Congenital Zika Viral Infection

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DISCLOSURE

The content of this presentation does not relate to any product of a commercial entity; therefore, I have no relationships to report.
Objectives for this Presentation

1. Review importance of this emerging virus
2. Provide overview of transmission, epidemiology and characteristics of this infection in pregnant women and infants
3. Discuss current recommendations for diagnosis and management of infection
4. Review established and emerging strategies for prevention of infection
Congenital Zika

- Early fetal loss
- Constellation of anomalies
- Consistent and unique - neural tube defects
- Consequences of direct neurological damage
- Associated with severe intracranial volume loss
- Specific cranial morphology syndrome
- Specific brain anomalies
- Ocular anomalies
- Congenital contractures
- Can be divided into structural and functional components (overlap)
Zika Virus (ZKV)

- Encapsulated, single stranded RNA virus
- Member of flavivirus family (others include West Nile, Dengue, Yellow Fever, Tick-Borne Encephalitis)
Presentation of Human ZKV in Adult Humans

• Signs/symptoms similar to dengue, chickungunya which are frequently found in the same geographic areas

• However, serologic surveys (e.g., Yap) indicate up to 80% of those infected are asymptomatic.
Presentation of Human ZKV
History of ZKV

- Discovered in 1947 in Uganda in blood of a rhesus macaque
- Nigeria – 3 human cases in 1953
- 13 reported cases in next 54 years, although serologic surveys indicated 6-10% prevalence in Uganda, other tropical areas
History of ZKV

• First large outbreak on Micronesian island of Yap in 2007

• Roughly 5000 infections in a population of 6700
History of ZKV

• Further subsequent outbreaks in French Polynesia and SE Asia
• Brazil beginning in March 2015, with >1.5 million cases
  ✓ Dramatic increase in Guillian-Barre
  ✓ 4300 cases of congenital microcephaly
• Retrospective confirmation of increased CNS problems in Yap, Polynesia
History of ZKV

• Subsequent spread to Central America, Mexico and Caribbean
• First US cases were associated with travel
• Endogenous cases now reported in southern Florida and Brownsville, TX
Transmission of ZKV

• Mosquito borne
  ✓ *Aedes aegypti*
  ✓ *Aedes albopictus*
  ✓ Possibly others
Distribution of Vector Mosquitoes in US, 2016
Transmission of ZKV

• Sexual
  ✓ ZKV may persist in semen up to 188 days
  ✓ Puerto Rico, 2016 – prospective study in 150 PCR+ adults with serial urine, serum, semen, saliva, vaginal specimens
    o Median/95 %ile for PCR+ in serum: 14 / 54 d
    o Median/95 %ile for PCR+ in urine: 8 / 39 d
    o Median/95 %ile for PCR+ in semen: 34 / 81 d
Transmission of ZKV

• Other
  ✓ Blood donors – 3% PCR+ in Polynesian
  ✓ Postnatal mother-infant
  ✓ Breast feeding not contraindicated
  ✓ Transplacental/Amniotic fluid
  ✓ Unclear - at least one in Utah in 2016
Pregnant Mouse Model of Perinatal ZKV
Cugola et al, Nature 2016
Congenital ZKV Infection

- As with other congenital infections, disease and defects usually occur after maternal infection in first or early second trimester
- Fetal loss
- IUGR
- LBW
- Reported with presumed and laboratory confirmed CZS
Congenital ZKV Infection

- Microcephaly (<3 %ile)
- Overriding sutures
- Redundant scalp skin
- Prominent occiput
- Thin cerebral mantle
- Cerebral calcifications
- Ventriculomegaly

- Cerebral atrophy
- Small corpus callosum
- Contractures
- Clubfoot
- Chorioretinitis
- Marked hypertonia
- Seizures
ZKV is Neurotropic

- Many CNS manifestations
- Histologic and microbiologic evidence when other sites have become negative
- Preferentially affects neuroblasts, rather than glioblasts
- Apoptosis is prominent, although inflammation is present
Cranial Morphology

- Severe microcephaly (>3 SD below mean)
- Infection consistent with fetal brain disruption sequence (FBDS)
  - Severe microcephaly
  - Overlapping cranial sutures
  - Redundant scalp skin
  - Severe neurologic impairment
- Extreme craniofacial disproportion
- Depression of frontal and parietal bones, can overlap
- Prominent occiput
- Decreasing OFC in utero
Congenital ZKV Microcephaly

- Extreme craniofacial disproportion
- Depression of frontal and parietal bones, can overlap
- Prominent occiput
- Decreasing OFC in utero

Cranial Morphology Computerized Tomography

Brain Finding

- Striking volume loss
  - Enlarged extra-axial space
  - Ventriculomegaly
- Poor gyral development
  - Few and shallow sulci
  - Irregular “beaded” cortex (polymicrogyria)
- Flatten Pons
- Small cerebellum
- Occipital shelf
- Intracranial calcifications

Fetal Brain Disruption Sequence

- Result of loss of brain volume
- Decrease in intracranial pressure
- Not specific to the etiologic agent
- Gross brain pathology resembles CMV
- Intracranial calcifications different than CMV
  - CMV – periventricular
  - ZIKA - Subcortical
Optic nerve hypoplasia with the double-ring sign, increased cup-disc ratio, attenuated blood vessels, gross pigment mottling, and chorioretinal scar in the macular region.

Contractures
ZKV During Pregnancy - CDC
ZKV Diagnosis in Pregnancy

• Assess all pregnant women at each prenatal visit with 3 questions
  1. Do you live in/travel to areas with active ZKV?
  2. Have you traveled to a ZKV area during pregnancy OR up to 8 wks before conception?
  3. Have you had sex without a condom or shared sex toys with a partner who lives in/traveled to a ZKV area?
ZKV Diagnosis in Pregnancy

• If answer to any of 3 questions was ‘Yes’, assess for signs/symptoms of ZKV disease

  ✓ Do you have or have you had in the last 12 wks, fever, rash, joint pain or conjunctivitis?
ZKV Diagnosis in Pregnancy

• If signs/symptoms ‘Yes’
  ✓ ZKV RT-PCR serum, urine
    o If + → recent ZKV
    o If - → check ZKV IgM and dengue IgM
  ✓ If ZKV and dengue IgM - → no recent ZKV
  ✓ If ZKV or dengue IgM + or equivocal → probable ZKV, dengue or flavivirus infection
    o Plaque reduction neutralization test (PRNT)
ZKV Diagnosis in Pregnancy

• If no signs/symptoms but meets travel or contact criteria 2-12 wks after exposure
  ✓ ZKV IgM and dengue IgM on serum
  ✓ If ZKV IgM and dengue IgM -, no recent ZKV
  ✓ If ZKV IgM + or equivocal, presumptive ZKV or flavivirus infection
    o ZKV RT-PCR on serum, urine; if + → recent ZKV
    o If ZKV RT-PCR -, proceed to PRNT
ZKV Diagnosis in Pregnancy

• Problems with ZKV antibody testing
  ✓ Cross-reactivity with other flaviviruses, hence need for PRNT if no prior flavivirus infection
  ✓ ‘Original antigenic sin’ due to prior flavivirus infection precludes interpretation of results
PRNT Interpretation for ZKV

- ZKV ≥10 and dengue <10 → recent ZKV
- ZKV ≥10 and dengue ≥10 → recent flavivirus infection; which one?
- ZKV <10 → no recent ZKV
Mother with Recent ZKV

- Serial fetal imaging if pregnancy continues
  - Sensitivity not ideal; better as GA increases
  - In one prospective Brazilian study (N=42), 29% abnormal (with 19% abnormal due to CNS)
- Sensitivity of AF PCR+ unclear
Neonatal ZKV Diagnosis

• Test if either:
  ✓ Mother with lab evidence of ZKV in pregnancy
  ✓ Abnormal clinical/imaging finding(s) and possible maternal epidemiologic link
• All blood tests should be baby blood, **NOT** cord blood
Neonatal ZKV Diagnosis

• RT-PCR of serum and urine in first 2 days
  ✓ Of all PCR+, 37%+ in serum but not urine
  ✓ Of all PCR+, 10%+ in urine but not serum
• Negative PCR does not exclude ZKV; if PCR –
  ✓ Check ZKV IgM serum and CSF (if sampled)
  ✓ If + → PRNT
Neonatal ZKV Diagnosis

• If ZKV RT-PCR and IgM -, still need
  ✓ Serial CNS imaging
  ✓ Serial physical and neurologic exams
  ✓ CBCDP, liver function tests
  ✓ Serial ABR
  ✓ Ophthalmology exam
  ✓ TSH, fT4 at 2 wks and 3 months
  ✓ Consider other congenital infections
Postnatal CNS Changes After Normal Birth OFC
van der Linden et al, MMWR 2016
Epidemiology of Perinatal ZKV in US, 2016

- From US Zika Pregnancy Registry
  - 1,297 pregnancies with possible ZKV
  - 972 infants from completed pregnancies
    - 51 (5%) with some laboratory evidence of ZKV
    - 10%, if restrict to confirmed ZKV
    - Of mothers with confirmed 1st ZKV, 15% of infants had ZKV birth defects
    - Postnatal CNS imaging obtained in only 25%
    - At least one postnatal ZKV test in only 65%
ZKV Treatment

• Currently only supportive treatment is available

ZKV Prevention

• Travel restrictions during pregnancy
• Restrict sexual contact with residents of and travelers to endemic areas
• Protection from vectors
  ✓ Repellent
  ✓ Permethrin treatment of clothing
  ✓ Bed nets
  ✓ Window screens
ZKV Prevention

• Vector control
  ✓ Eliminate breeding sites
  ✓ Larvicides
  ✓ Insecticides

• Vaccine
  ✓ 99% nucleotide homology in American strains
  ✓ Trials underway
  ✓ Timely administration (probably childhood)
Antibody Protects Developing Fetus from Zika Virus Pregnant Mice

- Researchers from Washington University in St. Louis and Vanderbilt
- Screened 29 anti-Zika antibodies from humans who had recovered from Zika infection
- ZIKV-117 efficiently neutralized in the lab five Zika strands (represents worldwide diversity of the virus)
- Gave antibody to pregnant mice either one day before or one day after they were infected.
- Markedly reduced the levels of virus in pregnant females, their fetuses, and placentas
- Placentas appeared to be normal
- No damage to fetal blood vessels
- No growth restriction
- Appears to have prevented the virus from crossing the placenta

Zika Virus

• Adult male mice
• Lethal dose of Zika virus
• 5 days after initial infection
• Antibody protected mice
ZIKV-117

- Can persist in certain parts of the body
- Eyes, testes
- Can cause long-term damage in mice
- Don’t know if antibody can clear it
Zika Virus Infection and Associated Neurologic Disorders in Brazil

• Letter to editor NEJM April 20, 2017
• Frequency of congenital microcephaly during the 2016 Zika season much lower than previous 2 years
• Despite only modest change in frequency of Zika infection
• Strongly suggests (but does not prove) that something else besides just Zika may be an important factor
• Zika is still definitely a causative virus
• Could a co-factor enhance pathogenicity/virulence of Zika
Perinatal ZKV

- CDC 24/7 consult line: 770-488-7100
- UDOH: 801-538-6191 or 888-374-8824 (888-EPI-UTAH)
- CDC and AAP websites
- Zika Screening Tool for Pregnant Women