

INFECTIONS DURING PREGNANCY

Heidi L Thorson, MD FACOG
Minnesota Perinatal Physicians
Maternal-Fetal Medicine
Clinical Genetics

October 11, 2019



Minnesota Perinatal Physicians, part of Allina Health, offers expert consultative care for all maternal health concerns, pregnancy complications and fetal abnormalities.

In collaboration with Children's Minnesota, we also provide care at Midwest Fetal Care Center – the only advanced fetal care center in the Upper Midwest.

Disclosures

- none



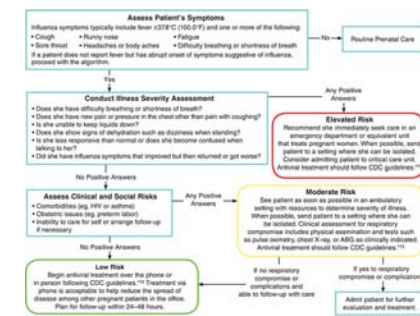
Infection during Pregnancy: Outline & Objectives

- Identification of common infections affecting pregnancy
- Understand and initiate appropriate work up for infections during pregnancy
- Understand and initiate appropriate management of pregnancies complicated by infection.



Influenza and pregnancy

- Pregnant women more susceptible to serious flu related complications
 - Changes in immune status, hemodynamic status (heart and lungs) place pregnancy women at risk
- Flu vaccine recommended
- Influenza treatment: oseltamivir 75 mg twice daily for 5 days
- Post exposure prophylaxis: oseltamivir 75 mg once daily for 7–10 days (twice daily for 5 days)
- Studies evaluating risk of miscarriage
 - VSD 2010-2011, 2011-2012 increased risk of miscarriage if received vaccine the previous year
 - Larger VSD follow up study 2012-2013, 2013-14, 2014-15 no increased risk regardless of previous season vaccination



ACOG CO 753

Cytomegalovirus (CMV)

- Most common cause of in utero infection
 - 0.5-1% (2.2%) of pregnant women affected
 - Higher rate of perinatal infection in 3rd trimester
 - More severe outcomes with earlier infection
- Adult infection frequently asymptomatic
 - Fatigue weakness, fever, lymphadenopathy
 - Less than 5% of pregnancy women with primary infection are symptomatic
- Primary infection – increased risk of fetal CMV infection
 - 30-40% vertical transmission rate
- Recurrent or Reactivation – lower transmission and less severe
 - 0.2 – 8% vertical transmission rate



Cytomegalovirus - Prognosis

- Severity of disease and manifestations based on timing of infection and affinity of nervous tissue to different CMV strains
- CMV most common infectious cause of mental retardation, sensorineural deafness, visual impairment
- Detectable anomalies in fetus associated with poorer outcome
- Accurate diagnosis important for treatment of infant
 - 90% of congenitally infected infants are asymptomatic at birth
 - 30% sequelae in first year of life
 - 10% hearing loss early in life



Cytomegalovirus - Ultrasound

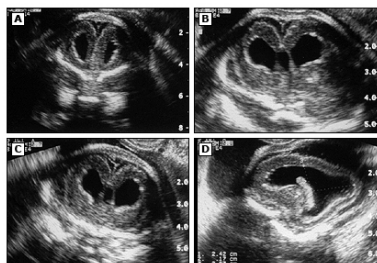
- Hepatic and Splenic calcifications
- Hydrops
 - Pleural effusions
 - Ascites
 - Anasarca
 - Scalp edema
 - Placentomegaly
- Cardiomegaly
- Ventriculomegaly
- Central nervous system
 - Microcephaly
 - Periventricular echogenic halo
 - Linear calcifications in basal ganglia
 - Punctate cerebellar calcifications
 - Intraventricular hemorrhage
 - Porencephaly
 - Lissencephaly
 - Subependymal cysts
 - Microphthalmia
- Echogenic bowel, kidneys
- Hepatomegaly, splenomegaly



CMV



Periventricular calcifications



Courtesy of Ana Monica Gudo, MD.
2019 update



CMV



Leyder et al; AJOG Nov 2016

Echogenic bowel



Courtesy of Beryl R Benacerraf, MD.
2019 update



Cytomegalovirus - Testing

- Maternal blood serologic testing
- Delineating acuity of infection
 - CMV immunoglobulin
 - IgM, IgG and IgG avidity
- Amniocentesis – CMV PCR
 - At least 7 weeks from presumed maternal infection
 - After 21 weeks gestation



Cytomegalovirus - Treatment

- No licensed treatments for pregnancy women
- Treatments in nonpregnant women –
 - Not approved in pregnancy
 - Not been shown to prevent CMV infection in the fetus
- Hyperimmunoglobulin therapy promising but investigational
 - Seroconversion – can be referred



Parvovirus B19

- Replication occurs primarily in erythrocyte and erythroblasts
- Children "slapped-cheek" – rash, low-grade fever, mild influenza-like symptoms
- 10% risk of fetal death due to anemia
- 17% < 20 weeks
- 6% > 20 weeks



Parvovirus B19– ultrasound

Frequent findings

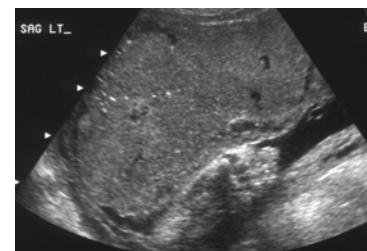
- Hydrops
 - Pleural effusions
 - Ascites
 - Anasarca
 - Scalp edema
- Placentomegaly
- Polyhydramnios
- Cardiomegaly

Less frequent

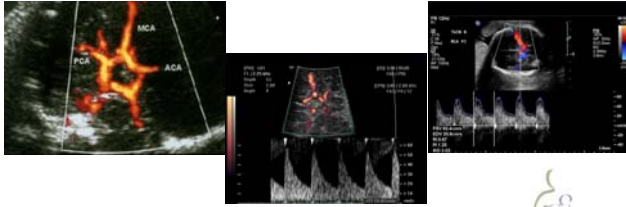
- Ventriculomegaly
- Microcephaly
- Hepatosplenomegaly
- Hepatic calcifications
- Echogenic small bowel



Placentomegaly



MCA Doppler



Parvovirus B19

- Middle Cerebral Artery – Peak Systolic Velocity – elevated in severe anemia
- Hydrops 5-10% in first trimester to 1% at 20 weeks
- Hydrops develops 3-12 weeks after maternal infection
- Hydrops – most develop between 16-32 weeks of gestation



Parvovirus B19 testing

- Maternal serology IgG and IgM
- IgG positive, IgM negative – immunity
- IgG negative, IgM negative – susceptible
 - Repeat testing in 2-4 weeks if concern for exposure, clinical symptoms
- IgGpos/neg, IgM positive – Recent infection
 - Ultrasound every 1-2 weeks with MCA PSV Doppler
 - Continue 10-12 weeks post exposure
 - Severe anemia based on MCA PSV – intrauterine transfusion



Toxoplasmosis

- Toxoplasma gondii – cat is definitive host
 - Typically outdoor cats
- Consuming raw or undercooked meat
 - United States seroprevalence lower ~10-14%
- Acute maternal infection in pregnancy 0.2-1%
 - First trimester infection less likely 2-10%, more severe, more likely to spontaneously abort
 - Infection >20 weeks – high congenital infection rate 20-30%, less severe



Toxoplasmosis - ultrasound

Frequent findings

- Central nervous system
 - Random intracerebral calcifications
 - Ventriculomegaly
- Hepatic calcifications

Less frequent

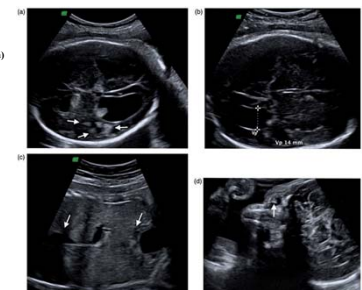
- Microcephaly
- Microphthalmia
- Cataracts
- Hepatosplenomegaly
- Hydrops
 - Pleural effusions
 - Pericardial effusions
 - Ascites
 - Anasarca
 - Scalp edema



Toxoplasmosis

Ultrasonographic images of fetal toxoplasma infection. (a) White arrows indicate periventricular calcification, (b) ventriculomegaly; lateral ventricle width: 14.09 mm, (c) hepatomegaly; white arrows indicate liver borders from diaphragm to urinary bladder and (d) white arrow indicates the fetal cataract.

Rajapakse et al; Pathogens and Global Health August 2017



Toxoplasmosis - testing

- Amniocentesis – at least 4-5 weeks after maternal exposure
- Real-time PCR rapid and more sensitive for detecting *T. gondii* in amniotic fluid
- Serologic testing
 - IgG – prior infection of onset unknown
 - IgG positive and IGM negative – excludes recent infection
- Serologic testing in first trimester is preferred
- Samples in second trimester may not exclude first trimester infection



Toxoplasmosis - testing

- Toxoplasmosis-specific IgM enzyme immunoassay – positive 18 months after infection
- Toxoplasmosis IgM lacks specificity
- IgG negative on two occasions with positive IgM; the IgM should be considered false positive
- Prior to initiation of management for acute toxoplasmosis all IgG/IgM positive tests should be sent to reference laboratory
- Toxoplasmosis Serology Laboratory, Palo Alto, CA for IgG avidity testing
 - High avidity in first 12-16 weeks of pregnancy rules out infection acquired during gestation
 - Low avidity IgG is suspicious for recent infection, may have with low avidity for months



Toxoplasmosis

- Treatment for women diagnosed at reference laboratory
- Spiramycin is recommended (1st and early 2nd trimester)
 - Acutely infected – reduces placental transfer
- Pyrimethamine/sulfadiazine & leucovorin (late 2nd and 3rd trimesters)
 - More effectively eradicates parasites in placenta and fetus
- Maternal therapy of fetal outcome not well studied, more likely to be effective in absence of fetal manifestations on ultrasound.

Varicella

- Adults – fever and generalized malaise typically precede classic rash of chickenpox
 - Begins on face and scalp, spreads to the trunk, minimally limb involvement
- Pneumonia – 5-10% of adults with chickenpox
 - Untreated – high morbidity and mortality for mother
- Primary infection <20weeks
 - Low birth weight, hypoplasia of extremity, skin scarring, localized muscle atrophy, encephalitis, cortical atrophy, chorioretinitis, microcephaly
 - ~6% fetal transmission –
 - 1/3 with clinical manifestations, usually cutaneous
 - Congenital abnormalities < 2

Varicella

Frequent findings

- Ventriculomegaly
- Cerebral calcifications
- Clubfeet
- Limb contractures
- Limb atrophy
- Decreased limb movement
- Polyhydramnios

Less frequent

- Cataracts
- Microcephaly
- Microphthalmia
- Myocardial echogenicity
- Lung echogenicity
- Renal echogenicity
- Oligohydramnios



Varicella



Source: W.A. Hogg, B. Collins, L. Wilkins, London 1981:
Sander's Structural Fetal Abnormalities, Third Edition,
www.elsevier.com
Copyright © McGraw Hill Education. All rights reserved.



Source: W.A. Hogg, B. Collins, L. Wilkins, London 1981:
Sander's Structural Fetal Abnormalities, Third Edition,
www.elsevier.com
Copyright © McGraw Hill Education. All rights reserved.

Varicella



Source: W.A. Hodge, B. Cohen, J. Wilson, London: H.B. Saunders' Structural Fetal Abnormalities, Third Edition, www.elgim-international.com
Copyright © McGraw Hill Education. All rights reserved.

Varicella – Testing & Management

- If varicella syndrome suspected
 - IgG and IgM
 - Amniotic fluid – PCR for varicella
- Oral acyclovir or valacyclovir for mild maternal varicella
- Serial ultrasound – limb abnormalities, ventriculomegaly, fetal growth restriction
 - Poor prognosis
 - Antiviral medication to treat fetus after ultrasound recognition, not recommended
- Peripartum infection associated with ~25% risk of life-threatening neonatal infection
- Maternal zoster outbreak **NOT** associated with risk of fetal infection or malformation

Syphilis, congenital

- Primary, Secondary or Tertiary syphilis
- Latent infection – lacking clinical manifestations – detected by serologic testing
 - Early latent – acquired within last year
 - Late or unknown duration – all other cases
- In absence of timely & effective penicillin treatment – congenital syphilis 50% of babies with primary or secondary syphilis during pregnancy
- Maternal early latent – 40% risk of congenital syphilis
- Late Latent – 10% risk of congenital syphilis

Syphilis, congenital - ultrasound

Frequent findings

- Hepatosplenomegaly
- Hydrops
 - Pleural effusions
 - Pericardial effusions
 - Ascites
 - Anasarca
 - Scalp edema

Less frequent

- Intracerebral calcifications
- Echogenic bowel
- Bowel dilation – enterocolitis
- Hepatic calcifications
- Long-bone shortening
 - Abnormal curvature; focal bowing
- Placentomegaly
- Polyhydramnios



Syphilis, congenital

- Ultrasound stigmata only consistently identified after 18-20 weeks, fetus can develop an inflammatory reaction
- All pregnant women should be tested for syphilis – new ob labs
- Women at high risk for syphilis – tested twice during second trimester 28-32 weeks and at delivery
- Jarisch-Herxheimer reaction – few hours after first dose of antibiotic – fever, chills, rigor, hypotension, headache, tachycardia
 - Contact provider – fever, contractions, decreased fetal movements
- Late congenital syphilis > 2 years of age
 - Hutchinson triad – (Hutchinson teeth, interstitial keratitis, 8th nerve deafness), MR, seizures, saddle nose deformity, frontal bossing, saber shins, CN palsies

Zika - Screening

- At each prenatal visit, screen for exposure before and during pregnancy
- Exposure history:
 - Current or recent residence in an area where mosquito-borne transmission of Zika reported
 - Recent travel to an area where mosquito-borne transmission of Zika reported
 - Unprotected sexual contact with a person who resides in or has traveled to an area where mosquito-borne transmission of Zika reported
- Signs and Symptoms: 3-14 days after exposure, last <1week
 - Maculopapular rash, Arthralgia, Conjunctivitis, Fever
 - Ultrasound findings consistent with congenital Zika virus syndrome

Zika - Testing

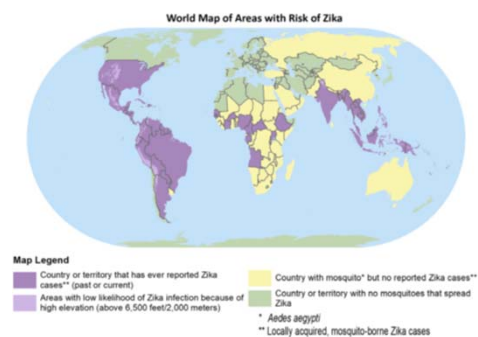
- Zika – real-time reverse-transcription PCR (rRT-PCR)
- Symptomatic women – up to 12 weeks after symptom onset
 - Nucleic acid test of serum and urine as well as IgM testing
- Asymptomatic women with exposure
 - Limited not ongoing – do not warrant routine lab testing – discuss with patients, increased risk of false positive
 - Ongoing exposure – reside or travel at least weekly; NAT testing 3x during pregnancy
- Amniocentesis
 - After 21 weeks gestation (18-21 weeks)
 - 6-8 weeks after maternal infection

Zika

- United States Zika Pregnancy and Infant Registry – 1450 confirmed or possible infection
 - 6% of offspring with at least one Zika-associated birth defect
 - 9% neurodevelopmental abnormalities, potentially related to Zika
 - 1% had both birth defects and neurodevelopmental abnormalities
- Severe microcephaly with partially collapsed skull
- Thin cerebral cortices with subcortical calcifications
- Macular scarring and focal pigmentary retinal mottling
- Congenital contractures (arthrogryposis)
- Marked Early hypertonia

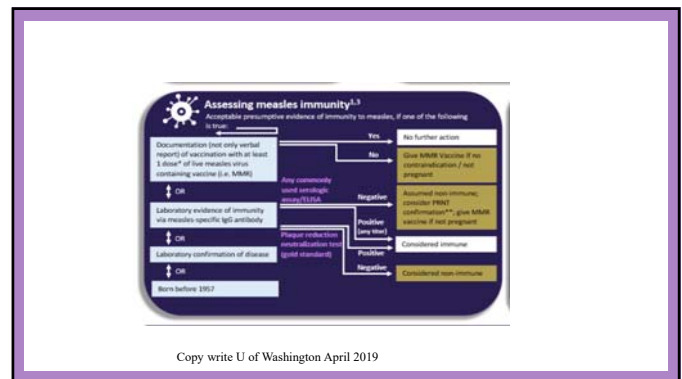
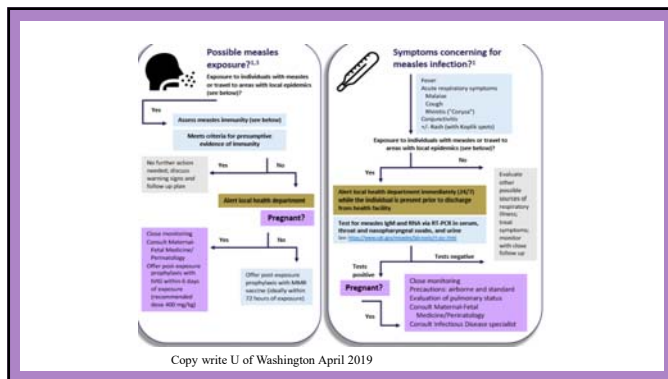
Zika - Prevention

- In 2018 and 2019, there have been no reports of Zika virus transmission by mosquitoes in the continental United States
- Do not travel to high risk areas and use precautions/avoid sex with someone who recently traveled to a high risk area
- Prevent mosquito bites
- Preventing infection through sex



Measles

- 7-21 day incubation period
- Two doses of MMR vaccine series 97% effective
 - 92-95% of individuals in a community must be immune to prevent transmission
- Pregnant women and young children among those at highest risk
 - Increased risk of hospitalization and pneumonia
- Pregnancy risks to fetus, miscarriage, stillbirth, low birth weight, preterm delivery
- Pregnant women with exposure but without immunity may be eligible for IVIG
- MMR not recommended during pregnancy due to theoretical risks on fetus



HSV

- One of the most common sexually transmitted infections
- Women with recurrent genital HSV, ~75% Expect recurrence during pregnancy
- 1200-1500 cases annually in US – not reportable disease
- Neonatal herpes acquired during intrapartum period, in utero/postnatal infections rare
 - 80% of infected infants are born to mothers with no reported history
 - 14% women with prodromal symptoms or clinical recurrence at delivery (genital region)
 - Cesarean delivery recommended
- Women with recurrent lesions at delivery – transmission 3%



HSV - treatment

Table 1. Recommended Doses of Antiviral Medication for Herpes in Pregnancy

Indication	Acyclovir	Valacyclovir
Primary or first-episode infection	400 mg orally, three times daily, for 7-10* days	1 g orally, twice daily, for 7-10* days
Symptomatic recurrent episode	400 mg orally, three times daily, for 5 days or 800 mg orally, twice daily, for 5 days	500 mg orally, twice daily, for 3 days or 1 g orally, daily, for 5 days
Daily suppression	400 mg orally, three times daily, from 36 weeks estimated gestational age until delivery	500 mg orally, twice daily, from 36 weeks estimated gestational age until delivery
Severe or disseminated disease	5-10 mg/kg, intravenously, every 8 hours for 2-7 days, then oral therapy for primary infection to complete 10 days	

*Treatment may be extended if healing is incomplete after 10 days.
Adapted from Sexually transmitted diseases treatment guidelines, 2006 [published erratum appears in MMWR Recommen Rep 2006;55(9):1-4]. Centers for Disease Control and Prevention. MMWR Recommen Rep 2006;55(9):1-4.



Referral process and programs

- Easy referral/consultation process- provider referrals only
- Perinatologist consultation: 612-863-4502
 - Referral/appointments: 612-863-4502 (for any clinic location – six throughout Mpls/St. Paul)
 - Patient transfers available 24/7: 612-863-1000

How we support referring providers

- comprehensive multidisciplinary team
- consultations 24/7
- advanced technology ultrasound imaging
- genetic counseling and testing, including prenatal screening, CVS and amniocentesis
- coordinated case management

Unique partnerships & programs

- Neonatal care in conjunction with Children's Minnesota
- Maternal Obstetric Medicine Surgical program
- Obstetric Intensive Care program
- Genetics program
- Morbidly Adherent Placenta program
- Fetal Echo and Early Fetal Echo programs
- Cardiopregnancy program in conjunction with Minnesota Heart Institute



THANK YOU

