Carrying the TORCHH-Z: Congenital Infections

Jennifer A. Jolley, MD
Associate Clinical Professor
University of California, Irvine
Department of Obstetrics and Gynecology
Division of Maternal-Fetal Medicine

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Outline
• Overview of congenital infection
• The role of the prenatal care provider
• Specific infections:
  • Impact
  • Diagnosis
  • Management

Congenital Infections
• Pregnant women have unique susceptibilities to many infectious diseases
• Alterations in immunity to allow tolerance of fetus
• Anatomic and physiologic changes
• Mother-to-baby transmission can occur
  • In utero: Congenital
  • Around the time of delivery: Perinatal
  • Breastfeeding: Postnatal
• Most infections during pregnancy are typically not serious
  • UTI, respiratory, skin
• Others are associated with obstetrical complications including embryopathy and fetopathy

TORCHH-Z Infections
• T: Toxoplasmosis
• O: Other: Parvovirus, Syphilis, Enteroviruses
• R: Rubella, Rubella
• C: Cytomegalovirus
• H: Herpesvirus, Varicella
• H: Hepatitis, HIV
• Z: Zika

General concepts: Congenital infection
• All viruses and most bacteria can pass through the placenta
• The fetus does not make IgM until >20 weeks
• Evidence of infection does not imply fetal damage
• Infections can lead to miscarriage, growth restriction, preterm birth, neonatal sepsis, long term sequelae
  • Fetus affected not only by direct transmission but as consequence of maternal infection: preterm birth, growth restriction
• Some infections can cause specific fetal abnormalities and ultrasound findings
### General concepts: Fetopathy
- In general, fetal infections have more severe consequences when they occur in the first trimester
  - Disrupt organogenesis
- Second and third trimester infections can cause neurologic impairment or growth abnormalities
- In general, primary infections are substantially more damaging than re-infections and reactivations

### Obstetricians & Infection
- Reported counseling of pregnant women about prevention of perinatal infections
  - 79-88%: Toxoplasma, Hepatitis B, and Influenza
  - 50-68%: Varicella, Listeria, Parvovirus
  - <50%: CMV, Pertussis, Lymphocytic choriomeningitis virus
- Preconception counseling ideal
  - Possibility of prevention
  - Chance to make behavioral changes


### Unique opportunities for prevention of perinatal infections
- Limited time frame for disease transmission
- Health care provider plays key role in prevention implementation
  - Preconception, prenatal, intrapartum
- Interventions can greatly reduce disease
- Perinatal GBS disease: estimated 39,000 cases prevented 1993-2004
- Congenital rubella syndrome: 1 case in US 2004

### CDC’s recommendations for preventing infections in pregnancy
- Protect yourself from Zika virus
  - If you are pregnant, do not travel to areas with Zika
- Wash your hands with soap and water
  - Especially after using bathroom, handling pets, getting saliva on your hands
- Wash your hands often when around children
- Avoid unpasteurized (raw) milk and foods made from it
- Do not touch or change dirty cat litter
- Stay away from wild or pet rodents and their droppings
- Get tested for STDs including HIV and Hepatitis B
- Talk to your healthcare provider about vaccinations
- Avoid people who have an infection
- Ask your doctor about Group B strep

https://www.cdc.gov/pregnancy/infections.html

### Zika virus
- First reported May 2015 in South America
  - Dominated headlines in 2016
- Transmitted by Aedes aegypti & Aedes albopictus mosquitoes, sex, and vertical transmission from mother to fetus
- 80% of cases are asymptomatic
- No vaccine or treatment
- Number of Zika cases is declining
  - In most places epidemic is over
  - Virus likely to be endemic

### Zika virus disease
- At least one of following symptoms
  - Acute onset of fever, rash, arthralgia, conjunctivitis
- And laboratory confirmation of Zika virus infection
- Only 20% will exhibit recognizable symptoms
  - Most will have mild, nonspecific symptoms
- Incubation period 3-14 days
- Once infected, likely protected from future infections, although this is based on limited data
What we know about Zika

• Zika can pass from pregnant patient to her fetus
• Congenital infection can cause microcephaly and other severe brain defects
• Zika spreads through mosquitos and sex without condoms
• There is no vaccine to prevent or medication to treat Zika

What we don’t know about Zika

• If it’s safe to travel to an area with Zika during pregnancy
• How likely it is to contract Zika and have effect on pregnancy
  • Incidence of infection
  • Rate of vertical transmission
• The rate of birth defects with congenital infection

Birth defects reportedly linked to Zika: Congenital Zika syndrome

• Microcephaly
• Brain malformations
  • Ventriculomegaly
  • Anencephaly
  • Arhinencephaly
  • Corpus callosum abnormalities
• Calcified deposits in the brain indicating possible brain damage
• Excess fluid in the brain cavities and surrounding the brain
• Absent or nearly formed brain structures
• Abnormal eye development
  • Anophthalmia
  • Microphthalmia
• Congenital hearing loss
• Congenital contractures from damage to the brain that affects nerve or muscle and bones
  • Arthrogryposis
  • Club Feet
• Early hypertonia and symptoms of extrapyramidal involvement

Zika in the US: January-October 2017

• US States
  • 291 symptomatic Zika virus disease cases reported
  • 287 cases in travelers returning from affected areas
  • 3 cases acquired through presumed local mosquito-borne transmission
  • 1 case acquired through sexual transmission
• US Territories
  • 582 symptomatic Zika virus disease cases reported
  • 582 cases acquired through presumed local mosquito-borne transmission
  • 0 cases acquired through other routes
What’s happening in the United States?
Outcomes of pregnancies with possible Zika virus infection in US 2015-2017

What is our role?
• Screen
  • All pregnant women in the U.S. and U.S. territories should be assessed for possible Zika virus exposure and symptoms at each prenatal care visit
• Inform
  • Avoid travel to areas where Zika virus has been reported
  • If traveling, precautions against mosquito bites
  • Consistently using condoms or abstaining if sex partner at risk
• Test
  • Pregnant women who have potentially been exposed by travel or sex
  • Symptomatic women
  • Algorithms and explanations of limitations of tests available on CDC/ACOG websites
• Report
  • To state Health Department

If you have a patient who has tested positive
• Referral to Maternal-Fetal Medicine
• Counseling regarding pregnancy options
• Detailed fetal neurosonographic evaluation
  • If anatomy normal, repeat US 3-4 weeks
  • 20 fetuses with HC between 2-3 SD below mean had normal HC at birth 90% of time
  • >3 SD or more below mean: Isolated fetal microcephaly
• >5 SD: Pathologic microcephaly
• Normal ultrasound findings during the antenatal period do not rule out neonatal sequelae of Zika infection developing or manifesting after birth!!
  • Delayed findings have been reported

Avoiding exposure is best
• Delay travel to Zika areas if pregnant
• When traveling, take all precautions to avoid mosquito bites: DEET, cover skin, treat clothing
• Communicate to pregnant women that repellants can be used safely
• Follow protective measures day and night as Aedes aegypti bites dawn, day, dusk

Pregnant women should not travel to any area where there is a risk of Zika virus infection because Zika infection in a pregnant woman can cause severe birth defects in fetuses and infants.

World Map of Areas at Risk of Zika
**Avoiding Zika in pregnancy**

- Women with Zika and asymptomatic women with possible exposure to Zika should wait at least 8 weeks after symptom onset to attempt pregnancy.
- Men with possible Zika virus exposure, regardless of symptom status, should wait to attempt pregnancy until 6 months after symptom onset (if symptomatic) or last possible Zika exposure (if asymptomatic).
- Those living in areas with ongoing transmission of Zika virus may decide to delay pregnancy until the epidemiology of local transmission demonstrates no additional transmission.

**Zika resources**

- Any questions about who to test and when can be addressed online through resources such as ACOG advisory, CDC website.
- Contact MotherToBaby
  - 1-866-626-6847
  - Chat live or send email through website
- Local health department

**CMV (Cytomegalovirus)**

- Most common congenital viral infection
  - Leading non-genetic cause of congenital deafness
  - CDC estimates that 30,000 infected infants are born each year.
- In the US, 30-50% of pregnant women have never been infected with CMV
  - Rates of seroprevalence increased for women in lower SES, developing countries, Non-Hispanic black and Mexican-American, >25-30yo, higher parity, with kids <3yo
- 1-7% of nonimmune patients will have a primary infection during pregnancy
  - Only 30% will transmit to fetus
  - Rate of transmission increases as pregnancy progresses, but disease is less severe with later transmission

**How do you get CMV?**

- Direct contact with body fluids: urine, saliva, vaginal secretions, semen, blood

**Congenital CMV**

- Majority of congenital infections are asymptomatic
  - Normal ultrasound does not completely exclude the possibility of a symptomatic neonate or development of long-term neurological morbidity
- But 5-20% are overtly symptomatic
  - SGA, microcephaly, ventriculomegaly, chorioretinitis, splenomegaly, thrombocytopenia
  - Result from viral replication in different organs
  - Stillbirth also possible
  - 5% mortality rate
  - 50-60% of survivors with severe neurologic morbidity
The CMV virus causes microcephaly in babies, and it’s much more widespread than Zika

- Microcephaly and seizures are common manifestations
- Neurologic signs are only signs in 30% of cases
- Destructive effect on proliferating and migrating neurons
- Associated with several migrational disturbances
  - Polymicrogyria
  - Lissencephaly
  - Pachygyria
  - Neuronal heterotopias

How to diagnose?

- Test:
  - Pregnant women with mononucleosis-like illness
  - Fetal anomaly suggestive of CMV
  - If woman requests the test
  - CMV IgM and IgG
    - Presence of CMV IgM not helpful for timing onset because only present in 75-90% with acute infection, can remain positive for a year
    - IgG avidity helpful to determine acuity
      - High avidity (>65%) suggests that primary infection occurred >4-6 months ago
      - Over time antibody maturation → higher avidity
      - Low avidity (<30%) suggests a recent primary infection
      - Low to moderate avidity 9-18 weeks following infection
      - Amniocentesis for CMV DNA PCR: Best option

How to avoid transmission of CMV?

- Greatest impact a prenatal care provider can have is educating patients on preventative measures
- Wash your hands!
- Especially after:
  - Changing diapers
  - Feeding young child
  - Wiping a young child’s nose or drool
  - Handling children’s toys
  - Don’t share food or drinks with young children
  - Do not put a child’s pacifier in your mouth
  - Do not share a toothbrush with a young child
  - Clean toys, countertops, other surfaces that come into contact with children’s urine or saliva

CMV Epidemiology and Fetal Risks Summary

CMV in the literature

- Congenital CMV leading cause of birth defects and developmental delays in the US
  - Only 13-22% of women in the US have heard of it
- Research assesses:
  - Quantity and accuracy of CMV info included on pregnancy-related websites and reference books
  - Whether CMV information was included less often than information about other birth defects
  - CMV less likely to be included as a topic than other infections or birth defects
  - Fewer sentences about CMV than tox, Down syndrome, or HIV

Thackeray et al. Matern Child Health J 2014; 18:584-591
OB role in counseling about CMV

- Less than half of OB/GYNs in the US report counseling their patients about how to prevent CMV infection
- Greatest impact an OB can have is educating patients on preventative measures

*STOP CMV*

Syphilis

- Transmitted sexually and vertically
  - Treponema pallidum readily crosses placenta
  - Frequency increases with advancing gestational age
  - Severity decreases with advancing gestational age
- Clinical stages
  - Primary: ulcer at infection site
  - Secondary: rash, mucocutaneous lesions, lymphadenopathy
  - Tertiary: cardiac, neurologic, ophthalmic, gummatous lesions
- Latent syphilis: seroreactive but no clinical manifestations
- Transplacental transmission can occur during pregnancy or delivery
  - 60-100% transmission during primary or secondary syphilis
  - 40% early latent infection
  - 8% late latent infection

Congenital syphilis

- Congenital infection associated with
  - Perinatal death
  - Preterm delivery
  - Low birth weight/growth restriction
  - Congenital anomalies
    - Deformed bones
    - Notched teeth: Hutchinson's teeth
  - Active neonatal syphilis
    - Deafness and neurologic impairment, meningitis, seizures

http://www.medthical.com/syphilis.html
Prenatal ultrasound findings

- Placentomegaly 62%
- Hepatomegaly 57%
- Ascites 17%
- Bone abnormalities
  - Biometry 3 standard deviations below normal
  - Bowing, thickening
- Sonographic signs of fetal or placental syphilis indicate a greater risk for fetal treatment failure

Congenital syphilis roars back

- Recent sharp increase in the number of congenital syphilis cases
- After period of decline from 2008-2012
  - Rates increased by 38% between 2012-2014
  - From 8.4 to 11.6 cases per 100,000 live births
  - 334 cases versus 458 cases in 2014
- Parallels a national increase in primary and secondary syphilis among women during the same time period
  - Primary and secondary syphilis are the most infectious stages of sexually-transmitted adult syphilis
  - Of 458 congenital syphilis cases in 2014, 22% mothers received no prenatal care
  - Of women who had prenatal care but were never treated, 15% were never tested for syphilis during their pregnancy
CDC Letter November 2015

• “Every case of congenital syphilis is a needless tragedy”
  • “The resurgence of congenital syphilis points to missed opportunities for
    preventions. Physicians, health departments, and the public health
    community must do a better job of protecting mothers and newborn babies
    from this dangerous infection.”
• Easy to treat with antibiotics when in early stages of disease
• Appropriate treatment dramatically decreases transmission rate
  • From 70-100% to 1-2%

What we can do: Testing

• Know who to test and when
• Screen all pregnant women at the first prenatal visit
• For communities and populations in which the prevalence of syphilis is high
  and for women at high risk for infection:
  • Perform serologic testing twice during the third trimester
    ▫ 28–32 weeks gestation
    ▫ Again at delivery
• Test any woman who has a stillbirth after 20 weeks gestation
• No mother or neonate should leave the hospital without maternal serologic
  status having been documented at least once during pregnancy, and if the
  mother is considered high risk, documented at delivery

Treatment

• Benzathine Penicillin G
• Coordinate with health department or infectious disease specialist
• Providers should ensure that the clinical and antibody responses are
  appropriate for the patient’s stage of disease
• Inadequate maternal treatment is likely if delivery occurs within 30
  days of therapy, clinical signs of infection are present at delivery, or
  the maternal antibody titer at delivery is fourfold higher than the pre-
  treatment titer

Summary: How not to carry the TORCHH-Z

• Prevention of maternal infection by modifying habits that increase
  contact with agents of communicable disease
• Education about preconceptional and antenatal screenings and
  prevention strategies
• Ensure that missed opportunities for prevention don’t occur