Perinatal Viral Infections: from A to Zika

Dr. Amanda M Moen
Gillette Children’s Specialty Healthcare
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• I have no financial disclosures.
• I have no conflicts of interest to disclose.
• I am a pediatric neurologist, and welcome the input of the obstetricians in attendance.
- Discuss congenital cytomegalovirus (CMV) infection in comparison to congenital CMV syndrome
- Discuss diagnosis and management of congenital forms of CMV
- Discuss risk reduction strategies to reduce rate of congenital CMV
- Discuss congenital Zika syndrome in comparison to CMV
- Discuss diagnosis and management of congenital Zika syndrome
- Discuss risk reduction strategies to reduce risk of congenital Zika Syndrome

Objectives
CYTOMEGALOVIRUS: THE UNDER DISCUSSED PERINATAL ENDEMIC
• Most common congenital viral infection worldwide.
• Nearly 40,000 babies per year born in US with perinatal CMV exposure.

Cytomegalovirus (CMV)
• Primary infection:
  • Mild febrile respiratory infection
  • Infection may be similar to mononucleosis (“mono”)
  • Asymptomatic in up to 90% of cases
  • Common in young children
  • Spread by contact with body fluids – saliva, nasopharyngeal secretions, urine, blood, semen and breast milk

• Non-primary infection:
  • Reactivation of latent virus resulting in ability to shed and spread virus
    OR
  • Infection with a second strain of CMV resulting in symptoms and viral shedding
• CMV Seroprevalence: 58% of women age 15-44 years test positive implying prior infection
• Rate of CMV seroconversion is 1-7% per year worldwide
• The 42% of women who are seronegative are at higher risk of having an infant with congenital CMV if they contract CMV while pregnant

CMV in the Community
• High risk populations for CMV exposure:
  • Pregnant women: 2.3% seroconversion per year
  • Health Care workers: 2.3% seroconversion per year
  • Daycare providers: 8.5% seroconversion per year
  • Parents of young children:
    • Seronegative child: 2.1% seroconversion per year
    • Seropositive/shedding child: 24% seroconversion per year
Congenital CMV:

- **Primary Maternal Infection:**
  - 35-40% fetal infection rate if infection occurs in 1st or 2nd trimester
  - 65% fetal infection rate if infection occurs in 3rd trimester
  - Accounts for 25% of congenital CMV cases
- **Nonprimary Maternal Infection:**
  - 1% fetal infection rate
  - Accounts for 75% of congenital CMV cases
- Outcomes in infants are the same in both groups.

**CMV in the Community**
• **Recommendation from CDC is against routine screening of ALL pregnant women.**

• **WHY?**
  
  • No vaccine is available to prevent infection in seronegative women.
  
  • Seropositive women remain at risk of fetal infection from reactivation of latent virus and/or reinfection with a new viral strain.
  
  • There is no evidence that antiviral drug treatment of primary infection in pregnant women prevents or mitigates sequelae of CMV infection in the neonate.
  
  • The only randomized trial of use of intravenous immunoglobulins (IVIG) to prevent congenital infection did not establish a benefit.
  
  • Although fetal infection can be detected, there is no way to accurately predict whether or not the fetus will develop significant sequelae.
  
  • Routine screening can lead to unnecessary, and potentially harmful, intervention.

**Prenatal Screening for CMV?**
Whom to test?
• Pregnant women who present with a mononucleosis-like illness
• Pregnant women with a fetal anomaly suggestive of CMV on prenatal ultrasound
Ultrasound markers of possible fetal CMV infection:

Non-CNS Findings:
- Hyperechogenic fetal bowel
- Fetal growth restriction
- Ascites or pleural effusion
- Hepatosplenomegaly
- Hepatic calcifications
- Amniotic fluid abnormalities
- Hydrops fetalis
- Placental enlargement
Ultrasound markers of possible fetal CMV infection:

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CMV – Prenatal Diagnosis
Ultrasound markers of possible fetal CMV infection:

CNS Findings:
• Periventricular calcifications
• Ventriculomegaly
• Microcephaly
• Polymicrogyria
• Cerebellar hypoplasia
• Periventricular abnormalities – echogenicity or pseudocysts
• Large cisterna magna

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CMV – Prenatal Diagnosis
• Prenatal Diagnostic Testing:
  • Amniocentesis for CMV DNA polymerase chain reaction (PCR) testing allows confirmation of fetal infection
• Treatment:
  • Antivirals (ganciclovir, foscarnet, cidoforvir) can be use to treat severe end organ damage in adults with disseminated CMV.
  • BUT:
    • Do not decrease perinatal transmission of the virus
    • Do not decrease risk of infectious sequelae in the fetus
    • Drug-related risk to the fetus are unknown
  • Single randomized trial of intravenous immunoglobulins showed no benefit to the fetus.
  • Prenatal care and delivery in women with confirmed fetal CMV infection is ROUTINE.

Thus, all treatment is supportive and in preparation of caring for an infant with possible symptomatic or asymptomatic congenital CMV.

CMV – Prenatal Diagnosis
• Consider delay of confirmatory testing in suspected congenital CMV if prenatal diagnosis will not impact treatment.

• Postnatal Diagnosis:
  • Birth to 3 weeks: urine or saliva testing with CMV PCR to detect viral RNA
  • 3 weeks to 1 year: Retrospective testing of dried blood samples used for newborn screening with CMV PCR
  • Older than 1 year: Confirmative testing not possible as most states dispose of dried blood spots 1 year post-birth.

CMV: Postnatal Diagnosis
Symptomatic Newborns: 10-15% of infants with congenital CMV will have symptoms at birth.

Common Symptoms:
- Petechiae (54 to 76 percent)
- Jaundice at birth (38 to 67%)
- Hepatosplenomegaly (39 to 60%)
- Small size for gestational age (39 to 50%)
- Microcephaly (36 to 53%)
- Sensorineural hearing loss (SNHL, present at birth in 34%)
- Lethargy and/or hypotonia (27%)
- Poor suck (19%)
- Chorioretinitis (11 to 14%)
- Seizures (4 to 11%)
- Hemolytic anemia (11%)
- Pneumonia (8%)

Life threatening CMV infection: 8-10% of newborns with symptomatic CMV

CMV – Symptomatic Newborns
• Outcomes in infants with Symptomatic CMV infections at birth:
  • Mortality rate: 5%
  • Survivors:
    • Cerebral palsy with motor or cognitive deficit: 50% AND/OR
    • Hearing loss: 50%
    • Visual impairment: 20%
    • Normal outcome: 50%
• Treatment of symptomatic newborns
  • IV ganciclovir
  • Symptomatic treatments
• Represents the vast majority of infants with congenital CMV infections.
• Includes infants with failed hearing screen but no other symptoms at birth.
• Accuracy of diagnosis declines the later the patient presents for evaluation.
• Outcomes:
  • Hearing loss: up to 25%
  • Rates of motor, visual, and cognitive deficits are unclear
**Case Study: CS**

- Term SGA infant
- Uncomplicated prenatal course
- Mild feeding difficulty over the first 1-2 weeks of life
- Passed routine hearing screen in the nursery
- Presented to clinic at age 6 months with gross motor developmental delays

**Exam:**
- Microcephaly – OFC 39 cm (OFC 33.5 cm at birth)
- Hypotonia
- Inconsistent startle response to loud noise
Head Circumference: “OFC”
<table>
<thead>
<tr>
<th>Age</th>
<th>Head circumference (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth (CGA 40 weeks)</td>
<td>34-35</td>
</tr>
<tr>
<td>2 months</td>
<td>38</td>
</tr>
<tr>
<td>3 months</td>
<td>40</td>
</tr>
<tr>
<td>4 months</td>
<td>41</td>
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<tr>
<td>6 months</td>
<td>42-43</td>
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<tr>
<td>12 months</td>
<td>45-46</td>
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<tr>
<td>24 months</td>
<td>47-48</td>
</tr>
<tr>
<td>5 years</td>
<td>50-51</td>
</tr>
</tbody>
</table>

**Expected head circumference in children (50th percentile)**
Baby Girl CS: MRI Brain findings

A. Periventricular Calcifications
B & C. Bilateral Polymicrogyria / Cortical Malformation

Case Study: CS
Baby Girl CS Evaluations:

- Extensive blood testing showed positive serum CMV IgG (remote infection)
- Audiology evaluation showed bilateral severe sensorineural hearing loss
- Evaluation of stored blood spot from newborn screening confirmed presence of CMV infection at birth

Diagnosis:

- Congenital CMV syndrome with associated hearing impairment, motor delays, and brain malformation.

Case Study: CS
Baby Girl CS Outcome at age 8:

- She went on to develop cerebral palsy with moderate limitations in motor development requiring ongoing interventions including use of a walker to ambulate.
- She went on to have bilateral cochlear implants but continues to have hearing limitations.
- She divides her time between a mainstream and special education classroom due to mild-to-moderate learning disabilities.
- She requires treatment with antiepileptic medications due to recurrent seizures related to her brain malformation.

Case Study: CS
Behavioral Risk Reduction Interventions

• All pregnant women should be aware of CMV prevention measures; however, no actions can eliminate all risks of becoming infected with CMV.

• The following measures may reduce the risk of transmission:
  • Practice good personal hygiene throughout pregnancy, especially hand washing with soap and water after contact with diapers or oral and nasal secretions (particularly with a child who is in daycare). Wash well for at least 15 to 20 seconds.
  • Avoid kissing children under age 6 on the mouth or cheek; instead, kiss them on the head or give them a hug.
  • Do not share food, drinks, or oral utensils (e.g., fork, spoon, toothbrush, pacifier) with young children.
  • Clean toys, countertops, and other surfaces that come into contact with children’s urine or saliva.
Vaccination:

- Not available for CMV at this time

- Vaccine development is actively ongoing at this time but will not likely be available for a number of years
ZIKA VIRUS: THE NEW PERINATAL EPIDEMIC
• RNA virus predominantly transmitted by mosquitos.
• Related to other Flaviviruses that are also transmitted by mosquitos: Dengue, Yellow fever, Chikungunya, West Nile, St. Louis encephalitis,
• First identified in monkeys in Uganda in 1947
Aedes Aegypti distribution in 2015

Moritz UG Kraemer, et al. - elifesciences.org/content/4/e08347, File:Global Aedes Aegyptus distribution.gif
2014 in French Polynesia: An outbreak of Guillain-Barre syndrome – acute weakness after a viral infection – resulted in recognition of human Zika viral infection
It is estimated that 85-90% of infected individuals are asymptomatic.

Clinical symptoms include: low-grade fever, transient arthralgia, joint swelling, viral rash, conjunctivitis, and headaches.

Symptoms start 3-12 days after exposure.

Symptoms last 2-7 days.

Rate of Guillain-Barre syndrome in French Polynesia was estimated to be 2.4 cases per 10,000 Zika infected individuals.
Clinical symptoms of children and infants infected with Zika postnatally do not appear to be different than adults.

The most common symptom in addition to fever, and rash is joint pain and swelling often presenting as a limp.

Zika Infection: children and infants
• In March of 2015, an outbreak of a viral illness with conjunctivitis, low-grade fevers, and rash was noted in Brazil. This was found to be secondary to Zika virus.

• In December 2015-January 2016, doctors began noting an increased number of infants in Brazil born with severe microcephaly.

Prenatal Zika Infection: the microcephaly epidemic

Image Credit: NPR
Like all perinatal infections, Congenital Zika Syndrome likely has a spectrum of severities.

Due to the newness of this diagnosis, at this time only the most severely affected infants are being recognized.

As infants with this syndrome in Brazil are still under 1 year of age, long-term effects and outcomes are not yet known.
A cohort of 45 infants (44 pregnancies) with confirmed or presumed prenatal Zika in Brazil are being followed and early findings have been published.

The following slides summarize what is currently known about that cohort.

Congenital Zika Syndrome
Microcephaly is often severe.
Microcephaly ranges from 2 to 7 standard deviations below average at birth.
Babies of mothers with known Zika infection during pregnancy with NORMAL head circumference at birth have also been identified and are being monitored.

Congenital Zika Syndrome: Microcephaly

Image Credit: Mario Tama/Getty Images
Fetal brain disruption sequence

MD Cynthia A. Moore *, †, MD David D. Weaver *, †, MD Marilyn J. Bull *, †

* Department of Medical Genetics, Indiana University School of Medicine, Indianapolis USA
† Department of Pediatrics, Indiana University School of Medicine, Indianapolis USA

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Congenital Zika Syndrome: Fetal Brain Disruption Sequence:

- Profound microcephaly
- Overlapping sutures
- Occipital bone prominence – “occipital shelf”
- Scalp rugae

Image Credit: Radiological Society of North America,
• Brain Malformation Findings:
  • Brain volume loss: 100%  
    • Mild to moderate: 49%  
    • Severe: 51%  
  • Cortical Malformations: 98%  
    • Include: lissencephaly, polymicrogyria, other abnormalities of sulci and gyri  
  • Calcifications: 100%  
    • Location of calcifications (highest to lowest): grey matter-white matter junction, basal ganglia and thalamus, brainstem, cerebellum

Congenital Zika Syndrome: Brain Malformations
Brain Malformation Findings:
- Corpus Callosum Abnormalities: 85%
- Ventriculomegaly: 96%
- Cerebellar Abnormalities: 78%
- Brainstem Abnormalities: 40%

Congenital Zika Syndrome: Brain Malformations
Congenital Zika Syndrome: Infant #1
Congenital Zika Syndrome: Infant #2
Congenital Zika Syndrome: Infant #5
Congenital Zika Syndrome: Infants #6, #7, and #8
Presumed not Confirmed Zika
Congenital Zika Syndrome: Infant #9
• Other Congenital Findings:
  • Hearing loss
  • Eye anomalies
    • Chorioretinitis
    • Congenital cataracts
    • Optic nerve atrophy
    • Visual impairment
    • Strabismus
  • Severe Arthrogryposis (limb contractures)
Congenital Zika Syndrome: Congenital Cataracts
Congenital Zika Syndrome: Arthrogryposis

Congenital Zika syndrome with arthrogryposis: retrospective case series study BMJ. 2016; 354:i3899
Congenital Zika Syndrome: Infant #10
Congenital Zika Syndrome:

- Other clinical symptoms:
  - Feeding difficulties from time of birth
  - Spasticity
  - Tremors
  - Abnormal movements – dyskinesia and dystonia
  - Seizures – after age 6 months
Congenital Zika Syndrome: Prevention
• **Routes of Transmission:**
  - Mosquitos
  - Sexual
    - Virus isolated from human sperm up to weeks to months post-infection
  - Trans placental
  - Blood Transfusions
Pregnancy Planning

• Delay pregnancy if you live in a Zika endemic area.
• Avoid travel to Zika endemic areas if you are pregnant.
• Discuss your risk of Zika with your doctor before and during pregnancy if you believe you may have been exposed to Zika.
• If you or your partner has been exposed to Zika discuss how long to wait to become pregnant with your doctor.
## Suggested timeframe to wait before trying to get pregnant

### Possible exposure via recent travel or sex without a condom with a partner infected with Zika

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>Wait at least 8 weeks after symptoms start or last possible exposure</td>
<td>Wait at least 6 months after symptoms start or last possible exposure</td>
</tr>
</tbody>
</table>

### People living in or frequently traveling to areas with Zika

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Zika test</td>
<td>Wait at least 8 weeks after symptoms start</td>
<td>Wait at least 6 months after symptoms start</td>
</tr>
<tr>
<td>No testing performed or negative test</td>
<td>Talk with doctor or healthcare provider</td>
<td>Talk with doctor or healthcare provider</td>
</tr>
</tbody>
</table>
Infection Precautions for Pregnant Women

Protect yourselves from getting Zika from mosquito bites

Use insect repellent
- Protect yourself and your family from mosquito bites all day and night, whether you are inside or outside.
- Insect repellent is safe and it works! Read the label and follow the directions.

Cover your skin
- Wear long-sleeved shirts and long pants. For extra protection, treat clothing with permethrin.*

Mosquito-proof your home
- Use screens on windows and doors.
- Use air conditioning when available.
- Empty containers with standing water.

Once you’re pregnant, protect yourself from getting Zika from sex

Use a condom
- Use a condom every time you have sex during your pregnancy. To be effective, condoms must be used correctly from start to finish, every time you have sex. This includes vaginal, anal, and oral sex.

OR

Don’t have sex
- Don’t have sex during your pregnancy.

Talk to your healthcare provider
- If you think your partner may have or had Zika, tell your healthcare provider if you had sex without a condom.
Management of pregnant women with known or possible Zika Exposure
<table>
<thead>
<tr>
<th>Maternal Lab Result Interpretation</th>
<th>Prenatal Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent Zika Virus Infection OR presumptive recent Zika virus infection</td>
<td>Consider serial ultrasounds every 3-4 weeks to assess fetal anatomy and growth. Decisions regarding amniocentesis should be individualized.</td>
</tr>
<tr>
<td>No evidence of Zika or dengue infection</td>
<td>Prenatal ultrasound to evaluate for fetal abnormalities consistent with congenital Zika virus syndrome. If fetal abnormalities present repeat serologic testing. If fetal abnormalities absent base obstetric care on risk of ongoing Zika exposure.</td>
</tr>
<tr>
<td>Recent dengue virus infection</td>
<td>See existing guideline for dengue fever.</td>
</tr>
</tbody>
</table>
Postnatal Evaluation of Infants of Mothers with Zika Infection
<table>
<thead>
<tr>
<th>Maternal Lab Result Interpretation</th>
<th>Postnatal Lab Tests on the Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent Zika Virus Infection OR presumptive recent Zika virus infection</td>
<td>Cord blood and infant serum should be tested for Zika and Dengue virus and antibodies. If CSF obtained for other reasons it can also be tested. Testing of umbilical cord and placenta recommended. For fetal losses, testing of fetal tissues is recommended.</td>
</tr>
<tr>
<td>No evidence of Zika or dengue infection</td>
<td>Cord blood and infant serum should be tested for Zika and Dengue virus and antibodies if fetal ultrasound shows abnormalities concerning for congenital Zika syndrome.</td>
</tr>
</tbody>
</table>
Postnatal Evaluation of Infants with Zika Exposure

- Comprehensive Evaluation in the Newborn Nursery
  - Precise measurement of head circumference
  - Length and weight
  - Assessment of gestational age
  - Examination for neurologic abnormalities
  - Examination for dysmorphic features
  - A postnatal head ultrasound before discharge from the hospital
  - Hearing screen
  - Referred for a comprehensive ophthalmologic exam and evaluation of hearing by ABR testing before 1 month of age
  - Enroll all infants in the US Zika registry
• Management of infants with Negative Zika laboratory tests
  • Routine care
  • Routine monitoring of head circumference at every well child visit
  • Age-appropriate developmental screening
  • Enrollment in the US Zika registry regardless of infectious or symptom status of the infant.

Postnatal Evaluation of Infants with Zika Exposure
• For infants with findings consistent with congenital Zika syndrome:
  • Consider evaluation at a pediatric subspecialty facility
  • Complete blood count and metabolic panel, including liver function tests,
  • Comprehensive eye examination by an ophthalmologist,
  • ABR hearing testing,
  • Consultation with a neurologist
  • Consideration of advanced neuroimaging (MRI brain)
  • In addition, infants should be evaluated for other causes of microcephaly or intracranial calcifications, including genetic conditions and other congenital infections
• All confirmed symptomatic and asymptomatic cases.
• Registries for expectant mothers and prospectively for their babies in continental US and separate registry for Puerto Rico.

• See CDC website for details on registering identified or suspected cases.
• U.S. Zika Pregnancy Registry
• Puerto Rico Zika Active Pregnancy Surveillance System (ZAPSS)
US Registry
- **Minnesota**
  - Travel-associated cases reported: 47

- **US States**
  - Locally acquired mosquito-borne cases reported: 139
  - Travel-associated cases reported: 3,951
  - Laboratory acquired cases reported: 1
  - Sexually transmitted: 33
  - Guillain-Barre syndrome: 13
  - Total: 4,091

- **US Territories**
  - Locally acquired cases reported: 28,627
  - Travel-associated cases reported: 96
  - Guillain-Barre syndrome: 43
  - Total: 28,723*

**US numbers as of 10/26/2016**
• Congenital CMV is common and often goes undiagnosed.
• Delayed diagnosis is difficult due to high rate of CMV exposure after birth.
• Congenital CMV infection can be life threatening.
• Congenital CMV syndrome is recognizable and results in significant disabilities including hearing and visual impairment, cerebral palsy, learning disabilities, and epilepsy.

Take Home Points
• Congenital Zika Syndrome is severe and recognizable.
• High likelihood that we will be seeing infants with congenital Zika syndrome in the US due to travel and presence of mosquitoes in Florida and the southeast US.
• Precautions to reduce risk of infection with Zika include avoidance of Zika areas, use of precautions to prevent mosquito bites, and safe sex practices with individuals who may have been exposed to Zika.
Questions?

Thank you!
• CDC website: Zika and CMV
• Up-to-Date: Congenital CMV and Zika Virus Reviews.

References