ABSTRACT

Introduction/Background: Preventable reproductive tract infections are increasingly recognized as drivers of death in the 20% to 40% of fetal deaths and stillbirths worldwide. Objective: Develop “gedanken” (thought-based) strategies to prevent infection-caused fetal loss. Methods: Medical knowledge review and synthesis. Perinatal lethal infections are known to be caused by various potentially preventable pathways: 1) Bloodborne (via maternal circulation) infection of placental tissues, umbilical cord, amniotic fluid, 2) ascending infection through the cervix, decidua, and amnionchorion, 3) intratropic infection (amnionitis, membrane stripping), 4) preexisting (pregnancy) endometrial infections, and 5) zoonotic bloodborne infections. More recently recognized for “unlabeled” pathophysiologic pathways include 1) combined bacterial and viral infections in which viral infection or maternal-fetal “mismatch” sensitized the placenta to the effects of IFS (Influenza, parainfluenza), 2) “graft vs. host” phenomena by which prior infections could amplify production of HSPs (Heat Shock proteins) and other “immune molecules”, and 3) sterile inflammation or “autoaggressive” stimuli (caused by small particles or increased cell death from any cause). Results/Discussion: Successful primary and secondary prevention strategies include: 1) recognition and documentation of stillbirth; implicated microorganisms, 2) development of simple, inexpensive, accurate means to identify causal agents and boost host response mechanisms, 3) formula means to formulate evidence-based strategies to systematically prevent infection-caused late miscarriage, stillbirth, or neonatal infection.

DISCUSSION

AIMS

1) Review recognized infection causes of FDI in differing geographic regions.
2) Recognize clinically under-appreciated “pathophysiologic pathways” which may lead to locally important causes of FDI.
3) Comprehend newly recognized lethal organismal and cellular lethal processes.
4) Identify different medical and non-medical approaches or processes which may be used to reduce risks of prevalent causes of FDI.
5) Focus on opportunite clinical and public health research areas (low hanging fruit) which may be practically utilized to reduce risk of prevalent I-I caused FDI.
6) Review evidence-based primary preventive strategies which have been used effectively, but appear under appreciated or under used.

Table 1. Death Mechanisms of Processes, Not Commonly Acknowledged

<table>
<thead>
<tr>
<th>Process</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Necrosis</td>
<td>Direct cell death: toxic, physical, chemical, final product of apoptosis</td>
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<tr>
<td>Apoptosis</td>
<td>Programmed cell death</td>
</tr>
<tr>
<td>Autophagy</td>
<td>Self digestion</td>
</tr>
<tr>
<td>Death program</td>
<td>Several pathways leading to organ death</td>
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<tr>
<td>Sterile inflammation</td>
<td>Fatal tissue death</td>
</tr>
<tr>
<td>Senescence</td>
<td>Death - signaling by aging</td>
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</tbody>
</table>

Table 2. Proposed Infection Pathways to Fetal Death

<table>
<thead>
<tr>
<th>Name</th>
<th>Mode of Transmission</th>
<th>Aims</th>
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<tbody>
<tr>
<td>Maternal &quot;traditional&quot;</td>
<td>Bloodborn, ascending through cervix, persistent endometrial infection</td>
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<tr>
<td>Intratropic</td>
<td>Amnionitis, membrane stripping, prolonged infection</td>
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<tr>
<td>Complex</td>
<td>Viral infection &quot;sensitizing&quot; to IFS</td>
<td></td>
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<tr>
<td>Immunologic</td>
<td>Gravit vs Host &quot;maternal/fetal rejection&quot;</td>
<td></td>
</tr>
<tr>
<td>Gene-based</td>
<td>Infected sperm or ovum (Bacteria, viruses, parasites), In vitro contaminated</td>
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PREVENTION DEFINITIONS:

1) Prevent exposure,
2) Detect early (screen),
3) Mitigate damage (rehabilitation)
4) Systematically reduce damaging phenomena (policy)

RESULTS

There is considerable information available regarding infection caused FDI. More recently, understood death mechanisms are listed in Table 1. Proposed traditional and novel infection pathways to FDI are listed in Table 2. Selected important microorganisms associated with possible means for prevention are listed in Table 3.

RECOMMENDATIONS

1) The Burdens of Infection-caused FDI or stillbirth need to be systematically studied using epidemiologic, pathologic and public health techniques.
2) Behavioral, medical and vaccine-mediated primary prevention of FDI needs to be included in public policy prevention guidelines including FDI (preventive) GUIDELINES
3) Advance technologies including vaginal pH screening and microfluidic diagnostic techniques need to be systematically researched in large controlled trials.
4) Effective diagnostic pathology service/approaches for FDI (including placental triage) verbal autopsy and complete contemporaneous autopsy service should be made available.

REFERENCES