infection or symptoms should wait at least 8 weeks
• Condoms or abstain from sex

Preconception counseling

• Couples planning to conceive when one or both live in areas of active Zika virus transmission
  – If symptoms, test for Zika virus
    • If a woman is positive, wait at least 8 weeks gestation
    – If no symptoms, no testing recommended at this time
  – Mosquito prevention counseling
Zika and Fertility Treatment

- No reports to date of Zika virus through ART
  - Transmission via gametes or embryos is theoretically possible
  - FDA guidance for donated human cells, tissues and cellular and tissue-based products

Peri-conception Exposure

- Pregnant women who do not reside in areas with active Zika virus transmission who have had possible Zika virus exposure during the 8 weeks before conception (6 weeks before the last menstrual period) can be offered serologic testing within 2–12 weeks of this exposure.

Recommendations for Pregnant Women

- CDC Recommends all pregnant women consider postponing travel to areas of ongoing Zika virus transmission if possible
- If pregnant women have to travel, avoid mosquito bites (day and night)
  - Protective clothing
  - U.S. EPA-registered insect repellent
  - Screened-in or air-conditioned areas
Use EPA regulated insect repellent. Both DEET and Picardin are safe in pregnancy in appropriate dosing.

Evaluation- Maternal

• Screen all pregnant at each prenatal visit
• Test all pregnant woman with travel to an affected area (Algorithms) or exposure to a partner that has traveled
Evaluation- Maternal

• Test all pregnant woman with travel to an affected area or exposure to a partner that has traveled
  – No symptoms not living in area of active Zika virus transmission within 2 weeks of exposure
    • Serum and urine Zika rRT-PCR
      – A negative result requires further testing 2-12 weeks after exposure with a Zika IgM
  – No symptoms not living in area of active Zika virus transmission 2-12 weeks of exposure
    • Serum Zika IgM – if positive, send rRT-PCR

Evaluation- Maternal

• Test all pregnant woman with travel to an affected area or exposure to a partner that has traveled
  – Symptoms not living in area of active Zika virus transmission within 2 weeks of exposure
    • Serum and urine Zika rRT-PCR
      – A negative result requires further testing 2-12 weeks after exposure with a Zika IgM and a Dengue IgM. If positive, do PRNT
  – Symptoms not living in area of active Zika virus transmission 2-12 weeks of exposure
    • Serum Zika and Dengue IgM – if positive, send rRT-PCR

Evaluation- Maternal

• Symptomatic and asymptomatic pregnant women seeking care >12 weeks after symptom onset or exposure
  – Consider IgM testing
  – If fetal abnormalities concerning for Zika virus, rRT-PCR should be performed on maternal serum and urine.
  – A negative result does not rule out recent infection
Women residing in areas of ongoing risk for Zika virus transmission

- Asymptomatic women in first and second trimester
  - Serum Zika IgM
    - If positive, reflex rRT-PCR on same sample. If negative, send PRNT

Clinical management of a pregnant woman with suspected Zika virus infection

- Serial ultrasounds every 3-4 weeks to assess fetal anatomy and growth
  - Amniocentesis should be individualized if imaging suspicious for fetal infection.
  - Assay performance for amniotic fluid is uncertain at this time

Evaluation- Fetal

- If the ultrasound is abnormal or the maternal testing is positive for Zika infection, consider an amniocentesis after 15 weeks gestation
  - Limited knowledge of how good the AF PCR is, how long AF stays positive and if + AF PCR correlates with disease severity
- Send all pathology specimens and placentas for testing
Counseling for Zika Virus

- Demonstrative causation between Zika virus infection during pregnancy and adverse pregnancy outcomes
  - Unknown the rate of vertical transmission and rate at which an infected fetus manifests complications
- False positive and false negative testing not uncommon
- A reassuring ultrasound may not preclude later manifestation
- Congenital Zika infection may present well after birth


Counseling for Zika Virus

- Based on the available evidence, we think that Zika virus infection in a woman who is not pregnant would not pose a risk for birth defects in future pregnancies after the virus has cleared from her blood. From what we know about similar infections, once a person has been infected with Zika virus, he or she is likely to be protected from a future Zika infection.

Breastfeeding and Zika Virus

- Zika RNA has been reported in breastmilk
- No reports of infants getting Zika virus through breastfeeding
- Women may continue to breastfeed, even in areas where active Zika virus transmission is found
US Zika Pregnancy Registry and a CDC Zika hotline available
ZikaPregnancy@cdc.gov email
1-770-488-7100
ZIP Trial now enrolling