Research with pregnant women

Maggie Little, BPhil, PhD
Director, Kennedy Institute of Ethics
PHASES
PREGNANCY + HIV/AIDS
SEEKING EQUITABLE STUDY

NIH
Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies
PREVENT

Wellcome Trust
Disease burden in pregnancy

Nearly 4 million women give birth in the US each year

Many face medical conditions:
- Hypertension (approximately 5%; ~200,000)
- Diabetes (approximately 4%; ~160,000)
- Psychiatric illness (approximately 15%; ~600,000)
- Lupus, cancer, et cetera

Globally, pregnant women face HIV, malaria, TB, and more
“Pregnant women as drug orphans”
- Scaffidi, Mol, Keelan (2017)

1. 98% of drug treatments approved by the U.S. FDA since 2000 have insufficient data to determine teratogenic risk
2. 75% of drugs approved since 2000 do not have human pregnancy data
3. <98% of pharmacokinetic studies done provide any pregnancy-specific data

- McCormick, Best (2014)

Research “strategy” is to rely on data obtained in the clinical setting post-licensure
Post-licensure research “strategy”

1. Poor quality data
2. Long delays in safety determination
   • Mean time to assign risk level to drugs for pregnancy is 27 years

- Adam, Polifka, Friedman (2011)
Causes of reticence

1. Historical categorization of pregnant women as “vulnerable”
2. Misunderstandings about the regulations
3. Concerns about how to conduct research with pregnant women in an ethical way
4. Liability (duh)
5. Risk distortions
Four moral reasons for pursuing research with pregnant women

1. Achieving effective dosing
2. Reducing fetal risk
3. Combating reticence
4. Ensuring just access to trials involving prospect of benefit
Endorsement for responsible research with pregnant women

- WHO
- ACOG
- CIOMS
- 21st Century Cures Act
“...The Secretary of Health and Human Services shall establish a task force to be known as the “Task Force on Research Specific to Pregnant Women and Lactating Women.”

– 21st Century Cures Act, Section 2041, 2016
Framework for regulatory ethics of research with pregnant women

• Code of Federal Regulations of the U.S. Department of Health and Human Services ("Subpart B")
Pregnant women: no longer vulnerable

• Common rule update, effective January 2018
Regulatory disjunct: Subpart B

- No prospect of direct benefit
  - No more than minimal risk to the fetus

- Prospect of direct benefit
  - Reasonable ratio of risk to benefit
No prospect of direct benefit

No more than minimal risk to the fetus

“The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests”

- Subpart B
Prospect of direct benefit

- More complicated
- Whose risk? Whose benefit?

Reasonable ratio of risk to benefit
Evidence needed for enrollment of pregnant women

• Must have data on risks

• Types include:
  • Preclinical, including reprotoxicity in relevant animal models (determined by the specific theoretical or biologically plausible risks), and studies with human placental tissue or organoid models
  • Observational or opportunistic clinical experience of the study intervention in pregnant women
Preliminary evidence

• Hypothesis generating, not conclusion generating
• If it’s suggestive of something catastrophic, go precautionary principle
• If it’s suggestive of something minor but the potential benefit is good, investigate