Clinical Research in Pregnant Women: Process, Promise and Perils

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Achieving Excellence in Clinical Research: Scientific, Ethical and Operational Considerations
 Advocate Children's Hospital, Chicago, IL
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Disclaimer

- The opinions expressed here are those of the author and do not represent the official position of the U.S. National Institute of Health or the U.S. government.
- No conflicts of interest to disclose

BLUF

- Bottom Line Up Front: BLUF
- Clinical Research in Pregnant Women is "harder" than some other types of research.
- Clinical Research in Pregnant Women is being done
- ClinTrials.gov on 28 Sept 2016
  - ~1350 Trials open for enrollment today
  - ~358 trials specific to women
  - ~74 trials specific to pregnant women
  - 47 vaccine studies of HIV, TB,
  - 37 drug trials for depression and smoking cessation
  - 2 drug trials looking at seizure control
Clinical Research in Pregnant Women:
Process, Promise and Perils

Outline

- Clinical Research is a Collaborative Endeavor
- Objectives of DMID-supported maternal clinical research studies
- DMID Maternal Clinical Research Pathway
- Protocol design
  - Objectives
  - Inclusion/Exclusion
  - Safety Assessment
  - Halting Rules

Collaborative efforts:
Harmonization of terms and definitions, and adverse events grading

- DMID consultative conferences: NIH, FDA, CDC, Academia, Pharma, etc.
- WHO conferences
- BMGF stakeholders meeting
- Brighton Collaboration
- GAIA project:
  Save the date: Harmonized Safety Monitoring of Immunization in Pregnancy, International Consensus Conference
  March 29-30, 2016
  NIH, Natcher Conference Center, Bethesda, MD
Objectives of DMID-supported clinical research in pregnant women

• Spoiler Alert: DMID performs mostly Phase 1 and Phase 2 trials. Occasionally Phase 4 trials and rarely (twice) Phase 3 trials

• Primary endpoint: safety
  • local and systemic reactogenicity
  • frequent and common AEs

• Secondary endpoint: immunogenicity

• Exploratory endpoint: efficacy

DMID Maternal Immunization Research Pathway

Vaccines recommended during pregnancy in United States

No vaccine has been licensed by the U.S. FDA for use in pregnant women

Generally Recommended

• Seasonal Influenza Vaccine
• Tdap

Recommended ONLY when potential benefits outweigh potential risks

• hepatitis A and B
• Meningococcal
• Pneumococcal
• Inactivated polio
• Anthrax
• Japanese encephalitis
• Rabies
• Typhoid vaccines
• Vaccinia
• yellow fever vaccines.
Considerations for protocol design

Vaccine candidates to be studied in pregnant women should ideally meet the following requirements:

- Pre-clinical studies have been performed.
- Reproductive toxicology showed no fetal toxicity.
- Phase I-II clinical trials in healthy non-pregnant adults provided guidance on dosage, safety, and immunogenicity.
- Disease posing a special risk to the mother and/or the fetus.
- The study product is unlikely to cause harm to the mother or the fetus.

Munoz et al, Vaccine, 2013

Considerations for protocol design

Study protocol should include the following items:

- Background data and rationale for the study.
- Inclusion and exclusion criteria for enrollment.
- Safety parameters to be assessed: vital signs, local and systemic reactogenicity, laboratory values, and pertinent symptoms or medical events in the mother and the infant.

Considerations for protocol design

Study protocol should include the following items:

- Definition of AEs in the mother and fetus/infant, including events related to routine obstetric care that would not be considered AEs in the study.
- Description of a grading system of AEs
- Description and definition of AEs to be considered for study halting rules.
- Description of the evaluation to assess AEs’ relationship to the study product.
Natural history and burden of disease

<table>
<thead>
<tr>
<th>What is known</th>
<th>Knowledge gaps</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Background rates: incidence and prevalence in USA</td>
<td>• Background rates: incidence and prevalence in LICs</td>
</tr>
<tr>
<td>• Natural history and diseases burden in US</td>
<td>• Natural history and diseases burden in LICs</td>
</tr>
<tr>
<td></td>
<td>• Correlates of protection for some diseases</td>
</tr>
<tr>
<td></td>
<td>• Harmonized definitions across studies and trials</td>
</tr>
<tr>
<td></td>
<td>• Covariants-comorbidities affecting outcomes</td>
</tr>
</tbody>
</table>

Protocol design

• Types of studies:
  • Phase I: First in human (primary endpoint: safety)
  • Phase Ia: First in pregnant women (primary endpoint: safety),
  • Phase II in pregnant women: Dose ranging, formulation, and primary endpoint clinical efficacy, biomarkers, disease prevention or immunogenicity (exploratory efficacy)

• Types of studies:
  • Phase III in pregnant women: pivotal registration trials
  • Phase IV in pregnant women: Testing drugs approved in other populations or for other conditions or in other doses in the special population of pregnant women
Protocol design

• Study Design Decisions
  • Control group? / Placebo group?
  • Ethical issues / IRB Issues: Sub Part B
    • Risk benefit to mother
    • Risk benefit to the fetus
    • United States
    • International

Protocol Design: IRB Considerations

• Have there been studies that enable the assessment of risk to the pregnant woman and fetus?
  • Preclinical? pregnant animals? Non-pregnant women?
• If risk to the fetus? Is there the prospect of benefit to the pregnant woman?
• Is there the prospect of direct benefit to the fetus but no benefit to the pregnant woman? If yes, consent needed from the pregnant woman and the father of the child.

Protocol design

• Enrolment criteria:
  • Inclusion
    • Medical and past obstetrical history
    • Healthy
    • Disease State of Interest: Depression, gestational diabetes, influenza
    • Documentation of intrauterine pregnancy
    • Timing of enrolment [trimester]
    • Extent of prenatal testing
Protocol design

- Enrolment criteria:
  - Exclusion
    - Depends on agent being studied
    - Animal studies
    - Human data
  - Depends on measured outcomes
    - Do the outcome/endpoint measurements carry risk? Amniocentesis?
  - Comorbidities
    - What conditions will obscure the question you are trying to answer

Protocol design therapeutic: efficacy or biomarkers

- What is a most desired indication? Clinical efficacy!

- For a therapeutic study, the end point could be clinical efficacy
  - Microbiologic cure of UTI, relief from depression, suppression of seizures

- For a therapeutic study, the end point could be a biomarker
  - Normalized blood pressure or normal thyroid hormone levels

Protocol design vaccine: efficacy or immunogenicity

- What is a desired indication?
  - Clinical efficacy!

- What could be a vaccine surrogate outcome?
  - Immunogenicity:
    - Geometric mean titers (GMT) of neutralizing antibodies
    - Seroconversion and correlates of protection (CoP)
  - Persistence of antibodies: maternal, infant, serum, cord, BM IgA, duration of protection [kinetics of GMT above CoP], cell-mediated immunity
  - Efficacy (exploratory): effect on maternal infant’s illness (confirmed)

- Effect on infant immunization series (exploratory):
  - How to study and follow it?
Protocol design: Safety Assessments

- **Safety assessments:**
  - Vital signs
  - Safety laboratory tests
  - Solicited Adverse Events (Reactogenicity)
    - local and systemic
    - Ideal: not different from healthy adults or control group
  - Reported Adverse events in mothers and infants: definitions, grading and reporting
  - Duration of Follow up

**Constructed Tables of Normal Values**

**Laboratory Tests:**

- **Chemistry:**
  - Na, K, Ca, Mg, glucose, blood urea nitrogen, creatinine, BUN, urea, erythrocyte sedimentation rate, AST, ALT, GGT, bilirubin, albumin, total protein, cholesterol, triglycerides, glucose
- **Coagulation:**
  - Thrombin time, PT, APTT, INR
- **Hematology:**
  - Hemoglobin, WBCs, lymphocytes, ANC, eosinophils, monocytes, platelets
- **Urine analysis:**
  - Protein, glucose, blood/leukocytes

**Constructed Tables of Rates**

- **Pregnancy Outcomes:**
  - Pregnancy loss (spontaneous abortion, stillbirth); bleeding or blood loss (before delivery incl. abortion, pregnancy termination), rupture of membranes (premature, prolapsed), premature labor and delivery, intrauterine growth restriction, hypertensive disorders (hypertension, preeclampsia, eclampsia, HELLP), gestational diabetes, complications during delivery (chorioamnionitis)
- **Infant’s outcomes:**
  - Congenital anomalies, prematurity, admission to NICU (special care nursery),...
## Grading System for Adverse Events

### Table 1. Grading System for Adverse Events

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Approximately 10% outside the normal range; some cases may be attributed to the study condition, or to confounding variables.</td>
<td>Usually does not require an immediate intervention; may require additional monitoring or supportive care.</td>
</tr>
<tr>
<td>2</td>
<td>Approximately 20% outside the normal range; usually requires diagnostic workup and/or intervention.</td>
<td>Diagnostic workup and/or intervention is required.</td>
</tr>
<tr>
<td>3</td>
<td>&gt;20% outside the normal range; usually requires diagnostic workup and/or intervention.</td>
<td>Requires diagnostic workup and/or intervention.</td>
</tr>
<tr>
<td>4</td>
<td>Usually requires an immediate intervention, even if not potentially or immediately life threatening.</td>
<td>Immediate intervention is required, even if not potentially or immediately life threatening.</td>
</tr>
<tr>
<td>5</td>
<td>Life threatening</td>
<td>Life threatening</td>
</tr>
</tbody>
</table>

### Vital Signs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Values</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Temperature (°C or °F)</td>
<td>Fever</td>
<td>37-37.9°C (98.6-100.3°F)</td>
<td>38-38.4°C (100.4-101.1°F)</td>
<td>38.5-38.9°C (101.2-102°F)</td>
<td>&gt;39°C (&gt;102.1°F)</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>Tachycardia</td>
<td>&gt;100</td>
<td>91-100</td>
<td>85-90</td>
<td>≤84</td>
</tr>
<tr>
<td>Respiratory Rate (breaths/min)</td>
<td>Tachypnea</td>
<td>26-30</td>
<td>21-24</td>
<td>18-20</td>
<td>&gt;25</td>
</tr>
<tr>
<td>Blood Pressure (mm Hg)</td>
<td>Hypertension (systolic)</td>
<td>120-180</td>
<td>121-140</td>
<td>141-160</td>
<td>&gt;160</td>
</tr>
<tr>
<td>Hypotension (systolic)</td>
<td>Not applicable, unless symptomatic, or part of a clinical syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Toxicity tables for Safety Laboratory Tests

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Normal range for non-pregnant healthy adults</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal range per trimester</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>First trimester</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Second trimester</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Third trimester</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Sheffield et al., Vaccine, 2013
Laboratory values during first trimester of pregnancy

<table>
<thead>
<tr>
<th>Serum chemistries</th>
<th>Normal range for 1st trimester of uncomplicated pregnancy</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (135-143 mEq/L)</td>
<td>Hyponatremia</td>
<td>130-132</td>
<td>128-130</td>
<td>127-125</td>
<td>&lt; 125 or abnormal sodium with mental status changes, seizure</td>
</tr>
<tr>
<td></td>
<td>Hypernatremia</td>
<td>133-135</td>
<td>131-132</td>
<td>128-130</td>
<td>&gt; 132 or abnormal sodium with mental status changes, seizure</td>
</tr>
<tr>
<td>Potassium (3.7-5.0 mEq/L)</td>
<td>Hypokalemia</td>
<td>3.4-3.6</td>
<td>3.1-3.3</td>
<td>2.9-3.1</td>
<td>&lt; 2.9 or low K with paresis, ileus, life threatening arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
<td>5.1-5.2</td>
<td>5.1-5.2</td>
<td>5.1-5.2</td>
<td>&gt; 5.6 or abnormal K with life threatening arrhythmia</td>
</tr>
</tbody>
</table>

1. Sheffield et al., Vaccine, 2013
2. Abbassi-Ghanavati et al., Obstet Gynecol, 2009

Definitions and evaluations of selected adverse events in pregnant women participating in clinical trials

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Definition</th>
<th>Rates in the US; Risk Factors</th>
<th>Evaluation</th>
<th>AE category</th>
<th>SUSAR</th>
<th>Halting Rules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy loss</td>
<td>Spontaneous miscarriage or abortion in the first or second trimester of gestation, defined as early miscarriage if it occurs within 0 to 14 weeks of gestation, and late miscarriage when it occurs at 14 to less than 20 weeks of gestation.</td>
<td>Overall rates: 10-15% of all pregnancies in first or second trimester. Early fetal death: Up to 20% of pregnancies in first trimester. Late fetal death: Up to 2% of pregnancies in second trimester [29,30].</td>
<td></td>
<td></td>
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| Bleeding | First trimester | Second trimester | Postpartum |

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</table>

| Bleeding | First trimester | Second trimester | Postpartum |

Definitions and evaluations of selected adverse events in pregnant women participating in clinical trials

Munoz et al, Vaccine, 2013
Grading of adverse events in pregnant women participating in clinical trials and their children

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy loss during pregnancy</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>Early: &lt;14 weeks of gestation</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Late: 14 to &lt; 20 weeks of gestation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal death at or after 20 weeks of gestation</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Laboratory tests</td>
<td></td>
<td></td>
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<tr>
<td>Physical exam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic conditions</td>
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<tr>
<td>Laboratory tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Core dataset and AEs (definitions and grading) to be collected for safety monitoring of infants whose mothers received study agent during pregnancy

<table>
<thead>
<tr>
<th>Event definition</th>
<th>Normal range</th>
<th>Assessments of severity or toxicity</th>
<th>Life threatening (graded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
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</tr>
</tbody>
</table>

Munoz et al, CID, 2014

Munoz et al, Vaccine, 2013
Variants of normal and minor anomalies are NOT reported, graded or followed as AE, or SAEs. They are collected in the database as part of the medical examination and reported in the Final Study Report.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
</table>

From Munoz et al., Vaccine 2013 and Assessment of Congenital Anomalies in Infants born to Pregnant Women Enrolled in Clinical Trials, Rasmussen et al., CID, 2014

Safety oversight

• Stopping rules:
  • biological plausibility adverse events
  • time to event

• Safety oversight committees:
  • SMC, DSMB and ISM
  • Organizational Meeting
  • Data review meetings
  • Ad hoc meetings:
    • patient profile
    • additional information

Examples of study stopping rules:

• SUSAR:
  • SAE that occurs within 7 days of administration of vaccine

• Increased incidence/severity of an AE in the trial above reported background rate or above the rate in the control group.

• Stillbirth
• Pregnancy loss within 7 days of intervention
• Grade 3 hyperpyrexia within 7 days of intervention
• Premature labor and/or delivery within 7 days of intervention
• PROM within 7 days of intervention
• Severe, or life threatening vaginal bleeding within 7 days of intervention
• Grade 3 or 4 preeclampsia/hypertension within 7 days of intervention
Safety follow up

Type of vaccine (adjuvants)
- Mothers
  - AESI: autoimmune and neurologic
Duration of follow up
- Infants
  - Type of developmental outcome tests and duration of follow up

The End Game: Pregnancy Labeling!

Package Insert/Pregnancy Section

- Out with the “old” 1979 pregnancy and lactation labeling.
  - No more A, B, C, D, X labeling. Or rather it is being converted.

- The PLLR: Pregnancy and Lactation Labeling Rules went into effect on June 30, 2015
  - A major improvement of labeling.

The End Game: Pregnancy Labeling!

Package Insert/Pregnancy Section

- The PLLR has three sections:
  - Pregnancy
  - Lactation
  - Females and Males of Reproductive Potential
The End Game: Pregnancy Labeling!

Package Insert/Pregnancy Section

• The PLLR has three sections:
  • Pregnancy
    • Registry if available
    • Risk Summary, Clinical Considerations
    • Data.
  • Lactation
    • Females and Males of Reproductive Potential

• Lactation
  • Use of the drug during breast feeding
  • Amount of drug in breast milk
  • Potential effects on the baby.
  • Females and Males of Reproductive Potential

• Females and Males of Reproductive Potential
  • Need for pregnancy testing
  • Contraception
  • Concerns about subsequent infertility
The End Game: Pregnancy Labeling!

- To protect the pregnant women we care for and care about there is the need to know how to effectively and safely use vaccines and therapeutic agents during pregnancy.

- There is a need to protect pregnant women through research, not from research.

Thank you for your attention: Any Questions?