

RECOGNITION OF PATHOGENIC PATHWAYS TO
INTRAUTERINE INFECTION: KEYS TO IDENTIFYING
TESTABLE PRIMARY STRATEGIES TO PREVENT
PRENATAL INFECTION

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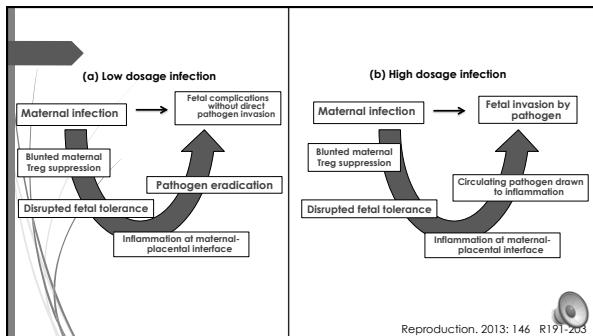




D. Trewdale mothers LHG
Helper Nature Immunol
7:241-246

- "The evolutionary adoption in mammals that allow implantation of their embryos in the mother's womb creates an immunobiological problem"
- "Contact with the mother's uterine tissue makes the fetus/trophoblast a target for her immune system."
- "Half the conceptus' genes are derived from the father. And the embryo and placenta are considered a semi-allograft to be normally rejected."
- During pregnancy the semi-allographic fetus is protected from assault by the powerful maternal immune system over time and by a NETWORK of immunological TOLERANCE





Background

- ▶ Research shows multiple microbes, molecules, nanoparticles (oral, resp, blood, GU, GI)
- ▶ Present in intrauterine tissues/organs (decidua, placenta, AF, meconium)
- ▶ Organism/molecule/products stimulate or moderate inflammatory/coagulation in host responses

Goals

- ▶ Perform Logic Analysis and literature review focusing on upper genital tract organs, tissues, decidua, trophoblast and fetal structures
- ▶ To identify and characterize how microbes, their products, and host response molecules may be transported to
 - ▶ URT and LRT organs, tissues, fetus
 - ▶ Gestational organs and tissues, e.g. decidua, Fallopian tubes, trophoblast, placenta, and fetal structures
- ▶ Speculate how to mitigate or prevent potentially injurious substances from reaching the female reproductive organs and tissues
- ▶ Identify potential primary prevention strategies
- ▶ Complete Logic Analysis matrix in order to identify personal, community, public health and policy recommendations to reduce risks of pathogenic microbial transport to reproductive tract tissues

Methods

- We conducted an updated English language PubMed and Medline computerized literature research
- We used search terms such as "uterine transport," "uterine transmission," "uterine activity," "Blood Brain Barrier," "host-microbial interactions," and "brain microvascular endothelial cells (BMEC)"
- We constructed a Logic Analysis matrix in order to identify personal and public health and policy recommendations to reduce risks of infection and inflammatory substances being transported to reproductive tract structures



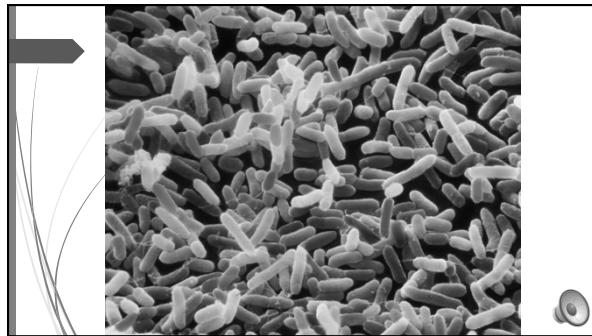
Results

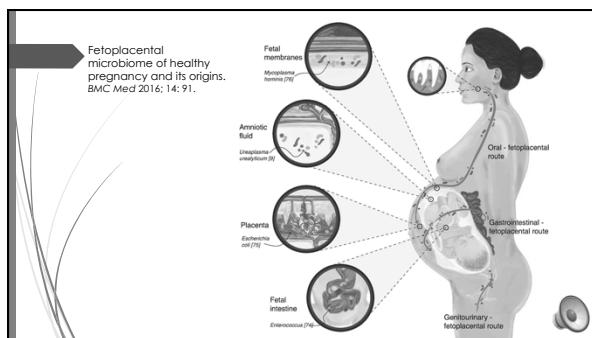
- Multiple pathways identified:
 - Sexually transmitted (penis in vagina)
 - Uterine peristalsis "upsuck"
 - Hematogenous (oral, periodontal, GI, GU, bacteremia)
 - Local spread
 - Lymphatic
 - Translocation
 - COUNTER CURRENT mechanism
 - Hygenic practices: talc, douching
 - Iatrogenic: membrane stripping
- No systemic, comprehensive studies

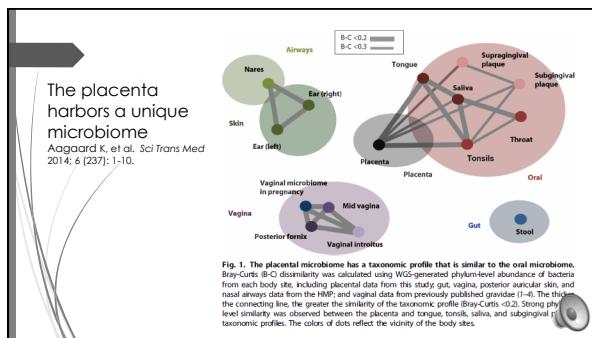


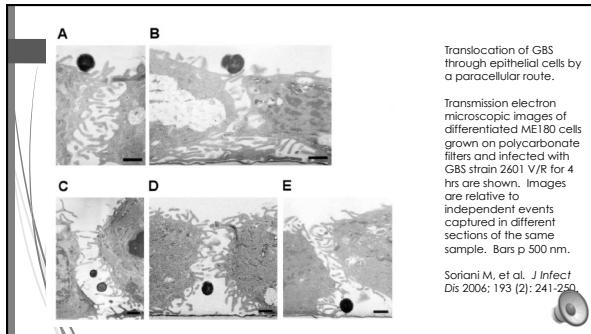
For video











→ "The World's Most Dangerous Animal"
Jerry Adler, Smithsonian 6.2016.27

Anophales (useless) mosquitoes reproduce in wet places
At 80 degrees F.

Molecular genetic approaches
Gates Foundation/WHO: @ 400K fatalities /year;
[↑ fetus / children]

The vector is the Achilles heel of malaria

Approach: inject lethal genes @ reproduction @ CRISPR

Aim: eliminate local populations

→ Risk of fetal death (SB) after (H1N1) pandemic influenza virus infection or vaccination.
Hoiberg SE, et al. NEJM 2013; 368 (4): 333-40.

- Mandatory registration @ 117,000 pregnancies
- Rate of FD @ 4.9/1,000 births
- Maternal Protection OHR
 - By vaccination .30 (.25-3.4)
 - Fetal death (n=496)
 - Mother with influenza 2.1 (1.27-3.49)
 - Mother vaccinated .88 (.66-1.17)
- Thus:
 - Protected mother 70%
 - 1 fetal death 12% (ND)
- Problems:
 - Vaccination program delayed, i.e., 12-week delay
 - Results similar to 1918 pandemic
- "Vaccination benefits fetus"

The vascular architecture of the supravaginal and vaginal parts of the human uterine cervix: a study using corrosion casting and scanning electron microscopy. Bereza T, et al. *J Anat* 2012; 221: 352-357.

Cervix sagittal section – vaginal part. The stars mark the large, exposed, pericanal veins. The capillaries joining the pericanal veins run parallel to the subepithelial vessels.
Scale bar: 1000 µm

The First Uterine Pass Effect

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Annals New York Academy of Sciences 1997; 828: 291-9

Counter concurrent multiplication loop in the kidney

- A circuit of fluid in the Loop of Henle – an important part of the kidneys allows for gradual buildup of the concentration of urine in the kidneys

Discussion

- We noted multiple pathways for microbes or their toxins, metabolites, breakdown products and other small/nano substances have access to reproductive tract tissues
- Rather than being "protected" or "sterile," it appears that upper tract tissues are endowed with considerable host defenses to deal with the multiple microbes in their environments
- Of the multiple pathways, we note that FIRST PASS or direct translocation and COUNTER CURRENT mechanisms are priority research areas



Possible research questions derived from review of pathobiology

<ul style="list-style-type: none"> ■ Dysbiosis/Microbiome/Infection <ul style="list-style-type: none"> ■ Oral microflora <ul style="list-style-type: none"> ■ Prevent/treat periodontal infection ■ Optimize oral health ■ Genito-urinary <ul style="list-style-type: none"> ■ Urinary tract infections "screen and treat" ■ Vaginitis: BV, yeast ■ STI ■ Gastrointestinal: Avoid exposure <ul style="list-style-type: none"> ■ Oral/enteric pathogens, i.e. Listeria ■ Zoonosis 	<ul style="list-style-type: none"> ■ Reproductive Tract <ul style="list-style-type: none"> ■ Avoid new exposure/partners ■ Barriers: vaccination, probiotics ■ Early life: hygiene hypothesis/exposure ■ Avoid transfusions
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How the Modern Lifestyle Wreaks Havoc on the Microbiome



The diagram illustrates how modern lifestyle factors contribute to the disruption of the microbiome across the human body. Factors include:

- Physical inactivity
- Cigarette smoke
- Chemical stress
- Unhygienic environment
- Inadequate and disturbed sleep
- Infant formula feeding
- Antibiotics and other drugs with antimicrobial activity
- Highly processed diet
- Exposure to harmful substances

www.Darwinian-Medicine.com



Fish oil enhances intestinal barrier functions and inhibits CRH pathways in weaned piglets after LPS challenge.
Zhu H, et al. *Br J Nutrition* 2016; 115: 1947-57.

- Stress induces injury in intestinal barriers in piglets, long chain n-3 PUFAs
- "↑ barrier effects in multiple animal models"
- Study: Cor
 - LC chain n-3 PUFA fish oil
 - ↑ intestinal barriers
 - 32 piglets challenged with LPS
- Results: Fish oil
 - ↑ intestinal barriers (villi)
 - ↓ translocated bacteria
 - ↓ mRNA of CRH-R1
 - ↓ TNF
- FO improves intestinal barrier function



Research suggestions

- Systems biology approach
 - Microbiome, innate immunity, physiologic functions, pharmacologic interactions
- Re-formulate accepted pathophysiology
 - Poly-microbial processes, microbiome interaction, reproductive/sex biology, multiple access pathways
- Identify behavioral, community, medical means to mitigate each process
- Examples:
 - Sexual partner selection, safer sex barriers, douching
 - Pre-conception care
 - Maintain local host defenses, oral health vs. periodontal disease
 - Pro-/Prebiotic
 - Nanotechnology, immuno-therapies
 - Biomarker/susceptibility screening



Selected papers about IUI/brain injury

- Patrick LA, et al. Development of a Guinea pig model of chorioamnionitis and fetal brain injury. *Am J Obstet Gynecol* 2004; 191 (4): 1205-11.
- McAdams RM, Juul SE. The role of cytokines and inflammatory cells in perinatal brain injury. *Neuro Sci Int* 2012; 2012: 561494.
- Burd I, Bovitz MA, et al. Inflammation-induced preterm birth alters neuronal morphology in the mouse fetal brain. *J Neurosci Res* 2010; 88 (9): 1872-81.
- Adams Waldorf KM, McAdams RM. Influence of infection during pregnancy on fetal development. *Reproduction* 2013; 146 (5): R151-62.
- Ma J, Aggaard KM, et al. High-fat maternal diet during pregnancy persistently alters the offspring microbiome in a primate model. *Nature Commun* 2014; 5: 3889.
- Allard MJ, Bergeron JD. A sexually dichotomous, (>male) autistic-like phenotype induced by Group B Streptococcus materno-fetal immune activation. *Austslan Res* 2016; 1647 doi: 10.1002/aur.1647 [Epub ahead of print].
- Aggaard KM. Author response to comment on "The placental harbors a unique microbiome." *Sci Transl Med* 2014; 6 (254): 254lis.
- Bashiri A, et al. Cerebral palsy and fetal inflammatory response syndrome: a review. *J Perinat Med* 2006; 34 (1): 5-12.



Selected papers about IUI/brain injury

- Burd I, et al. Models of fetal brain injury, intrauterine inflammation, and preterm birth. *Am J Reprod Immunol* 2012; 67 (4): 287-294.
- Coid CR, et al. Escherichia coli infection in mice and impaired fetal development. *Br J Exp Pathol* 1978; 59 (3): 292-297.
- Kaiser J. Placenta harbors bacteria, may impact fetal health. *Science* May 21, 2014.
- Larouche A, et al. Neuronal injuries induced by perinatal hypoxic-ischemic insults are potentiated by prenatal exposure to lipopolysaccharide: animal model for perinatally acquired encephalopathy. *Dev Neurosci* 2005; 27 (2-4): 132-142.

Transmission of diverse oral bacteria to murine placenta: evidence for the oral microbiome as a potential source of intrauterine infection.

Fardini Y, et al. *Infect Immun* 2010; 78 (4): 1789-96.

- Microbial infection is major cause of IAI, placental infection, SB, PTL, PTB, SGA and pre-eclampsia
- The current paradigm indicates that intrauterine infections predominately originate from the vaginal tract
- Impaired technologies show that other sources of commensal bacterial contribute to IUA, i.e., 16S rRNA gene-based PCR and clone analysis
- Study: showed that mouth flora are enriched concentrated in placenta mechanisms? Species specific

Transvaginal progesterone: evidence for a new functional "portal system" flowing from the vagina to the uterus.

Cincinelli E, de Ziegler D. *Hum Reprod Update* 1999; 5 (4): 366-372.

- "vaginal progesterone yields higher tissue concentrations than expected"
- How?
 - Direct diffusion
 - Infracervical aspiration
 - Absorption venous-lymphatic with countercurrent vascular exchange
- All mechanisms may work together

Vaginal pH self-screening as a KISS regimen in prevention of early preterm birth.

Hoyme UB. *EMJ Gyn Obs* 2012; 11: 44-47.

- "Self measurement of vaginal pH (>4.5) established screening procedure in Erfurt and Thuringia studies

The association between talc use and ovarian cancer: a retrospective, case-control study in two US states.

Cramer DW, Vitonis AE, et al. *Epidemiology* 2016; 27 (3): 334-346.

- Multiple studies of ovarian Ca and genital talc use started in the 1960's
- Study cases: 2,041 epithelial Ca vs 2,100 controls
- TALC USE
 - All OR 1.33 (1.16-1.52)
 - >2 yr OR 2.33 (1.32-4.57)
 - 1 serous, endometrioid
 - 1 menopause
- *expert witness

Centering pregnancy: the benefits of group prenatal care.

Rotundo G. *Nurs Womens Health* 2011; 15 (6): 508-17.

- Limited controlled trials
 - 1 PTB @ 33% (Ickovics JR, et al. *Obstet Gynecol* 2007; 110 (2 Pt 1):330-9
 - 1 PTB @ 41% in AA'a (Ickovics)
 - 1 Grady, Bloom (*J Midwifery Womens Health* 2004; 49 (5): 412-20)
- No Cochrane Reviews
- Limitations
 - Small sample sizes
 - Mostly whites
 - Conducted in the 1990's
 - No results: GDM, infant mortality, shoulder dystocia

Inflammation and brain edema: new insights into the role of cytokines and their receptors.

Stemotovic SM, Denilijevic OB, et al. Acta Neurochir Suppl 2006; 96: 444-50.

► (f) BBB breakdown

- Proinflammatory mediators
- Chemokines → PMNs (CCR2)
- PMN vasogenic edema
- CCL2/CCR2