Overview

Infections
  - Cytomegalovirus
  - Toxoplasmosis
  - Parvovirus

Epidemiology, Transmission, and Clinical Manifestations

Maternal and Fetal Diagnosis

Management in Pregnancy

Cytomegalovirus

- Most common congenitally acquired infection
  - Occurs 0.2-2% of all neonates
  - 40,000 infants infected annually in US
- Leading cause congenital hearing loss in US
- 50-85% prevalence in US by 40 years of age
- Cultured from urine, blood, throat, cervix, semen, stool, tears, breast milk

Transmission
  - Sexual, close contact, blood/tissue, occupational
  - Perinatal

Watts, 1999; Stagno, 1986; Stagno, 1982; Centers, 1989
Cytomegalovirus

- Seroprevalence among pregnant women
  - 77% among low-income
  - 36% among mid/high-income
- Seroconversion in pregnancy
  - 0.6-4.3% seronegative pregnant women
- Prevalence in pregnancy
  - Seropositive: 50-80%
  - Primary infection: 0.7-4%
  - Recurrent infection: 13.5%

CMV Clinical Manifestations

- Primary infection usually asymptomatic or mild flu-like symptoms
- Reactivation possible
  - Viremia
  - Positive IgM in presence of IgG
  - In setting of concurrent infections or stress
  - More common in immunocompromised

Mononucleosis syndrome

- Fever/chills, malaise, myalgia
- Mild hepatitis (elevated LFT's)
- Leukocytosis, atypical lymphocytes in blood x 6 weeks
- Less hepatomegaly, splenomegaly, pharyngitis than EBV
- Older patients, longer fever duration, less cervical LAN
- Negative Monospot or heterophile-agglutinin tests
- Meningoencephalitis, pericarditis, myocarditis
- Thrombocytopenia, hemolytic anemia
- Maculopapular rash, GI ulcers, pneumonia less common

CMV Transmission

- Vertical transmission greatest during 3rd trimester
- More serious fetal sequelae when infection in 1st trimester
- Vertical transmission
  - Primary maternal infection: 30-40%
  - Recurrent maternal infection: 0.15-2%
- Maternal immunity not protective
  - Reinfection with new strains attributed to all congenital infection in Brazil
  - 75% of congenital infections attributed to non-primary maternal infection in US

Watts, 1999; Stagno, 1986; Stagno, 1982; Griffiths, 1980

Yamamoto 2010, Wang 2011
CMV Transmission
- Most common congenitally acquired infection
  - Occurs 0.2-2% of all neonates
  - 40,000 infants infected annually in US
- Risk factors for neonatal transmission
  - Nulliparity, primary infection
  - Worse disease in premature infants
  - Transplacental transmission pathologic
  - Transplacental infection: symptomatic
  - Exposure to genital tract secretions: usually asymptomatic
  - Breast feeding: usually asymptomatic
    - Except premature infants!

Congenital CMV
- 85-90% infected infants → asymptomatic
  - 5-15% develop sequelae
  - Leading cause of congenital hearing loss in US
- 10-15% infected infants → symptomatic
  - 90% develop sequelae
  - Primary infection results in more severe neonatal manifestations compared to recurrent infection
  - Any sequelae based on infection status:
    - 25% (1º) vs. 8% (recurrent) (p=0.003)

Congenital CMV and Pregnancy
- Fetal ultrasound abnormalities
  - Ventriclemegaly, Microcephaly, Polymicrogyria, Cerebellar hypoplasia, Periventricular (pseudo) cysts
  - Hyperechogenic bowel, HSM
  - IUGR, Hydrops, Ascites/Effusions, Placentomegaly
  - Cerebral (periventricular) or Hepatic (multiple) calcifications
  - MRI may increase PPV for fetal brain abnormalities
  - Persistent changes (ventriculomegaly, periventricular calcifications, growth restriction, microcephaly, and hydrops)
    - Predictive of severe disease and high risk of long-term neurodevelopment impairment.

Watts, 1999; Fowler, 1992

Clinical Fetal Manifestations
Congenital/Perinatal

Ventriculomegaly and Periventricular Calcifications

CMV Infection in Fetus at 32 weeks
Bilateral Temporoparietal Cortical Malformation
Finely Irregular Appearance of Cortical Rim

CMV Infection in Fetus at 23 Weeks
Irregular Appearance of Frontoparietal Cortical Rim

CMV Fetal Manifestations
Echogenic Bowel

CMV Infection in Fetus at 32 weeks

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Congenital CMV

- Neonatal findings
  - Jaundice, petechiae → “blueberry corn muffin rash”
  - Hepatosplenomegaly
  - Hemolytic anemia
  - Mental and motor retardation
  - Sensorineural deficits

Watts, 1999; Feinler, 1992

Neonatal Manifestations

- Hepatosplenomegaly
- Hemolytic anemia
- Mental and motor retardation
- Sensorineural deficits

CMV Screening

- Routine screening not recommended by ACOG in pregnancy!
- Special considerations for CMV IgG screening
  - HIV-infected women
  - Immunocompromised (transplant patients)

CMV Maternal Screening

- If mononucleosis-like syndrome, known exposure, or fetal manifestations
  - Check CMV IgM/IgG +/- Avidity Studies prn
  - Serum tested 2-4 weeks apart
  - IgG seroconversion or fourfold increase (i.e. 1:4 to 1:16) IgG
  - IgM useful but not always reliable sign of primary infection
    - May persist for months
    - Appears in reinfection
    - False positive if RA
    - ≥30% of IgG value may suggest active infection
  - IgG avidity assay: Not standardized
    - High avidity c/w infection > 4 months ago
      - May not be helpful if 2nd or 3rd trimester (peri-conception infection)
    - Low avidity c/w more recent infxn (within 6 mo), but may persist
**CMV Prenatal Diagnosis**
- If documented 1\textsuperscript{st} maternal infection or high suspicion for recurrent infection
  - Amniocentesis (or Umbilical blood sampling)
  - PCR, routine cx, ?shell vial cx (early ag detection)
    - PCR generally preferred
  - PCR sensitivity 70-100%
  - Sensitivity higher after 21 weeks and by allowing a 6-week lag time between maternal infection and amniocentesis
  - AF Viral Load = prediction of sequelae in offspring
    - Higher VL in AF (>100,000 copies) associated with symptomatic fetuses or newborns

Ornoy 2006, Lazzarotto 2000, Revello 1999

**CMV Screening and Management**
- CMV in breast milk
  - CMV not contraindication to breast feeding in TERM infants
  - LPCH NICU and breastfeeding considerations for CMV
    - Colostrum OK
    - Assume mom + and < 32 weeks infants -> frozen breast milk
- CMV cervical excretion common during pregnancy
  - Not indication for c-section
- No treatment for CMV infection in healthy adults
  - Vaccines are in developmental stages
- Prevention
  - Avoid CMV-shedding infants (day-care center)
  - CMV-negative blood if maternal or fetal transfusion

**CMV Management**
- No current therapies for maternal or fetal CMV infection
- Ganciclovir crosses placenta in vitro
  - Case report of oral tx in pregnancy for clearance of intrauterine infection
- Reported use of ganciclovir and CMV IgG postnatally for congenital/perinatal disease
  - Treatment with IV ganciclovir remains controversial but may be considered in certain patients
  - Sensorineural hearing loss, microcephaly
  - Viral sepsis, pneumonitis, thrombocytopenia, retinitis
  - Prevention of long-term neurologic sequelae not proven

Pulyarida 2005, Kimberlin 2003

**CMV Congenital Infection Management during Pregnancy?**
- IVIG
  - Used for prevention and treatment
  - IVIG Tx: 1 of 31 infant with CMV disease vs. 7 of 14 women with no IVIG
  - IVIG Prevention: 6 of 37 women (16%) with congenital CMV infection vs. with 19 of 47 women (40%) with no IVIG
  - Limitations
    - Study design was neither randomized nor controlled
    - Interventions differed in the therapy and prevention groups
    - Study did not address the financial and logistic issues associated with screening large obstetrical populations for CMV infection and the expense of pursuing false positive results
    - Atypically high CMV symptomatic disease and asymptomatic infection rates
  - Case reports of potential regression of fetal manifestations?

**CMV Congenital Infection Management?**

- **Valaciclovir**
  - Maternal oral administration of VACV
  - 2 gm PO q 6 hours
  - Therapeutic concentrations in the maternal and fetal compartments
  - Decrease in fetal blood and amniotic viral load
  - However – limited data to predict long-term differences

*Jacquemard 2007*

**CMV Congenital Infection Management: Future Studies**

- **Valaciclovir Prospective Trial (Europe)**
- **IVIG Prospective Trial (MFMU Network)**
- **Valganciclovir PO Therapy for Symptomatic Congenital CMV Infections: Short-Term vs. Long-Term Prospective Trial (NIAID)**

**Toxoplasmosis Transmission**

- 11% adult women 15-44 yo in US are immune
  - France ~ 88% of adult population are immune
  - Infection during pregnancy in South America carries higher risk of serious fetal sequelae than does infection acquired in Europe or North America → more virulent strains?
- Risk of seroconversion in US during pregnancy?
  - 1 to 8 per 1000
- Undercooked meat of infected animals
  - 20% lamb, 20% pork, 8% beef; decreasing in U.S.
- Feces from infected cats (only if eat raw meat)
  - Ingested (or aerosolized) oocytes
  - Shedding in feces for 2 wks s/p 1°infection
  - Require 1 day to become infective s/p stooling
  - Contaminated soil, food, (unfiltered) water, cleaning cat litter
- Feces or insects in soil (oocytes infective for up to a year)

*CDC*
Toxoplasmosis

Transmission

- Pregnancy: 1-8 per 1,000?
- 1 per 1000-10,000 live births
- Acute infection during pregnancy
  - Reports from preconception infxn
  - Max 3 months prior
- Reactivation in IC’d women
- Transplacental transmission
  - 1st trimester: 10-15%
  - 2nd trimester: 25%
  - 3rd trimester: 60%
- Infection severity ↑ with ↓ gestation
- Perinatal transmission
  - Maternal immunity generally always protective
  - Reinfection=very RARE
  - Immunocompromised (parasitemia) may transmit

Elbez-Rubinstein 2009

Toxoplasmosis

Clinical Manifestations

- Immunocompetent adult
  - 90% asymptomatic 1°infxn
  - Nontender LAD (post cervical) in 7%-specific
  - Fatigue, fever, HA, malaise, myalgia, mono-like illness (neg heterophile test)
  - ± sore throat, rash, HSM, mild elevation transaminases, thrombocytopenia
  - Most common pathogens to cause chorioretinitis
    - Recurrence due to reactivation of localized disease
  - Immunocompromised: CNS, Pulmonary

- Fetus
  - Ventriculomegaly, intracranial calcification, IUGR, stillbirth

- Neonate
  - Up to 90% w/o symptoms at birth
  - Intracranial calcifications, hydrocephalus, microcephaly, seizures
  - Chorioretinitis (may be delayed for years)
  - Neurodevelopmental delay
  - LBW, jaundice, thrombocytopenia, HSM

Toxoplasmosis

Clinical Manifestations

<table>
<thead>
<tr>
<th></th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
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<tbody>
<tr>
<td>Congenital Toxo</td>
<td>9%</td>
<td>27%</td>
<td>59%</td>
</tr>
<tr>
<td>Subclinical</td>
<td>22%</td>
<td>74%</td>
<td>90%</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>78%</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td>SAb/IUFD</td>
<td>5%</td>
<td>2%</td>
<td>0%</td>
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</tbody>
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Toxoplasmosis

Prevention
- Education (↑knowledge; ↓seroconversion?)
  - Avoidance of risky behaviors
    - Eating raw or undercooked meat
    - Drinking unfiltered water
  - Gloves (and mask?) if contact with cat feces
    - Kitty litter, gardening
    - Daily litter changing may be okay because oocyte lifecycle
  - Cook meat fully, clean all kitchen surfaces
    - Internal temperature 67°C; Freezing below -12°C
  - Wash all fruits, vegetables, clean all kitchen surfaces
  - Use filtered water
  - Prevent contamination of food by insects

Toxoplasmosis

Screening
- Routinely screening for toxoplasmosis in pregnancy
  - NOT recommended in US
    - Low PPV in low prevalence populations
    - France, Austria = routine screening
    - Oregon: reversed mandated screening
    - Massachusetts: neonatal IgM testing since 1986
- Screen
  - Symptoms of toxoplasmosis
  - At high risk of recent exposure
    - Mononucleosis-like illness/negative heterophile test
- Need repeat testing to detect seroconversion
  - Minimum of two blood samples at least 2 weeks apart

Toxoplasmosis

Diagnosis
- IgM: peak at 1 mo; may persist for yrs (10-13 mo; up to 12 yrs)
  - Wide range in assay sens/spec
- IgG
  - Detectable 1-2 wks after infection; Persist for life
  - Repeat at 2-3 wk interval
  - 4x↑ suggests recent infxn
- IgG avidity test
  - High avidity Ab’s: infxn >3-4 months
  - Low avidity Ab’s: may persist past 3 months
  - Infection w/in past 4 months
- Toxoplasmosis Serological Profile (TSP)
  - Combination panel
    - Sabin-Feldman Dye IgG Test
    - AC/HS differential agglutination
    - IgG Avidity
    - IgM FInks

Toxoplasmosis

Treatment
- Spiramycin (no RCT, conflicting observational studies)
  - 1 gm orally q8 hours w/o food
  - Only available by FDA if serologically confirmed acute maternal infection (301-443-4280)
  - Concentrates in placenta but doesn’t cross well
  - 50-60% ↓risk of fetal infection
  - Doesn’t treat infected fetus
- If fetal infection documented (practices vary widely)
  - Spiramycin alternating with pyrimethamine/sulfadiazine
  - Concurrent Pyrimethamine and Sulfadiazine (folic acid antagonists), plus folic acid 5-20mg daily
  - Weekly CBC/plts
**Parvovirus**

- Parvovirus B19, erythema infectiosum, fifth disease
- Common childhood infection
- “Slapped cheek” appearance in children
  - Rare in adults
- “Lace-like” erythematous rash
  - Trunk and extremities
  - Less common in adults
- 30-40% of pregnant women are seronegative

**Parvovirus Manifestations**

- Facial Rash
  - “Slapped Cheek”
- Body Reticular Rash
  - “Lace-Like”

**Parvovirus Clinical Manifestations**

- Systemic symptoms x 1-4 days before rash
- Self-limited course (adults, children)
- Erythema infectiosum (rash)
- Arthritis, arthralgias
- Arthropathy (hands, wrists, knees, ankles)
  - 1-2 weeks
  - Preceding rash
  - Adults
- Transient aplastic crisis
  - Underlying chronic anemia (SCD, thalassemia)
- Anemia, leukopenia, transaminitis, thrombocytopenia, elevated LDH
- Chronic infection +/- anemia
  - Immunodeficient
  - Treatment: Transfusion, IVIG
**Parvovirus Transmission**
- Close contact (person-to-person), fomites, and/or large droplets, respiratory secretions, blood
  - Unlikely aerosol
- Viremia
  - Begins 6 days after exposure
  - Lasts 1 week (immunocompetent)
- Contagious before onset of symptoms
- Virus detected in blood/secretions 5-10 days after exposure
- No longer infectious after rash, arthralgias, arthritis
- IgG=immune to recurrent infections
  - Reinfection may be possible

**Parvovirus Perinatal Transmission**
- 65% pregnant women with baseline IgG (immune)
- Transplacental transmission
- Risk of transmission if acute infxn: 33-50%
- Most transmission w/o fetal/neonatal compromise
- 3.9% hydrops
- 6% fetal death
  - 11% if infection <20 wks gestation
- Risk factor for transmission
  - Maternal IgM positive status at delivery (later infxn?)
- Not risk factors
  - Maternal age, symptomatic maternal infxn, delivery route, maternal IgG titer, maternal IgG avidity, maternal viremia @ delivery

**Parvovirus Manifestations**
- Pregnancy
  - No change in natural history of parvovirus
  - But risk of preeclampsia if fetal hydrops
  - Especially if maternal infection <20 wks gestation
  - No fetal IgM (somewhat protective >20 wks)
  - Fetal loss
    - 1-12 wks post maternal infxn
    - Fetal loss if infxn <20 wks: 11%
    - Fetal loss if infxn >20 wks: <1%
  - IUFD in third trimester
    - 7.5% parvovirus

**Parvovirus**
- Transmission among adults/children
  - Respiratory; hand-mouth; blood products
- Seasonality: late winter-early summer
  - Peaks March-May (epidemics q 4-5 yrs)
- **Communicability**
  - 5-10 days after exposure
  - Up to 7 days after aplastic crisis (or longer if chronic parvovirus)
- Annual seroconversion risk among adults
  - 0.42% hospital workers
  - 1.5% pregnant women during endemic period
  - 13% pregnant women during epidemic period
- Risk of seroconversion
  - 50% if household member
  - 20-50% if other contact (childcare/school)
  - 16.7% of susceptible, exposed pregnant women
    - RR 2.8 if related child in household=source

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**Parvovirus Manifestations**

**Hydrops Fetalis**

**Parvovirus Diagnosis**

- Routine screening in pregnancy **NOT** recommended
- Incubation: 1-3 weeks
- IgM: within 10-12 days after inoculation (lasts 2-3 months)
  - 90% positive once symptomatic with rash
  - **BUT** 15% neg IgM in setting of maternal viremia!!!
  - CONSIDER PCR in case with high suspicion/IgM negative!!!
- IgG: approx 2wks after inoculation
  - IgG +, IgM neg: prior immunity vs. early clearing of IgM
  - IgG neg, IgM neg: retest in 3wks
  - IgG neg, IgM +: infected w/in past week
  - False + IgM (especially if other acute infections)
  - IgG +, IgM +: infected w/in past 6 months
- IgM detectable up to 10 months in some pts
- Viral culture difficult because viremia usually 1-3 days
- Repeat serologies in 2-3 weeks if originally negative

**Parvovirus Fetal Diagnosis**

and Management

- PCR of fetal tissue (amniotic fluid)
- Fetal IgM only appear after 22 wks
- May see ↑ MSAFP 4-6wks prior to hydrops
- Serial weekly US for 8-12wks after maternal infection
  - Hydrops, placentomegaly
- If hydrops:
  - Fetal middle cerebral artery (MCA) peak systolic velocity
  - Mild: daily ultrasounds
  - Moderate-Severe: PUBS/IUT: fetal Hct, wbc, plts, retic count
- High-dose IVIG??
  - Case report of resolution after single maternal dose
  - Limited studies
  - But transplacental passage of IgG unpredictable

**Summary**

- Routine screening in preconception or prenatal period **NOT** currently recommended for CMV, toxoplasmosis, parvovirus infections
- Primary maternal infection usually required for transplacental transmission and severe fetal/neonatal sequelae
- Primary maternal infection often asymptomatic or with non-specific symptoms
Summary

- Transmission and fetal/neonatal sequelae likelihood vary by gestational age of maternal infxn
- Repeat screening in 2-3 week if exposure
- Risk of transmission and severity of neonatal illness worse with 1st maternal infection
- Consider infectious etiologies in cases of specific fetal ultrasound findings
  - Parvovirus: non-immune hydrops and stillbirth
- Consider infectious etiologies in cases of maternal flu-like symptoms/findings
  - May mimic HELLP/PreE: thrombocytopenia, transaminitis

Resources

- Centers for Disease Control and Prevention
- Palo Alto Medical Foundation Toxoplasma Serology Laboratory
  - http://www.pamf.org/serology/
  - (650)853-4828

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