“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 senses are derived from the father. And the embryo and placenta are considered a semi-allograft to be normally rejected.”

“During pregnancy, the semi-allogrophic fetus is protected from assault by the powerful maternal immune system over time and by a network of immunological tolerance.”

D. Trewsdale mothers UHG
Helper Nature Immunol
7:241-246
Background

- Research shows multiple microbes, molecules, nanoparticles (oral, resp, blood, GU, GI)
- Present in intrauterine tissues/organisms (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
- Gastrointestinal 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
- Iatrogenic: membrane stripping
- Hygenic: talc, douching
- No systemic, comprehensive studies

For video


Translocation of GBS through epithelial cells by a paracellular route.

Transmission electron microscopic images of differentiated ME180 cells grown on polycarbonate filters and infected with GBS strain 2601 V/R for 4 hrs are shown. Images are relative to independent events captured in different sections of the same sample. Bars p 500 nm.


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

Anophales (useless) mosquitoes reproduce in wet places
A 1/2 degrees F.

Molecular genetic approaches
Gates Foundation/WHO: ~400K fatalities /year:
(1 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.

- Mandatory registration @ 177,000 pregnancies
- Rate of FD: 4/1,000 births
- Maternal Protection
  - Immunization: 30% (p<0.04)
  - Fetal death (SB): 0.8% (p=0.5)
- Mother with influenza: 2.1 (1.27-3.49)
- Mother vaccinated: 0.88 (0.51-1.49)
- Risk: 2.1 (1.27-3.49)
- Protecte mother: X10
- Fetal death: 0.056
- Problems:
  - Vaccination program delayed, i.e., 12-week delay
  - Results similar to 1918 pandemic
  - “Vaccination benefits fetus”

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

The First Uterine Pass Effect

DOMINIQUE DE ZIEGLER,* CARLO BULLETIT, BÉATRICE DE MONSTIER** AND ANNA-STINA JÅKKELÄINEN

*Columbia Laboratories
19 rue du Général Foy
75008 Paris, France

**Nyon Hospital
Nyon, Switzerland

1st Institute of Obstetrics and Gynecology
University of Bologna—Italy
Via Massarenti, 13
40138 Bologna, Italy

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:

- **Dysbiosis/Microbiome/Infection**
  - Oral microflora
  - Prevent/treat periodontal infection
  - Optimize oral health
  - Gastrointestinal
    - Oral microflora
    - Gastrointestinal pathogens, i.e. Listeria
  - Genitourinary
    - Urogenital tract infections, screening and treatment
    - Infection, BV, yeast
    - STIs
  - Gastrointestinal: Avoid exposure
  - Reproductive tract: Avoid new exposure/partners
  - Barriers: vaccination, probiotics

- **Early life:** hygiene hypothesis/exposure
- **Avoid transfusions**

Fish oil enhances intestinal barrier functions and inhibits CRH pathways in weaned piglets after LPS challenge.


- Stress induces injury in intestinal barriers in piglets, long chain n-3 PUFAs ↑ barrier effects in multiple animal models

Study: Con

- 1. Control
- 1. LPS
- 1. Fish oil
- 1. Fish oil + LPS

Results:

- Fish oil ↑ intestinal barriers (villi)
- Fish oil ↓↓ translocated bacteria
- Fish oil ↓ mRNA of CRH-R1
- Fish oil ↓ TNF

Research suggestions

- Systems biology approach
  - Microbiome, innate immunity, physiologic functions, pharmacologic interactions
- Meta-formulates accepted pathophysiology
  - Myocardial processes, microbiome interaction, reproductive axis biology, multiple access pathways
- Identify behavioral, community, medical means to mitigate each process
  - Sexual partner selection, safer sex barriers, douching
- Pre-conception care
  - Maintain local host defenses, oral health vs. periodontal disease
- Probiotics
  - Neurotechnology, immune therapies
- Biomarker/susceptibility screening

Selected papers about IUU/brain injury

Selected papers about IUI/brain injury


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


- Microbial infections are 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 bacteria 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.


- “vaginal progesterone yields higher tissue concentrations than expected”

- How?
  - Direct diffusion
  - Intracervical 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; 1: 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.


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 (1.30-4.57)

↑ serous, endometriod

↓ menopause

*expert witness

Centering pregnancy: the benefits of group prenatal care.


Limited controlled trials

| J FTB 475 in A A a ( chicas)
| J Grady, Bloom JJ Midwifery Womens Health 2004; 9 (3): 413-20
| 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.


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