CONGENITAL INFECTIONS

INSTRUCTOR: Laura Kasman, Ph.D. kasmanL@musc.edu Office BSB 208F

OUTLINE:

1) Definition of congenital infections / vertical transmission
2) The two most important risk factors for harm from a congenital infection
    i) Infection status of mother (primary or established infection)
    ii) Timing of exposure in pregnancy
3) Congenital infections by stage of pregnancy at greatest risk
    i) First trimester
        a) Cytomegalovirus
        b) Rubella virus
        c) *Toxoplasma gondii*
        d) Zika virus
    ii) Second and third trimester
        a) Hepatitis C
        b) *Listeria monocytogenes*
        c) Parvovirus B19
        d) *Treponema pallidum* (syphilis)
        e) HIV
    iii) Birth and perinatal period
        a) Group B Streptococcus
        b) Herpes simplex
        c) Varicella zoster
        d) Hepatitis B
        e) Neisseria gonorrhoeae
        f) Chlamydia trachomatis
        g) HPV
4) Prevention of congenital infections
    i) Immunization
    ii) Pharmacotherapeutics
    iii) Surgical birth

OBJECTIVES: After studying this unit you should be able to:

1. Explain the two most important risk factors for harm from a congenital infection in the fetus or newborn.
2. List infectious agents transmitted vertically with significant potential for harm in the fetus or newborn.
3. Describe the most common physical findings and pathophysiology of the congenital infections covered.
4. List measures to prevent vertical transmission of the infectious agents covered, if available.
5. Identify the most likely congenital infection given a clinical case scenario describing maternal history, timing of infection, and physical and laboratory findings in the child.

Pathogen name	**Fetal or perinatal death?**	**Permanent *developmental* defects in survivors?**	**Post-neonatal consequences only**	**Stage of pregnancy with *highest* risk**
Cytomegalovirus*	yes	yes	sometimes	1st trimester*
Rubella	yes	yes	-	1st trimester
Toxoplasma gondii	yes	yes	sometimes	1st trimester
Zika virus	yes	yes	-	1st trimester
Hepatitis C	-	-	yes	2nd or 3rd trimester
Listeria monocytogenes	yes	-	-	2nd or 3rd trimester
Parvovirus B19	yes	-	-	2nd or 3rd trimester
Treponema pallidum (syphilis)	yes	yes	-	2nd or 3rd trimester
HIV	-	-	yes	2nd or 3rd trimester and during birth
Group B Streptococci	yes	-	-	During birth
Herpes simplex	yes	-	-	During birth
Varicella zoster	yes	-	-	During birth
Hepatitis B	-	-	yes	During birth
Neisseria gonorrhoeae	-	-	yes	During birth
Chlamydia trachomatis	-	-	yes	During birth
HPV	-	-	yes	During birth

*CMV timing is difficult to determine, since congenital CMV infections occur in primary and secondary (reactivations) infections, both of which are often asymptomatic in the mother.

In all cases, the chart attempts to show period of highest risk, but infections at other times can have consequences.

Congenital Infections

Laura Kasman, PhD

BSB 208F

kasmanL@musc.edu

The purpose of this lecture is to bring together and organize information regarding infectious agents presented throughout the curriculum that have special consequences during pregnancy and the neonatal period.

Lecture Outline

1) Definition of congenital infections / vertical transmission

2) The two most important risk factors for harm from a congenital infection

3) Congenital infections by stage of pregnancy at greatest risk

    i) First trimester

    ii) Second and third trimester

    iii) Birth and perinatal period

4) Prevention of congenital infections

Definition of congenital infection

- **Congenital infection is one that is vertically transmitted** from a mother* to her fetus or neonate during pregnancy, childbirth, or via breast milk.

A subset of vertically transmitted infections are perinatal:

- **Perinatal transmission (WHO definition):** transmission directly from the mother to her child between the 22nd week of gestation and 1 week after birth.

*With mother defined as the person gestating the embryo and fetus in utero.

Vertical Transmission

Routes of vertical transmission

- Prepartum or transplacental
- Intrapartum (during delivery)
- Postpartum via breastfeeding

Not all congenital infections are transmitted by all routes.

Types of adverse outcomes from congenital infections

- permanent developmental defects apparent at birth
- fetal or perinatal death (with or without developmental defects)
- consequences apparent only after the neonatal period

#1 factor leading to an adverse outcome:

Mother is experiencing infection with the pathogen for the **first time** during the pregnancy

Why?

She has not built up adaptive immunity to it so

- Pathogen numbers will be higher
- No transplacental antibody transfer to protect the fetus / neonate

#2 factor in an adverse outcome:

The **timing of exposure** during gestation.

Why?

Pathogens have tropisms for specific tissues.

For transplacental infections, the developmental stage of a given tissue at the time of infection affects the outcome.

For infections transferred perinatally, maternal infection late in pregnancy will generally result in worse outcomes.

Congenital infections with greatest risk in the first trimester

Pathogens	Fetal or perinatal death possible?	Permanent developmental defects in survivors?	Post-neonatal consequences only
Cytomegalovirus*	yes	yes	sometimes
Rubella	yes	yes	-
Toxoplasma gondii	yes	yes	sometimes
Zika virus	yes	yes	-

*some uncertainty for CMV, since both primary and reactivation infections transmit transplacentally

Congenital Cytomegalovirus

Most common intrauterine infection in the U.S.

- 0.5-1.0% of births

Presentation:

- >90% asymptomatic at birth. If symptomatic - hepatitis, rash, retinitis and intracranial calcifications, microcephaly possible.
- Both asymptomatic and symptomatic may develop sequelae over months to years: sensorineural **hearing loss,** retinitis, microcephaly, cognitive impairment

Congenital Cytomegalovirus

Diagnosis:

- PCR of newborn saliva or urine in first three weeks of life
- or anti-CMV IgM

- Treatment: valaganciclovir if symptomatic, but no significant difference in long term outcomes
- Prevention: None yet

Congenital Rubella Syndrome

- Greatest risk following rubella in first trimester
- Transient abnormalities - “blueberry muffin spots”, low birth weight, pneumonitis, thrombocytopenic purpura, hepatosplenomegaly
- Permanent abnormalities – ocular and cardiac defects, microcephaly and deafness
- **Classic triad - cataracts, deafness, and heart defects**

#1 cause of congenital deaf-blindness worldwide.
Completely preventable with universal vaccination.

Congenital Toxoplasmosis

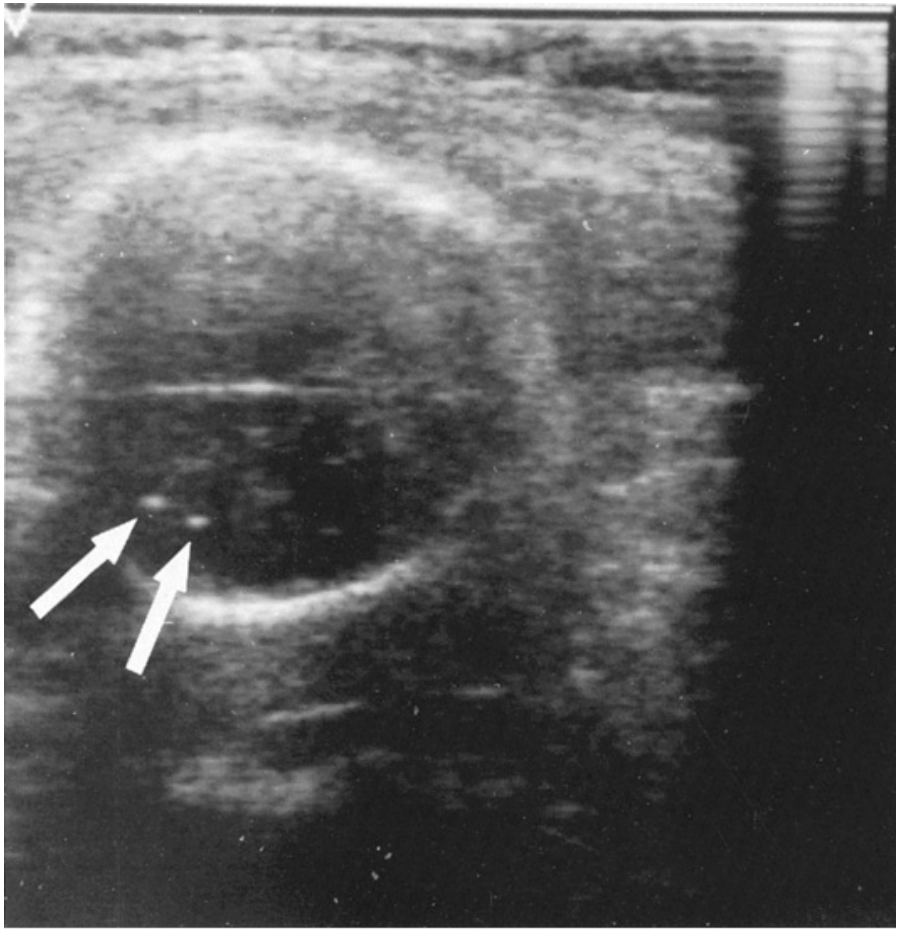
Presentation:

- classic triad includes chorioretinitis, intracranial calcifications, and hydrocephalus.
- Or asymptomatic at birth but develop learning and visual disabilities later in life.

- Prevention:
  - Avoid exposures during pregnancy (undercooked meat, soil or litter contaminated with outdoor cat feces)
  - Pre-existing immunity in mother from prior infection (about 10% of U.S. population)
  - Anti-toxoplasma drugs reduce fetal infection 50%

Severe Congenital Toxoplasmosis

Newborn with hydrocephalus, and sonographic image of intracranial calcifications (*arrows*) in a fetus at approximately 30 weeks. (Courtesy of Dr. Rigoberto Santos.)



Congenital *Toxoplasma gondii* epidemiology

- Transplacental transmission can occur at any time during pregnancy, but child is at greatest risk for severe disease if the mother is infected during the first trimester.

- About 20% of transplacentally infected fetuses develop severe disease, and 20% mild disease. The remaining 60% are asymptomatic.

Congenital Zika virus

Flavivirus spread by mosquitoes and semen

First seen in the Americas in 2016

Clinical Presentation:

- Microcephaly, brain damage, blindness, seizures, swallowing difficulties.
- May worsen after birth

- Treatment: None
- Prevention: Mosquito control, avoiding conception during mosquito season

PROTECT YOUR FAMILY AND COMMUNITY

HOW ZIKA SPREADS

Accessible Version: https://www.cdc.gov/zika/transmission/index.html

Most people get Zika from a mosquito bite

1

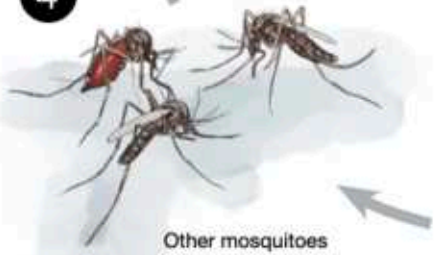
A mosquito bites a person infected with Zika virus

2

The mosquito becomes infected

3

The infected mosquito bites a person and infects them with Zika



4

Other mosquitoes bite that person and become infected

5

More members of the community become infected when they are bitten by those infected mosquitoes

Other ways people get Zika

During pregnancy
A pregnant woman can pass Zika virus to her fetus during pregnancy. Zika infection during pregnancy can cause serious birth defects and is associated with other pregnancy problems.

Through sex
Zika virus can be passed through sex from a person who has Zika to his or her sex partners.

Through blood transfusion
Zika virus may be spread through blood transfusion.

CDC

264550-A

Congenital Zika virus infection

- Too early to know the full range of other potential health problems caused by Zika virus infection during pregnancy.
- No reports of infants getting Zika through breastfeeding.
- No evidence that previous infection will affect future pregnancies.

Congenital infections with greatest risk in the 2nd and 3rd trimester

Hepatitis C virus

Listeria monocytogenes

Parvovirus B19

Treponema pallidum

HIV

No common features among the pathogens in this group

Congenital Hepatitis C

- HCV transmission from mother to child can occur in late pregnancy or during the birthing process (about 5% rate of transmission)
  - Co-infection with HIV appears to ~double the risk (~5 vs. ~10%); seen in HIV-untreated settings
  - NO association with associated viral genotype, mode of delivery, breastfeeding
- Clinical presentation: same as adults- no symptoms

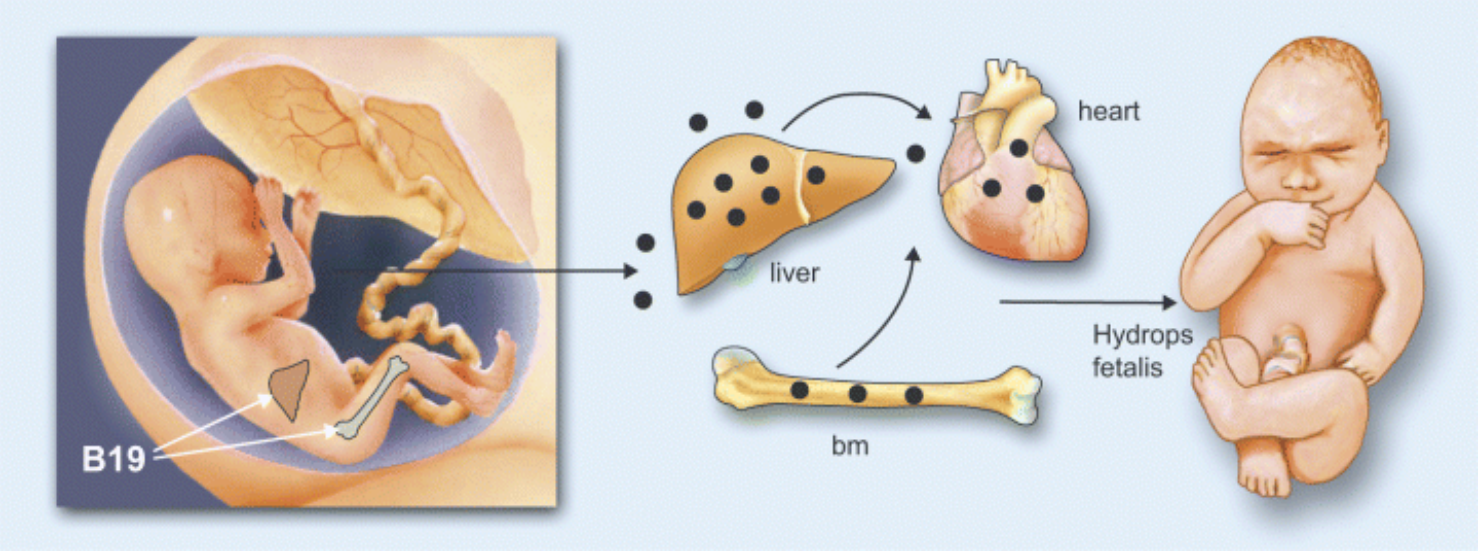
Congenital Hepatitis C

- Prevention: None except to treat mother before conception.
- Diagnosis: Antibody screen at ~ 12 months of age. Follow-up positive with RT-PCR. Diagnosis by RT-PCR is possible earlier but too early to treat so little reason.
- Spontaneous clearance can occur (up to 30% of infected infants) but is rare beyond age 3 years. Children who clear infection are negative for HCV RNA but remain antibody-positive.

Congenital *Listeria monocytogenes*

- Foodborne illness: Pregnant women are 10 times more likely to develop listeriosis from an exposure than other people
- Clinical presentation: Miscarriage or stillbirth, serious or fatal infections in newborns
- Prevention: Avoid consuming unpasteurized dairy and deli meats during pregnancy. May be treatable with antibiotics.
- Diagnosis: culture of blood, CSF or amniotic fluid

Congenital **Parvovirus B19**



- Highest risk of transmission in trimesters 1 and 2, when placental P-antigen is highest
- Infection of fetal hematopoetic cells causes fetal anemia, may progress to cardiac failure and **hydrops fetalis**
- Direct viral myocarditis also observed

Congenital **syphilis**

- May result in stillbirth, prematurity, or clinical manifestations. **Only severe cases are clinically apparent at birth.**
- Signs of early congenital syphilis, if present: thick, pale placenta, rhinitis/snuffles, hepatomegaly and a maculopapular rash that appears 2-3 weeks after birth
- **Preventable** by treating mother with Penicillin G as early in pregnancy as possible and the child at birth

Reproduced from: the Public Health Image Library, Centers for Disease Control and Prevention. Photo by Dr. Norman Cole.

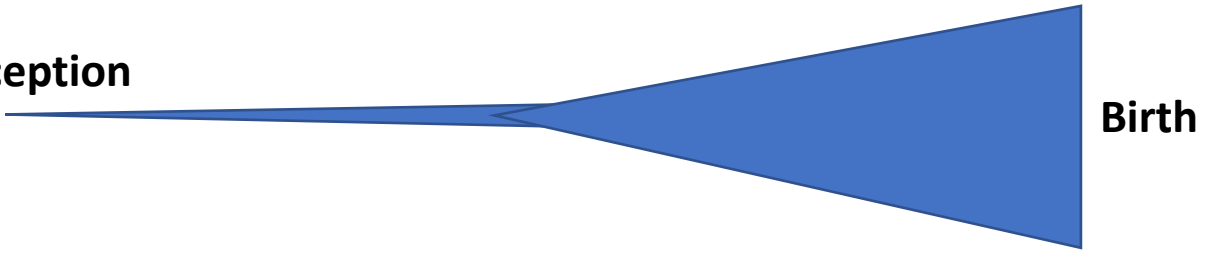
Baby is contagious.

Congenital syphilis transmission

	Risk of vertical transmission in untreated mothers by stage of infection
Early Syphilis	• Primary syphilis **60-90% chance** • Secondary syphilis **60-90% chance** • Non-primary, non-secondary syphilis **40% chance**
Late Syphilis	• Late latent syphilis. **Steadily decreases over time, to less than a 2% chance after 2 yrs**

Risk of vertical transmission in untreated mothers by time in gestation

Highest in **last 4 months** of gestation



Congenital **HIV**

- **Clinical presentation:** poor weight gain and the same opportunistic infections seen in adults.
- **Diagnosis:** same as for adults
- **Preventable: Yes**
- 25% transmission rate with no intervention
- <1% with combination of interventions:
  - antiretroviral suppression of mother's viral load
  - C-section delivery by 38 weeks if virus still detectable
  - antiretroviral treatment of newborn
  - No breastfeeding

Congenital infections with greatest risk during birth and the perinatal period

Group B Streptococcus **Herpes simplex** **Varicella zoster**	These cause fulminant, sometimes fatal infections in the newborn
Hepatitis B **HIV (also transplacental)**	These cause chronic, initially asymptomatic infections that currently last a lifetime
N. gonorrhoeae ***C. trachomatis*** **Human papilloma virus**	These usually cause symptomatic infections of the eyes and respiratory tract in the perinatal period, or longer in the case of HPV

Group B Strep

- Clinical presentation: Third trimester stillbirths, and neonatal infection in survivors
- 15-40% of pregnant women are colonized and without disease, and ~50% who are colonized will transmit GBS to their newborns
- Neonatal infection is most often a result of GBS ascending from the vagina into the amniotic fluid after onset of labor or rupture of membranes
- Neonatal infection may present 1-90 days after birth (If in first week, called "GBS early onset disease")
- Prevention: Universal screening in late pregnancy and Intrapartum **IV** antibiotics for those who test positive

α herpesviruses and neonates

- Both HSV and VZV can cause severe systemic infections in newborns
- **Much** less common than prevalence of HSV and VZV infections would suggest
- Most likely when mother is experiencing *primary* infection at **time of parturition**
- Maternal Ab provide protection in established infections

Routine screening of pregnant women NOT recommended. C-section only recommended if mother has lesions at parturition.

Congenital HSV and VZV infection

- Prevention: Suppressive anti-viral therapy with acyclovir starting at 36 weeks gestation reduces viral shedding and lesions. However, the majority of mothers having babies born with fulminant HSV do *not* have a history of HSV infection
- Congenital VZV incidence is now 1 in 500,000 in the U.S.
- Prompt treatment with acyclovir reduces mortality. Still, mortality ~20%, and severe sequelae common in HSV survivors.
- Rarely, transplacental infections occur with these viruses with similar severe outcomes.

Congenital Hepatitis B virus

Clinical Presentation:

- Asymptomatic at birth
- High risk (90%) of chronic HBV infection without treatment
- Greatly increased lifetime risk of hepatocellular carcinoma

Prevention: Yes

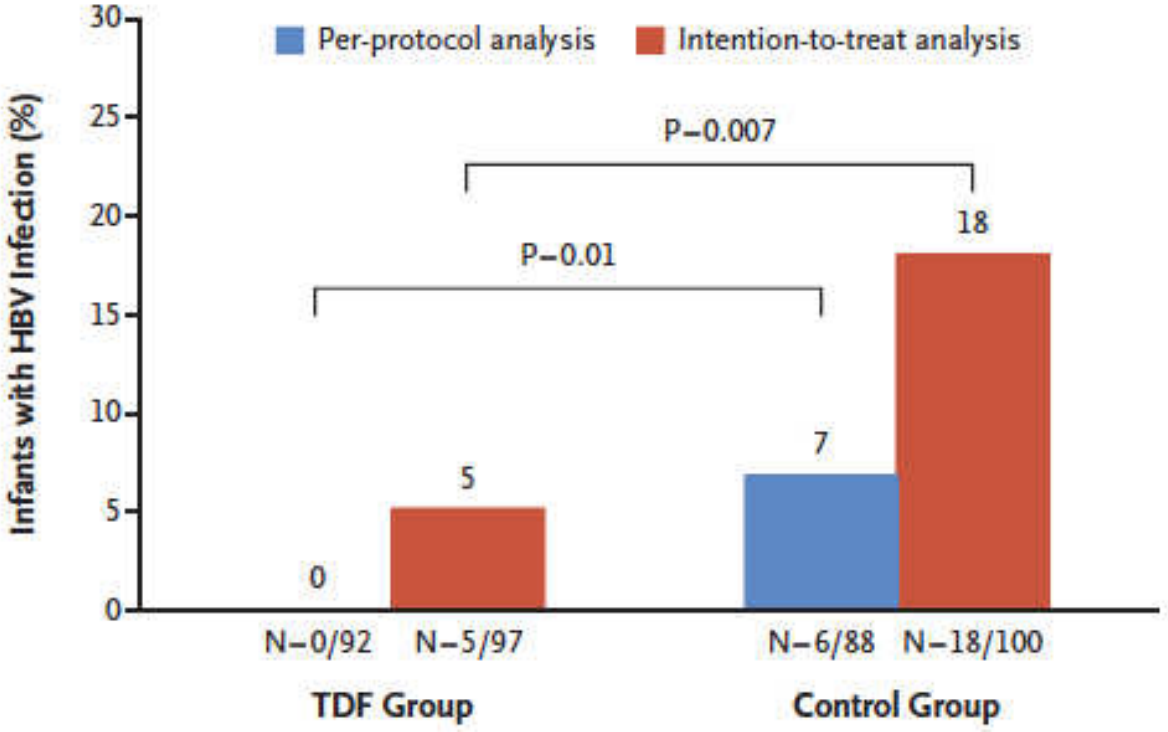
- Vaccination of mother before conception
- Passive and active HBV vaccination of baby at birth
- Tenofovir treatment of mothers with high viral loads in 3rd trimester
- C-section ***not*** effective because of blood exposure.

The NEW ENGLAND JOURNAL of MEDICINE

Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load

CONCLUSIONS

In a cohort of HBeAg-positive mothers with an HBV DNA level of more than 200,000 IU per milliliter during the third trimester, the rate of mother-to-child transmission was lower among those who received TDF therapy than among those who received usual care without antiviral therapy. (Funded by Gilead Sciences; ClinicalTrials.gov number, NCT01488526.)



Pan, et al, NEJM, 2016

Perinatal *N. gonorrhoeae* Infections Among Neonates

Neonatal conjunctivitis/ Ophthalmia neonatorum Monitor or systemic infection	**Treatment: Erythromycin 0.5% ophthalmic ointment** in each eye in a single application at birth*
Disseminated infection (e.g., sepsis, arthritis, and meningitis)	Ceftriaxone
	Prevention: Screen and treat during pregnancy

*topical erythromycin is not effective for Chlamydia conjunctivitis. It requires systemic antibiotics.

Perinatal *Chlamydia trachomatis* Serotypes D-K infections in neonates

- Serotypes D-K cause the common sexually transmitted *Chlamydia* disease
- Neonates born to infected mothers risk developing inclusion conjunctivitis and/or pneumonia
- **Prevention:** Test, treat, and test again for cure in 3rd trimester
- Topical/ ophthalmic erythromycin is not effective for Chlamydia conjunctivitis treatment in newborns. It requires systemic antibiotics.
- Azithromycin, single dose, is preferred therapy

Usually not symptomatic until 5-14 days after delivery

Can occur in C-section births, especially with ruptured membranes

Neonatal chlamydia conjunctivitis

12-day-old child with -day history of progressive lid swelling and discharge typical of chlamydial conjunctivitis.

Reproduced with permission from: Tasman W, Jaeger E. The Wills Eye Hospital Atlas of Clinical Ophthalmology, 2nd Edition. Lippincott Williams & Wilkins, 2001. Copyright © 2001 Lippincott Williams & Wilkins.

UpToDate®

Congenital C. trachomatis pneumonia

- Becomes symptomatic at 4 weeks of age or later
- Often preceded by inclusion conjunctivitis
- Common lab finding: Peripheral eosinophilia with normal total WBC

Chest radiograph in an infant with *Chlamydia trachomatis* pneumonia

Chest radiograph in a 10-day-old infant with *Chlamydia trachomatis* pneumonia. There is a diffuse interstitial pattern in both lung fields with normal heart size.

From: Hon KL, Leung AK. Chlamydial pneumonitis: a creepy neonatal disease. Case Rep Pediatr 2013; 2013:549649. https://www.hindawi.com/journals/cripe/2013/549649/. Copyright © 2013 Kam Lun Hon and Alexander K. C. Leung. Reproduced under the terms of the Creative Commons Attribution License 3.0

UpToDate

Congenital Human papillomavirus (1)

Clinical Presentation:

- Asymptomatic at birth
- Age 2-5 – develop hoarseness caused by Recurrent respiratory papillomatosis (RPP)
  - benign laryngeal tumor in children
  - HPV 6 and 11 are the most common types
- Disease usually regresses in puberty
- Rarely, spreads into the lungs, and undergoes malignant transformation.

Congenital Human papillomavirus (2)

Risk factors:

- First born child delivered vaginally
- Mother under 20 years of age with condyloma acuminata

Therapy:

- Ablative procedures, repeated as needed
- A review of 399 children with RRP, reported a mean number of surgical procedures per child of 4.4/year

Prevention: Yes

- Vaccination of parents with Gardasil 9 vaccine

TORCH infections (old mnemonic)

Toxoplasmosis

Other

Rubella

Cytomegalovirus

Herpes simplex

Syphilis, Parvovirus, HIV, Hepatitis B, Hepatitis C, Listeria, Zika, Gonococcus, Chlamydia, HPV

Summary of interventions to prevent congenital infections

- Immunization
- Pharmacotherapeutics
- Surgical birth

- Avoid exposures, especially during critical periods of gestation

Practice questions

Which of the following congenital infections is almost exclusively transmitted at the time of parturition?

A. Cytomegalovirus
B. Hepatitis B
C. Rubella
D. Toxoplasmosis
E. Syphilis

An 11-day old infant presents at the pediatrician's office with mucopurulent conjunctivitis. Which of the following pathogens is most likely responsible for these symptoms?

A. Chlamydia trachomatis
B. Neisseria gonorrhoeae
C. Herpes simplex virus
D. Syphilis
E. Toxoplasmosis

A prenatal screening anti-treponemal antibody test performed at 32-weeks gestation is positive, but a VDRL test is negative. The patient's record records a single intramuscular dose of Penicillin G one year ago. Is the patient at high risk of transmitting syphilis to the child?

A. Yes – patient is actively infected
B. No - patient was infected but is now cured
C. No - patient was infected but is now immune