PREVENTION OF NEONATAL INFECTIONS

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NEONATAL SEPTICAEMIA

- Early-onset: first week
- Late-onset: 7-28 days
- Perinatal septicaemia: first 24-36 hours

**Epidemiology**

- 1 to 5 cases/1000 live births
- 1990s: Group B Streptococcus, E. Coli, Enterobacter
- Differences depending on countries/continents
Pathogenesis

- Maternal infection
- Amniotic fluid infection (frequent)

Prevention

- Prevention of hematogeneous spread: maternal fever
- Prevention of ascending infection:
  - Risk factors:
    - Vaginal examinations ≥ 6 (Seaward 1997)
    - Duration of active labour ≥ 12h (Seaward 1997)
    - Rupture of membranes before labour ≥ 24h (Gunn 1970)
    - Group B Streptococcal colonisation (CDC 1996)
**Prevention**

- **Mother:**
  - vaginal disinfection during labour (*Taha 1997*)
  - induction of labour (*Hannah 1996*)
  - antibiotic prophylaxis (see GBS) (*Smaill 1994*)
  - antibiotic treatment if suspected chorioamnionitis

- **Neonate:**
  - surveillance (CBC, CRP) if risk factors
  - antibiotic prophylaxis
Problems

- Low incidence, but high mortality and morbidity
  - surveillance of many pregnancies to prevent one infection
  - surveillance of many neonates to prevent one infection

- Costs
  - diagnostic test
  - antibiotic treatment
  - hospitalisation and care
  - future costs because of sequelae

- Limitations:
  - women’s access to health services
  - anaphylaxis, bacterial resistance
EARLY-ONSET GROUP B STREPTOCOCCAL SEPSIS

- USA, Australia (before adoption of preventive strategies)
  - incidence of the neonatal GBS sepsis: 1.4-3.0‰
  - prevalence of maternal colonisation: 18-35%

- Europe:
  - incidence of the neonatal GBS sepsis: 0.2-1.0‰
  - prevalence of maternal colonisation: 7-15%
EPIDEMIOLOGY

Prevalence of maternal colonisation: 2 - 35%

↓

Vertical transmission to the neonate: 40 - 70%

↓

Early-onset GBS sepsis: 1 - 2% of the colonised neonates

Mortality: 6 - 20%     Sequelae: 10 - 20%
EARLY-ONSET GBS SEPSIS

- < 5 - 7 days
- 90% during the first 12 hours
- 1 - 2% of the colonised neonates
- rapid evolution
  - ARDS/septic shock
PREVENTION OF THE EARLY-ONSET GBS SEPSIS

• After delivery? ➔ TOO LATE, the fetus is generally infected before delivery
• Treatment of GBS colonised women?
  - during pregnancy: inefficient (recolonisation)
  - during labour: appropriate (Smaill 1994)
• Culture during labour? ➔ Results after > 36h
• Rapid tests? ➔ Low sensitivity (Yancey 1992)
• Treat all women during labour? ➔ Inacceptable
PREVENTIVE STRATEGIES

Consensus CDC & AAP & ACOG (1996)

Two equivalent strategies are accepted:

1. Strategy based on vaginal and anal culture screening at 35 - 37 weeks
2. Strategy based on risk factors
STRATEGY BASED ON CULTURE SCREENING AT 35 - 37 WEEKS

Risk factors
- Previous infant with GBS sepsis
- GBS bacteriuria this pregnancy
- Delivery before 37 weeks of gestation

Intrapartum prophylaxis

VAGINAL & ANAL GBS CULTURE AT 35-37 W

GBS -

Risk factors
- Intrapartum T° ≥ 38°C
- Membrane rupture ≥ 18h

No intrapartum prophylaxis needed

NO

GBS +

Intrapartum prophylaxis

Not done, results unknown

NO

YES

Intrapartum prophylaxis

Intrapartum prophylaxis
STRATEGY BASED ON RISK FACTORS

Risk factors
- Previous infant with GBS sepsis
- GBS bacteriuria this pregnancy
- Delivery before 37 weeks of gestation
- Intrapartum $T^\circ \geq 38^\circ C$
- Membrane rupture $\geq 18h$

YES \rightarrow Intrapartum prophylaxis

NO \rightarrow No intrapartum prophylaxis
ANTIBIOTICS

• IV antibiotics during labour: decrease the risk of vertical transmission by 90% (Smaill 1994)

• Administration (De Cueto 1998):
  – < 1h before delivery: vertical transmission 40%
  – 1-2h: transmission 28%
  – 2-4h: transmission 2.9%
  – > 4h (≥ 2 doses): transmission < 1%

• Proposed antibiotics:
  ➰ penicillin G or ampicillin
  ➰ allergy: clindamicin or erythromycin
MANAGEMENT OF THE NEONATE

Maternal antibioprophylaxis

YES

Sepsis signs

NO

Gestational age

≥ 35 weeks

Number of antibiotic doses given to the mother before delivery

≥ 2 doses

• No evaluation
• No therapy
• Observe ≥ 48 h at the hospital

< 35 w

< 2 doses

• Limited evaluation: CBC and blood culture
• Observe ≥ 48 h at the hospital
• If sepsis suspected: full evaluation and antibiotic therapy

YES

• Full evaluation: CBC and blood culture; chest radiograph or lumbal puncture if needed
• Antibiotic therapy
PREVENTIVE STRATEGIES

• The incidence of the early-onset GBS sepsis decreased from 1.4-2.0% to 0.2-0.8% in the USA and Australia (Schuchat 1999, Jeffery 1998, Isaacs 1999)

• Compliance: 50-90% (Cheon-Lee 1998, Lieu 1998)

• Side effects:
  - risk of anaphylaxis (Towers 1998)
  - risk of bacterial resistance (Morales 1999)
  - incidence of E. Coli sepsis (Towers 1998)
CURRENT POLICY IN OUR OBSTETRIC CLINIC

• No routine GBS culture during pregnancy
• Cervico-vaginal cultures, including GBS if:
  – preterm labour
  – preterm premature rupture of membranes
  – leucorrhrea
• Antibiotic treatment during labour if:
  – maternal fever (≥ 38°C)
  – positive GBS culture during pregnancy (urine or cervix)
  – preterm premature rupture of membranes before 34 weeks
GENEVA STUDY - OBJECTIVES

- To estimate the prevalence of maternal GBS colonisation, of risk factors, the predictive value of the GBS culture at 35-37 weeks of pregnancy.
- To analyse the impact of preventive strategies compared with the current policy in our clinic.

MATERIEL AND METHODES

- Prospective cohort study
- Rectovaginal GBS culture at 35-37 weeks (n = 264) and during labour (n = 334). Both cultures in 208 women.
- Decision and economic analyses.
RESULTS

Geneva epidemiological data concerning GBS:

- Incidence of the early-onset GBS sepsis: 0.4%
- Maternal colonisation (labour): 7.8% (95% CI: 5-11)
- Recto-vaginal culture at 35-37 weeks
  - sensitivity 33% (95% CI: 14-59)
  - specificity 95% (95% CI: 90-97)
- Prevalence of risk factors: 17.7% (95% CI: 14-21)
RESULTS

Prevalence of risk factors: 17.7%

- Premature delivery: 7.4%
- Rupture of membranes ≥ 18h: 8.8%
- Fever during labour: 1.6%
- GBS bacteriuria during pregnancy: 1.6%
- Previous infant with invasive GBS disease: 0.5%
# Predictive value of the antenatal culture

**GBS - Labour** 7.8%

<table>
<thead>
<tr>
<th></th>
<th>+</th>
<th>-</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GBS 35-37w</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>6</td>
<td>10*</td>
<td>16</td>
</tr>
<tr>
<td>-</td>
<td>12</td>
<td>177</td>
<td>189</td>
</tr>
<tr>
<td>TOTAL</td>
<td>18</td>
<td>187</td>
<td>205</td>
</tr>
</tbody>
</table>

* 3 cases excluded for antibiotherapy because of antenatal culture +

**Sensitivity** 33% 95% CI: 14 - 59%

**Specificity** 95% 95% CI: 90 - 97%

**PPV** 38% 95% CI: 16 - 64%

**NPV** 94% 95% CI: 89 - 97%
### Predictive value of the risk factors

<table>
<thead>
<tr>
<th></th>
<th>GBS - Labour</th>
<th>RF 17.7%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
<td>+</td>
<td>-</td>
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<tr>
<td>+</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>-</td>
<td>18</td>
<td>259</td>
</tr>
<tr>
<td>TOTAL</td>
<td>26</td>
<td>308</td>
</tr>
</tbody>
</table>

- **Sensitivity**: 31% 95% CI: 13 - 49%
- **Specificity**: 84% 95% CI: 80 - 88%
- **PPV**: 14% 95% CI: 5 - 23%
- **NPV**: 94% 95% CI: 91 - 96%
## PREVENTIVE STRATEGIES

<table>
<thead>
<tr>
<th></th>
<th>Expected sepsis/ $10^6$ births</th>
<th>Prevented sepsis/ $10^6$ births</th>
<th>Cost / $10^6$ births</th>
<th>Marginal cost effectiveness ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current policy</td>
<td>378</td>
<td>--</td>
<td>$4,970,000</td>
<td>--</td>
</tr>
<tr>
<td>Risk factors</td>
<td>309</td>
<td>69</td>
<td>$11,146,000</td>
<td>$89,500</td>
</tr>
<tr>
<td>Screening</td>
<td>276</td>
<td>102</td>
<td>$29,933,000</td>
<td>$698,200</td>
</tr>
</tbody>
</table>
SENSITIVITY ANALYSIS: prevalence of maternal colonisation

Number of deaths / 1,000,000

Current policy
Screening
Risk factors

Sensitivity of antenatal culture screening = 33%
SENSITIVITY ANALYSIS: Sensitivity of the antenatal GBS culture for predicting colonisation at delivery

Prevalence = 10.6%

Cut-off value:
Sensitivity = 28%
Number of deaths = 59

Current policy
Screening
Risk factors

Number of deaths / 1 000 000

Sensitivity of the antenatal culture (35-37w)
## PREVENTIVE STRATEGIES

<table>
<thead>
<tr>
<th>Proportion of treated women</th>
<th>Anaphylaxis/10^6 births</th>
<th>NNT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current policy</td>
<td>6%</td>
<td>6</td>
</tr>
<tr>
<td>Risk factors</td>
<td>13.5%</td>
<td>13.5</td>
</tr>
<tr>
<td>Screening</td>
<td>16.5%</td>
<td>16.5</td>
</tr>
</tbody>
</table>

*NNumber of women needed to treat to avoid one neonatal GBS sepsis*
### EFFECTIVENESS AND COST

#### EFFECTIVENESS RATIO: sensitivity analysis

<table>
<thead>
<tr>
<th>Prevalence of maternal GBS colonisation</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CE*</td>
</tr>
<tr>
<td>7.8%</td>
<td>89 500</td>
</tr>
<tr>
<td>20%</td>
<td>43 000</td>
</tr>
<tr>
<td>30%</td>
<td>33 000</td>
</tr>
<tr>
<td></td>
<td>$E^\dagger$</td>
</tr>
<tr>
<td>7.8%</td>
<td>69</td>
</tr>
<tr>
<td>20%</td>
<td>171</td>
</tr>
<tr>
<td>30%</td>
<td>257</td>
</tr>
</tbody>
</table>

| Screening | Sensitivity 33% | CE* |  
|-----------|-----------------|
|           | 698 300         |
| 7.8%      | 295 000         |
| 20%       | 207 000         |
|           | $E^\dagger$    |
| 7.8%      | 102             |
| 20%       | 255             |
| 30%       | 382             |

| Sensitivity 87% | CE* |  
|-----------------|
| 7.8%            | 155 000 |
| 20%             | 79 000  |
| 30%             | 62 000  |
| $E^\dagger$    |
| 7.8%            | 234    |
| 20%             | 584    |
| 30%             | 876    |

* Marginal cost effectiveness ratio in $/prevented sepsis

† Effectiveness of a preventive strategy compared to the current policy (prevented sepsis/10^6 births)
CONCLUSIONS

- **Effectiveness:** strategies based on risk factors and screening are more effective than the current policy.

- **Cost:** preventive strategies have important costs; the screening strategy has the highest cost in our context.

- **Cost effectiveness:** important increase of the cost per averted sepsis if adoption of a screening strategy.
CONCLUSIONS

Prevention decreases the incidence of the early-onset GBS sepsis

Problems:
- detection of high-risk mothers and neonates: incomplete
- high costs for the screening strategy and for the antibiotic prophylaxis
- is it reasonable to give antibiotics to 20-40% of women in labour?
- could we afford a cost to prevent a GBS sepsis case between $33,000 and $700,000?
- probably a good option in countries with high incidence of GBS sepsis and with important health resources
CHOICE OF A PREVENTIVE STRATEGY

• low incidence of the early-onset GBS sepsis in Geneva
• high cost of the preventive strategies
• significant increase of the proportion of women receiving antibiotics during labour

Implementation of a preventive strategy does not seem justified in our clinic
CONCLUSIONS

Search for alternative attitudes:

• Antibioprophylaxis limited to women with positive GBS screening presenting with risk factors *(Jakobi 1996)*


• PCR rapid test *(Bergeron 2000)*

• Vaccine: not yet available *(Harrison 1998)*
DISINFECTION OF THE BIRTH CANAL

(Taha TE et al. BMJ 1997;315:216-20)

- **Objective:** Does disinfection of the birth canal during labour reduce infections in mothers and babies postnatally?
- **Design:** Alternate periods of intervention (chlorhexidine 0.25%) and no intervention in a tertiary centre in Malawi
- **Participants:** 6965 women giving birth over a 6 month period to 7160 babies
# RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>No</th>
<th>Rate*</th>
<th>No intervention</th>
<th>Rate*</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=3743)</td>
<td></td>
<td></td>
<td>(n=3417)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Admissions due to sepsis</td>
<td>29</td>
<td>7.8</td>
<td></td>
<td>61</td>
<td>17.9</td>
<td>0.43 (0.28-0.67)</td>
</tr>
<tr>
<td>• Mortality due to sepsis</td>
<td>9</td>
<td>2.4</td>
<td></td>
<td>25</td>
<td>7.3</td>
<td>0.33 (0.15-0.70)</td>
</tr>
<tr>
<td><strong>Mothers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=3635)</td>
<td></td>
<td></td>
<td>(n=3330)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Admissions due to sepsis</td>
<td>6</td>
<td>1.7</td>
<td></td>
<td>17</td>
<td>5.1</td>
<td>0.37 (0.13-0.82)</td>
</tr>
<tr>
<td>• Admissions overall</td>
<td>107</td>
<td>29.4</td>
<td></td>
<td>134</td>
<td>40.2</td>
<td>0.73 (0.57-0.94)</td>
</tr>
</tbody>
</table>

* Rates are per 1000 live births (infants) and per 1000 deliveries (mothers)
Influence of prevalence on the decision to implement an intervention

<table>
<thead>
<tr>
<th></th>
<th>Malawi</th>
<th>Geneva</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>18‰</td>
<td>1‰</td>
</tr>
<tr>
<td>RR</td>
<td>0.43</td>
<td>0.43</td>
</tr>
<tr>
<td>DR</td>
<td>10‰</td>
<td>0.6‰</td>
</tr>
<tr>
<td>NNT</td>
<td>100</td>
<td>1600</td>
</tr>
</tbody>
</table>

Prevalence of a disease influences the absolute effectiveness and the decision to implement an intervention.
CONCLUSIONS

- Cleansing the birth canal with chlorhexidine reduced early neonatal and maternal postpartum infections.

- The simplicity and the low cost of the procedure suggest that it should be considered as standard care to lower infant and maternal morbidity and mortality.

- Other studies showed similar results: Burman 1992, Adriaanse 1995.