Reluctance to include pregnant women in clinical research: Physiological changes and complexity

Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)
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David M. Haas, MD, MS
Munsick Professor of OB/GYN
Vice-Chair for Research
Indiana University School of Medicine
DISCLOSURE

• No direct financial conflicts of interest
• Research funding related to medication studies in pregnancy from NIH, industry, university, foundation sources
Reluctance- why?

- History of missteps (next talk)
- Pregnancy-induced differences
- Complexity
  - Regulations and laws
  - Lactation
  - Participant reluctance
Women are different when they are pregnant

Cardiovascular system and blood
- Increases in plasma volume, cardiac output, stroke volume, and heart rate
- Decreases in serum albumin concentration and serum colloid osmotic pressure
- Increases in coagulation factors and fibrinogen
- Compression of the inferior vena cava by the uterus

Liver
- Changes in oxidative liver enzymes, such as cytochrome P450

Lungs
- Increase in tidal volume and minute ventilation

Stomach and intestines
- Nausea and vomiting
- Delayed gastric emptying
- Prolonged small bowel transit time
- Gastrointestinal reflux

Nature Reviews | Cardiology
Changes throughout pregnancy

**Mean (±SD) Dose-Normalized Glyburide Concentration-Time Curves in GDM (n = 40) and Non-Pregnant T2DM (n = 25) Subjects**

- **GDM** - Solid line
- **T2DM** - Dotted line

**Glyburide Plasma Concentration (Dose-Normalized, ng/ml/mg Dose)**

- **Time (hours):** 0, 2, 4, 6, 8, 10, 12

**Box plots showing CI-D ratio (umol/L/mg/day) at different time points:**
- **Prior to pregnancy (n=12)**
- **First trimester (n=10)**
- **Second trimester (n=10)**
- **Third trimester (n=11)**
- **3.5 days after birth (n=9)**
- **2 weeks after birth (n=9)**
- **4 weeks after birth (n=9)**

**B**

- **% Increase in CYP2C9 Activity Within Subjects Compared to Postpartum:**
  - 14-16 Wks
  - 24-28 Wks
  - 36-40 Wks
  - **p<0.001**

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For detailed analysis and interpretation, please refer to the original research paper.
Changes throughout pregnancy

- Labs change
- Physiologic outcomes can be difficult to distinguish from side effects
Same patient?

- Start with differences and differences can develop as it goes
- Can present analytical challenges
Complexity

• Regulations
  – 2 participants, increased regulatory requirements
  – Different laws in different states about pregnant minors
  – Protection as vulnerable population
  – INDs needed for medication studies
  – Tight protocols that aren’t generalizable
Lactation

- Attempts to protect babies from any risks
- Women have conditions that need treating
- Navigating balance of need for data and breastfeeding encouragement
- Little data
  - Sampling issues
  - Modeling of effect
  - Short/long-term outcomes
Participants themselves are complex

- Protective feelings, fear of “research”
- Anxiety with adverse conditions
- Health literacy
- Participant-centered study design

- Protection through research, not from research