Primary and Secondary Prevention of Fetal Death Caused by Maternal Infection

JA McGregor, MD,CM[1,2] M Perhach[2]

Institutions: [1] LA Best Babies Network, California Hospital Medical Center, Los Angeles, CA; [2] Group B Strep International, Pomona, CA

"Prevention is better than cure" – Desiderius Erasmus

ABSTRACT

Objective: Potentially preventable reproductive tract infections (RTIs) are increasingly recognized as causes of fetal death (stillbirth [SB]) worldwide. Our objective is to develop "gedanken" (thought-based) strategies to prevent infection caused SB.
Methods: Medical knowledge reviews and synthesis.
Results:
(1) Perinatal lethal infections are known to be mediated by a) maternal bloodborne infection of gestational tissues; b) ascending infection through the cervix; c) iatrogenic; d) preexisting (prepregnancy) endometrial infections; and e) zoonic infections.
(2) More recently recognized common "pathogenic pathways" potentially linked to SB include a) bacterial and viral infections which sensitize the endometrium to LPS or other bacterial products; b) graft vs. host phenomena; c) sterile inflammation associated with autophagic or programmed cell death processes.
(3) Possible novel primary or secondary prevention strategies may include a) systematic recognition and documentation of SBs , and implicated microorganisms; b) development of simple, inexpensive accurate diagnostic methodologies ; c) fermentation of means to prevent common ascending cervicovaginal microbes and d) recognize how systematic maternal vaccination can prevent viral intrauterine infections.
Conclusion: Prevention of many infection caused stillbirths may be possible using contemporary techniques.

BACKGROUND

• FD or stillbirth (SB) is increasingly recognized to be caused by potentially preventable maternal infections and associated inflammation. McClure and Goldenberg maintain that infection causes 40% to 20% of fetal deaths in developing and developed countries respectively.[1] Review of possible opportunities for evidence-based clinical, pathophysiological and epidemiologically based preventive strategies is required to allow for clinical opportunities for reducing risks of FD which remain persistently as high as 1% in many populations. Recently both national (CDC-P) and international agencies (WHO) have focused attention on identifying recognized and "novel" or "emerging" causes of fetal death, so as to reduce the "burdens" of this often ignored or marginalized cause of death.

AIMS

1) Review recognized infection causes of FD in differing geographic regions.
2) Recognize clinically under-appreciated "pathophysiologic pathways" which may lead to locally important causes of FD
3) Comprehend newly recognized lethal organismal and cellular lethal processes
4) Identify different medical and non-medical approaches or processes which may be used to reduce risks of prevalent causes of FD
5) Focus on opportune clinical and public health research areas ("low hanging fruit") which may be practicably utilized to reduce risk of prevalent I-I caused FD
6) Review evidence-based primary preventive strategies which have been used effectively, but appear under appreciated or under used.

METHODS

• Review and analysis of available research indexed in Medline, PubMed, and/or Cochrane data bases for the topics: "infection", "stillbirth", "fetal death", "inflammation", and "sepsis" or "septic"

• Analysis of relatively recently recognized biologic mechanisms of lethality available databases using the key words: "death program", "lethal programming", "killing" as well as "apoptosis", "programmed cell death" and "autophagy". Along with "surviving sepsis", "sepsis", "infection and inflammation" and "death".

•Construct an "action matrix" each common and "important" infectious process with possibly effective means of 1º prevention.

• Focus on group B streptococcus (GBS) as a cause of morbidity which may be further prevented by utilization of possible new technologies, i.e., microbiologic "rapid" diagnosis and "point of care" (POC) diagnostic and complementary immunologic approaches i.e., vaccination.[2,3]

PREVENTION DEFINITIONS:
1º Prevent exposure,
2º Detect early (Screen, treat),
3º Mitigate damage (rehabilitation)
4º Systematically reduce damaging phenomena (policy)

RESULTS

There is considerable information available regarding infection caused FD. More recently, understood death mechanisms are listed in Table1. Proposed traditional and novel infection pathways to FD are listed in Table 2. Selected important microorganisms associated with possible means for 1º prevention are listed in Table 3.

Table 1. Death Mechanisms of Processes, Not Commonly Recognized

Process	Definition
Necrosis	Direct cell death: toxin, physical, chemical final product of apoptosis
Apoptosis	Programmed cell death
Autophagy	Self digestion[7,11]
Death program	Several pathways leading to organismal death
Sterile inflammation	Fetal-maternal conflict[9]
Senescence	Death - signaling by aging

Table 2. Proposed Inflection Pathways to Fetal Death

Name	Mode of Transmission
Maternal "Traditional"	Bloodborn, ascending through cervix, persistent endometrial infection
Iatrogenic	Amniocentesis, membrane sweeping, prolonged induction
Complex	Viral infection "sensitizing" to LPS[10]
Immunologic	Graft vs Host "maternal/fetal rejection"
Gamete-based	Infected sperm or ovum (bacteria, viruses, prions, transposons) *In vitro* contaminated

Table 3. Common and Important Pregnancy Infections Amenable to Primary Prevention

Virus	Vaccine	Behavioral	Medical
Varicella	√		
Influenza	√		√
Mumps	√		
Rubella	√		
Parvovirus	√	√	
HIV		√	
CMV		√	
Bacteria			
GBS			√
Listeria		√	
Protozoal			
Toxoplasmosis		√	
Malaria		√	√

DISCUSSION

GBS associated FD is an example of possible **Primary Prevention** of infection FD

1) **Epidemiologic Research.** Means to prevent GBS caused early neonatal sepsis and death have focused on strategies intended to reduce exposure at birth by IAP. That this "dogma" is incorrect and that GBS can be an important preventable cause of FD has been highlighted by Katz, Wendel, and McDonald who described convincing evidence of GBS crossing intact fetal membranes and causing FIRS or perinatal depression or death.[4,5] Measurement of this phenomenon requires large epidemiologic surveillance such as in available through the CDC-P, ABC program and an advanced population surveillance program such as in Ontario, Canada.
2) **Quality Improvement Approaches** to preventing GBS FD. It has been shown by Thomsen et al that screening for GBS UTI/ASB and treatment reduces risks of loss, as well as PROM and PTB.[6] This observation has not been followed up with large well controlled experiments. Specific culture screening for UTI/ASB is recommended by the USPSTF but not ACOG.
3) **Technologic Advances in Identifying GBS Presence**[13,14] are now available for evaluation (microfluidics, rapid antigen/nucleic acid systems). These may be shown to be useful as rapid, "Point of Care" (POC) techniques which could be used to more rapidly exclude GBS presence, and thus avoid unneeded antibiotic treatment, as well as other uses to benefit mothers, babies and adults.
4) **New Treatment Modalities for GBS Disease** may include defensins (cationic membrane-active proteins) and peptides (such as occurs naturally in vernix and vaginal fluid) as well as various probiotics.
5) **New Clinical Diagnostic Systems** are now available for GBS infection which can be used in expanded, non-technical settings.[14]
6) **Vaccination Strategies** as proposed by Baker and Kasper may provide protection against prenatal onset GBS disease (PO-GBS-EOS). A recent modeling study estimated that GBS vaccination could prevent 4% of U.S. preterm births and 60-70% perinatal disease.[2] Maternal immunization is already routine for tetanus, pertussis, HBV and influenza. Other possible advances include:
   a. Maternal micronutrient supplementation
   b. Augmented provider, payor, patient, community education and
   c. Quality control research, as well as
   d. Refined antimicrobial primary prevention strategies (in long acting antibiotic preparations, oral treatment)

RECOMMENDATIONS

1) The Burdens of Infection-caused FD or stillbirth need to be systematically studied using epidemiologic, pathologic and public health techniques.
2) Behavioral, medical and vaccine-mediated primary prevention of FD needs to be including in public policy prevention guidelines including PAY FOR PERFORMANCE GUIDELINES
3) Advance technologies including vaginal pH screening and microfluidic diagnostic techniques need to be systematically researched in large controlled trials.
4) Effective diagnostic pathology services/approaches for FD (including "placental triage" verbal autopsy and complete contemporary autopsy service should be made available

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