Primary Prevention of Fetal Death and Congenital Infection Caused by Maternal Infection Using a Checklist-enabled Acronym Prompt "LESS BABY TORCHEZ"

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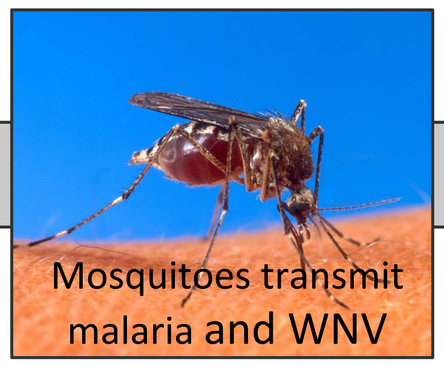


Abstract

Introduction:
Background: Maternal (vertical) infections causing fetal death (FD) (including stillbirth [SB]) or congenital infection (CI) are microbiologically and geographically diverse, often medically "neglected," considered "orphans" or "emerging," and are not systematically reported. These features make primary prevention preferable to "screen and treat" secondary prevention strategies. Use of checklists (CLs), which can guide medical providers and inform susceptible patients or "at risk" populations, are industrially recognized as effective tools to organize approaches to complex tasks such as pregnancy care. **Objectives:** Using established microbiologic, epidemiologic, and systems-based pregnancy care knowledge, we collaboratively modified a widely-known medical-teaching mnemonic "TORCH" for 1) recognizing/ remembering important and preventable "textbook" causes of vertical infections which may lead to FD including SB, or CI, and 2) enabling a teaching device for both pregnancy providers and patients to enable locally practicable evidence-based, behavioral prevention strategies. **Material and Methods:** We employed a systematic literature review and responded to parent enquiries via crowdsourcing. **Results:** We propose "LESS BABY TORCHES" as follows to enable, inform, and guide primary behavioral prevention of FD or Cis. (See table.) **Conclusions:** 1) We derived an expanded behavior-oriented checklist that may be individualized on the basis of location, season, environment, lifestyle, food style, and personal factor (immunization status) evidence-based prevention strategies. 2) Individually generated checklists can enable behavior change and generate patient problem lists for providers, payors, and policy makers. 3) Generated checklists may be incorporated into electronic medical records (EMRs) and be adapted to become quality performance standards (HEDIS, USPHS, WHO) which may also lessen morbidity costs and liabilities.

Cost-effectiveness of screening and Rx for BV in EARLY PREGNANCY among women at LOW RISK for PTB.
Kekki M, Kurki T, et al. *Acta Obstet Gynecol Scand* 2004; 83 (1): 27-36.

- "BV is important risk factor for PTB"
- Detected 10-30% pregnant women, often asymptomatic
- Rx BV in HIGH RISK women reduces risk

Risk of invasive Haemophilus influenzae infection during pregnancy and adverse outcomes.
Collins S, Ramsay M, et al. *JAMA* 2014; 311 (11): 1125-32.

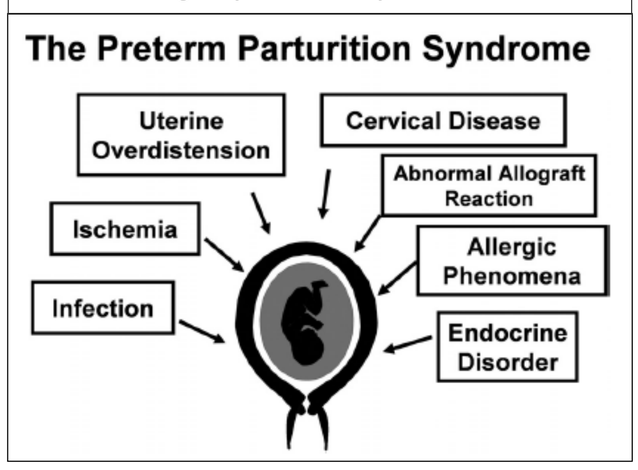
- Unencapsulated H. inf causes non-invasive URI's in adults and children
- Public Health England – 4 year period, 144 cases
  - Fetal loss
  - Extreme PTB
- Prevent? Vaccination in childhood, prompt antibiotic

Global report on PTB and Stillbirth (SB): evidence for effectiveness of intervention.
Barros FC, Bhutta ZA, Rubens CE, et al; The GAPPS Review Group. *BMC Pregnancy Childbirth* 2010; 10 Suppl 1: S3.

- Analyzed 2,000 intervention studies systematically → 2008 → 49 relevant and adequate
- PTB: 11 intervention High → Medium → Low
- SB PREVENTION
  - Screening and treatment SYPHILIS (1940's)
  - Treatment for malaria (Cochrane)
  - *Insecticide treated mosquito netting (Cochrane RR.67), "INTs"

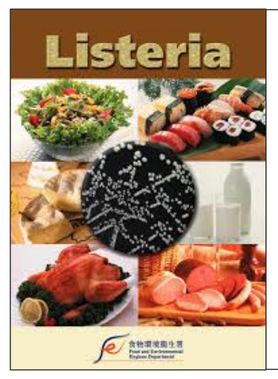
*Primary prevention

Pathological processes implicated in PTB:




Human Microbiome

1965 Acronym
Culture, serology, animal
Toxoplasmosis
Others
Rubella (measles, varicella)
Cytomegalovirus, coxsackie
Herpes, HBV



Listeria monocytogenes cytoplasmic entry induces fetal wastage by disrupting maternal Foxp3+ regulatory T cell-sustained fetal tolerance.
Rowe JH, Way SS, et al (Cincinnati) *PLoS Pathog* 2012; 8 (8): e1002873.

- Listeria: → disseminated infection in pregnancy → pregnancy → abortion/SB
- Model: very small inocula → fetal wastage
- Showed listeria ↓↓ maternal Foxp3+ regulatory T cell suppression
- ↓ TOLERANCE

2016 Acronym
Culture, serology, X non-culture

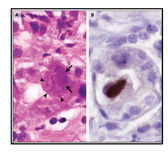
	Agents	Behaviors
L	*Listeria* **L**eishmaniasis	Food preparation Bite avoidance
E	**E**nteroviruses	Hygiene, food preparation
S	**S**yphilis, **s**exually transmitted infections (STIs)	Avoid new sex contacts, use condoms
S	**S**easonal: influenza, West Nile Virus (WNV)	Immunization Avoid bites
B	Group **B** *streptococcus* (GBS)	Assume CDC/ACOG recommendations
A	**A**symptomatic bacteriuria (ASB)	ASB/Urinary tract infection (UTI) screening
B	***B**orrelia* species	Lyme disease (tick) precautions
Y	Barn**y**ard leptospirosis	Hygiene
T	***T**oxoplasma gondii* **T**uberculosis	Food preparation Vaccination
O	**O**thers, e.g., varicella-zoster virus	Vaccination, etc.
R	**R**ubella, measles, pertussis	Vaccination
C	**C**ytomegalovirus (CMV)	CMV precautions, handwashing
H	**H**erpes simplex 1 and 2 viruses (HSV-1, HSV-2) **H**epatitis A, E viruses (HAV, HEV)	Behavior Hepatitis precautions, vaccination
E	**E**merging infections	
Z	**Z**oonosis: **Z**ika, malaria, dengue, WNV, coxiella, Lyme, rickettsia, yellow fever, leishmaniasis, arena viruses	No mosquitoes! No kissing bugs! No ticks!

A RCT of hyperimmune globulin to prevent congenital CMV. Revello MG, CHIP Study Group. *NEJM* 2014;370; 1316.

- Congenital CMV @ 1% major cause mortality/ morbidity
- 2005 uncontrolled study of 1° infection ↓ intrauterine transmission 40→16%
- ∴ RCT 124 pregnant women 5-26 wks. Rx placebo vs. HIG-CMB q 4 wk until 36 wks or ⊕ CMV in AF, endpoint congenital infection @ birth or AF

CMV: Prevention, Diagnosis, Therapy
Kotton CN. Am J Transplant 2013; Suppl 3: 24-40.

- Most common cause transplant morbidity, childhood deafness
- Prevention
  - Universal prophylaxis
  - Preemptive therapy
- Others
  - Childhood "parties"
  - No blood transfusion, kissing, urine, handwashing


CMV-infected lining cells of gastric crypts

Antenatal interventions for preventing transmission of CMV from mother-to-fetus during pregnancy.
McCarthy FP, Rowlands S. *Cochrane Database Syst Rev* 2011; CD008371.

- No RCTs
- Pre-conception immunity
- Chemoprevention

"Being a woman is difficult since it consists of dealing with men." Joseph Conrad (1847-1921)

Causes of death among STILLBIRTHs (SBs).
Stillbirth Collaborative Research Network Writing Group (Silver R, Dudley D) *JAMA* 2011; 306 (22): 2469-79.

- SBs @ 1/160 pregnancies in US ≥ 20 weeks
- X ≈ Number of Infant Deaths
- "Systemic Evaluation"
- 663 women enrolled"
  - Probable case of death 61%
  - Possible cause >6%
  - Obstetric conditions 29%
  - Placental conditions >3%
  - Structural 14%
  - "Infection" 12.9% (↑ AA)
  - Umbilical cord 10.4%

Atul Gwande's Checklist
1° Prevention vs. Infection-caused Fetal Death

1. **Hygiene:** Food choice/preparation - Avoid deli food stored a long time, under-cooked, cross-contamination *(E. coli*, Listeria, Salmonella)
2. **Respiratory:** Enterovirus, hanta virus (aerosolized mouse droppings)
3. **Bites (zoonosis):** Malaria (mosquitos), Rocky Mountain Spotted Fever (ticks), Lyme (ticks), West Nile Virus (mosquitos)
4. **Invasive:** Blood transfusion, organ transplant → CMV

Prevention Strategies
Vaccination: Childhood, adult, maternal influenza
Oral hygiene/care: Periodontal disease, dental hygiene, root canal

Strategies for Partner Notification for STIs, including HIV.
Ferreira A, et al. *Cochrane Database Syst Rev* 2013; Issue 10: CD002843.

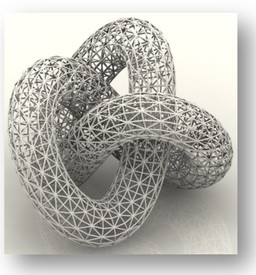
- Enhanced patient referral
- Expedited partner therapy
  - Contact referral
  - Provider referral
- No optimal strategy

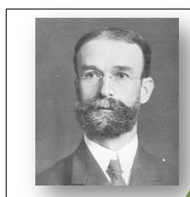
"Infectious diseases cause adverse pregnancy outcomes including stillbirth, perinatal complication and death in childhood."*

12% in US**
7.6 mm worldwide

*Edwards MS (UT) *JAMA* 2013; 311: 1115-6.
**Stillbirth Collaborative Network Writing Group. *JAMA* 2011; 306: 2459-68.

"Complex systems are characterized by many independent components where low level actions produce high level results." J. Werfel. *Science* 2014; 343: 754.





Theobald Smith's Equation

***Can infants be protected by MATERNAL VACCINATION?**
Esposito S, Bosis S, et al (Milan) *Clin Microbiol Infect* 2012; 18 Suppl 5: 85-9.

- Best example: anti → pertussis, influenza, **H. influenzae B, pneumococcus
- *Maternal immunization vs. viral disease
  - Englund J, Glezen WP (Wyeth) RSV antibody in breast milk
  - GBS???

**PLoS 2013 Bishchoff SC (may need ↑ dose)