Ethical Considerations for Enrolling Pregnant Individuals in Clinical Studies

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Toward the Responsible Inclusion of Pregnant Women in Medical Research

THE SECOND WAVE INITIATIVE

PHASES
PREGNANCY + HIV/AIDS
SEEKING EQUITABLE STUDY

PREGNANCY RESEARCH ETHICS FOR VACCINES, EPIDEMICS, AND NEW TECHNOLOGIES
PREVENT

NIH

Wellcome
History of exclusion

• **First wave:**
  • Early 1990s, women and their health interests under-represented in research
  • 1993 NIH Revitalization Act
  • Women now a majority of research participants; gaps remain

• **Second wave:**
  • Pregnant people and their health interests still under-represented in research
  • Result is a dearth of information to guide care
  • Second Wave Initiative: ethics requires inclusion
Critical evidence gaps and their costs

- may be given drugs at the wrong dose.
- may be given drugs that carry unacceptable risk.
- may be denied access to critically needed drugs.
Barriers

- Drug development and approval pathway
- Risk reasoning
- Protectionism
- Lack of training and experience
- Legal and logistical challenges
- Justificatory asymmetry
- Myths and misconceptions

“quixotic quest” to eliminate fetal risk
Risk shifting

Research

Clinical
Three Conceptual Shifts

- *Vulnerable population* → *Complex population*
- *Protection from research* → *Protection through research*
- *Presumptive exclusion* → *Fair inclusion*
Ethical Foundations

Reproductive Justice

The right to have children
The right not to have children
The right to nurture children in a safe and healthy environment

https://www.sistersong.net/reproductive-justice
Pregnancy and HIV/AIDS: Seeking Equitable Study

26-member international, interdisciplinary Working Group
Qualitative research, workshops, consultations

Ending the evidence gap for pregnant women around HIV & co-infections:
A CALL TO ACTION

Pregnancy and HIV/AIDS:
Seeking Equitable Study

The PHASES Working Group
Pregnancy and HIV/AIDS: Seeking Equitable Study
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The PHASES Working Group
Pregnancy and HIV/AIDS: Seeking Equitable Study

PHASES Guidance (July 2020)

Ending the evidence gap for pregnant women around HIV & co-infections: ethics guidance from the PHASES project

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Abstract

Integrating HIV-affected pregnant people have been an important focal point for HIV research, although evidence gaps remain regarding prevention, co-infections, and safety and efficacy of new antiretroviral therapies in pregnancy. Such gaps can result in harm without safe data, and gaps may harm reproductive rights to the needs of women living with HIV/AIDS (PLWH) and their children. The starting point for addressing these gaps is to ensure that the research is inclusive and equitable, and this requires the development of an interdisciplinary framework to address prevention, care, and treatment in PHASES.

Keywords: Pregnancy, HIV/AIDS, antiretroviral therapy, prevention, research

1 INTRODUCTION

Since the early 1990s, the management of pregnancy has been an important focus for the research community. The objective was to identify and develop effective prevention and treatment interventions for HIV transmission. Although the available evidence has been equivocal, evidence continues to evolve, resulting in improved outcomes for pregnant women and their children.

In developing a framework for the future, PHASES recognizes the need for a comprehensive, multidisciplinary approach to addressing the complex health issues faced by pregnant women, infants, and children living with HIV/AIDS. This approach is designed to promote equitable access to care and treatment, while also addressing the social determinants of health that impact the well-being of these populations.
Recommendations (12)

Building Capacity (3)

1. Affirm the need for research with pregnant people: Organizations with influence over the development, research, regulatory approval, guidance development, and use of HIV/Co-infections drugs should affirm the imperative for responsible research with pregnant people to achieve a timely and equitable evidence base.

2. Formulate a global network for advocacy and resources: The global HIV/Co-infections research and advocacy communities, supported by funders, should formulate a network dedicated to advancing needed research with pregnant people. This network should facilitate research with pregnant people by creating a portfolio of shared resources to empower researchers to pursue, and enable oversight committees to effectively evaluate, studies that meet the needs of people who are pregnant.

3. Enhance training: Those involved in the conduct, monitoring, oversight, and community consultation of research in the HIV/Co-infections space should be provided training in the ethical and legal issues relevant to research with pregnant people.

Supporting Inclusion (3)

4. Design for inclusion: Researchers designing trials in HIV/Co-infections should commit to a goal of integrating pregnant people whenever possible and optimizing opportunities to gather pregnancy-specific data.

5. Review for and facilitate inclusion: Review pregnancy-related studies, research ethics committees, and funders of HIV/Co-infections research should require proposed clinical trials protocols to provide justification wherever pregnancy is indicated as a criterion for exclusion or removal from a trial, and should proactively support and incentivize inclusive designs.

6. Ensure equitable research on pregnant persons’ own health: Advocates in HIV/Co-infections research should commit to equitable promoting the study of pregnant persons’ own health needs as a key pillar of effort and funding. Research into total health outcomes should be matched by relevant maternal outcomes assessments to ensure that decisions about whether and which options to pursue during pregnancy are made with equitable consideration of the pregnant person’s health.

Achieving Priority Research (3)

7. Integrate pharmacokinetic (PK) studies: Plans for pregnancy-specific PK pharmacokinetic studies should be integrated into new drug development plans and performed as early as possible, ideally before licensure, for all new preventives and therapies anticipated to be used during pregnancy.

8. Enhance post-approval safety evaluations: The HIV/Co-infections research community should commit to a more robust and regularized structure of post-approval safety evaluations to ensure both adequate pharmacovigilance and pregnant people’s timely access to important drugs. This includes expanding prospective registries, conducting timely prospective observational studies for drugs in widespread use during pregnancy, and conducting prospective cohort studies of unintended exposures to probe safety signals that shed light on the way of pregnant people accessing important drugs.

9. Address legacy evidence gaps: Currently approved HIV/Co-infections preventives and treatments should be reviewed for critical pregnancy-related evidence gaps that interfere with safe, evidence-based use in pregnancy, and research should be conducted to address those gaps.

Ensuring Respect (3)

10. Ensure access to life-saving experimental drugs: Pregnant people should be guaranteed fair access to participate in trials and special access programs for experimental interventions that offer potential life-saving benefit in contexts where no or poor alternatives exist.

11. Respect and support decisional authority: When a pregnant person of legal standing is capable to participate in research, their voluntary and informed consent should be sufficient to authorize participation. Accommodations should be made to facilitate a pregnant person’s ability to engage the father, family, or other personal supports, and to promote understanding of the benefits and risks of research participation.

12. Contextualize risk findings: Those conducting HIV/Co-infections research with pregnant people should anticipate possible adverse events and proactively develop communication strategies for adequately contextualizing them against baseline rates of such events. Communication of overall findings should take care to contextualize potential risks of an intervention against its potential benefits and the risk/benefit profiles of alternatives, and should include benefits to the pregnant person and those that would accrue secondarily to the child should the pregnant person’s health be benefited.

*Updated toward gender-inclusive language.*
7. Integrate pharmacokinetic (PK) studies

Plans for pregnancy-specific pharmacokinetic (PK) studies should be integrated into new drug development plans and performed as early as possible, ideally before licensure, for all new preventives and treatments anticipated to be used during pregnancy.

- Drug industry – commit to pursuing PK studies
- Regulators – encourage and require up to authority
- Funders – support post-approval when not achieved by industry
Ethical complexities

consent  risk  timing
Consent

HHS requirements – paternal consent

Consent of pregnant woman [Subpart A]

Consent of pregnant woman and father [Subpart B]

PDB mother?

PDB fetus?

PK

(if minimal risk to fetus and information cannot be obtained by other means)
Risk (and benefit)

Either
woman or fetus (or both)

Reasonable ratio of risk to benefit
e.g. Phase III

Neither
woman nor fetus

Fetal RRR capped at minimal risk
e.g. Phase I/II, PK

PDB?
(Prospect of Direct Benefit)

- Contrasts pediatrics, which allows “minor increase over minimal risk”
- Opportunistic studies offer a potential workaround, but at a cost...

Little, PRGLAC 2017
Timing

• Human pregnancy data usually gathered post-approval, if at all
  • Avoids risk conundrum (e.g., PK studies)
  • Avoids exposure to investigational drug or vaccine
  • Addresses (some) liability concerns
  • Financially advantageous

• Delays are extensive, and consequential
  • Average delay for PK data for ARTs (HIV) = 6 years
  • In the meantime, pregnant persons may receive ineffective treatment
    • Risks to woman and fetus (Cobicistat)
    • Compromise trial results (Glyburide)

• Earlier, clinically actionable PK data are an ethical priority
Conclusions

• Broad recognition that research in pregnancy is an *ethical imperative and a matter of reproductive justice*
  • Pregnant people deserve protection, access, and respect

• PK studies are a crucial element of this imperative

• Immediate opportunities for progress, though complexities remain
  • Consent in accordance with Subpart A
  • Many studies can be conducted without RRR (“low hanging fruit”)
  • Minimal risk standard is limiting, more stringent than pediatrics
  • Timing and incentives require attention
Thank you!

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