Prenatal-onset Group B Strep (POGBS) Sepsis is a Distinct Cause of Perinatal Mortality/Morbidity

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GBS Pathobiology

[Diagram of GBS Pathobiology]
Suggestions

1. Demand autopsy for all perinatal deaths
2. Demand genetic, multi-specialty consultation and planning meeting
3. Change coding form to include final pathology

Background: Original Reports of GBS Antenatal Infection


“The burden of prenatal-onset GBS disease has not been assessed adequately and no effective prevention techniques have been identified before the intrapartum period.”

CDC MMWR Nov 19 2010;59:RR-10
Infection as a Predominant Cause of Perinatal Mortality (SB +Neonatal)

KK Christensen (Lund) 1982;Ob/Gyn 59:499

Perinatal death (Sweden) rates lowest in world. No deaths from “classic” infections i.e., rubella, syphilis, toxoplasmosis, listeriosis

- Intensively investigated microbial (10 cultures) suspected death 1979-1980
- 11 fetal deaths; 14 neonatal deaths (DOL 1-28)
- Intrauterine mortality 0.27%
  - 1 late miscarriage
  - 7 (21% lethal infections)
  - Microbe 7/21
  - GBS 2 (LM=GBS) (1-GBS intra-membranes, not in labor
  - Coxsackie B2
  - Others 3

- "Autopsy is recommended in all cases of perinatal / neonatal deaths plus microbial exam"

Maternal GBS Related Stillbirth: A Systematic Review

C Nan et al 2015;BJOG

"Limited epidemiologic data makes determining the incidence of GBS associated stillbirth difficult"

Search strategies: CDC Active Bacterial Core Surveillance definitions ≥ 20 wks

GBS at autopsy or by culture

From placenta, AF or other

Normally sterile sites from stillborn

Differences in definition did not allow for pooled estimates to be calculated.

GBS related SB vary 0.04- 0.9/ 1000 birth (range 0-12.1 % of stillbirths)

Are some cases of EOGBS disease actually POGBS disease?

Intrapartum Evidence of Early-Onset GBS


- Estimates of neonate with early onset GBS sepsis have clinical evidence of FETAL INFECTION during labor or delivery.
- 143,384 live born neonates: 94 Dx with EOGBS ; 93/94 within First Hour

- Features:
  - Premature birth
  - c% for "distress"
  - Depression Apgar < 3
  - Cord gas pH, 7.0 8E ≥ 12 mmo/L
  - Chorioamnionitis 62% vs 8%, p<0.001

- "Compelling Evidence" fetuses with EOS have signs of sepsis peripartum"
- Supports concept GBS is spectrum that precedes birth"
For Practitioners- SB Workup:
■ “Fetal blood culture, placenta, swab for GBS and search for histologic funisitis are mandatory actions within the SB workup”
■ “Send placenta roll, segment of cord.”

The Pathobiology of Antenatal GBS Disease differs from LOSGBS > EOSGBS=POGBS
GBS (pathobiont) highly adapted to human gut, vagina, urethra
A) LOS Disease:
1. 90% GBS St17clone
2. Expresses HvSA signature virulence factor/adhesin (CovR/S gene system) [facilitates vessel and BBB invasion and attachment]
B) EOS mixed ↑ virulence factors (sialic acid pilo/toxin: NETS, hemolysin), lipopeptides, lectin proteases (↑ invasion)
C) Host binds GBS antigens, nucleic acids using toll-like receptors and inflammation
D) Transmission factors: EOS vs LOS PID 2014;33:1211-18
“Need comprehensive models”

Maternal and Fetal Inflammatory Response in Unexplained Fetal Death
S Blackwell, R Romero, S Hassan et al
J Mat Fet Med 2003;14:151-7
Prospective study in 44 women with fetal death
Amniotic fluid sampled by AMNIOCENTESIS
Placenta and membranes cultured and examined
Fetal inflammation
Maternal infection > Fetal infection > MIAC
(21%) (2%) (1 case GBS)
“Fetus may not mount an inflammatory reaction in FD, similar to C Christiansen 1982; Tafari (1976 mycoplasma)”
Factors Associated with Intrapartum Transmission of GBS

Prospective Cohort Study of women with vaginal positive GBS at 35 wks

502 neonates with 458 exposed to IAP; throat and rectal neonatal cultures at 24-48 hrs after birth

Factors associated with GBS transmission:
1) Lack of IAP exposure (p<0.01)
2) Intrapartum fever ≥ 37.5 °C (p<0.01)
3) Heavy maternal colonization (p<0.03)
4) African ethnicity (p<0.01)

ND in IAP exposed between 1 and 12 hours after birth

Fetal Infections in Antepartum Stillbirth: A Case Series
F Monari, F Facchinetti et al (Italy) Early Hum Dev 2013;89:1045

What are BEST SAMPLES for identification of fetal infection?
Study: Multiple maternal /fetal samples; Each case discussed in audit; N=109 cases

- Best: fetal cord blood culture/ histology
  - 4 GBS
  - 2 Listeria
  - 1 coag negative staphylococci
  - 1 Pseudomonas aeruginosa

Recommended:
1) Fetal blood culture (cord, heart)
2) Placental culture
3) Cord sample (funisitis)

Prenatal-onset GBS Sepsis as a Distinct Cause of Stillbirth and Perinatal Mortality (SB/ND)

Summary:
Prevalent “dogma” is that GBS exposure and subsequent infection occurs only during passage through the GBS colonized birth canal. This notion is the basis of present CDC-P, ACOG, AAP and other guidelines.

Non-congruent observations by Katz, Tudela, Wendel, Sheffield and Christiansen and others suggest GBS can cross intact fetal membranes and cause both SB and perinatal depression with depressed APGARS and neonatal death (ND)

Contemporary findings JUSTIFY the term Prenatal onset of GBS (POGBS)
Suggestions

1) Request/encourage FULL AUTOPSY for all perinatal deaths
2) Present reasonable testing alternatives and scenarios to parents and encourage them to consider giving permission to try to find a cause and information for future pregnancies
3) Request/demand 6 week multi-specialty consultation and planning meeting
4) Assess need for ongoing counseling (grief/genetic/perinatal)
5) Change coding form to include final determinations
6) Annual family/staff-oriented meeting to recognize perinatal losses

Recommendations

1) Implement collection of surveillance (ABC) for putative POGBS Disease
2) Reconvene well-funded study groups to explore novel strategies to reduce risks of PO and LO GBS disease
3) Foster verbal or other autopsy (operational) procedures designed to guide patient / fetal care
4) Parents demand autopsy

If your baby dies or is stillborn, demand a complete AUTOPSY and followup consultation meeting (@ six weeks PP) to explain results and plan ahead.

CJ Baker 2018
GIGO: The Coding of Underlying Cause of Death from Fetal Death Certificates: Issues and Policy Considerations.

Recent plans to implement nationwide coding for underlying cause of fetal death promulgated... not implemented.

**Study**
- Coding criteria 5 states: CA, WI, AR, NC, ME
  - 5/5 different coding instructions; but similar distributions
  - Unspecified conditions 20-30%
  - Congenital anomalies 7-10%
  - Deemed "Not Valid/useful" 30-40%

A. "to obtain better data researchers must focus on improving fetal death reporting, which entails comprehensive autopsy, placental and laboratory evaluation"
B. Systematic vital records query procedures
C. Implement multiple cause of death coding

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**Proposed Working Definitions of Prenatal-Onset GBS Disease**

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<thead>
<tr>
<th>Comment</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Proven</td>
<td>GBS Positive from sterile site (brain, blood)</td>
</tr>
<tr>
<td>Likely</td>
<td>GBS Positive from surface or histology + syndrome</td>
</tr>
<tr>
<td>Possible</td>
<td>GBS Positive culture + clinical syndrome</td>
</tr>
<tr>
<td>Atypical</td>
<td>GBS Positive in milk, mastitis; CXR, pneumonitis</td>
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</tbody>
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* (after TSS)