Recognition of Pathogenic Pathways to Intrauterine Infection: Keys to Identifying Testable Primary Prevention Strategies

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Background: Research shows that various microbes (bacteria, viruses, yeasts/fungi, parasites) arising from endogenous sources (vagina, cervix, and gastrointestinal, genitourinary, others) are frequently present in the upper reproductive tract and gestational (decidua, placenta, membranes, amniotic fluid, meconium) tissues. These molecules (their toxins, metabolic products, breakdown products) may stimulate or moderate inflammatory/coagulation "host" (mother, fetus, trophoblast) responses.

Goals:

1. We sought to perform a <u>logic analysis</u> and literature review.
2. To <u>identify</u> and <u>characterize</u> how microbes and their products may be transported to
   a. upper genital tract organs and tissues, and
   b. gestational organs and tissues, e.g., decidua, Fallopian tubes, trophoblast, placenta and fetal structures
3. Speculate how to mitigate or prevent potentially injurious substances from reaching the female upper tract and gestational tissues and organs.
4. To <u>identify</u> possibly primary preventive strategies to reduce risks of transport of potentially damaging substances to reproductive tract organs and tissues.

Methods:

1. We conducted an updated English language PubMed and Medline computerized literature research.
2. We used search terms as *"uterine transport," "uterine transmission,"* and *"uterine activity."*
3. We constructed a logic analysis matrix in order to identify personal and public health and policy recommendation to reduce risks of microbial transport to reproductive tract structures.

References:

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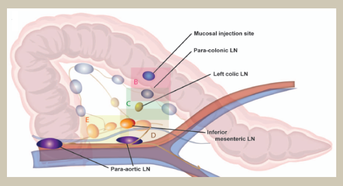
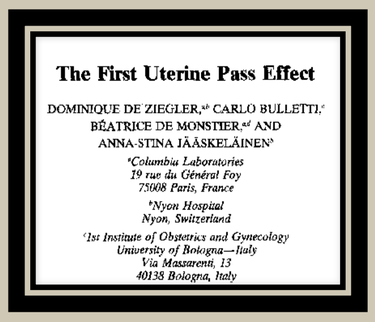
Results:

1. Multiple pathways identified:
   - Uterine peristalsis in non-pregnant (i.e., sperm, talc) and pregnant
   - Hematogenic, i.e., oral, periodontal, UTI, bacteremia, bacteriuria)
   - Lymphatic
   - Translocation, i.e., intestinal, GI tract
   - COUNTER CURRENT mechanism
   - Locally spreading, i.e., STI, surgical
   - Hygienic practices i.e., perineal talc powder, douching
   - IATROGENIC, i.e., membrane "stripping," labor induction, amniocentesis
   - Breastfeeding
   - Placenta phagy
2. No systematic, comprehensive studies



"lymphatic draining pattern" Smedley J, et al. *PLoS One* 2014; 9 (3): e92830.



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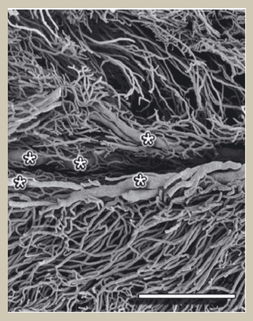

"counter current mechanisms" Bereza T, et al. *J Anat* 2012; 221: 352-357.

Research suggestions:

1. Systems biology approach
   - Regarding microbiology of reproductive tract, pregnancy, microbiology
   - Physiologic reproductive functions
2. Re-formulate pathophysiology
   - Polymicrobial infection
   - Host immunity
   - "Normal presence of microorganisms"
3. Biology of sex functioning
   - Non-reproductive
   - Reproductive

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4. Einer-Jensen N, et al. Physiological and pharmacological aspects of local transfer of substances in the ovarian adnexa in women. *Hum Reprod Update* 2000; 6 (2): 132-138.
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Discussion:

1. We noted multiple pathways for microbes or their toxins, metabolites, breakdown products and other small/nano substances to have access to upper reproductive tract tissues.
2. 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.
3. Of the multiple pathways, we note that FIRST PASS or direct translocation and COUNTER CURRENT mechanisms are priority research areas.

Conclusions:

1. There is RAPID TRANSPORT of fluids, LARGE/SMALL MOLECULES from the vagina/cervix via MULTPLE PHENOMENA:
   - Uterine peristalsis ("upsuck")
   - Local diffusion
   - FIRST PASS
   - Lymphatics/venous plexus
   - COUNTER CURRENT processes
2. These observations prompt consideration of NEW APPROACHES <u>intrauterine</u> and <u>transovarian</u> therapeutics.
3. These may include NANOTECHNOLOGY and immune therapies.
4. UNKNOWN if similar mechanisms occur in GU and GI tracts

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