Maternal immunization: development and evaluation of vaccines for use in pregnancy

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Development and evaluation of vaccines for use in pregnancy

- Immune response during pregnancy
- Safety assessment
- Challenges and opportunities in the development and evaluation pipeline
  - Novel vaccine platforms
  - How and when to include pregnant women in the evaluation of vaccines intended for broad use
- Not discussed today
  - Challenges and opportunities related to implementation
Immune response during pregnancy
Pregnancy and immunity

• “Pregnancy…[promotes] a modulated immunologic condition, not a state of immunosuppression.”

• Influenced by increasing levels of estradiol and progesterone during gestation
  – Promote Th2 responses and humoral immunity, with relative suppression of Th1 and CD8 responses
  – Temporary thymic involution
  – Innate immunity is maintained or enhanced

• T cell responses may be particularly important in controlling viral replication and suppression of Th1 and CD8 may contribute to disease pathogenesis (e.g., hepatitis E)
Changes in Hormone Levels and Immune System Characteristics during Pregnancy.


<table>
<thead>
<tr>
<th>First trimester</th>
<th>Second trimester</th>
<th>Third trimester</th>
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<td></td>
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<td>Increased severity:</td>
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<td>Influenza</td>
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<td>Hepatitis E</td>
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<td>Herpes simplex virus</td>
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**Monocytes and phagocytosis**
- Dendritic cells
- Polymorphonuclear cells
- α-Defensins
- Regulatory T cells

**CD4+ T cells**
- CD8+ T cells
- B cells
- Natural killer cells
- Cytotoxicity

**Progesterone**

**Estradiol**
Pregnancy and vaccine responses

• Most studies focus on antibody response

• Data vary:
  – Comparable antibody responses to IIV, Tdap
  – Diminished antibody responses reported:
    • HBV: (n=73; not ss)
    • IIV: (n=51; no difference in rates of seroconversion or seroprotection)
    • Yellow fever (n=216)

• No evidence of reduced vaccine efficacy, though numbers are small
Transplacental transport of IgG during pregnancy

• Placental transfer is highly selective for monomeric IgG, and occurs by receptor-mediated active transport
• Transport requires healthy placenta
• IgG1 = IgG3 > IgG4 > IgG2
• No transfer of IgM, IgA, IgE
• Begins at 17 wks; increases with gestation
• By 33 weeks maternal = fetal IgG levels and by 40 weeks fetal > maternal IgG levels
• HIV and hypergammaglobulinemia interfere with transport; placental malaria (??)

Fig. 1. Comparison of IgG concentrations in forty-six paired maternal cord sera

De Moraes-Pinto et al. J Infect Dis. 1996 May;173(5):1077-84
Optimizing transplacental antibody transfer

- Recent studies indicate that transfer of PT and FHA antibodies to term and preterm infants is optimal when mothers receive Tdap in the 2\textsuperscript{nd} trimester
- Data needed for other vaccines
Assessment of vaccine safety during pregnancy
GAIA (Global Alignment of Immunization Safety Assessment in pregnancy): guidance for safety monitoring in clinical trials during pregnancy

• “harmonize data collection for safety monitoring in the course of clinical trials of vaccines in pregnant women...a minimal set of high-priority parameters in various settings”

• Guidance developed by Brighton Collaboration Immunization in Pregnancy Working Group based on literature review and consensus development

• Guidance includes recommendations for documentation, collection, and presentation of:
  • baseline epidemiologic data, maternal demographic data, maternal clinical data, fetal data, birth/neonatal data, and data on adverse events following immunization
Safety monitoring in clinical trials during pregnancy: additional considerations

• Think about safety monitoring/pharmacovigilance in the context of maternal immunization
  – Normal events related to pregnancy, labor and delivery may be considered AEs in other contexts
  – Inconsistent approaches to clinical definitions (e.g. postpartum hemorrhage) across regions/countries
  – Importance of baseline data on adverse maternal, fetal, and infant outcomes that are relevant to the setting(s) in which clinical trials are conducted
Challenges and opportunities in development and evaluation of vaccines for use in pregnant women
Maternal vaccines: primary target for protection

- **Maternal/fetal disease**
  - Malaria*
  - Hepatitis E
  - Lassa fever
  - Ebola

- **Infant disease (acquired)**
  - RSV*
  - Pertussis
  - Tetanus

- **Infant disease (congenital)**
  - Zika
  - CMV

- **Maternal & infant disease**
  - Influenza
  - HSV
  - GBS*

*Vaccines specifically being developed for use in pregnancy
Maternal immunization: vaccine development

- What type of immunity is needed?

  - Ab
  - Sterile immunity

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<tr>
<th>RSV</th>
<th>HSV</th>
<th>Zika</th>
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<td>GBS</td>
<td>CMV</td>
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- What is the development pathway for novel vaccine technologies in pregnant women?
  - Nucleic acid vaccines
  - Replication defective vectors
Maternal immunization: vaccine evaluation

• When should a vaccine being developed for general use be evaluated in pregnant women?
  – Potential risks and benefit of vaccine
  – Risk of disease
  – Who decides?

• For any vaccine being evaluated in WOCA
  – What are plans for follow-up of unanticipated pregnancies?
  – In the event of an urgent threat, can trial completion (e.g., additional doses) be considered
  – Pregnancy is not an adverse event
Development of vaccines for use in pregnant and non-pregnant populations: the example of Hepatitis E vaccine

- 20 million cases HEV and 44,000 deaths annually; endemic and epidemic
- Highest disease incidence in young men, usually self-limited
- Pregnant women at high risk of severe disease:
  - Mortality 5-25%
  - High rates of spontaneous abortion and stillbirth in survivors
- Hecolin (HEV 239; recombinant peptide with alum)
  - Licensed in China based on phase 3 trial: 97,356 evaluable subjects; 37 pregnant women received 54 doses of vaccine
  - Vaccine efficacy after three doses was 100.0% (95% CI 72.1–100.0)
  - WHO position paper:” Due to the lack of sufficient information on safety, immunogenicity and efficacy in the following population subgroups, WHO does not recommend routine use of the vaccine in children below 16 years of age, pregnant women, chronic liver disease patients, and patients on organ transplant waiting lists, and travellers”

http://www.who.int/immunization/policy/position_papers/2015_up_hepe_may_2015_summary.pdf?ua=1

Zhu FC et al Lancet 2010; 376: 895–902
Effectiveness Trial to Evaluate Protection of Pregnant Women by Hepatitis E Vaccine in Bangladesh (NCT02759991)

- Phase IV effectiveness study of HEV 239 in women ages 16 to 39 years (active comparator HBV vaccine)
- iccddr,b, Norwegian Institute of Public Health, Innovax, GLOBVAC
- N=20,745; cluster randomized trial in Matlab, Bangladesh
- Vaccine administered at 0, 1, 6 months
- Primary outcome measure:
  - Determine the effectiveness of hepatitis E virus (HEV) vaccine in preventing HEV disease during pregnancy among women in rural Bangladesh
  - Women screened for pregnancy every 2 weeks during the study
- Pregnant women excluded from enrollment
• PREVENT:
  – will provide ethics guidance to promote the interests of pregnant women and their offspring in vaccine development efforts for priority pathogens and emerging epidemic threats
  – A collaborative project of the Johns Hopkins Berman Institute of Bioethics, the UNC Center for Bioethics, and the Kennedy Institute of Ethics at Georgetown University
  – Funded by the Wellcome Trust
Maternal immunization: a new paradigm

• ‘Old School’:
  – License a vaccine based on data in healthy, non-pregnant adults
  – Generate post-licensure data to support use in pregnancy

• New paradigm:
  – Develop purpose-built vaccines for use in pregnancy to prevent maternal/fetal/infant disease (RSV, GBS, malaria)
  – Include pregnant women in prelicensure clinical trials of other new vaccines if potential benefits outweigh potential harms
Potential roles for PDVAC with respect to maternal immunization

• Support stakeholder discussions pertaining to:
  
  – evaluation of novel vaccine platforms (e.g. nucleic acid vaccines, replication defective vectors) in pregnancy
    • are there common considerations that transcend specific products?
  
  – considerations for inclusion of pregnant women at earlier stages of vaccine development
    • particularly for vaccines intended for use beyond pregnancy
    • magnitude and immediacy of threat to health and vaccine platform will likely inform discussions
Thank you