Perinatal Infections

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Definitions

- congenital
  - contracted *in utero*
- perinatal
  - from completion of 24 weeks gestation until 1-4 weeks after birth
- postnatal

- neonatal

Intrauterine and perinatal infection

- infection diagnosed *in utero*
- congenital infection, symptomatic or asymptomatic at birth
- acquired around the time of birth and manifest later

Effects of maternal infection

- no evidence of damage
- subclinical infection without evidence of damage
- abortion
- stillbirth
- death in infancy
- intrauterine growth retardation (IUGR)
- congenital defects
- late onset of congenital disease

Common infecting agents

- Viruses
- Bacteria
- Protozoa
- Rickettsiae/Chlamydiae

- (Fungi are rare, as a cause of intrauterine infection – an increasing cause of late-onset neonatal sepsis)

Intrauterine and perinatal infection

Diagnosed *in utero*

Parvovirus B19

Manifest at birth

Toxoplasma gondii

Cytomegalovirus

Treponema pallidum

Hepatitis C

Rubella

Varicella/Zoster

Hepatitis B

HIV

Intrauterine and perinatal infection

Acquired around the time of birth and symptomatic later

Herpes simplex
Hepatitis B
Hepatitis C
HIV
Group B β haemolytic streptococci
E. coli
Listeria monocytogenes
Chlamydia trachomatis
Neisseria gonorrhoea

Torch syndrome

Toxoplasma

Others (Varicella/Zoster, Treponema pallidum)

Rubella

Cytomegalovirus (CMV)

Herpes simplex

Mechanisms of infection

- Intrauterine
  - blood borne transplacental infection
  - ascending infection
- During delivery
- Postnatal infection
  - breast milk
  - cross infection
  - the environment

Period of transmission

Virus	Congenital	Natal	postnatal
Rubella	+*	-	-
Cytomegalovirus	+	+*	+
Varicella-zoster	+	+	-
Herpes simplex	+	+*	+
Hepatitis B	+	+*	+
HIV	+	+*	+

* *Principal time of transmission*

What should we know?

- The risk posed by the agent to the fetus
- Timing of infection in relation to risk
- Frequency of damage
- Nature of damage
- Availability of diagnostic tests
- Whether treatment is available
- Preventive measures

Antenatal screening: Justification

- Will give information “for action” to prevent or reduce the adverse consequences of the infection

- Treatment or prophylactic measures will usually be instituted

Problems with screening for infection: it gives a “snapshot” in time

- Women remain at risk of acquiring infection during the pregnancy? Repeat tests

- A woman may be in the “window period” before signs of the infection appear

Antenatal screening programmes

YES	NO
Rubella	CMV
HBV	Herpes simplex
HIV	Parvovirus B_{19}
Syphilis	

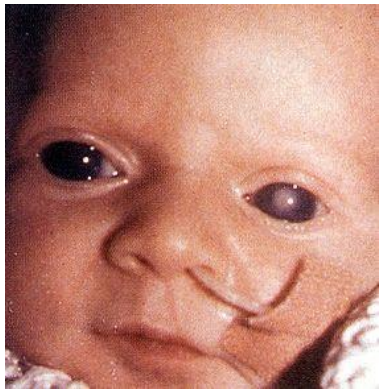
Rubella

An RNA togavirus

- 1941 McAlastair Greig suggested an association between maternal rubella, congenital heart disease and cataracts

- 1962 virus isolated

- 1969 live vaccine developed



Timing of infection: Risk of damage

Infection at

• 0-8 weeks	80% detectable defects
• 9-12 weeks	52% detectable defects
• 13-20 weeks	16% ?
• 20+ weeks	no increased risk

Rubella: Nature of damage

Rubella Syndrome

- PDA
- Cataracts
- Hearing deficits
- Encephalitis
- Interstitial pneumonia
- Sensory abnormalitis: Eye/Ear
- Bony radiolucencies

Expanded Rubella Syndrome

- Small for gestational age
- Microcephaly
- PDA
- Pulmonary stenosis
- Hepatosplenomegaly/ lymphadenopathy

Rubella

- Routine infant immunization - **MMR** at 15 months and 4 years

➢ **Measles** causes fever, rash, cough, runny nose, and red, watery eyes. Complications can include ear infection, diarrhea, pneumonia, brain damage, and death.

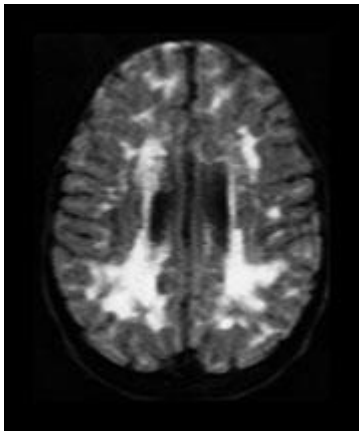
➢ **Mumps** causes fever, headache, muscle aches, tiredness, loss of appetite, and swollen salivary glands. Complications can include swelling of the testicles or ovaries, deafness, inflammation of the brain and/or tissue covering the brain and spinal cord (encephalitis/meningitis) and, rarely, death.

➢ **Rubella**, causes fever, sore throat, rash, headache, and red, itchy eyes. If a woman gets rubella while she is pregnant, she could have a miscarriage or her baby could be born with serious birth defects. You can protect against these diseases with safe, effective vaccination.

- Routine screening test in pregnancy - a convenient time to screen healthy normal women
- Women who are non-immune are offered vaccine postnatally
- [pre-conceptual screen, premarital screen]

Congenital CMV

- The most common congenital infection worldwide; rate estimated at 0.5 to 2.5%
- 95% are asymptomatic at birth, 10-15% may develop symptoms later



- microcephaly, hydrocephaly
- periventricular cerebral calcification
- deafness, cerebral palsy
- seizures
- microphthalmia
- chorioretinitis, blindness
- interstitial pneumonia
- petechiae/purpura
- anemia
- lymphadenopathy

Congenital CMV

- Prevention - there is no proven preventive intervention
- Treatment - there is limited evidence that treatment of infants with neurologic symptoms, with ganciclovir iv x 6 weeks, may help, however, when the drug is stopped the viral load increases again

Toxoplasmosis

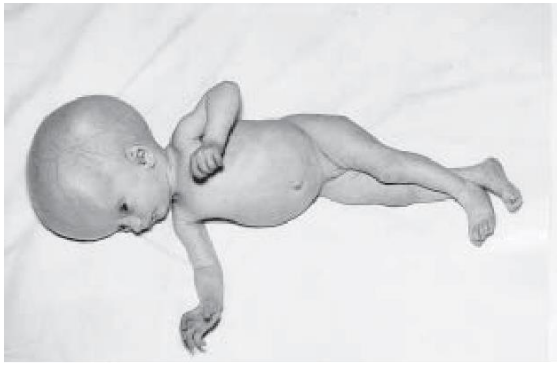
Toxoplasma gondii

- The cat is the primary host
- Other animals and birds

- 25% of women have antibody indicating previous infection
- Human infection is believed to result from eating undercooked infected meat or handling infected soil or cat litter

Congenital toxoplasmosis

- Classic triad
  - hydrocephalus, intracranial calcification, chorioretinitis
- Non-specific signs
  - hepatosplenomegaly, jaundice
  - thrombocytopenia
  - growth retardation, rash



A Girl with hydrocephalus due to congenital toxoplasmosis. (From Dubey JP, and Beattie CP. Toxoplasmosis of animals and Man. CRC

Sequelae

- Only 10% of infected babies are clinically symptomatic at birth
- The most common clinical sequel is chorioretinitis
  - by the age of 20, 60-85% have had chorioretinitis which may be unilateral or bilateral
- Deafness, low IQ

Treatment of congenital toxoplasmosis

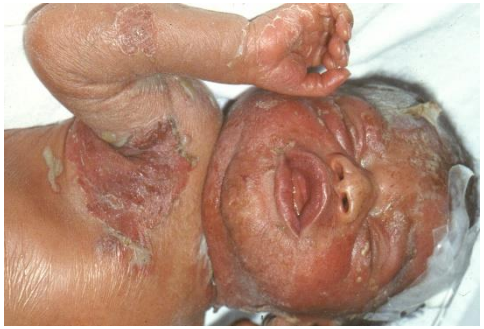
- ***In utero* diagnosis and treatment**
  - France, Austria, Switzerland
  - Few controlled studies
  - Meta-analysis “5 studies showed that antenatal treatment was effective, four that it was not” (spiramycin is given until the 16th week of pregnancy, followed by at least 4 weeks of combination therapy with pyrimethamine, sulfadiazine, and folinic acid)

Postnatal diagnosis and treatment

- Treatment for the entire first year of life will improve outcome (pyrimethamine, sulfadiazine, and folinic acid)

Congenital syphilis

- Fetal death and miscarriage
- Stillbirth



- Congenital infection which may be asymptomatic at birth and manifest later

Congenital syphilis

- Most likely to occur if a mother has untreated primary infection during present pregnancy
- The risk of transmission decreases with subsequent pregnancies

Positive treponemal serology

- Treat mother unless previous treatment and serological response has been documented
- Repeat serology monthly
- Screen for other STDs
- Partner(s) should be treated

- Assess infant
  - Depends on maternal results and treatment, (X-rays and CSF exam may be required in infant)
- **Treat the infant in virtually all cases**

Neonatal therapy
Recommended Regimens

- **Aqueous crystalline penicillin G** 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
  OR
- **Procaine penicillin G** 50,000 units/kg/dose IM in a single daily dose for 10 days
  OR
- **Benzathine penicillin G** 50,000 units/kg/dose IM in a single dose

Listeriosis

Listeria monocytogenes

- A zoonosis
- soft cheeses, pate

- Infection *in utero* may result in stillbirth or a live infant with congenital infection
- Uncommon (but the third most common organism causing early onset neonatal infection)

Parvovirus B19

- “Slapped Cheek Syndrome” or Fifth Disease
- A common febrile exanthematous infection of childhood
- Symptoms include a “lacy” rash, influenza-like symptoms and arthropathy
- Some 50% of women of child-bearing age are immune

Parvovirus B19

- When acquired by a non-immune pregnant woman the transmission rate to the fetus is about 33%
- anemia, cardiomyopathy, hepatic dysfunction, hydrops fetalis (fetal death may occur)

- Diagnosis by specific IgM
- Exchange transfusion *in utero* is appropriate therapy in severe cases

Parvovirus B19

„B19 multiples in the bone marrow where it is cytotoxic for erythroid progenitor cells; this results in temporary arrest of erythropoiesis” - this effect is not typically seen in the normal child or adult

- Severe anemia is most frequent with infection of the fetus and in individuals with chronic haemolytic anemias such as sickle-cell disease
- Myocarditis occasionally reported

Varicella zoster virus

- Infection in the first 20 weeks may result in congenital varicella syndrome
- The risk of CVS with chickenpox in the first 20 weeks is approx. 2%
- Acute varicella in the time period from 2 days before to 5 days after delivery is associated with a high risk of severe disseminated varicella in the newborn

Varicella zoster: Prevention

- Specific VZ immunoglobulin if administered within 96 hours of exposure will usually modify the illness

- If administered up to 9 days there may be attenuation

Varicella zoster: Prevention

- If a mother has chickenpox in the time period 2 days before to 5 days after delivery, the infant should be given VZIG and carefully observed; if any lesions develop, iv aciclovir should be given

Herpes simplex

- The principal risk of transmission is with **primary** maternal infection at the time of delivery

- The risk is smaller with recurrent herpes at time of delivery

Prevention of neonatal herpes

- Recognition
- Elective Cesarean section in primary herpes at term or <4 hours after membrane rupture
- Some obstetricians would also recommend elective section when recurrent genital herpes is present at term

Herpes simplex

- Recognition of primary herpes can require a high index of suspicion
- Type 1 infection typically produces less severe symptoms and relatively little local manifestation compared with type 2 infection
- The infection may be confined to the cervix

Hepatitis B

- Chronic HBV infection with persistence of HBsAg occurs in
  - up to 90% on infants infected vertically,
  - 30% of children 1 to 5 years old infected after birth
  - in 5 to 10% of older children, adolescents and adults with HBV infection

Hepatitis B

- The development of the carrier state following vertical transmission has been estimated to increase the risk of chronic liver disease x20 times, hepatoma x86 times
- In addition, horizontal transmission of the infection may occur in childhood (vaccinating one child protects 3 others)

HBV: Perinatal transmission

- Neonate should receive Hepatitis B vaccine
- Administration of HBIG will further reduce the risk of transmission

HBV: Prevention of vertical transmission

- Routine linked antenatal HBV testing would be cost-effective because of the morbidity prevented by identifying carrier mothers and giving immunoprophylaxis to their infants

- This is the case even in areas of low endemicity

Hepatitis C

- Most transmission is around the time of birth
- Vertical transmission rate is about 7%
- Outcome - may become chronic carriers
- Identify mothers at risk

Diagnosis in the neonate should be postponed until after the child reaches 1 year of age because infants may have transient viremia.

Treatment for HCV infected children has not been studied extensively.

Ribavirin are not currently approved for pediatric use; however, recent studies in children have shown potential benefit. More effective and less toxic therapies for young patients with HBV and HCV are needed, as are methods to interrupt perinatal transmission of HBV and HCV.

HIV - Vertical transmission

- perinatal in most cases
- transmission rate 15 - 25%
- role of Caesarean section in reduction of transmission in some cases

HIV - Vertical transmission

- Transmission can be decreased by approximately 2/3 by administration of anti-retrovirals
  - to the mother in pregnancy, in labour
  - to the infant for the first 4 weeks - this is post-exposure prophylaxis

HIV

- >90% of cases of pediatric HIV are due to vertical transmission

- Prevention is dependent on identification of infected mothers and
  - antiretroviral therapy, antepartum and intrapartum with post-exposure prophylaxis to the infant
  - caesarean section in selected cases

Chlamydia trachomatis

- Acquisition occurs in some 50% of infants born vaginally to infected mothers and in some delivered by Cesarean section with intact membranes

- The nasopharynx is the common site of primary multiplication in the infant
  - conjunctivitis in 15-50%
  - pneumonia in 5 - 20%

Chlamydia: Prevention

- Opportunistic screening of women “at risk”
  - DNA detection methods suitable for use on urine specimens
- Recommendation
  - all women attending STD clinics
  - single women < 25 years
  - women with multiple sex partners
  - women with a new sex partner

Perinatal infections in the hospital

- **sepsis**
- **meningitis**
- **pneumonia**
- urinary tract infection
- conjunctivitis
- omphalitis
- otitis media

Perinatal infections in the community

- skin infections → omphalitis
- bronchiolitis → pneumonia
- diarrhoea
- otitis media
- urinary tract infection
- conjunctivitis (orbital cellulitis)
- **sepsis**
- **meningitis**

Diagnosis of neonatal sepsis

- Difficult
- Signs are subtle and non-specific
  - respiratory distress
  - lethargy
  - poor feeding
  - jaundice
  - vomiting and diarrhoea

Risk factors

- Maternal history
  - Traumatic delivery
  - Prematurity
  - Maternal Peripartum Sepsis
  - Prolonged Rupture Of Membranes
    - PROM >24 hours (infection rate of 1/100 with chorioamnionitis: 10/100)
    - Irrespective of the time interval, membrane rupture - delivery, infection rates are 5 times higher in infants born before term

Characteristics

Early-Onset

- Within first 24 hours, range (0 - 6d)
- Fulminant, Multisystem, Pneumonia frequent
- Mortality rate of 15-50%

Late-onset

- At 3 to 4 weeks, range 7d to 3 mo
- Slowly progressive,
- Focal; Meningitis frequent
- Mortality rate of 10-20%

Neonatal sepsis

- **Group B Streptococcus**
- **E. coli**
- **other Gram negative bacilli such as Proteus, Klebsiella**
- **Listeria monocytogenes**

Others including:

- Staphylococcus aureus
- Coagulase-negative Staphylococci
- Candida species
- Pseudomonas
- Enterobacter

Neonatal sepsis: Problems

Difficulties with making a laboratory diagnosis

- Mother had antibiotics
- Infant has received antibiotics
- Small sample size, especially in the premature or growth retarded infant
- Frequent isolation of “normal flora”

Neonatal sepsis

- Many neonatologists/units perform screening swabs

- Ear swab, umbilical swab, gastric aspirate, in addition to blood culture

Group B Streptococcus (GBS)

- Historically the case-fatality rate has been estimated to be 5-20% for neonates and 15-32% for adults

- Fatality rate in early-onset sepsis in the most recent studies was 6%. This reduction in rates may be because of advances in neonatal care.

GBS epidemiology

- **Reservoir** - Gastrointestinal tract
- The genitourinary tract is the most common site of secondary spread
- Colonisation rates may vary by geographical area, race and age
- In most populations studied 10-30% of pregnant women were colonised

GBS epidemiology

- Neonatal disease: “1 to 4 cases /1,000 live births”
- USA 1990, multistate surveillance 1.8 cases /1,000 live births
- Early-onset accounts for >75% of neonatal cases

GBS infection - Prevention

- Early-Onset GBS infection is primarily an intra-uterine infection
- Therefore it ***may*** be prevented by intrapartum chemoprophylaxis
- In Late-Onset GBS infection the route of entry is unclear
- This is not amenable to prevention by chemoprophylaxis

GBS infection - Prevention

Pregnant women should receive antibiotics through the vein (IV) during labor if:

- They test positive for GBS bacteria during their current pregnancy
- They have GBS bacteria in their urine anytime during their current pregnancy
- They had a previous baby who developed GBS disease

Prevention of congenital and perinatal infection

- Serological screening in pregnancy
  - Rubella, syphilis, Hepatitis B, HIV: “routine”
  - Hepatitis C: in certain groups
  - Handwashing
  - CMV, toxoplasmosis
- Modification of “at risk” behaviour
  - Blood borne viruses
  - Sexually transmitted infection

Prevention of congenital and perinatal infection

- Avoidance of certain foods
  - pate, soft cheeses, undercooked meats
- Screening for GBS carriage is performed in USA and AUS
  - from 35 weeks
  - intrapartum penicillin in carriers and those who deliver earlier (not screened)
- Active herpes at term - avoid vaginal delivery