Opportunities in Clinical Research to Reduce Maternal Morbidity and Mortality

Cynthia Gyamfi-Bannerman, MD, MS
Samuel SC Yen Endowed Chair Professor and Chair, Dept of Obstetrics, Gynecology, and Reproductive Sciences
UC San Diego School of Medicine
Maternal Morbidity and Disparities

Rate of severe maternal morbidity per 10,000 delivery hospitalizations:
- Overall rate of severe maternal morbidity with blood transfusions
- Blood transfusions
- Severe maternal morbidity without blood transfusions

Percentage of Deliveries:
- 5.3% among deliveries with any morbidity
- 4.6% among deliveries without severe morbidity

CDC.gov

Department of Obstetrics, Gynecology, and Reproductive Sciences
US Maternal Mortality and Disparities

Kassebaum, Lancet, 2016
What do we do about it?
Randomized Clinical Trials

Pros

• The “gold standard”
• Limits bias in selection, direct comparison between 2 groups
• Can establish causation

Cons

• Strict inclusion criteria limits generalizability
Clinical Trials and Pregnant People

• 2 broad categories
  • Interventions to improve pregnancy outcomes
    • Preterm birth
    • Preeclampsia
    • Intrahepatic cholestasis of pregnancy
  • Interventions for common medical conditions that co-exist with pregnancy
    • Hypertension
    • Diabetes
    • COVID-19

Source: cbinsights.com
How do we perform clinical trials in obstetrics?

• Investigator initiated studies
  • NIH or other government funding
  • Industry

• NICHD MFMU
  • Only obstetric clinical trials research network
NICHD MFMU Origins

• Obstetrical management, especially for high-risk patient, had often adopted practices without objective evaluation

• To address the need for well-designed clinical trials in maternal fetal medicine, the NICHD established the MFMU Network in 1986
MFMU Network

• 12 University based academic medical centers
• **ONLY** federally funded obstetric clinical trials research network
• The MFMU Network conducts clinical studies to improve maternal, fetal and neonatal health with greatest priority given to randomized trials
• The aim is to:
  • **Reduce morbidity** to mom and baby, related to preterm birth, fetal growth abnormalities & maternal complications
  • **Address maternal mortality**
  • Provide rationale for evidence-based, cost-effective, obstetric practice
Pravastatin for the Prevention of Preeclampsia in High-Risk Women: A Pilot Study

Obstetric-Fetal Pharmacology Research Units (OPRU) Network
The National Institute of Child Health and Human Development
Primary Research Question

• What are the **Pharmacokinetic** properties and maternal and fetal **safety** profiles of **pravastatin** when used as a prophylactic daily treatment in pregnant women at high risk of preeclampsia?

ClinicalTrials.gov

NCT01717586
## Results – Maternal Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=10)</th>
<th>Pravastatin (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preeclampsia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Severe features</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>GHTN</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Highest BP mm Hg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>152.4 ± 23.1</td>
<td>144.2 ± 18.4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>96.8 ± 17.1</td>
<td>91.8 ± 16.1</td>
</tr>
<tr>
<td><strong>GA at delivery, weeks</strong></td>
<td>36.7 ± 2.1</td>
<td>37.7 ± 0.9</td>
</tr>
<tr>
<td><strong>Indicated PTD &lt; 37 wks</strong></td>
<td>5 (50)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>RR 0.17, 95% CI (0.02-1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Length of hospital stay</strong></td>
<td>4 [3 - 7]</td>
<td>3 [3 - 4]</td>
</tr>
</tbody>
</table>
A Randomized Controlled Trial of Pravastatin for the Prevention of Preeclampsia in High Risk Women
How the MFMU has changed lives

• The *Eunice Kennedy Shriver* NICHD is named after JFK’s sister

• His first son, Patrick Bouvier, died of respiratory distress in 1963
  • He was 35 weeks
Antenatal Betamethasone for Women at Risk for Late Preterm Delivery


Published April, 2016
Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery

A single course of betamethasone is recommended for pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.
The importance of leveraging different study designs
Top 3 Causes of Maternal Mortality

- Hemorrhage
- Preeclampsia
- Venous thromboembolism

1987
Top 3 Causes of Maternal Mortality

• Cardiovascular conditions
• Preeclampsia
• Venous thromboembolism
Top 3 Causes of Maternal Mortality

- Cardiovascular conditions
- Cardiomyopathy
- Venous thromboembolism
Top 3 Causes of Maternal Mortality

- Cardiovascular conditions
- Cardiomyopathy
- Sepsis
Pregnancy related deaths 2014-2017


- Other cardiovascular conditions: 15.5%
- Infection or sepsis: 12.7%
- Cardiovascular disease: 11.5%
- Maternal hemorrhage: 10.7%
- Thromboembolism or other cerebrovascular accidents: 9.6%
- Pregnancy hypertension: 8.2%
- Disorders of pregnancy: 6.6%
- Anemia: 5.5%
- Other complications: 0.4%
- Other noncardiovascular medical conditions: 12.5%
# Pregnancy Complications in Nulliparous Women

## Table 2: Frequency of perinatal outcomes according to maternal age group

<table>
<thead>
<tr>
<th>Perinatal Outcomes</th>
<th>Total</th>
<th>&lt;35 years (a)</th>
<th>35–39 years (b)</th>
<th>≥40 years (c)</th>
<th>p</th>
<th>a vs.b</th>
<th>a vs.c</th>
<th>b vs. c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational diabetes mellitus</td>
<td>101</td>
<td>27 (5.7)</td>
<td>57 (14.3)</td>
<td>15 (17.2)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>58</td>
<td>20 (4.2)</td>
<td>29 (7.2)</td>
<td>8 (9.2)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>62</td>
<td>22 (4.6)</td>
<td>31 (7.7)</td>
<td>8 (9.2)</td>
<td>0.033</td>
<td>&lt; 0.001</td>
<td>0.457</td>
<td></td>
</tr>
<tr>
<td>Ablation placenta</td>
<td>7</td>
<td>2 (0.4)</td>
<td>4 (1.0)</td>
<td>1 (1.1)</td>
<td>0.073</td>
<td>0.051</td>
<td>0.865</td>
<td></td>
</tr>
<tr>
<td>Spontaneous preterm delivery before 34 weeks</td>
<td>83</td>
<td>39 (8.2)</td>
<td>36 (9.0)</td>
<td>7 (8.0)</td>
<td>0.469</td>
<td>0.754</td>
<td>0.601</td>
<td></td>
</tr>
<tr>
<td>Spontaneous late preterm delivery between 34 and 37 weeks of gestation</td>
<td>71</td>
<td>34 (7.2)</td>
<td>28 (7.0)</td>
<td>9 (10.3)</td>
<td>0.342</td>
<td>0.044</td>
<td>0.038</td>
<td></td>
</tr>
<tr>
<td>Prolonged rupture of membranes</td>
<td>41</td>
<td>21 (4.5)</td>
<td>16 (4.0)</td>
<td>4 (4.6)</td>
<td>0.780</td>
<td>0.913</td>
<td>0.612</td>
<td></td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>80</td>
<td>21 (4.5)</td>
<td>48 (12.0)</td>
<td>11 (11.5)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.560</td>
<td></td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>21</td>
<td>7 (1.5)</td>
<td>12 (3.0)</td>
<td>2 (2.3)</td>
<td>0.072</td>
<td>0.134</td>
<td>0.411</td>
<td></td>
</tr>
<tr>
<td>Placenta previa</td>
<td>24</td>
<td>13 (2.8)</td>
<td>9 (2.2)</td>
<td>2 (2.3)</td>
<td>0.613</td>
<td>0.218</td>
<td>0.891</td>
<td></td>
</tr>
<tr>
<td>Post-term pregnancy</td>
<td>66</td>
<td>41 (8.7)</td>
<td>21 (5.3)</td>
<td>4 (4.6)</td>
<td>0.021</td>
<td>&lt; 0.001</td>
<td>0.139</td>
<td></td>
</tr>
<tr>
<td>Operative vaginal delivery</td>
<td>16</td>
<td>9 (1.9)</td>
<td>6 (1.5)</td>
<td>1 (1.1)</td>
<td>0.451</td>
<td>0.112</td>
<td>0.207</td>
<td></td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>396</td>
<td>175 (37.1)</td>
<td>167 (41.8)</td>
<td>44 (50.5)</td>
<td>0.029</td>
<td>&lt; 0.001</td>
<td>0.040</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%)
Gaps in current approach

• Developing centers with infrastructure to enroll pregnant women (of all risk levels) to answer pertinent research questions
• Levering EHRs to gather and analyze data on a general, large-scale population of pregnant individuals
• Identifying and addressing barriers to research in under-represented groups
• Leveraging implementation science to study proven interventions in groups where the outcomes can be improved
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Need Alternatives to Diversify Research Opportunities
Opportunities: Maternal Morbidity and Mortality

• Continues to increase
• Single OB research network with limited funding
• Need more research networks focusing on pregnancy complications
  • MFMU: investigator initiated
  • Additional future research networks: RFA rapid response and study implementation
• Need infrastructure for nimble response to priority research areas
Opportunities: Clinical Research in Community Settings

Integrating Research into Community Practice
— Toward Increased Diversity in Clinical Trials

Janet Woodcock, M.D., Richardae Araojo, Pharm.D., Twyla Thompson, Pharm.D., and Gary A. Puckrein, Ph.D.

Woodcock et al, NEJM, 10.2.2021

• Engaging community clinicians in research
  • Offering training, mentorship and access

• Levering these relationships to enroll a more diverse population in clinical trials

• “Lack of trial access is a particularly problematic barrier for both clinicians and patients.”
Opportunities: Expanding traditional mechanisms to allow for follow-up

• Traditional R01 funding for clinical trials provides 5 years to study a pregnancy intervention and outcomes related to that intervention
  • Does not allow for long-term infant follow-up
  • Does not allow for maternal follow-up, particularly beyond 6-weeks postpartum

• Need to study the life-course that is the continuum of pregnancy, postpartum, fetal programming, infant and childhood outcomes, subsequent pregnancy
  • Maintaining prospective cohorts
  • Incorporating detailed pregnancy questions into ongoing pediatric cohorts
Opportunities: Moving beyond the RCT

• Considering multilevel clinical trials
• Affect at least two levels of influence—for example, the patient and the health care provider
• Usually includes community input
• Economies of scale to study interventions on target population
• Cons: allow for interactions, makes interpretation of which intervention is leading to the effect more challenging
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Opportunities: Including Pregnant People in non-Obstetric Clinical Trials

• Prototype: Exclusion of pregnant individual in the COVID trials

• September 29, 2021—CDC Urgent Health Advisory: recommending vaccination of pregnant people
  • 22 of 161 deaths from COVID in pregnancy occurred in August (13.7%)

• Chronic medical conditions and pre-existing conditions are related to maternal morbidity

• Interventions to mitigate chronic medical conditions are not studied in pregnant people
Opportunities: Inclusion in Clinical Trials

• NIH requires that women and underrepresented groups are included in clinical trials

• “women and members of minority groups and their subpopulations must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research”

• Exclusion of women, children, gender, race must be justified

• Exclusion of pregnancy needs no justification
Opportunities: Studying non-obstetric interventions in pregnancy

- Once inclusion of pregnant people should be considered, non-pregnancy interventions would be studied in pregnancy
  - Behavioral interventions
  - Mental health
  - Technology
- Reduces the need to replicate findings in pregnant populations
- Is the ethically correct solution
Opportunities: Leveraging EHR data

• Pregnancy data generated copiously in the EHR
• Coordination of this effort at the national level
• Common variables; variable dictionary
• Epidemiologic data to identify morbidities, outcomes of newly introduced interventions, and implementation barriers
• Collect data on underrepresented groups and those less likely to be involved in clinical trials
  • Access and/or desire
Conclusions

• Numerous opportunities to study maternal morbidity and mortality
• Need to move beyond single clinical research network in obstetrics
• Need to allow for follow-up and life course evaluations in current time-limited mechanisms
• Need to leverage EHR data
• NEED to justify exclusion of pregnant people in ALL clinical trials
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Professor and Chair, Dept of Obstetrics, Gynecology, and Reproductive Sciences
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