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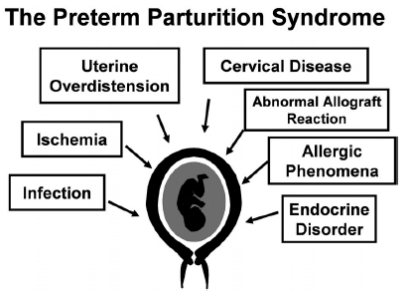
Primary Prevention of Fetal Death and Congenital Infection Caused by Maternal Infection using a Provider Checklist-enabled Mnemonic Prompt "LESS BABY TORCHEZ"

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



Mazaki-Tovi S, Romero R, et al. Semin Perinatol 2007; 3 (13): 142-158

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%

MNEMONIC

1965 Mnemonic
- Culture and serology
- Animal

Toxoplasmosis
Others
Rubella
Cytomegalovirus
Herpes

2018

- Culture, serology
- X non-culture

	Agents	Behaviors
L	*Listeria* Leishmaniasis	Food preparation Bite avoidance
E	Enteroviruses	Hygiene, food preparation
S	Syphilis, sexually transmitted infections (STIs)	Avoid new sex contacts, use condoms
S	Seasonal: influenza, West Nile Virus (WNV)	Immunization Avoid bites
B	Group **B** *streptococcus* (GBS)	Assume CDC/ACOG recommendations
A	Asymptomatic bacteriuria (ASB)	ASB/Urinary tract infection (UTI) screening
B	*Borrelia* species	Lyme disease (tick) precautions
Y	Barnyard leptospirosis	Hygiene
T	*Toxoplasma gondii* Tuberculosis	Food preparation Vaccination
O	Others, e.g., varicella-zoster virus	Vaccination, etc.
R	Rubella, measles, pertussis	Vaccination
C	Cytomegalovirus (CMV)	CMV precautions, handwashing
H	Herpes simplex 1 and 2 viruses (HSV-1, HSV-2) Hepatitis A, E viruses (HAV, HEV)	Behavior Hepatitis precautions, vaccination
E	Emerging infections	
Z	Zoonosis: Zika, malaria, dengue, WNV, coxiella, Lyme, rickettsia, yellow fever, leishmaniasis, arena viruses	No mosquitoes! No kissing bugs! No ticks!

Complexity

Complex systems are characterized by many independent components where low level actions produce high level results.

J. Werfel
Science 2014; 343: 754

Occam's Razor

Sir William Hamilton, 9th Baronet, Scottish metaphysical philosopher

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

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

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

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

Theobald Smith's Equation

Infection Outcome

$$\frac{\text{Number x Virulence}}{\text{Host Defenses (Innate, Acquired)}}$$

Immunology in the skin

- http://www.nature.com/ni/multimedia/skin/index.html

7:30 mins
Nature Immunology

Regulatory T cells and the immune pathogenesis of prenatal infection

- Placental mammals benefit via placenta
- Sit Peter Medaway 1950's ↓ ↓ immune responses vs. graft rejection
- Research (Fisher):
  - Maternal regulatory t cells (f) fetal tolerance

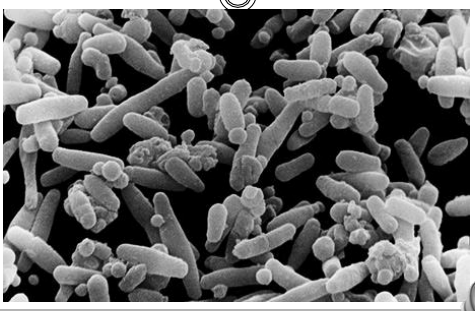
Rowe J, Way SS, et al. Reproduction 2013; 146 (6): R191-203

WE ARE NOT ALONE

- 2013 "top advances" in science
  - Person: 90% microbes, 10% human cells
  - i.e., we are "superorganisms," multi-chimera

1. Shared genome "hologenome"
2. Immune system – intentions
3. Metabolism
4. Reproduction (wasps)
5. Modulate emotions
6. Brain functioning: autism, schizophrenia
7. Interactive ↔ "Pregnancy bacteria" (Howerton)
8. "How to be a good SYMBIOT?"

Human Microbiome



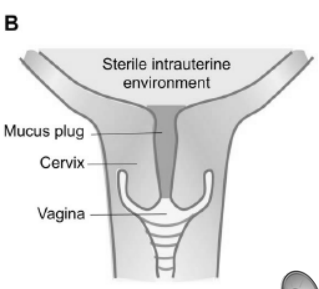
Cervical mucus properties stratify risk of PTB*

A Critchfield, et al (Tufts) PLoS One 2013; 8 (8): e69528

- "Ascending infection from vagina is a well-documented cause of preterm birth" – protected by dense and protective cervical mucus
- Study:
  - Examined SPINNBARKIET in "low" and "high" risk women
  - Fluorescent microbeads = "high risk," "more permeable"
  - ↑ Spinnbarkeit biomarker for PTB

- *Romero R, Gonzalez R. Short cervix ≈ MICA. Am J Obstet Gynecol 1992; 167 (3): 1086-91
- Vaisbuch E, Hassan SS, Romero R. Cervix <15 mm ≈ MICA. Am J Obstet Gynecol 2010; 202 (5): 433.e1-8

Cervical mucus stratify risk for PTB



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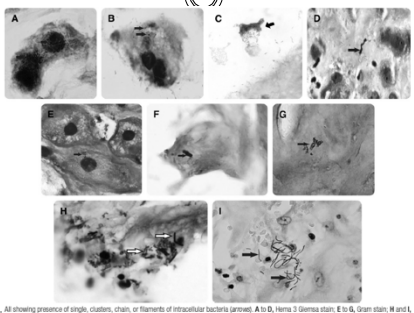
Intracellular bacteria in placenta basal plate



All showing presence of single, clusters, chain, or filaments of intracellular bacteria (arrows). **A** to **D**, Hema 3 Giemsa stain; **E** to **G**, Gram stain; **H** and **I**, Brown–Hopps stain.

Onest. Bacteria in human placental basal plate. *Am J Obstet Gynecol* 2013.

Gram positive rod

Death is an Active Process

Kaplan MJ, Radic M. J Immunol 2012; 189 (6): 2689-95

- Death pathways (f) FAS, toxins
  - Apoptosis
  - Autophagy
  - Necrosis
  - NETS (neutrophil extracellular trap)
- Beneficial?
- Recycle
- Reversible? Anti-FAS? Anti-Caspase?

How cells DIE: Signaling death 2014

Zhang J, Chan F. Science 2014; 343: 1322-23

- Programmed cell death (PCD) "apoptosis"
  - Signal: Fas and Fadd (f) TNFα
  - Cell recycling
  - Not inflammatory
- Programmed necrosis "necroptosis"
  - Signal: TLR3, TLR4, T cell receptor
  - Highly inflammatory kills virus, bacteria

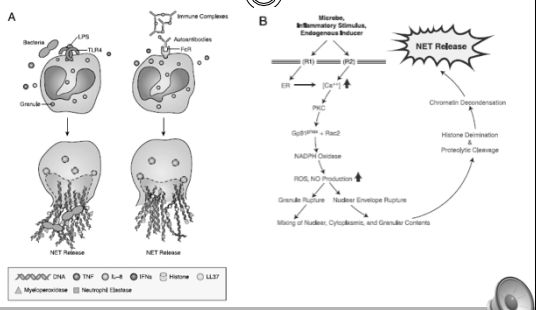
NETS: Neutrophil Extracellular Traps: Double-edge sword of innate immunity

Kaplan MJ, Radic M. J Immunol 2012; 189 (6): 2689-95

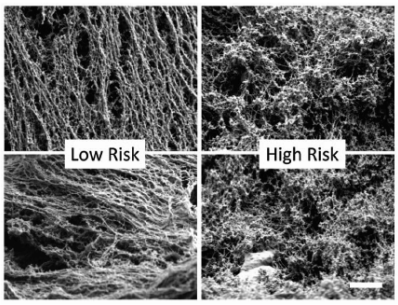
- Discovered 2004
- PMN "eject" nuclear chromatin and bactericidal proteins
- See: Infection, sepsis, DIC, vasculitis

Death is an Active Process

Kaplan MJ, Radic M. J Immunol 2012; 189 (6): 2689-95



Bead permeability assay



Critchfield AS, et al. PLoS One 2013; 8 (8): e69528

Cost-effectiveness of screening and Rx for BV in EARLY PREGNANCY among women at LOW RISK for PTB

Kekki M, Kurki T, PaavonenJ, et al. Acta Obstet Gynecol Scand 2004; 83 (1): 27-36

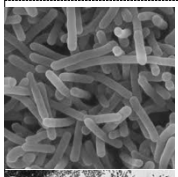
- "BV is important risk factor for PTB"
- Detected 10-30% pregnant women, often asymptomatic
- Rx BV in HIGH RISK women reduces risk

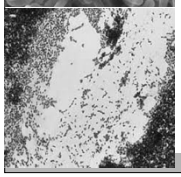
Study Decision Tree (Prior Study)		
	Screening + Clinda Rx	**Placebo**
Sensitivity Analysis	Rate PTB @ 2% ND overall for cost	
Results	Rx cost saving if PTB is 7.3%	

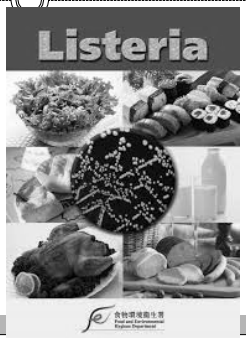
Mosquitos transmit malaria and WNV

Ticks transmit Lyme disease and RMSF and others

Listeria







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

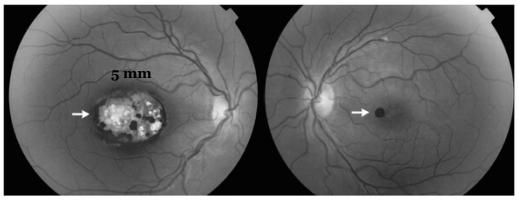
- Listeria: → disseminated infection in pregnancy → pregnancy → abortion/SB
- Model: very small inocula → fetal wastage
- Showed listeria ↓ ↓ maternal Foxp3+ regulatory T cell suppression
- ↓ TOLERANCE

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

Toxoplasmosis



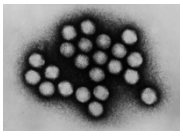
Chorioretinal toxoplasmosis (serologic testing was positive for *Toxoplasma gondii* IgI antibody (low level) and negative for IgM antibody. Hafidi A, Daoudi R. NEJM 2014; 270 (4): 361

Toxoplasmosis: Mice lose fear of cats

Mechanism of placental viral infection

Koi H, Zhang J, Parry S (Penn) Ann N Y Acad Sci 2001; 943: 148-56

- Models
  - Adenoviruses
  - HSV
  - CMV
- Efficient transduction
- Apoptosis
- Inflammation



Herpes

CMV

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

	HIG	Placebo	P=
CMV	33%	44%	0.13
Clinical/lab outcomes			ND
∴ND with HIG-CMVg. 1° prevention or infection before pregnancy			

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

CMV: Prevention, Diagnosis, Therapy

Kotton CN. Am J Transplant 2013; Suppl 3: 24-40

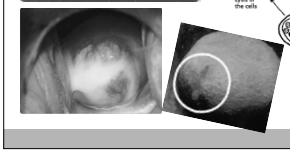
- Most common cause transplant morbidity, childhood deafness
- Prevention
  - Universal prophylaxis
  - Preemptive therapy
- Others
  - Childhood "parties"
  - No blood transfusion, kissing, urine, handwashing
- Wang D. *Progress on pursuit of human cytomegalovirus vaccines for prevention of congenital infection and disease.* Vaccine 2014 pii: S0264-410X(14)00426-5. doi: 10/1016/j.vaccine.2014.03,057 [Epub ahead of print]

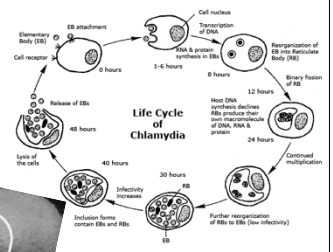
Passive immunization during pregnancy for congenital CMV

Nigro G, et al; Congenital CMV Collaborating Group; NEJM; 2005; 353 (14): 1350-62

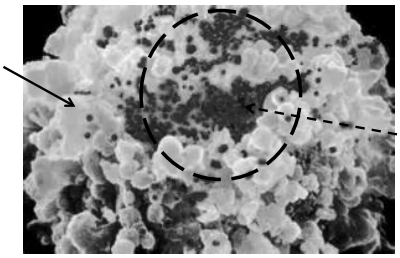
- Dx Greek women with evidence 1° CMV <20 wk
- Treatment of CMV hyperimmune globulin is safe
- ↓ congenital infection, aOR 0.32 (0.1 to 0.94); 95% CI, p<0.4
- 2-year follow-up (monthly injection)

Chlamydia





CD4+ T lymphocyte infected with HIV



Host cell (green) is infected by and produces HIV particles (red)
Electron micrograph by Dr. David Hockley from an infected culture provided by Dr. Robin Weiss; University College London, London

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4. Invasive
   A. Blood transfusion, organ transplant → CMV

LESS BABY TORCHES

- "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

*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)