Infectious Complications of Pregnancy

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Five Pillars

• Pregnancy Immunology
• ToRCHeS(Z?)
• Syphilis
• Arboviruses
• Human Immunodeficiency Virus
Pregnancy Immunology

• Prior to seminal paper by Sir Peter Medawar in 1953, model was “no contact between mother and fetus
Pregnancy Immunology

• Medawar’s paper proposed three possible theories:
  
  – Anatomic separation of fetus and mother (since refuted by observed bidirectional microchimerism, i.e., small amount or number nonhost cells or DNA from one individual harbored in another)
  – Antigenic fetal immaturity (disproven by abundant evidence of fetal immune function, including expression of polyclonal Tcell responses and CD4 cell differentiation)
  – Immunological maternal inertness (discredited by clinical experience that, during pregnancy, host organisms survive most, but not all, infections)
Pregnancy Immunology

• Current Theory: Maternal Tolerance

• Allows host to retain ability to elicit necessary responses to infections
Pregnancy Immunology

• Maternal tolerance is complex and not yet fully understood, but regulatory T cells (Treg) appear vital to expression of paternal and fetal genes without maternal destruction.

• Treg are specialized CD4 cells which elaborate CD25 receptors, which can suppress self-reactive lymphocytes and thus allow immunologic self-tolerance.
Pregnancy Immunology

• Copulation, conception, and pregnancy

• Also alter levels of vasoactive intestinal peptide, leukocyte inhibitory factor, CD4 Th1/Th2 ratio, uterine natural killer cell activity and likely MANY other immunopeptides to permit IMPLANTATION and PLACENTATION
Pregnancy Immunology

- Maternal tolerogenic environment permits
- BIDIRECTIONAL COMMUNICATION
- With fetal antigen presentation and permissive maternal response
Pregnancy Immunology

• RANTES = Regulated on Activation, Normal T cell, Expressed and Secreted

• Made by peri-implantation endometrium and trophoblasts

• Increase Treg and decrease CD3 to prevent apoptosis

• Suppress maternal allogeneic responses to paternal and fetal antigens
Pregnancy Immunology

• Both mother and fetus extremely vulnerable
Pregnancy Immunology

• Many pregnancy complications (preeclampsia, prematurity, stillbirth) are linked to maternofetal tolerance disorders
Pregnancy Immunology

- Pregnancy CAN predispose to unique susceptibility to some infections, including Listeriosis and Brucellosis among many others.
Pregnancy Immunology

• Enhanced susceptibility may be an undesired consequence of expansion of Tregs needed for fetal tolerance.
Pregnancy Immunology

• Maternal infections compromise maternofetal tolerance and lead to COMPLICATIONS.
ToRCHeS

- Toxoplasma gondii
- Rubella
- Cytomegalovirus
- Herpes simplex
- Syphils
ToRCHeS

- Toxoplasma gondii ubiquitous, protozoan, zoonosis
- Usually transmitted to humans in undercooked pork or lamb or by contaminated water or food
- Congenital toxoplasmosis almost always requires that mother be infected while pregnant.
- Congenital infection asymptomatic vs neurologic or ocular
Toxoplasmosis

- Diagnosis: amniocentesis for PCR or serology or PCR after birth
- Prevention: avoid undercooked meat, contaminated food and water, raw milk, raw shellfish
- Screen all pregnant women for Toxoplasmosis
- Usual acute maternal manifestation, if any, is regional lymphadenopathy
Toxoplasmosis

• Congenital infection is worse if occurs earlier in pregnancy

• Vertical infection may be 50% in pregnant women with untreated acute toxoplasmosis

• Testing problematic and confusing but improved
Rubella

- Formerly called third disease (after measles – first, and scarlet fever – second)
- In 1941 association between maternal Rubella and congenital defects
- In 1962 Rubella virus identified
- In 1969 vaccine approved.
- Last major US Rubella epidemic affected 12.5 million people and left 30,000 US children affected by congenital Rubella, which has essentially disappeared from the US
Rubella

• Congenital Rubella manifestations: deafness, cataracts, glaucoma, mental retardation, heart disease

• Vaccinate non-immune women (NON-PREGNANT)
Cytomegalovirus

- Largest virus infecting humans
- Infants infected during gestation by mothers with primary CMV infection during pregnancy at high risk for severe congenital infection
- Congenital infection may manifest as fulminant hepatitis, microcephaly, chorioretinitis, intracranial calcifications, etc
- Fetal infection by mothers with preexisting CMV infection often with no symptoms
- 1-2% of US women carry CMV cervically
- No treatment approved during pregnancy
Herpes Simplex

- Worldwide
- 22% of pregnant women in US HSV-2 seropositive
- Risk of neonatal HSV low (1 in 6,000-20,000 live births) considering the high seroprevalence
- CSD not indicated unless visible lesions, primary maternal HSV late in pregnancy, or viral shedding (by culture or PCR) near delivery
- Neonates infected in the first 6 weeks (most at delivery) have 70% chance of catastrophic CNS HSV infection with death or significant morbidity
Syphilis

• Congenital syphilis referred to as CS in this section
Incidence has increased by 12.6% from 2014 to 2015 (487 cases)
• Outcomes of CS can be catastrophic, including miscarriage, stillbirth, prematurity, low birth weight, death in early neonatal period
• Up to 40% of babies born to mothers with untreated syphilis may suffer from CS
All pregnant women should be tested at first prenatal visit, and in high incidence areas, including ours, should be tested again in third trimester and perhaps at delivery (depends on risk assessment, partner history, etc).
CS

- Newborn screening complicated by maternal antibody transfer to fetus
- Clinical decisions regarding neonatal treatment often hinge on maternal diagnosis and treatment history, physical exam, and lab and X-ray findings, and comparisons of maternal and fetal nonspecific treponemal ab’s (RPR usually) after delivery
• Any neonate at risk for CS also needs screening for HIV
• Proven or Highly Probable CS
• Neonate with abnl physical findings, RPR 4-fold higher than mother’s RPR, and positive darkfield or PCR of a lesion or nasal discharge
• Neonate evaluation=CSF VDRL, CBC, LFT’s, indicated Xrays, eye and hearing evaluations
CS

• Possible CS Definition:

• Normal neonate PE with RPR >4-fold higher than mother’s RPR, mother without history of diagnosis or adequate treatment completed 4 weeks prior to delivery (not EDC)

• OR mother not treated with penicillin-containing regimen
• CS Less Likely Case Definition:
• Normal PE, RPR<4-fold higher than mother’s RPR, mother adequately treated >4 weeks prior to delivery. And mother without evidence of reinfection or relapse
CS

• CS Unlikely Case Definition:
• Normal PE and RPR<4-fold higher than mother’s RPR, mother with history adequate treatment prior to pregnancy, and mother’s RPR, if positive still, serofast at low titer (RPR <1:4) throughout pregnancy
• If neonate with positive RPR being watched because perceived to be at low risk for CS, RPR should be negative at 6 months of age.
• All Reported Syphilis Cases in Texas in 2011 (6,161) and in 2015 (8,247)
• Congenital Syphilis in Texas 2015 487 (12.6% increase from 2014)
Arboviruses

• Any virus transmitted by arthropods
• Will only discuss West Nile Virus today
• Vertical transmission rare as is transmission via breast milk
Arboviruses

• Diagnosis should be considered in any infant born to a mother infected with West Nile Virus during pregnancy or while breastfeeding.
Arboviruses

- Pregnancy does not appear to predispose to West Nile Virus infection
Arboviruses

- Pregnant women during West Nile Virus season should be advised to avoid mosquitos, protective clothing, and EPA-approved insect repellent.
Arboviruses

• May be transmitted through breast milk but current guidance allows breastfeeding women to continue despite history of West Nile Virus.

• No person-to-person spread (except through vertical, breast milk, organ transplantation, and rarely prior to screening, blood products)
Zika Virus

• As of 9/6/17, 5,441 US and DC Zika Virus cases and 37,009 cases in US territories
• To date, 2,155 cases of pregnant women with any lab evidence of Zika Virus infection and 4,481 cases in US territories
• One local transmission case in US in 2017 (in Texas)
• Worldwide, incidence declining as well
Zika Virus History

• Febrile illness in Rhesus macaque in 1947 in Zika Forest, and virus identified and named Zika Virus in 1952
• Episodic human cases from 1954 onward
• Large outbreak in Yap Island (archipelago between Palau and Guam) in 2007 studied with PCR technology
• Other Pacific Ocean outbreaks followed
Zika Virus History

- In 2014 in Brazil, FIFA World Cup and va’a World Sprint Canoe race
- Followed by gradual appearance of a new febrile illness (not malaria, Dengue, or Chikungunya) eventually confirmed to be Zika Virus
- Subsequently, increased incidence of microcephaly reported leading to epidemiologic investigation of possible association of Zika Virus with microcephaly
Zika Virus Clinical Presentation

• Only 20% symptomatic
• FRAC – fever, rash, arthralgias, conjunctivitis
• Also GBS, transverse myelitis
Zika Virus Transmission

- Vector-to-person
- Sexual
- Maternofetal
Zika Virus and Microcephaly

• Other Microcephaly Causes
• Craniosynostosis
• Rubella
• CMV
• Toxo
• Malnutrition
• Syphilis
• Toxins (ETOH, drugs, other)
Zika Virus and Microcephaly

• Zika Virus can initiate FETAL BRAIN DISRUPTION SEQUENCE if Zika Virus infection occurs in first or early second trimester

• Brain AGYRIC (lissencephaly)

• Zika Virus known to be NEUROTROPIC since 1950’s (based on mouse models)
Zika Virus and Microcephaly

• Zika Virus reaches fetus through chorionic villae and trophoblasts before placental vessels have formed.
• HIGH affinity for neuronal and microglial AXL and Tyr3 receptors
• Infected cells APOPTOSE
Zika Virus Testing

• If glial cells infected, glial SCAFFOLDING fails to form and neuronal migration, required for forebrain development, cannot occur, leading to microcephaly.

• Microcephaly is a continuum and can be associated with seizures, developmental delays, intellectual disability, movement and balance issues, poor feeding, swallowing dysfunction, vision and hearing impairments.
Zika Virus Testing

- Serum and urine RNA (nucleic acid amplification test or NAAT) testing covered under emergency use authorization
- IgM hard to interpret because other Flavivirus exposures or YF vaccine can cause false positive Zika Virus IgM’s
- Plaque reduction neutralization testing not commercially available for confirmation
Zika Virus Testing

• Test anyone with possible Zika Virus exposure and recent symptoms
• “Possible Zika Virus Exposure” includes living in, traveling to, or having a sex partner who has traveled to, areas with local Zika Virus transmission.
Zika Virus Testing

- Test symptomatic pregnant women if they present within 12 weeks of symptom onset and have history of possible Zika Virus exposure
- Test asymptomatic pregnant women with ongoing possible Zika Virus exposure
- Test pregnant women with possible Zika Virus exposure and prenatal ultrasound consistent with congenital Zika Virus infection
- Infants born to women with Zika Virus infection
- Infants with findings c/w congenital Zika Virus infection
Zika Virus Transmission

• No evidence of transmission through breastfeeding

• Assess for Zika Virus exposure risk at every prenatal encounter
Perinatal HIV Transmission

• 37 million HIV infected worldwide
• 1 million HIV infected in US
• 200,000 undiagnosed and HIV infected in US
• 2 billion persons worldwide with TB (10.4 million with active TB)
Perinatal HIV Transmission

• 1.2 million of HIV infected persons worldwide also with ACTIVE TB
Perinatal HIV Transmission

• 50,000 new US HIV cases annually
• 8500 HIV infected US women give birth annually
• Perinatal transmission risk <1%
• 86 perinatal cases in 2015 (US)
Perinatal HIV Transmission

• At zenith 1650 US perinatal HIV cases (in 1991)
• In 1994 widespread implementation of AZT to expectant HIV positive mothers, IV AZT during labor, and postexposure AZT to infants born to HIV positive mothers
• 86 perinatal HIV infections in US in 2015
Perinatal HIV Transmission

• Additional Interventions:
  - No breastfeeding
  - No pre-chewing food for babies
  - Maternal HIV viral load suppression
  - Scheduled CSD if maternal VL > 1000
  - Early maternal diagnosis and HIV treatment
Perinatal HIV Transmission

- Current risk <1%
- No recent Tarrant County perinatal HIV transmission
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