Maternal Infections in Pregnancy

Jane Ellis, MD, PhD

Associate Professor, Division of Maternal-Fetal Medicine

Department of Gynecology and Obstetrics

Emory University School of Medicine, Atlanta, Georgia

Medical Director, Emory Regional Perinatal Center at the Grady Health System

Obstetric Director, Maternal and Infant Grant
Co-chair, Georgia Maternal Mortality Review Committee
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Objectives

- To identify the symptoms, diagnosis and treatment of selected maternal infections – CMV, HIV, HSV, syphilis
- To review the potential maternal and/or fetal consequences of these infections
- To outline potential strategies for reducing occurrence of these diseases

Infections in Pregnancy to Note

- Influenza
- Emerging infections -
 - ► Ebola, Nipah
- Respiratory diseases
- Zika, West Nile, malaria and other mosquitoborne diseases

- Food borne diseases listeria
- Tick borne diseases
- Mumps, measles, rubella
- STDS
- TORCH
- Many others!

Maternal Effects of Infections

- Many common symptoms of pregnancy mimic infections – nausea, fatigue, myalgia
- Due to pregnancy, mom may be more frequently or more severely affected by certain disease processes due to immunologic changes during pregnancy

General Principles

- Ask questions at New OB visit and at each subsequent visit –
 make sure patient is answering the question asked
- Document maternal symptoms
- Never hesitate to take a peek below!
- Maintain a high index of suspicion

General Comments on Maternal Infections

- Can have significant maternal complications
- Infections during pregnancy can be associated with adverse pregnancy outcomes such as stillbirth, preterm birth, lowbirth weight and SAB
- Appropriate prevention, diagnosis and treatment of maternal infections can reduce the associated maternal/fetal/neonatal morbidity and mortality
- Never incorrect to refer to Internal Medicine, MFM or ID

General Comments on Maternal Infections

- Maternal infection incidence depends on many determinants such as socioeconomic, access to health care, poverty, education, etc.
- Direct correlation between poverty and high incidence of maternal and neonatal infections
- With diversity of causative agents and diversity of transmission and pathogenesis of maternal and neonatal infections, it is difficult to propose a general approach to management of of maternal infections
- Each requires a specific measure for prevention, diagnosis, screening and treatment

Mother to Child Transmission of Infections

- MTCT can occur
 - In utero (congenital)
 - During delivery
 - Via breastfeeding
- Routes of infection to embryo and fetus
 - Hematogenous spread as a result of maternal viremia, bacteremia or parasitemia
 - Ascending from upper vagina via cervix to uterus and amniotic fluid

Organisms which may cause IUI and common routes of infection

Hematogenous spread

- TORCH infections
- Varicella-herpes zoster
- Listeria
- Syphilis
- Mumps
- Coxsackievirus B
- Poliomyelitis virus

Ascending infections

- E. coli
- B-hemolytic strep A and B
- Herpes simplex
- Proteus
- Klebsiella
- Pseudomonas
- Clostridium perfrignes
- Candida albicans

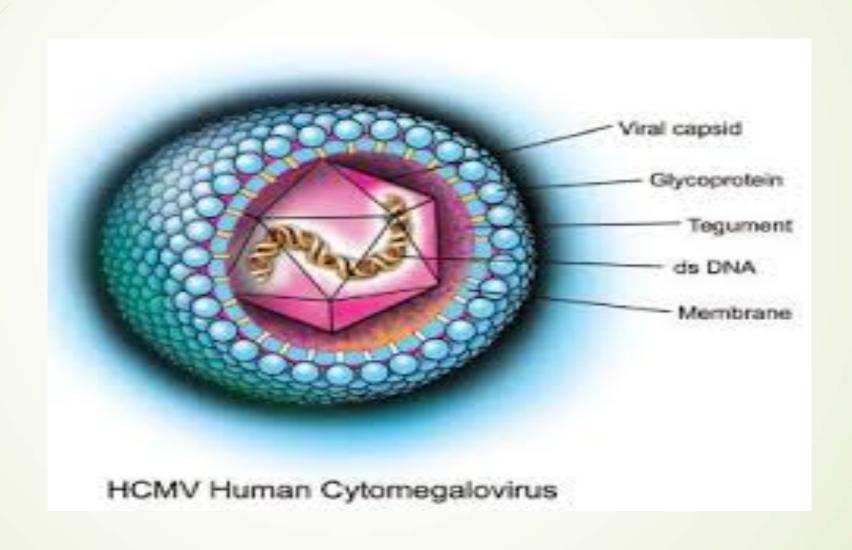
Diagnosis of Maternal Infections

- Based on careful history, PE and other diagnostic approaches (labs, US, Xray)
- Signs and symptoms of infections may be vague and attributed to pregnancy
- Symptoms should be documented
- Appropriate lab studies/imaging usually needed to develop differential and make the diagnosis

Treatment of Maternal Infections

- Disease specific
- Wil often involve treatment of maternal symptoms

Cytomegalovirus



Cytomegalovirus

- Is a DNA virus and a member of the Herpesviridae family
- Humans are the only known host
- Can cause latent infection
- Transmitted horizontally as a result of organ donation, blood transfusion, sexual contact and contact with infected urine or saliva
- Most pregnant women acquire the infection as a result of contact with own young children or children in daycare or preschool setting
- Neonates may acquire during contaminated blood or vaginal secretions during delivery or via breastmilk

CMV - Case Scenario

- 27 year old G1P0 at 24 weeks by 13.2 week US, missed appointment for 20 week anatomy scan
- US ordered because fundal height was 20 cm
- Findings:
 - Placenta thickened at 6.4 cm
 - AFI in low-normal range for EGA
 - EFW at 15th percentile for EGA
 - Fetal bowel was brightly echogenic, no other abnormalities noted
- Maternal history
 - Employed as preschool teacher
 - Prolonged "flu-like illness" at 14 weeks gestation, no treatment

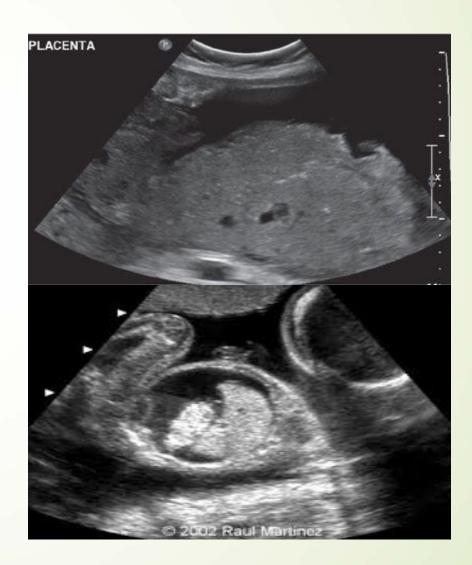
- Clinical features and incidence
 - Mild maternal symptoms, usually flu-like syndrome
 - ➡ High seroprevalence 59% of reproductive age women test +; nearly universal by middle age
 - → 520,000 women of CBA experience a primary CMV infection each year
 - CMV is most common viral infection causing congenital malformations and is leading cause of sensorineural hearing loss; is leading viral cause of brain damage in children
 - Risk of primary CMV infection ranges between 1-4% in seronegative women
 - Large population based study of infants showed birth prevalence of CMV is 0.5%

- Approximately 35,000 infants are born infected with CMV; 8000 experience sequalae in US each year
- Likelihood of infection does not vary by trimester but the earlier the exposure the higher the likelihood of infection and more likely to have sequela
- Primary infection in pregnancy in 1st tri results in risk of transplacental infection of 40%
- Timing of transmission is weeks to months after maternal infection
- 11% (5-15%) of infected infants exhibit symptoms shortly after delivery rash, jaundice, hepatosplenomegaly, microcephaly
- If reactivated or recurrent maternal infection only 5-10% of infants infected and usually asymptomatic at birth
- Late sequela include minor visual and auditory deficits and developmental delays which may becomes obvious around elementary school age

- Maternal symptoms of infection
 - 90% of women infected during pregnancy remain asymptomatic
 - When symptoms occur are mild, include low grade fevers and myalgia
 - Labs may show ↑ in lymphocytes and liver enzymes
 - If Mom is immunocompromised symptoms may be severe
 - Usually suspicion for fetal infection raised by ultrasound findings
 - Findings include IUGR, microcephaly, intracerebral calcifications, fetal ascites, placentamegaly, echogenic bowel and cerebral ventriculomegaly

Cytomegalovirus – US Findings





- Diagnosis
 - Maternal diagnosis typically made by CMV IgM and IgG serology
 - IgM assays have excellent specificity (95%) and sensitivity (100%)
 - ► IgM peaks during first 1-3 months after primary infection but can persist between 18-39 weeks
 - +IgM may not indicate primary infection since may be elevated in reactivated or recurrent infection
 - Primary CMV infection suggested when IgG converts from negative to positive in presence of +IgM on serum testing separated by several weeks
 - Primary vs recurrent CMV infection can be differentiated by an antigen avidity test – low in primary but as amount of antibody increases avidity increases

CMV – Summary of Maternal Diagnostic Tests

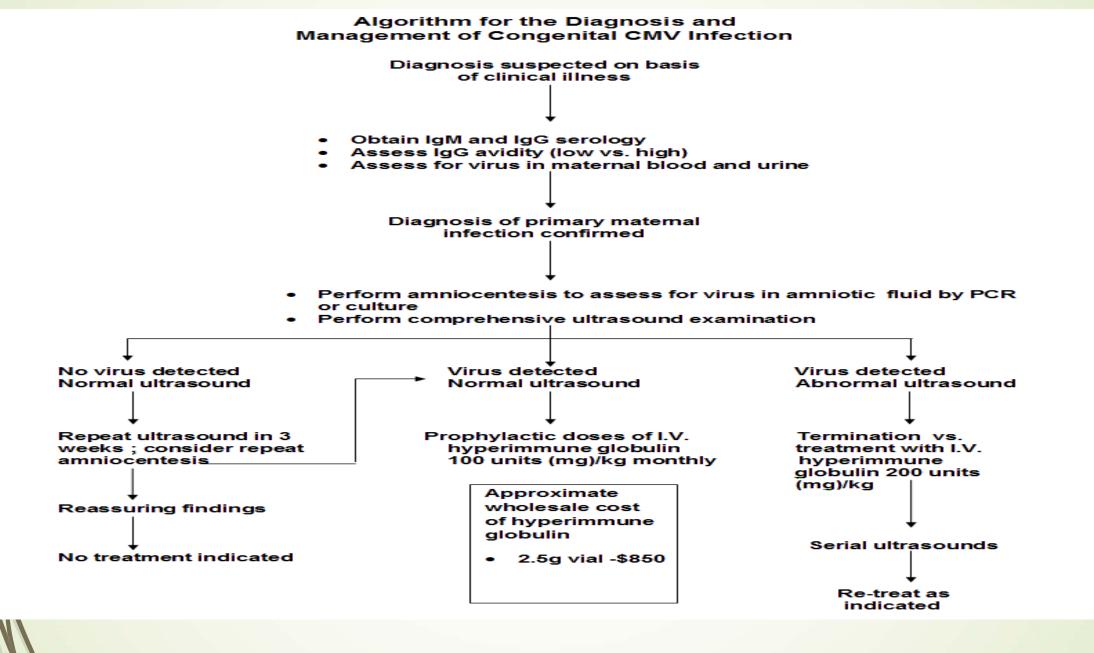
Type of Infection	Serum PCR	Urine PCR	IgM	IgG
Acute	Positive	Positive	Positive	Absent for low avidity antibody
Recurrent or Reactivated	Usually negative	May be positive	Usually negative but secondary response can occur	Positive for high avidity antibody

CMV - Treatment

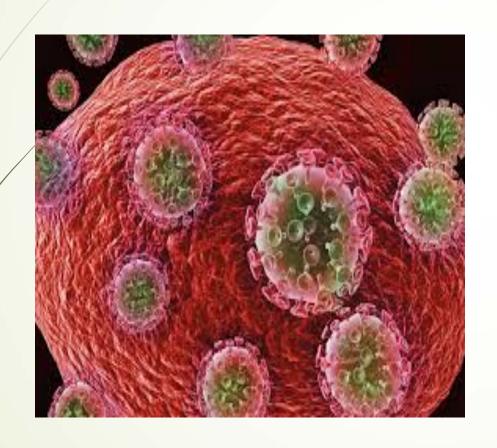
- Once diagnosis made pregnancy termination is an option depending on EGA
- Use of antiviral agents such as ganciclovir, foscarnet and cidofovir
 - May be of moderate effectiveness in treating maternal CMV infection, especially if immunocompromised
 - No proven value in preventing or treating congenital CMV
- Most promising agent is hyperimmune globulin 6 ACOG has not supported its use outside of research protocols
- CMV vaccine in early stages of development

CMV - Prevention

- Pregnant women susceptible to CMV should be counseled on importance of careful handwashing and cleaning surfaces when interacting with young children
- In day care setting wearing glove, handwashing extremely important when changing diapers
- Wash hands after handling toys or objects kids place in mouth
- If maternal blood transfusion required or IUT use CMV-negative blood
- Safe sex practices
- Vaccine development?



HIV in Pregnancy





HIV in Pregnancy

- Horror stories from early years of HIV
- First HIV clinic for pregnant women in US at Grady
- Reduction in MTCT of HIV one of most effective public health initiatives in US
- No treatment 25-30% chance of transmission
- Prior to current treatment 2000 HIV+ babies born in US each year; in 2015 86 HIV+ babies born
- Use of AZT reduced MTCT by 68%, from 25.5% to 8.3%

HIV in Pregnancy

- Implementation of HIV testing, counseling, public information campaigns, rapid of dissemination of information, ARV, csections prior to labor and discouragement of breastfeeding in HIV+ moms risk of transmission ↓ to 1-2%
- Prenatal testing important 30% of pregnant women not tested; another 15-20% receive no prenatal care
- Exact mechanism of MTCT HIV remains unknown intrapartum, during delivery, breastfeeding
- Greatest risk for vertical transmission is thought to be advanced maternal disease with high viral load

Epidemiology of HIV

- Early in AIDS epidemic women rarely diagnosed with HIV/AIDS
- By 2005 women represented 27% of 46,000 new cases transmission most commonly by heterosexual contact
- More common among African American and Hispanic women
- Women of color account for 80% of new cases in US
- Greatest risk was among young women
- In 2017 36.7 million people worldwide were infected with HIV

Pathogenesis of HIV

- ► HIV infection occurs in 4 major stages
 - Acute viral illness
 - Latent stage
 - Symptomatic stage
 - -AIDS

Screening/Diagnosis

- All pregnant women screened at new OB, if risk factors occur, in 3rd trimester
- Rapid HIV test available for women at time of delivery with no testing
- Initial screening with enzyme immunoassay (EIA) for HIV-1 and HIV-2
- If +, follow up with Western blot or IFA
- If both +, infection; if both -, unlikely to be infected; if EIA + and confirmatory negative should repeat
- CDC recommends universal screening for pregnant women with "opt out" strategy

Management During Pregnancy

- Essentially same as other other pregnant women labs, US, regular schedule of visits
- CVS/amnios questionable
- Viral load and CD4 count at new OB, near delivery and at other points
- Should receive vaccines for pneumococcal infection, influenza, hep A and B, tdap, meningococcal infection
- Test for other STDs syphilis, GC, chlamydia, Hep B and C
- Should be screened for TB, CMV, toxo
- Single most important intervention is initiation of HAART

Management During Pregnancy

- HAART easier said than done!
- ACTG-076 trial demonstrated that treatment of pregnant women with prophylactic zidovudine (AZT) reduced rate of perinatal transmission from 26% to 8%
- Subsequent studies demonstrated that use of combination chemotherapy reduce PNT to <2%
- Multiple agents available at least 45 medications available in US
- At a minimum Combivir and Kaletra should be used safe, well tolerated, highly effective
- Other medications needed for TB, CMV, etc

Management During Pregnancy

- If medication started, serial assessments of VL made
- If no response should order HIV genotyping to assess for resistance
- Adjustments to medications if resistance noted
- All meds with potentially serious maternal side effects
- Only Efavirenz (Sustiva) clearly teratogenic to fetus and should be avoided

Delivery

- If VL <1000 copies/mL near delivery vaginal delivery possible unless other contraindications exist
- Avoid invasive procedures during labor amniotomy, scalp electrodes, scalp pH assessment, episiotomy
- If VL > 1000 copies/mL c-section at 38 weeks recommended
- IV AZT should be initiated 3 hours prior to c-section and during labor if vaginal delivery
- If patient presents for labor or delivery with unknown HIV status, rapid HIV test available with results in 1 hour
- If suspicious for HIV, treat as above until test results available

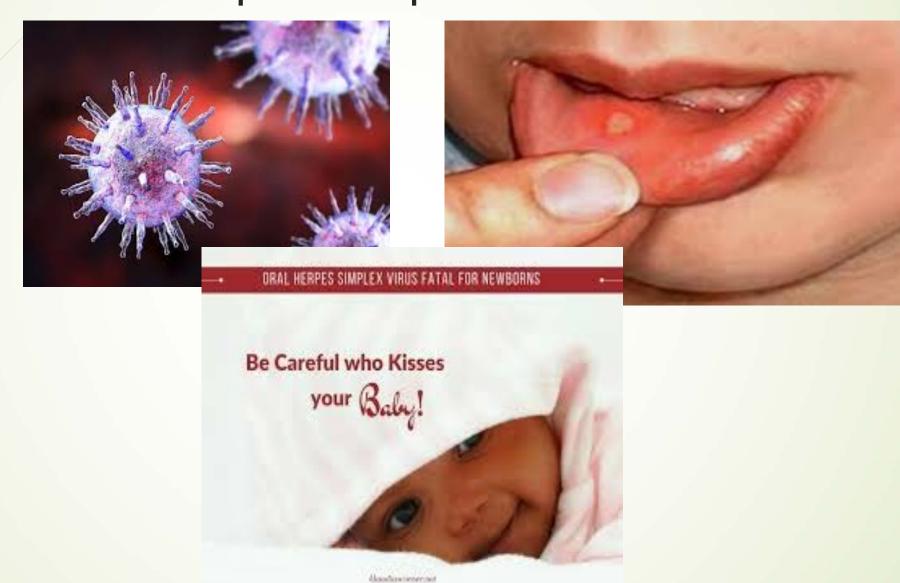
The Fetus and the Newborn

- Transmission may occur intrapartum, during delivery (most likely) and via breastfeeding
- Goal of HAART is to reduce transmission to the fetus
- ► Factors increasing risk of transmission history of affected infant, high maternal viral load, preterm delivery, invasive procedure, intrapartum exposure to maternal secretions, chorio, concurrent STDs, vag delivery with high viral load
- Infants born to HIV+ patients receive ART for at least 6 weeks
- No breastfeeding

Postpartum

- Discussion of birth control options
- Routine postpartum care
- Refer for follow up to Internal Medicine/ID physician with expertise in lifelong management of HIV

Herpes Simplex Virus 1 and 2



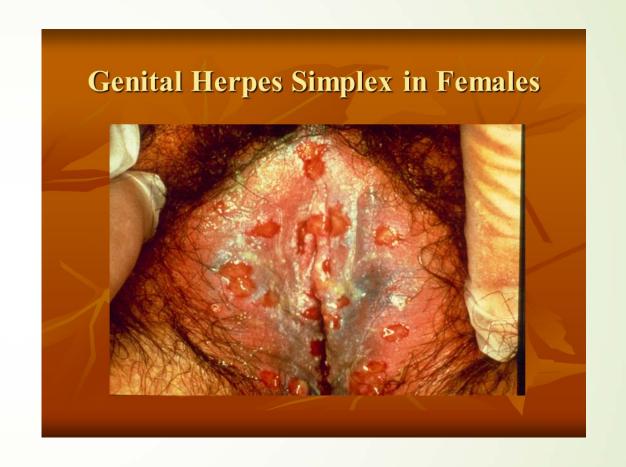
Herpes Simplex Virus (HSV)

- HSV herpesvirus family
- Prevalence to serum antibodies to HSV-2 increasing in US;
 45 million cases of infection
- In adults results in infections of oral cavity, skin, genital tract
- HSV-1 and HSV-2 can both cause infections of these areas
- Genital herpes spread by sexual contact
- Is not more severe or protracted in pregnancy

Herpes Simplex Virus

Three syndromes of genital herpes

- First episode primary genital herpes: no antibodies, severe local symptoms, lesions lasting 3-6 weeks, regional adenopathy, constitutional symptoms, rarely viral meningitis



Herpes Simplex Virus

- Three syndromes of genital herpes
 - ► First episode nonprimary genital herpes initial clinical infection with either HSV-1 or HSV-2 with antibodies to the other serotype
 - More like recurrent infection; tends to be less severe
 - Recurrent genital herpes milder and shorter episode, lesions last 3-10 days, shortened course reflects preexisting antibodies

Clinical Diagnosis of HSV

- Clinical diagnosis made on basis of painful crops of lesions in various stages of progression
- With primary infection have tender inguinal adenopathy, fever, other constitutional symptoms, ill appearing
- Lesions resolve without scarring in 3-6 weeks
- Clinical recurrences are variable about 50% have recurrences in 6 months

Laboratory Diagnosis of HSV

- Clinical diagnosis may not be enough as patients may present after symptom resolution and classic presentation not present
- Diagnosis can have social and future implications so confirm by labs
- Made by viral culture vesicular fluid has highest yield
- Can be made by Tzanck smear or pap smear
- PCR to detect HSV DNA is probably best test results available in several hours
- Use of newer IgG assays can distinguish between HSV-1 AND HSV-2
- Unclear if pregnant women should be routinely screened for HSV

Treatment of HSV

- During clinically evident episodes treatment consists of supportive measures oral analgesics, topical anesthetics, strict attention to hygiene
- May see frequent bathing with drying of perineum with hair dryer
- Acyclovir 400 mg po tid is highly effective for primary/recurrent episodes
- Suppression with acyclovir safe and effective for up to 6 years
- Valacyclovir 1000 mg po bid is better absorbed, longer half life, more expensive; 1000 mg po qd for suppression
- Acyclovir and valacyclovir safe during pregnancy

Management of HSV During Pregnancy

- Routine prenatal care
- Ask all pregnant women about history of herpes
- Treat if outbreak occurs during pregnancy
- Confirm diagnosis by PCR or culture if outbreak occurs
- For women with recurrent infection prophylaxis with acyclovir at 36 weeks until delivery
- No recommendation now for serial cultures at 34-36 weeks in asymptomatic women with history of HSV
- US if ventriculomegaly or echogenic bowel, consider TORCH titers

Management of HSV During Pregnancy

- Instruct to come to hospital if history of HSV and early labor or PROM; if asymptomatic risk of infection is low
- If labor or PROM, careful vaginal/perineal exams to rule out active lesions
- C-section if active lesions noted
- Since neonatal infection severe and maternal treatment not always effective, mainstay of management is to prevent contact of fetus and infected maternal material – c-section
- Avoidance of skin-to-skin if maternal active lesions present

Herpes Simplex Virus –The Fetus and Neonate

- Transplacental infection resulting in congenital infection is rare
- Maternal seroconversion to HSV-2 during pregnancy rarely results in LBW, PTD, growth restriction, stillbirth or neonatal death
- Neonatal herpes potentially devastating, usually acquired during vaginal delivery by contact with infected lower maternal genital tract
- Neonatal herpes more likely to occur with primary maternal infection due to lack of maternal antibodies – less likely (but no zero) with recurrent infection
- Difficult to tell if infection primary or recurrent
- If disseminated herpes occurs in neonate risk of death exceeds 40% even with treatment

HSV Prevention

- Condom use
- Ask partner about history of STDs
- Limited number of partners
- Avoid sexual activity if genital lesions
- Ask partner to be tested for STDs
- Alternate forms of sexual intimacy
- Treatment with antivirals for outbreaks, prophylaxis

Syphilis



Syphilis

- Chronic systemic infection caused by spirochete
 Treponema pallidum
- Human is only known host
- Is sexually transmitted
- Recognized that infection in pregnant woman can result in stillbirth, congenital abnormalities and active disease at birth
- Routine screening of pregnant women recommended

Syphilis - Epidemiology

- 1937 prediction that 10% of Americans would be infected with syphilis
- Rates declined and reached a nadir in 2000 due to public health initiatives and availability of penicillin
- Uptrend in rates in late 1970s and early 1980s, then a downtrend due to safe-sex education related to HIV/AIDS
- Uptrend again in late 1980s and increase I number of congenitally acquired cases
- Low of 108 cases in 1978, 350 cases in 1986, 3850 in 1992 with an incidence rate of 100/100,000 live births
- 90% of cases in AA/Hispanic patients; 50% in women with no PNC increase in "crack" epidemic, decrease in funding syphilis control, treatment of gonorrhea with spectinomycin, revised guidelines for reporting congenital syphilis

Syphilis - Epidemiology

- Rates declined and reached a nadir in 2000 due to public health initiatives and availability of penicillin
- latest epidemic peaked in 1990 >112,000 cases of primary/secondary syphilis reported yielding rate of 18.4/100,000 population
- Nadir in 2002 with only 450 cases reported
- CDC launched its National Syphilis Elimination Program in 1999

Syphilis - Epidemiology

- The states with the highest syphilis rates are as follows, with DC at No. 1 and Georgia at No. 5:
- D.C. has 84.5 cases per 100,000 people
- New York has 47.8 cases per 100,000 people
- Nevada has 45.4 cases per 100,000 people
- California has 45.0 cases per 100,000 people
- Georgia has 40.3 cases per 100,000 people
- Maryland has 30.7 cases per 100,000 people
- Virginia has 15.5 cases per 100,000 people
- AJC, April 25, 2018

Syphilis - Pathogenesis

- T. pallidum transmitted through sexual contact and is acquired in 50-60% of partners after one exposure to person with primary syphilis
- Can gain entrance through break in mucosal surface; mean incubation time is 21 days (10-90 days)
- Infection occurs in stages –primary, secondary and tertiary
 - Stages can overlap and may not be clinically distinct

Syphilis

- Primary: patient develops a painless chancre (10-90 days), lasts 2-6 weeks; usually on penis, cervix, vagina
- Secondary: stage during which syphilis disseminate; can infect any organ; skin rash over whole body, fever, muscle pain; highly contagious mucocutaneous lesions present; 2-3 months after onset of chancre, followed by latent phase of many years with no symptoms even if not treated
- Latent: period of no symptoms but seropositive results
 - Early latent: infection acquired within past year
 - ►Late latent: any other time frame; not contagious sexually but can pass infection transplacentally
- Tertiary: several years to decades following infection; takes the form of neurosyphilis, cardiovascular syphilis or late benign syphilis
- Without treatment 1/3 of patients progress to tertiary syphilis

Syphilis - Diagnosis

- Most definitive method dark field microscopic exam or direct fluorescent antibody tests of lesion exudates or tissue
- Presumptive diagnosis nonspecific tests for reagin-type antibodies and specific antitreponemal antibody tests
- Nonspecific tests VDRL and RPR
 - Used for screening all pregnant women at new OB and at 28 weeks minimum; no mother-infant pair should leave hospital with unknown maternal status
- Treponema-specific tests –used to confirm diagnosis of + VDRL or RPR
- After treatment nonspecific tests become negative while specific may remain weakly positive for life

Syphilis - Diagnosis

- Reinfection or persistence of active syphilis hard to differentiate
- With successful treatment VDRL titer should decrease or become negative/very low within 6-12 months of treatment for early syphilis or 12-24 months late syphilis
- Rising titers may indicate need for additional diagnostic tests or retreatment

Maternal Treatment

- All pregnant women with history of sexual contact with a person with syphilis who has any positive testing for syphilis should be treated
- Women who have been treated who have a fourfold risk in titer should be retreated
- Penicillin G is the agent of choice and is only agent effective for treating maternal syphilis, preventing transmission to the fetus, and treating established fetal infection
- If pregnant woman is allergic to penicillin must be desensitized and treated with pen G

Maternal Treatment – CDC Guidelines 2016

Stage	CDC STD Treatment Guidelines	WHO STI Guidelines
Primary/Secondary	2.4 MU benzathine penicillin G IM x1 once	2.4 MU benzathine penicillin G IM x1 once
Early Latent	2.4 MU benzathine penicillin G IM x1 once	2.4 MU benzathine penicillin G
Late Latent/Unknown Duration	2.4 MU benzathine penicillin G IM x1 per week for 3 weeks	2.4 MU benzathine penicillin G IM x1 per week for 3 weeks
Tertiary without evidence of neurosyphilis	2.4 MU benzathine penicillin G IM x1 per week for 3 weeks	No set recommendation
Neurosyphilis	Aqueous crystalline penicillin G 18-24 MU per day for 10-14 days; 3-4 MU IV every 4 hours or continuous IV for 10- 14 days	No set recommendation

Maternal Treatment

- Pregnant women treated for syphilis during latter half of pregnancy may be at risk for preterm labor or fetal distress if Jarisch-Herxheimer reaction occurs
- CDC recommends repeating serologic titers at 28-32 weeks
- Titers may be checked more frequently if risk of reinfection high

- Occurs when T. pallidum is transmitted from a pregnant woman to her fetus
- May lead to stillbirth, neonatal death, and infant disorders such as deafness, neurologic impairment, and bone deformities
- Transmission can occur during any stage of syphilis; risk is much higher during primary and secondary syphilis
- Fetal infection can occur during any trimester of pregnancy
- Wide spectrum of severity exists; only severe cases are clinically apparent at birth
 - Early lesions (most common): Infants <2 years old; usually inflammatory</p>
 - Late lesions: Children >2 years old; tend to be immunologic and destructive

- Clinical spectrum includes stillbirth, neonatal death, nonimmune hydrops, clinically apparent syphilis during early months of life, and classic stigmata of late congenital syphilis
- Most severe outcomes occur with maternal primary and secondary syphilis
- About 2/3 of infants asymptomatic at birth and develop symptoms at 3-8 weeks – symptoms include maculopapular rash, snuffles, mucus patches in oral cavity, enlarged liver, jaundice, LAD
- Untreated/inadequately treated disease will progress to Hutchinson teeth, mulberry molars, 8th nerve deafness, saddle nose, saber shins

- May be difficult to diagnose due to transfer of nonspecific and specific treponemal maternal antibodies to fetus
- If any of following occur should conclude congenital syphilis present
 - Mother had untreated/inadequately treated syphilis durig pregnancy
 - + treponemal test and
 - Evidence of congenital syphilis on PE
 - Evidence of congenital syphilis on long bone Xrays
 - Reactive CSF VDRL test
 - Elevated CSF white blood cell count or protein concentration
 - Reactive test for FTA-ABS -19S-IgM antibody
- Treatment with penicillin according to CDC/AAP protocols

- Unlikely to occur if mother adequately treated but should be of concern if
 - Mother has untreated syphilis at delivery
 - Mother has serologic evidence of relapse or reinfection after treatment
 - Mother received treatment with non-penicillin regimens
 - Mother was treated < 1 month before delivery</p>
 - Mother with no documented history of treatment
 - Mother who does not demonstrate an adequate response despite treatment
 - Mother with treatment before pregnancy but with insufficient serologic follow-up to ensure appropriate response

Prevention of Maternal-Fetal Syphilis

- Safe sex practices
- Serologic screening of all pregnant women at appropriate intervals during pregnancy
- Treatment with penicillin per CDC recommendations

Effects of Maternal Infections

- In utero transmission is variable and may depend on type of infection, EGA and maternal immunologic status
- In general if infection is primary or acquired early in gestation effects may be more serious
- Ascending infections can cause funisitis and chorio and lead to PPROM/PROM and PTD
- Hematogenous or viral infections can infect placenta and lead to deciduitis, villitis and fetal infections

Effects of Maternal Infections on Fetus/Neonate

- **LBW**
- PTB
- Miscarriage and stillbirth
- Developmental anomalies toxo, CMV
- Congenital diseases syphilis
- Postnatal persistence of infections TB, syphilis, malaria may persist for months/years

General Guidelines for Prevention of Maternal Infections

- Handwashing
- Avoidance of sick contacts
- Modification of maternal behavior safe sex practices
- Educating women on infection prevention strategies
- Preconceptual and antenatal screenings to ensure early disease detection
- Maternal immunization when possible

Thank you! ■ jellis@emory.edu

General References

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- www.cdc.gov
- www.perinatology.com
- www.smfm.orgxc dc