

# Prenatal-onset GBS (POGBS) Sepsis is a Distinct Cause of Stillbirth and Perinatal Mortality

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## ABSTRACT

**Objective:** Intrauterine infection is increasingly recognized as a possibly preventable cause of stillbirth. (McClure, Goldenberg, Semin Fetal Neonatal Med 2009, 14(4):182-9.) 1) Conduct an expert systematic review and analysis of GBS disease knowledge in order to justify recognition of distinct Prenatal-onset GBS (POGBS) sepsis, distinct from Early-onset (EO) and Late-onset (LO) GBS infection. 2) To correlate patient experiences, we conducted a quasi-experimental "internet commons" inquiry of parent contacts who had suffered GBS SB.

**Materials:** 1) Computer-based national data bases were utilized to update knowledge of GBS infectious disease. 2) An English language 7 question survey was constructed, pretested, and disseminated to selected GBSI contacts using the internet.

**Methods:** Meta analysis

**Results:** 1) Much is known about GBS disease. Despite this knowledge, preventative regimes remain inconsistently applied, and in the best of circumstances are incompletely (85-90%) successful in reducing EOGBS infection and do not address LO or prenatal-onset GBS infections. GBS demonstrates tropism for estrogenized tissues, produces multiple cytotoxins and proinflammatory signaling molecules (DAMP and RAGE molecular cascades.) 2) There were 27 responders of which 10 suffered stillbirth due to GBS. Of these 16 mothers had been identified as GBS carriers, and only 5 of these had positive urine cultures. Some GBS+ mothers recalled invasive "membrane stripping" for induction of labor with subsequent SB. Placentas were not uniformly examined. Autopsies were infrequent, but noticeably demonstrated GBS in the spleens of 2 of 8. Only 6 mothers recalled peripartum fever. Most cases (20) were manifest near term gestation, but 3 occurred at preivable gestation.

**Conclusion:** 1) There is sufficient knowledge to support the CDC-P proposed (MMWR 2010, Volume 59/RR-10) classification of prenatal-onset GBS POGBS sepsis as a distinct entity. 2) Our limited, uncontrolled investigation supports clinical notions that a) GBS loss or SB occurs in a bimodal gestational time distribution with the preponderance of cases occurring near term (POGBS); and b) that mothers do not reliably demonstrate fever or "textbook" findings of potentially lethal intrauterine infection. Other observations are precluded by the limited, uncontrolled nature of our retrospective, self-reported sample.

## BACKGROUND

- Group B streptococcus (GBS) was identified as a leading cause of perinatal infection in the 1970s.
- The 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 the present CDC-P, ACOG and AAP guidelines to prevent GBS Early-onset Sepsis (EOS).
- Non-congruent observations by Katz and more recently Tudela, Wendel, and Sheffield suggest that GBS infection also occurs before birth across intact fetal membranes and causes both stillbirth (SB) and perinatal depression (PD) with depressed Apgars and neonatal death.
- Systematic epidemiologic investigations may allow for investigations to possibly reduce risks of pre-labor onset of GBS infections.

## GOALS

- 1) Review and Analyze prior observations including:
  - a) Animal models
  - b) Microbiologic findings
  - c) Microbiologic
  - d) Immunologic
  - e) Clinical experimentationswhich can justify naming "prenatal-onset of early GBS neonatal infection (PO-GBS-EOS)
- 2) Provide rationale for expanded epidemiologic studies
- 3) Suggest strategies which may reduce risks of PO-GBS-EOS

## METHODS

- 1) Review/Analyze available information justifying "official" designation of prenatal-onset GBS infections
- 2) Evaluate this proposal using historical "causal criteria," i.e., Kock's postulates & Bradford Hill causal criteria
- 3) Apply pathophysiologic principles including innate and acquired immunologic prevention strategies (i.e., vaccination, microecologic, and clinical strategies to reduce risk of perinatal GBS infection including SB (20-28 weeks) and very early PTB and/or late miscarriage (16-20 weeks)

## RESULTS

- 1) Prenatal-onset GBS intrauterine infection has been previously described (Katz, Tudela, Benirschke, others)
- 2) GBS is the commonest or among the commonest microorganisms isolated from normally "sterile" sites after passage through the vagina, between membranes, within placenta, cord blood, heart blood or spleen at autopsy.
- 3) GBS demonstrates pathophysiologic virulence capacities which can explain:
  - a) Intrauterine infection with intact fetal membranes
  - b) Invasive fetal infection
  - c) Lethal factors leading to placental or fetal death
- 4) Multiple studies/analysis demonstrate feasibility and practicability of **ACTIVE GBS VACCINATION**

## CONCLUSIONS

- 1) GBS, similar to other "perinatal pathogens," is an apparent cause of intrauterine infection (1° chorioamnionitis "CAM" or intraamniotic infection "IAI" can cause SB and very early PTB and possibly EM)
- 2) Intrauterine infection or prenatal-onset GBS may explain GBS selective culture-based antibiotic chemoprophylaxis (IAP)
- 3) Recognition of PO-GBS-EOS can allow renewed experimentation in order to further reduce risks of GBS perinatal disease including rapid "Point of Care" microbial testing as well as adjuvant VACCINATION or other novel strategies

## RECOMMENDATIONS

- 1) Reconvene well-funded national study group to explore novel strategies to further reduce risk of GBS neonatal disease burden
- 2) These strategies can be separate or in combination with culture-guided IAP:
- 3) VACCINATION
- 4) Microecologic
- 5) Clinical Strategies - screen UTI/ASB
- 6) Further refine microbials screening, i.e., early in pregnancy, UTI/ASB, and in labor or after ROM
- 7) Improve operational procedures to enhance efficacy of IAP

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