The epidemiology and pathogenesis of intrauterine and perinatal infection.

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Intrauterine and perinatal infection:

• Epidemiology:
  Developing v Developed World

• Spectrum of Pathogens

• Pathogenesis

• Impact of Infection
Pregnancy and childbirth the leading cause of death in women of reproductive age in developing countries
Global Maternal and Child Mortality & Rates

Maternal Deaths
- 500,000 pa (<1% occur in developed countries)
- 1. hemorrhage, 2. infection and 3. unsafe abortion

Perinatal Deaths
- ~1% in developed countries
- 3.3 million stillbirths
- 4 million neonatal deaths

• Neonatal mortality rates
  • Developing 30-40 per 1000 livebirths
  • Developed 3 per 1000 livebirths

www.who.int 2005 Making every mother and child count
Direct causes of neonatal deaths 2000

Infectious causes of neonatal deaths 2000

## Australia 2006: Births and Perinatal Deaths

- **280,078 live births** (3.6% increase from 2005)
- **8.2% preterm births** (7.3% in 2005)
- **816 perinatal deaths**
- **2091 stillbirths** (27% unexplained)
- **Neonatal mortality rate** 3 per 1000 livebirths
- **Perinatal mortality rate** 10.3 per 1000 births

Causes of infection in pregnancy and the newborn
Congenital infections

TORCHES CLAP
- Toxoplasma gondii
- Rubella virus
- Cytomegalovirus
- Herpes simplex virus
- Enteroviruses
- Syphilis

- Chickenpox (VZV)
- Lyme disease
- AIDS
- Parvovirus B19

Congenital Toxoplasmosis

Histology
Pseudocyst containing tachyzoites

Imaging

Sakaie & Gonzalez, NeuroAIDS Vol.2, (7), 1999

Cand.med. Fábio Bombarda, Faculdade de Medicina de Marília, Brazil.

Olaf Dammann INIS ppt.
Maternal Infection in the Developing World

Systemic infections:
- malaria
- pneumonia
- tuberculosis
- typhoid fever
- pyelonephritis

STIs:
- Syphilis
- HIV
- Hepatitis

VPDs
- Spontaneous abortion
- Stillbirth
- Preterm labour
- Preterm birth
- Low birth weight
- malformation
- Infection
## Viruses associated with Congenital Infection

<table>
<thead>
<tr>
<th>ANTE</th>
<th>PERI &amp; POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella</td>
<td>HSV 1, 2</td>
</tr>
<tr>
<td>CMV VZV</td>
<td>VZV</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Enteroviruses</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>HIV</td>
</tr>
<tr>
<td>HIV</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>Hepatitis C,</td>
<td>HTLV-1</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>HPV</td>
</tr>
<tr>
<td>Lassa Fever</td>
<td></td>
</tr>
<tr>
<td>Japanese Encephalitis</td>
<td></td>
</tr>
</tbody>
</table>
Bacteria associated with Congenital Infection

<table>
<thead>
<tr>
<th>STDs</th>
<th>Genitourinary and gastrointestinal flora: (incl yeasts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T pallidum, N gonorrhoea, C trachomatis</td>
<td>Group B streptococci, E coli</td>
</tr>
<tr>
<td></td>
<td>Mycoplasma spp, Ureaplasma spp</td>
</tr>
<tr>
<td></td>
<td>Enterococci, Staphylococci, AnO2 streptococci, coliforms</td>
</tr>
<tr>
<td></td>
<td>Gardnerella vaginalis, Fusobacterium spp</td>
</tr>
<tr>
<td></td>
<td>Bacteroides spp</td>
</tr>
<tr>
<td>Pathogen</td>
<td>Transmission risk</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>1(^\circ) ~50%, non 1(^\circ) &lt; 1%</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>no data re predictors for risk</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>up to 90% (90% then chronic carriers)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>~6% (to 45% with HCV/HIV co infection)</td>
</tr>
<tr>
<td>Herpes Simplex Virus</td>
<td>1(^\circ) &amp; &gt;34/40 30-50%, recurrence to 3%</td>
</tr>
<tr>
<td>HIV</td>
<td>Varies with VL, CD4 count, GA, ROM &gt;4 hr</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>50% risk of transmission mother to fetus</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>1(^{st}) trimester: 50-100%, 2(^{nd}): 20% 3(^{rd}): &lt;1%</td>
</tr>
<tr>
<td>Varicella zoster virus</td>
<td>Highest risk in 2(^{nd}) trimester: 2%</td>
</tr>
<tr>
<td>L monocytogenes</td>
<td>Highest mortality 2(^{nd})/3(^{rd}) trimester 40-50%</td>
</tr>
<tr>
<td>M tuberculosis</td>
<td>Most cases occur airborne after delivery</td>
</tr>
<tr>
<td>Group B strep</td>
<td>20% women colonised, GBS bacteruria</td>
</tr>
<tr>
<td>T pallidum</td>
<td>risk related to maternal disease stage</td>
</tr>
<tr>
<td>T gondii</td>
<td>Risk of infection and damage varies w GA</td>
</tr>
</tbody>
</table>
Pathogenesis of infection:
Transmission of infection: mother to baby

- occurs across mammalian species
- causing injury, malformation, sepsis and death
Modes of intrauterine and perinatal infection:

- Transplacental
- Iatrogenic
- Ascending
- Perinatal
- Breast milk
- Nosocomial
Transplacental Infection

- Infection spread haematogenously via placenta
- Follows acute or reactivation maternal infection
- Blood borne viruses, bacteria, parasites
- Asymptomatic, vague non specific symptoms
- Fetal infection: malformation, death, preterm labour, growth restriction, developmental
Transplacental Infection: Congenital Rubella

- 57% WHO member countries vaccinating (100% industrialised)
- 100,000 babies per annum with congenital rubella globally [Robertson 2003]

- Teratogenic: fetal damage via 2 mechanisms
  1. generalised, progressive vasculitis > parenchymal hypoplasia
  2. cellular deletion via mitotic arrest and apoptosis [Plotkin 2005]

- Most severe impact early, coincident with organogenesis
Transplacental Infection: Congenital Rubella

- Rubella infected cells have reduced lifespan
- Infected organs have reduced cell number
- Ocular, Auditory, Cardiovascular, CNS, other

Fields virology
Banatvala JE et al Lancet 2004
Congenital Rubella Syndrome:

• **Ocular:**
  – Cataracts, glaucoma, pigmentary retinopathy, microophthalmia, iris hypoplasia, cloudy cornea

• **Auditory:**
  – Sensorineural deafness

• **Cardiovascular:**
  – Patent ductus arteriosus, pulmonary artery stenosis, VSD, myocarditis

• **Central nervous system, other organ systems:**
  – Microcephaly, developmental delay, meningoencephalitis, behavioural disorders, speech disorders, IUGR, thrombocytopenia, hepatitis, hepatosplenomegaly, bone lesions, pneumonitis, lymphadenopathy, diabetes mellitus, thyroid disorders, progressive panencephalitis.
Congenital Rubella Syndrome:

- preventable disease
- vaccine response in 95% >11 months age
- long term efficacy >90%
- congenital rubella syndrome rare in developed world
- those at risk are unvaccinated, migrants, nonimmune
- …complacency would be unwise…
Iatrogenic Infection

- Intrauterine sampling, instrumentation
- Risk low
- Bacteria (skin and gut flora), viruses, yeasts
Perinatal Infection
Perinatal Infection

- Infection acquired around time of delivery
- **Contact** with infective lesions/blood or
- **Colonisation** and infection eg (Group B strep)
- Prevention strategies effective
- HIV, HPV, GBS, HBV, HCV, HSV, etc
Perinatal Infection: HSV infection

• Maternal: genital, orolabial

• Risk greatest when 1° infection in late gestation

• Lower risk before 30-34 weeks: similar to recurrence in pregnancy

• Nosocomial

• 85% acquired perinatally, true IUI ≤5%

• Significant M&M

Palasanthiran P et al Eds ASID 2002
Breast milk Infection

- Bacteria, Viruses, Parasites detected in BM
- Those reported to cause disease:
  - GBS, L. monocytogenes, C burnetii
  - HIV, CMV, HBV, HTLV1, HSV, rubella
  - Toxoplasmosis (case)
- HIV, HTLV1,2 advise against BF
  (developed setting) ?GBS

Jones CA 2001
Breast milk infection with GBS

- Late onset infection
- GBS colonises ducts
  - Clinical mastitis
  - Infant ingests bolus
  - Colonises oropharynx
  - Invasive infection
- Twins

Kotiw M
Ascending infection

- Vaginal flora, low pathogenicity
- Polymicrobial
- Enterococci, Staphylococci, AO2 streptococci, coliforms, Ureaplasma, Mycoplasma, GBS
- Common (and causative) preterm births
Ascending Intrauterine infection: Key Points

Clinically:
1. Asymptomatic

Immune responses:
1. Maternal *then*
2. Fetal

Histological Diagnosis:
1. Chorioamnionitis (maternal)
2. Umbilical vasculitis ± funisitis (fetal)

Goldenberg NEJM 2000
Histological Chorioamnionitis in Preterm Births: n=3928

Lahra MM, Jeffery HE. AmJOG 2004
Russell P AmJDiagGO 1979
Ascending infection

• 50% early preterm births

• IUI: inflammation protective
  ➢ + fetal hypothalamic-pituitary-adrenal axis
  ➢ labour
  ➢ glucocorticoid production (endogenous steroid)
  ➢ fetal lung maturation

BUT:

➢ Low gestation: adverse outcome
Preterm birth

- Cerebral palsy
- Chronic Lung Disease
- Impairment of vision and hearing
- Learning difficulties: reading and maths
- Other neuro developmental problems
Intrauterine infection

chorioamnionitis

fetal inflammatory response

labour

lung maturation

delivery

reduced RDS, CLD

survival

sepsis

CNS injury

GA

CLD

CP

injury
Neonatal sepsis

• Preterm at high risk for sepsis

• Early versus late

• Early (perinatal): GBS, E coli

• Late (nosocomial): CoNS, gram + /-ve, yeast

• Treatment associated with risk
Neonatal sepsis

- n=761 < 30 weeks
- 31% episode/s sepsis

- RF for CLD

  CoNS: 3.17 (2.08 - 4.83)
  Other bacteraemia: 2.46 (1.42 - 4.27)
  Candidaemia: 8.68 (1.65 - 43.63)

Lahra MM Paediatrics 2009
Summary

Developing: poverty, overcrowding, deprivation

Developed:

- Intrauterine infections ~ 50% preterm births
- Preterm birth: significant M&M
- Unresolved PH issue
- Most neonatal sepsis nosocomial
- Sepsis associated with adverse outcome
- Potentially modifiable risk factor
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