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Infections in pregnancy
Infections in Pregnancy

• STDs/HIV and other infections (B strep, malaria)

• Direct infection of fetus/infant

• Indirect effects of inflammatory response in fetus or mother
Routes of Intrauterine Infection

**Pregnancy**
- Hematogenous Transplacental
  - Syphilis, HIV, malaria
- Ascending Infections
  - Gonorrhea, Chlamydia, Group B Strep

**Intrapartum**
- HIV, Hepatitis B, HSV-2, HPV
- Gonorrhea, Chlamydia, Group B Strep

**Lactation**
- HIV
- Syphilis
## Maternal-Infant Infections During Pregnancy

### STDs
- Viruses (HIV, HSV-2, HPV)
- Bacteria (Syphilis, Gonorrhea, Chlamydia)
- Trichomonas

### Other Genital Tract
- BV
- Group B Strep

### Other Systemic Infections
- Parastitic (Malaria)
- Viruses (Rubella, Hepatitis B, CMV)
- Bacterial (TB)
Fetal/Infant outcomes

- Pregnancy Loss, perinatal and infant Death

- Direct infection of fetus/new born (congenital)

- Effects via preterm birth and low birth weight
Birth Outcomes

Outcomes:
- Preterm Delivery <37 weeks (PTD)
- Premature rupture of membranes (PROM)
- Low birth weight (< 2500 gm)

Etiology:
- HIV
- Syphilis
- Gonorrhea/Chlamydia
- BV
- Trichomonas
- Chorioamnionitis
**Frequency of transmission to infants**

- **Syphilis** ~ 70% of infants affected in primary, secondary and early latent maternal syphilis
  - SAB/stillbirth/infant death
  - congenital syphilis
- **Gonorrhea** ~ 45% ophthalmia → blindness
- **Chlamydia** ~ 50% low grade ophthalmia or pneumonia
- **HIV**: 14-44% infants infected without treatment
Pregnancy outcome with treated and untreated active syphilis, Tanzania

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>Untreated active syphilis %</th>
<th>Treated active syphilis %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>24.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>32.7</td>
<td>6.3</td>
</tr>
<tr>
<td>Preterm</td>
<td>20.0</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Watson-Jones *et al JID* 2002;186:186 and 194
Placental membrane infections

- Chorioamnionitis, funistis (cord), amniotic fluid infection, fetal infections
- Probably due to organisms from the vagina which ascend into the uterus early in pregnancy
- Often asymptomatic
- Direct effects of infection
- Indirect inflammatory effects
Anatomy of Chorioamnionitis, Amniotic Fluid and Fetal Infections (Goldenberg NEJM 2000)

Inflammatory Response in Fetus and Mother

- Inflammatory response to infection

```
Fetal ← Infection → Maternal

CrH → Cortisol

Prostaglandin

Contraction

Preterm Delivery

Cytokines

IL-1,2; TNFα

Metalloproteins

PROM
```
Preterm Delivery (PTD)

- Delivery < 37 weeks
- ~ 10% births in US (higher in African American mothers)
- 70% perinatal deaths are PTD
- 50% of long-term neurologic morbidity PTD
- Most serious morbidity/mortality in PTD < 32 weeks and very low birth weight (VLBW < 1500 g)
Bacterial Vaginosis (BV)

- BV is the most common vaginal infection
  - 10-50%
- Disturbances in the vaginal flora
  - loss of peroxide producing lactobacilli,
  - increase in predominantly anaerobic flora,
  - increase in vaginal pH
- Most women are asymptomatic
- BV implicated in chorioamnionitis, PTD, PROM, and PID
BV Diagnosis

- **Clinical (Amsel criteria)**
  - Raised (alkaline pH)
  - Discharge
  - Amine odor (KOH whiff test)
  - Clue cells

- **Gram stain morphology (Nugent’s score)**
  - 0-4 normal
  - 4-6 intermediate
  - 7-10 BV (low or no Lactobacilli, anaerobes, Mobiluncus)
BV and Preterm Delivery (PTD) or Low Birth Weight (LBW)

- **Observational studies**
- BV and PTD RR $\sim 1.6$
- BV associated with chorioamnionitis and amnionotic fluid infections
  - Elevated cytokines
  - Elevated prostaglandin $\rightarrow$ PTD
Treatment of BV

- **Metronidazole or Clindamycin** ~ 70-85% cure over 1 month
- Treats anaerobic overgrowth, but does not restore Lactobacilli
- BV tends to be recurrent following treatment because of depletion of lactobacilli
  - Role of bacteriophages?
# Trials in high risk women (prior preterm delivery or other risk factors)

<table>
<thead>
<tr>
<th>References</th>
<th>Treatment in pregnancy</th>
<th>RR of PTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGreggor AJOG 1995</td>
<td>Clindomycin</td>
<td>0.52*</td>
</tr>
<tr>
<td>Ugwumadu Lancet 2003</td>
<td>Clinindomycin</td>
<td>0.42*</td>
</tr>
<tr>
<td>Morales AJOG 1994</td>
<td>Metronidazole</td>
<td>0.46*</td>
</tr>
<tr>
<td>Mc Donald BJOG 1997</td>
<td>Metronidazole</td>
<td>0.14*</td>
</tr>
<tr>
<td>Hauth NEJM 1995</td>
<td>Metronidazole</td>
<td>0.63*</td>
</tr>
<tr>
<td>Andrews AJOG 2006</td>
<td>Metronidazole (preconception)</td>
<td>1.1</td>
</tr>
</tbody>
</table>
## Trials in low risk women or general populations

<table>
<thead>
<tr>
<th>References</th>
<th>Tmt</th>
<th>RR PTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carey NEJM 2000</td>
<td>Mtz</td>
<td>1.0</td>
</tr>
<tr>
<td>Goldenberg AJOG 2006</td>
<td>Mtz</td>
<td>1.0</td>
</tr>
<tr>
<td>HIV+</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>HIV- (LMP subgroup)</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>McDonald BJOG</td>
<td>Mtz</td>
<td>0.96</td>
</tr>
</tbody>
</table>
• BV treatment during pregnancy reduces PTD in high risk women with BV in most trials
• PTD not reduced in lower risk women
• Metronidazole alone less efficacy than combined metronidazole plus macrolide antibiotics (clindomycin, erythromycin, azithromycin)
  – Possibly via suppression of TNFα
Treatment of Trichomonas in pregnancy
Metronidazole in women with Trichomonas (MFNU Study)  
(Klebanoff NEJM 2001;345:487)

- 617 women asymptomatic trichomonas randomized to Metronidazole 16-23 weeks & 24-29 wks.

- **PTD**
  - Metronidazole = 19.0%
  - Placebo = 10.7%
  - RR = 1.8 (1.2-2.7)

- **VLBW <1500 gm**
  - Metronidazole = 5.4%
  - Placebo = 3.8%
  - RR = 1.4 (0.7-3.0)
Rakai Trial; Trichomonas Treatment (Kigozi AJOG 2003)

- Subanalysis of women with Tv in Rakai trial
  - Treatment arm n = 94
  - Control arm n = 112

- LBW RR = 2.49 (1.12-5.50)
- PTD RR = 1.28 (0.81-2.02)
- Mortality RR = 1.58 (0.99-2.52)
Other treatment of infection in pregnancy

- Presumptive treatment
- Birth canal cleansing
- Syndromic management
Presumptive STD Treatment in Pregnant Women (Gray AJ OG 2001)

• Intervention arm - single, oral, directly observed therapy:
  - azithromycin 1 gm, cefixime 400mg., and metronidazole 2 gram

• Control arm
  - iron/folate

• Serologic syphilis IM benzathine penicillin 2.4 million units
  - Home tmt in intervention
  - Referral for free tmt in control
## Baseline Maternal Infections in Pregnancy (Rakai, Uganda)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV</td>
<td>50%</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>25%</td>
</tr>
<tr>
<td>Syphilis</td>
<td>10%</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>2%</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>3-4%</td>
</tr>
</tbody>
</table>
## Maternal STDs Postpartum

<table>
<thead>
<tr>
<th>Maternal STDs</th>
<th>Intervention vs Control RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td>1.0 (0.8-1.3)</td>
</tr>
<tr>
<td>BV</td>
<td>0.75 (0.7-0.8)</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>0.3 (0.2-0.5)</td>
</tr>
<tr>
<td>Gon/Chlamydia</td>
<td>0.4 (0.3-0.7)</td>
</tr>
</tbody>
</table>
## Infant Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intervention vs control RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonorrhea/chalmydia</td>
<td>0.38 (0.2-0.7)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>0.70 (0.51-0.96)</td>
</tr>
<tr>
<td>Preterm</td>
<td>0.73 (0.54-0.99)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>0.83 (0.71-0.97)</td>
</tr>
</tbody>
</table>
Presumptive Ceftriaxone in pregnancy

(Temmerman J Repro Med 1995)

- Nairobi trial 209 women ceftriaxone IMI, 191 control, at 28-32 weeks

- **Birthweight**
  - Ceftriaxone = 3209 g
  - Placebo = 3056 g \((p = 0.01)\)

- **Low Birth weight**
  - Ceftriaxone = 4.0%
  - Placebo = 9.2% \((p = 0.08)\)
Presumptive treatment (Rakai) vs syndromic management (Mwanza) in pregnant women

Presumptive treatment more effective than syndromic management in reducing STIs
Infections at Time of delivery

- Maternal genital tract infections contaminate infants during passage through birth canal during labor and delivery
  - ingestion/inhalation
  - transdermal
- Antisepsis during labor can reduce infections with STDs and other pathogens (e.g., Grp B strep)
- Viral STIs (HSV-2, HPV, HBV)
  - Antiviral drugs
  - C-section
Genital Tract Cleansing During Labor
(Taha Brit Med J 1997;315:216-9)

- Randomized trial of Chlorhexadine (0.25%) washing of birth canal in labor. n=3,500 per arm
  - Neonatal sepsis admissions RR = 0.44 (p<0.002)
  - Neonatal mortality RR = 0.78 (p<0.06)
  - Mortality due to sepsis RR = 0.33 (p<0.005)
  - Maternal re-admissions RR = 0.33 (p<0.02)
Group B Streptococcus (GBS)

- 15-30% of women asymptomatic carriers
- Transmission rate to baby 40-75%
- Neonatal sepsis Early onset (< 1 week)
  - Incidence = 0.3%, case/fatality = 10-50%, common in preterms
  - Late Onset (> 1 week)
  - Incidence = 0.05%, case/fatality = 10-15%
- Common infection but rare outcomes
- Treatment ampicillin, penicillin
- Prevention trials all unsuccessful
Prevention of Infection in Pregnancy

• Primary prevention:
  - Prophylaxis (condom use)
  - Safe sex

• Secondary prevention
  - Screening and treatment (e.g. syphilis HIV)
  - Mass treatment (e.g., metronidazole + macrolide in populations with high BV?)
  - Cleansing of birth canal during labor

• Treatment of new born
  - Screening and diagnosis can be problematic
HIV incidence during pregnancy
(Gray et al Lancet 2005)

<table>
<thead>
<tr>
<th></th>
<th>Pregnant</th>
<th>Lactating</th>
<th>Neither preg/lact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident cases/women years (wy)</td>
<td>23/997</td>
<td>40/3043</td>
<td>275/24,161</td>
</tr>
<tr>
<td>Incidence/100 wy</td>
<td>2.3</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Adjusted IRR (95%CI)</td>
<td>2.0 (1.3-3.1)</td>
<td>1.2 (0.8-1.6)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

HIV incidence during pregnancy was also significantly higher than during lactation Adj IRR = 1.76 (1.05-2.94)
Mother to child HIV transmission (MTCT)

- Rates and timing of transmission
- Prevention trials
- Breast milk transmission
Epidemiology

- Most children with HIV are infected by vertical transmission
- HIV seroprevalence rates of 30-35% among pregnant women in some African settings
- In countries with very large populations, lower seroprevalence rates can still result in large numbers of infected children
HIV prevalence among pregnant women in South Africa, 1990 to 1999

Source: Department of Health, South Africa
Timing and rate of MTCT
no breastfeeding

<table>
<thead>
<tr>
<th>Timing</th>
<th>Absolute rate</th>
<th>Relative proportion of all transmissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine</td>
<td>5-10%</td>
<td>25-35%</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>10-20%</td>
<td>65-75%</td>
</tr>
<tr>
<td>Total</td>
<td>15-30%</td>
<td>100%</td>
</tr>
</tbody>
</table>

DeCock JAMA 2000;283:1175
## Timing of transmission with breastfeeding for 18-24 months

<table>
<thead>
<tr>
<th>Timing</th>
<th>Absolute rate</th>
<th>Relative proportion of transmissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine</td>
<td>5-10%</td>
<td>20-35%</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>10-20%</td>
<td>35-50%</td>
</tr>
<tr>
<td>Breast 2 months</td>
<td>5-10%</td>
<td>20-25%</td>
</tr>
<tr>
<td>Breast &gt; 2 mths</td>
<td>5-10%</td>
<td>20-25%</td>
</tr>
<tr>
<td>Total</td>
<td>30-45%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Perinatal Transmission of HIV

Maternal Placental Chorioamnionitis

Duration of Ruptured Membranes

Breast Feeding

ART Rx

C-Section

HIV-1 RNA

ART Rx
Maternal Factors and perinatal MTCT

- Stage of maternal infection
- HIV viral load (1 log increase in VL RR of MTCT RR ~2.5)
- Viral subtypes
- Antiretroviral therapy
- Coinfections (STIs, chorioamnionitis, malaria)
- Factors associated with delivery (instrumentation, C/S)
HIV diagnosis in infants

- Complicated by presence of maternal antibodies

- Under 18 mths of age use:
  - HIV DNA PCR
  - HIV RNA PCR

- > 18 months use EIA/WB
ACTG 076 Trial

- Multicenter clinical trial conducted in US and France

- Placebo vs AZT:
  - AZT beginning at 14 wks gestation
  - Given intravenously during labor
  - Given to infant for 6 weeks
ACTG 076 - Outcome

- Target sample size 748 women
- Interim analysis done with 364 women, trial stopped
- Transmission rate in AZT arm was 8.3% compared to 25.5% in placebo arm
- Reported adverse events balanced between two groups, although mean Hgb levels lower in infants receiving AZT
Incidence of Perinatally-Acquired AIDS
United States, 1985-June 2000*

*Reported through December 2000
HIV Perinatal Transmission Rates in short-course AZT Trials

ACTG 076  Thai CDC  W Africa CDC 4-6 wks  W Africa Pooled 18 mos

Short course AZT

AZT  Placebo
HIVNET 012 trial, Uganda

- **NVP**
  - Mom: 1 dose
  - Baby: 1 dose

- **AZT**
  - IP doses
  - 7 days
HIVNET 012: Cumulative transmission during long-term follow up

Sustained reduction in MTCT, despite breast milk transmission
## Chorioamnionitis and MTCT Observational studies

<table>
<thead>
<tr>
<th>Study (Country)</th>
<th>Transmission Rate with Chorio (%)</th>
<th>RR of Transmission (Chorio/no chorio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Louis JAMA 1993; 269:2858 (Zaire)</td>
<td>40</td>
<td>4.2 (1.3-13.7)</td>
</tr>
<tr>
<td>Temmerman, Am J Obstet Gynecol 1995:172:700 (Kenya)</td>
<td>---</td>
<td>7.9 (1.3-47.4)</td>
</tr>
<tr>
<td>Landesman NEJM 1996:334:1617 (US)</td>
<td>45.5</td>
<td>2.45 (1.3-4.8)</td>
</tr>
<tr>
<td>Wabwire-Mangen AIDS Retrovirol 1999: (Uganda)</td>
<td>25.5</td>
<td>2.87 (1.0-7.9)</td>
</tr>
</tbody>
</table>
Trials of chorioamnionitis and MTCT

- Two trials of presumptive treatment of chorioamnionitis showed **no effect on MTCT**

  - Rakai Uganda (Gray Amer J Obstet Gynecol 2001)
  
  - NIH (trial stopped prematurely due to no impact)
Factors Associated with Transmission Through Breastfeeding

- Maternal viral load and CD4 count
- Duration of breastfeeding
- Type of breastfeeding
- Subclinical and clinical mastitis
- Breast milk viral load
- Low vitamin A (no effect)
Randomized Trial of Breastfeeding vs Formula Feeding Nduati et al: JAMA

- 425 HIV infected women in Nairobi randomized to breast or bottle feeding
- Median follow-up of 24 months
- Data from 401 mother-infant pairs in final analysis
- Compliance was 96% in breastfeeding arm and 70% in the formula arm
Transmission Rate by Feeding Method *(Nduati et al, JAMA 2000)*
Morbidity and Mortality in Breastfed and Formula-Fed Infants of HIV-Infected Women

(Mbori-Ngacha, JAMA 2001;286:2413-20)

Two year mortality rates similar in the 2 arms even after adjusting for HIV infection status.

(Is 2 years too short?)
% Mortality among HIV-Infected Women by Feeding Method

Nduati et al. Lancet
Why breast feeding might increase maternal mortality

- Depletion of nutritional reserves
  - More rapid weight loss
  - More OIs

- No effects of breastfeeding on maternal deaths in SA trial (Kuhn AIDS 2005)
Method of Infant Feeding and breast milk HIV Transmission

- Conducted a vitamin A intervention trial in South Africa
- Evaluated transmission rates by feeding practice among 551 mother-infant pairs
- Compared the following:
  - Never breastfed (n = 157)
  - Exclusively breastfed (n = 118)
  - Mixed feeding (n = 276)
MTCT by Feeding Practice

![Bar chart showing MTCT by feeding practice across different ages and feeding practices.](image)
Why mixed feeding may increase MTCT

- Mixed feeding increases risk of
  - Intestinal infection (gastroenteritis, diarrhea)
  - Allergies
  - Recruitment of HIV target cells into gut
Breast feeding vs formula feeding

- The objective is to maximize AIDS free survival of infants

- UNICEF recommends women be informed of risks and advised to:
  - Formula feed
  - Exclusively breast feed for 4-6 months then abruptly wean
Randomized trial of abrupt weaning at 4 months vs continued breast feeding: Zambia (Sinkala CROI 2007, Abst 74LB)

- 998 HIV+ women who exclusively breastfed randomized to:
  - Abrupt weaning at 4 mons
  - Continued breast feeding
- At 24 months HIV/death:
  - Abrupt weaning 17%
  - Continued breast feeding 19%
- Among HIV-infected infants mortality was reduced by breastfeeding
### Post-weaning gastroenteritis mortality, Malawi

(Kafulafula CROI 2007, Abst 773)

<table>
<thead>
<tr>
<th></th>
<th>Gastroenteritis mortality/1000 by age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 mth</td>
</tr>
<tr>
<td>Early weaning</td>
<td>4</td>
</tr>
<tr>
<td>Delayed weaning</td>
<td>1</td>
</tr>
</tbody>
</table>
HIV and Fertility

- Studies in Uganda and US show lower pregnancy rates and increased rates of pregnancy loss in HIV+ women (Gray et al Lancet 1998)

- Reduction in pregnancy rates are associated with duration of HIV infection and viral load

Pregnancy rates are lower in HIV+ than HIV- women
Odds of pregnancy associated with HIV viral load, Rakai (Ngyen et al 2006)

Log_{10} HIV Viral Load

Adj Log OR of pregnancy

Inflection point ~ 56,000 cps/mL
Policy Implications
Reduced Fertility in HIV-Infected Women

• HIV Surveillance
  - Antenatal surveillance underestimates HIV prevalence in reproductive age women
  - 70% of UNAIDS data from antenatal surveillance underestimates the global burden of HIV
Malaria and pregnancy

• Malaria associated with
  - LBW
  - PTD
  - SAB and stillbirth

• Effects mainly in nulligravid women (but in HIV+, malaria effects at all gravidities)

• Routine malaria prophylaxis in pregnancy
Malaria and HIV in pregnancy

• Malaria more common and parasitemia is higher in HIV+ than HIV-

• **MTCT and placental malaria (pm)**
  – Placental malaria MTCT = 33%
  – No placental malaria MTCT = 14%
  – Adjusted RR = 5.6, p = 0.02

• HIV Viral load higher in women with malaria