Zika Virus

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Do we really need to talk about this?
• Unheard of by most providers until 11 months ago
• Does not cause major health risks to most people
• Does not seem likely to spread in most parts of the U.S.
• Major fetal implications seem relatively rare even among infected women

How often do you talk about Zika in your practice?
A. At least once every clinic
B. Often
C. Occasionally
D. Rarely
E. Never
Zika Virus

Do we really need to talk about this?

- 5 million Californians travel to Mexico alone annually
- Over 90 million people travel to Central/South America, the Caribbean and Mexico annually
- Zika virus is not likely to go away and may become more of an issue with ongoing changes in our climate
- We are learning more and more about the less obvious effects on infected fetuses
- Lifetime cost of caring for one child with microcephaly is >$10 million
- Our patients are worried

OUTLINE

- Background of Zika virus
- “Congenital Zika Syndrome”
- What healthcare providers should do
- Emerging topics

Zika Virus

- Single-stranded RNA arbovirus
- Arthropod-borne
- Flavivirus family
- Related to dengue, West Nile, yellow fever, Japanese encephalitis
Transmission

• *Aedes* species of mosquitoes
  – Poor flyers (small range for each mosquito)
  – Bite during day and nighttime
  – Attracted by standing water, more common in less developed areas
  – Also transmits dengue, chikungunya and yellow fever

Maternal → fetal

• Sexual transmission
  • Blood transfusion (none in the US)
  • Laboratory exposures (1 in the US)
  • Transplants

Clinical Presentation

• 20-40% of infected people recall symptoms
• Mild febrile illness with viral exanthem
• Maculopapular rash, conjunctivitis, arthralgias, myalgias
  – typically ~ 7 days after exposure, lasting 3-4 days
• Rare:
  – Guillain-Barre
  – Myositis
  – Congenital Zika Syndrome


The Zika Virus Timeline

- 1947 Virus Identified
- 1952 First Human Cases
- 2007 Yap Island Outbreak
- 2013-2014 French Polynesia Outbreak
- Sept, 2015 Increase in reported cases of microcephaly in Northeast Brazil
- Nov 24, 2015
- May, 2015
- Jan 15, 2016
- Nov 17, 2015
- Feb 1, 2016
- July, 2016 First reported transmission in United States (Miami Dade, Florida)
- Nov 17, 2015
- Nov 24, 2015
- Jan 15, 2016
- Feb 1, 2016
- Public Health Emergency of International Concern

Spread of Zika Virus

Countries and territories showing historical distribution of Zika virus, 1947 - 2016

Where Zika-Transmitting Mosquitoes Live in the US

- Aedes aegypti
- Aedes albopictus

Zika Virus in the United States

Laboratory-confirmed Zika virus disease cases reported to ArboNET by state or territory (as of October 3, 2016)

- 27,000 locally-acquired cases
- 137 locally-acquired cases
**Current Statistics as of 10/19/2016**

**U.S. States**
- Travel associated cases reported: 3,878
- Locally acquired vector-borne cases reported: 137
- Sexually transmitted cases reported: 32

**U.S. Territories**
- Travel-associated cases reported: 88
- Locally acquired vector-borne cases reported: 27,314

**Pregnant Women with any laboratory evidence of Zika**
- US States: 899
- US Territories: 1,927

**Pregnancy Outcomes for Women with Laboratory Evidence of Possible Zika Virus**

- **United States:**
  - Liveborn infants with birth defects: 23
  - Pregnancy losses with birth defects: 5

- **US Territories:**
  - Liveborn infants with birth defects: 1
  - Anticipated number in Puerto Rico is 100-300
  - Pregnancy losses with birth defects: 1

**Background of Zika virus**
- **“Congenital Zika Syndrome”**
- What healthcare providers should do
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**CONGENITAL ZIKA VIRUS IS A REAL CLINICAL ENTITY.**

A. Definitely true
B. Probably true
C. Unlikely
D. Definitely not true
Congenital Zika Syndrome

- Microcephaly
- Severe cortical malformations
- Abnormalities of the posterior fossa
- Ventriculomegaly
- Intracranial calcifications
- Ophthalmologic abnormalities
- Intrauterine Growth Restriction
- Intrauterine Fetal Demise
- Subtle effects??
- Long-term outcomes??

Microcephaly

- Many causes – genetic, infectious, exposures, etc.
- Cytomegalovirus & alcohol
- Newborn head circumference > 2 SD below mean
- Reduced brain volume
- Seizures
- Intellectual disability
- Cognitive differences
- Motor disability
- Behavioral problems

Evidence of Congenital Zika Syndrome

- Epidemiological evidence
- Microbiologic evidence
- Clinical evidence
Epidemiological Evidence - Brazil


- 5-6/100,000 live births
- First reports of autochthonous Zika virus infections in Brazil
- Really probably closer to 250/100,000 by the end of 2015

Epidemiological Evidence - French Polynesia

Cauchemez et al:
- 8 microcephaly cases identified Oct, 2013 – April, 2014
- Baseline prevalence 2/10,000 (95% CI 0 – 8)
- Zika-associated risk 95/10,000 (95% CI 34 – 191)
- Modeling suggests a period of risk in the 1st trimester

Besnard et al:
- 4,787 births between March, 2014 – May, 2015
- 19 cases of unexplained congenital brain malformations (3/1,000)
- 14-fold increase in congenital microcephaly, 31-fold increase in brainstem dysfunction spatially & temporally related to ZIKV outbreak

Microbiologic Evidence

- Zika virus infects cells of the central nervous system ("neurotropism")
- Nerve cells infected with ZIKV in vitro show apoptosis
- ZIKV receptors exist in many maternal/fetal compartments
- Critical proteins that facilitate ZIKV entry into the fetal compartment and neural cells have been identified
- Mouse and primate models demonstrate brain injury with degeneration of nerve progenitor cells and neuronal tissue when infected with Zika virus

Clinical Evidence

- Case reports, case series, one case-controlled trial
- Fetuses and newborns among mothers living in or traveling to areas with Zika virus transmission with:
  - Growth restriction (identified in 3rd trimester)
  - Microcephaly plus other brain abnormalities
  - Intraocular findings (cataracts, calcifications)
  - Intrauterine fetal demise
  - ZIKV identified in abortuses, amniotic fluid, newborn serum/urine, CNS tissue
Among 42 ZIKV positive women with ultrasound follow-up:
- 2 (4.8%) IUFDs (infections at 25 & 32 weeks)
- 12 (29%) had abnormal ultrasound results
  - Microcephaly
  - Cerebral calcifications/other CNS abnormalities
  - Vermian agenesis, Blake’s pouch cyst
  - Abnormal cerebral or UA arterial flow
  - Oligo/anhydramnios
  - IUGR
- 6 live-born: 3 generally well, 2 with significant neurologic abnormalities, 1 with IUGR

Clinical Evidence – Case Series
Brasil et al

Among 42 ZIKV positive women with ultrasound follow-up:

1,501 cases of microcephaly in Brazil
- 602 with evidence of Zika virus
- NON-Zika cases had:
  - Newborns with larger head circumferences
  - Lower first-week mortality (14 vs 51/1,000 – rate ratio 0.28)
  - Fewer rashes (21% vs 61% – rate ratio 0.34)
- Rashes in the third trimester were associated with brain abnormalities despite normal head sizes.
- 20% of likely cases had normal head circumference
- Sensitivity of microcephaly to detect definite/probable cases was 83% (95% CI 79 – 86%)

Clinical Evidence – Case Series
Franca et al

• 32 cases, 62 controls
• Cases: neonates with microcephaly (> 2 SD below the mean controlled for sex/GA)
• Controls: live neonates without abnormalities
• OR for microcephaly and laboratory confirmed Zika virus = 55.5 (8.6-∞)
• OR in cases with brain abnormalities = 113.3 (14.5 - ∞)

Clinical Evidence – Case Control Study
de Araujo et al

Shepard’s Criteria for “Proof” of Human Teratogenicity

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Evidence</th>
<th>Met?</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Proven prenatal exposure</td>
<td>Microcephaly seen with lab-proven Zika-infections occurring during pregnancy</td>
<td>Yes</td>
</tr>
<tr>
<td>* Solid epidemiologic evidence (≥ studies, RR ≥ 6)</td>
<td>Temporal &amp; geographic associations. 2 epidemiological studies published.</td>
<td>Yes</td>
</tr>
<tr>
<td>* Careful delineation of clinical cases</td>
<td>Phenotype well-described. Consistent with fetal brain disruption sequence.</td>
<td>Yes</td>
</tr>
<tr>
<td>* Rare exposure/rare defect</td>
<td>Zika infections &amp; microcephaly have occurred in travelers</td>
<td>Yes</td>
</tr>
<tr>
<td>Teratogenicity in experimental models</td>
<td>Evidence of teratogenicity in mice and primates</td>
<td>Yes</td>
</tr>
<tr>
<td>Biologically plausible</td>
<td>Findings consistent with other viral exposures, ZIKV is neurotropic and infects nerve progenitor cells, ZIKV isolated from tissues of affected fetuses/neonates</td>
<td>Yes</td>
</tr>
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Do you screen for risk for Zika exposure in your pregnant patients?

A. Yes, at every visit
B. Yes, at least once in pregnancy
C. If the patient mentions travel
D. Not really

So...What do we do?

- Screen for travel, test for exposure
- Advise
- Provide options & support
- Stay up-to-date
- Advocate

Screen and Test

- Screen for exposure: travel or unprotected sex with someone who traveled to areas with active transmission (cdc.gov/Zika)
- Consider using EHR as trigger
Symptomatic pregnant women with exposure:
- rRT-PCR testing of serum and urine up to 2 weeks after symptom onset
Asymptomatic pregnant women with exposure:
- anti-Zika IgM testing 2-12 weeks after the last date of possible exposure
- rRT-PCR testing of serum and urine < 2wks after the last possible exposure or if anti-Zika IgM positive
  - Negative rRT-PCR results should be followed up with plaque reduction neutralization testing to measure virus specific neutralizing antibodies

Microcephaly – not entirely straightforward
- Suspect: greater than 2 SD below the mean for GA
- Diagnose: greater than 4-5 SD below the mean
Ventriculomegaly
Intracranial calcifications
IUGR
Placental abnormalities
Doppler abnormalities

Who Should Have Follow-Up Ultrasounds?
- Positive ZIKV testing opting to continue pregnancy
- Travelers who were not tested

Who Probably Does NOT Need Follow-Up Ultrasounds?
- Patients who did not travel or have unprotected sex with a partner who traveled to an area with Zika transmission
- Negative anti-ZIKV IgM within 12 weeks of travel

Fetal brain MRI – potentially useful, but limited access, specialized interpretation
Postnatal Testing

- Infants born to women with laboratory evidence of Zika:
  - Neonatal serum sample for IgM/rRT-PCR testing
  - Pathologic evaluation of fetal tissue

Advice for Pregnant Women

- Avoid travel to areas with Zika transmission
- FDA-approved mosquito repellents, protective clothing
- Condoms if partners have traveled
- Contraception for those not wanting to conceive
- Reassure the worried-well
- Zika is new, counseling in the face of uncertainty is not
- Patient-centered, preference based

Advice for Couples Considering Pregnancy

- Avoid travel to areas with Zika transmission
- FDA-approved mosquito repellents, protective clothing
- Women: wait at least 8 weeks after symptoms or last possible exposure
- Men: Wait at least 6 months after symptoms or last possible exposure

Provide Options & Support

- For those at high-risk or with obvious findings:
  - Expectant management
    - Serial ultrasounds
    - Antenatal testing
    - Resources, counseling, support
  - Termination
Stay Up to Date

• Information about Zika is rapidly changing

Stay Up to Date

• Consider designating someone to coordinate Zika response
  • UCSF “Zika Response Coordinator”
    – Responds to patient queries
    – Follows-up on testing
    – Stays up-to-date on guidelines and recommendations
    – Counseled over 500 patients
    – Tested 125+ patients for Zika exposure
    – Screened more than 6,000 office visits since Zika Travel Screen inception in June
    – Saved obstetric providers 300-400 care hours in 6 mos

Advocate

• Funding
  – Federal, international
  – Vaccine development, vector control, education, family planning services, surveillance programs, support for affected families

• Policy
  – Family planning
  – Vector control strategies

Conclusions – The Dry Ink

• Congenital Zika Syndrome (CZS) is probably real and seems to have the potential to be quite serious
• Zika virus is primarily transmitted by mosquitoes that do not reside in the Bay Area for now, but over 40 million Americans travel to affected areas each year
• Prior Zika virus infection appears to provide protective immunity
• Caring for women at high risk for fetal-CZS requires careful counseling and providing pregnancy options when appropriate
The Wet Ink

- Probability of an affected fetus in an infected mother
- Long term outcomes of Zika
- Ameliorating or exacerbating factors (genetic/co-exposures)
- Critical windows in pregnancy
- Economic, social and other consequences from a missing birth cohort

Conclusions

- Monitor pregnant patients for exposure
- Suggest avoidance of exposure when possible pre-pregnancy and during pregnancy
- Provide careful, patient-centered counseling
- In time, “CZS” will likely to take it’s place with other infectious diseases in pregnancy – another “O” in “TORCH”

Thank You