Performing Drug Safety Research During Pregnancy and Lactation: Biomedical HIV Prevention Research as a Template

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Abstract

Evidence-based guidance regarding use of nearly all pharmaceuticals by pregnant and lactating women is limited. Models for performing research may assist in filling these knowledge gaps. Internationally, reproductive age women are at high risk of human immunodeficiency virus (HIV) acquisition. Susceptibility to HIV infection may be increased during pregnancy, and risk of maternal-child transmission is increased with incident HIV infection during pregnancy and lactation. A multidisciplinary meeting of experts was convened at the United States National Institutes of Health to consider paradigms for drug research in pregnancy and lactation applicable to HIV prevention. This report summarizes the meeting proceedings and describes a framework for research on candidate HIV prevention agent use during pregnancy and lactation that may also have broader applications to other pharmaceutical products.

Introduction

DRUG SAFETY DURING PREGNANCY AND LACTATION is a largely neglected area of research.¹ This knowledge gap has been facilitated by valid concerns regarding potential risks of fetal and infant exposure, leading to systematic exclusion of pregnant/lactating women from research on pharmaceuticals.² However, this approach has contributed greatly to limited safety and pharmacokinetic data for these populations.³ This dearth of data is especially important given the normal physiologic adaptations to pregnancy, which may produce profound alterations in drug metabolism, with important safety and efficacy implications. Recognition of the need for drug safety research in pregnancy and lactation is gaining momentum as a public health priority.^{4,5} Recent draft guidance published by the U.S. Food and Drug Administration (FDA) has highlighted the advantages of including pregnant women in safety research during drug development, particularly in the case of anti-human immunodeficiency virus (HIV) vaginal microbicides.⁶

The limitations of excluding pregnant women from early stage drug trials were especially apparent during the 2009

H1N1 influenza pandemic,⁷ given the well-documented history of increased susceptibility of pregnant women to complications and death from influenza.⁸ Subsequent research has begun to inform optimal therapy with oseltamivir for pregnant women.⁹ Nevertheless, inclusive and comprehensive study of safety and pharmacokinetics could have improved maternal and fetal outcomes. Here, a separate example of the need for drug research in pregnancy and lactation and a template for that research are provided.

Drug Research During Pregnancy and Lactation: HIV Chemoprevention

Heterosexual transmission now accounts for the majority of new human HIV infections worldwide, with women of reproductive age comprising a large proportion of these new cases.¹⁰ Women-controlled approaches for prevention of HIV infection are recognized as a critical component in combating the pandemic.¹⁰ Two such approaches under investigation are topical microbicides and oral preexposure prophylaxis (PrEP). Biomedical HIV prevention is an important

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area for research during pregnancy and lactation that may inform investigations in other disciplines.

Many advances in HIV prevention have occurred recently. Earlier identification and treatment of HIV-infected persons has been demonstrated to reduce the risk of sexual transmission.¹¹ Several tenofovir-based regimens (coitally dependent tenofovir vaginal gel, oral tenofovir disoproxil fumarate (TDF), and oral TDF/emtricitabine) have demonstrated efficacy in the prevention of transmission in some studies but not in others.^{12–16} While such disparate results are challenging for researchers, regulators, and policy makers, research continues and topical antiretroviral drugs may be available to women in the near future. Although some oral formulations of these products have been studied in the context of HIV treatment in pregnant women, their risk-benefit ratio is not yet established for HIV-uninfected pregnant and lactating women.

There are many compelling reasons to investigate candidate HIV prevention agents during pregnancy and lactation.^{7,17} Pregnant women remain sexually active and may increase the frequency of intercourse near term to initiate labor.^{18–20} Pregnancy increases susceptibility to HIV acquisition as well as potentially increasing infectivity to male partners.^{21–23} Two recent studies emphasize the critical importance of preventing incident HIV during pregnancy to decrease risk of vertical transmission.^{24,25} Additionally, unintended pregnancies among clinical trial participants present significant challenges to the conduct and interpretation of HIV prevention trials, an issue highlighted by the Institute of Medicine.²⁶

Similar data support the need for proactive investigation of candidate HIV prevention agents during lactation. Many countries with high HIV prevalence also have high rates of extended duration of breastfeeding (30%–80% at 2 years of age).^{27–29} In some cultures, rates of sexual concurrency for men may increase during the postpartum period, increasing lactating women's risk of HIV exposure and acquisition.^{30,31} Acute maternal infection during lactation also increases risk for transmission to the infant.^{32–34}

The increased risk of HIV acquisition during pregnancy and the increased transmission risk to the infant with new infection during pregnancy and lactation compel the identification of safe and effective HIV prevention strategies for these populations. Given the unique nature of this research, an expert meeting, "Next Steps for Testing Microbicides and PrEP in Pregnancy," was convened in November 2010 at the National Institutes of Health (NIH) in Bethesda, Maryland. Many of the challenges discussed are also applicable to research in pregnancy and lactation in general and can inform this critical area. The goals of the meeting are shown in Table 1. In light of the recent draft guidance published by FDA,⁶ it is useful to review potential strategies to address these unique challenges.

Meeting Proceedings

A panel of 52 investigators and government representatives from the United States and Africa with expertise in international HIV prevention research, infectious diseases research in pregnancy, lactation, maternal-fetal pharmacology, and neonatology attended. State-of-the-science updates were given in the field of HIV prevention and topics relevant for any investigations undertaken during pregnancy:

TABLE 1. OBJECTIVES OF "NEXT STEPS FOR TESTING MICROBICIDES AND PREP IN PREGNANCY," BETHESDA, MARYLAND, NOVEMBER 29–30, 2010

1. Review current knowledge on HIV prevention agents in pregnancy and lactation.
2. Frame the domestic and international perspectives on feasibility and priorities of research during pregnancy and lactation.
3. Delineate a paradigm for the study of drugs in pregnancy and lactation applicable to nearly all current and future pharmaceutical products, with a focus on HIV prevention agents.

trimester-specific drug safety concerns, current U.S. regulations, domestic and international perspectives on research in pregnancy and lactation, and ethical considerations.

General safety considerations

Drug safety is a paramount consideration for any pharmaceutical research conducted in reproductive age women, given the potential for inadvertent exposure during early pregnancy. Drug safety profiles become especially critical when intentional exposure during pregnancy or lactation is planned. Thus, animal and clinical safety data and U.S. Food and Drug Administration (FDA) guidelines should be carefully reviewed. Reproductive toxicity studies required by the FDA prior to licensure include:

- Segment I: fertility and early embryonic development to implantation,
- Segment II: embryonic-fetal development (teratogenicity), and
- Segment III: perinatal and postnatal development, including maternal function.

Presenters discussed normal fetal development and potential vulnerabilities during different periods. While exposures can have deleterious effects after the first trimester, organ sensitivity to teratogens is generally decreased after that time. In general, drug exposures in the second and third trimester carry little risk of malformations but have rare potential for malfunction (e.g., altered kidney function). Many drugs cross the placenta and can have pharmacologic actions in the fetus that can be beneficial (antimicrobials for in-utero infections) or deleterious (fetal hypothyroidism secondary to maternal hyperthyroid therapies).

Second trimester discussions focused on potential indirect effects caused by intravaginal medications. Alterations in vaginal flora and inflammatory mediators can be associated with preterm labor, preterm birth, preterm premature rupture of membranes, or chorioamnionitis^{35–37} and have a critical role when studying intravaginal products. Ideal topical drugs would be efficacious with no impact on vaginal flora or immunology. Cervicovaginal biomarkers such as H₂O₂-producing lactobacilli, bacterial vaginosis-associated organisms, cervical cytokines interleukin (IL)-6 and IL-8, and matrix metalloproteases should be evaluated during trial participation for their ability to predict adverse effects on the cervicovaginal environment and pregnancy outcome.

During study design, it is important to consider characteristics of the drug and its potential use during pregnancy.

Table 2 outlines a list of questions for consideration before evaluation of new drugs during pregnancy.

Domestic perspectives on research in pregnancy

A recent evaluation of drugs approved from 1980–2000 found that in greater than 90% the potential teratogenic risk is still unknown, and that very few drugs actually have an approved indication in pregnancy, although many are prescribed.³⁸ Despite the lack of pregnancy data, pregnant women frequently use both prescription and over-the-counter medications.^{39–41} Although sizable alterations in physiology during pregnancy and lactation can have substantial impact on drug metabolism and pharmacokinetics, these areas are also understudied.^{9,42,43} It was agreed that most drugs lack adequate data for informed prescribing during pregnancy.^{5,7,38,39}

The U.S. Code of Federal Regulations provides specific requirements regarding the participation of pregnant women in clinical research.⁴⁴ These regulations were enacted to protect the fetus but have the negative effect of discouraging drug research in pregnancy prior to licensure and widespread public use. Paradoxically, this design may actually result in uncontrolled exposures of far more fetuses once the drug is licensed. Furthermore, harm resulting from exposure following licensure may be more difficult to detect without the

data collection power of clinical trials.^{7,40,45} Collection of data on fetal effects as part of well-controlled and carefully monitored clinical trials is an effective way to obtain information addressing safety during pregnancy.

International perspectives on research in pregnancy

Maternal–child health investigators attending from Africa stated that a restrictive regulatory environment for research during pregnancy and lactation currently exists. One approach to the study of drugs during pregnancy that may be more acceptable to local regulatory agencies is the development of pregnancy exposure registries. A combination of pregnancy registry data and controlled, sequentially larger trials during pregnancy may also represent an acceptable approach.

Ethical justifications for ongoing and future research

The ethical imperative to investigate medications during pregnancy is a well-recognized concept with documented justification.^{5,7,46–48} The current regulatory approach limiting research efforts in pregnancy can be considered in conflict with the ethical principle of justice given that medication use (and fetal exposure) during pregnancy is common. Informed use of medical therapies during pregnancy is necessary to optimize care (principal of beneficence) and there is

TABLE 2. RECOMMENDED CONSIDERATIONS PRIOR TO THE EVALUATION OF INVESTIGATIONAL DRUGS IN PREGNANCY

<i>Question</i>	<i>Rationale</i>
1. What is the rationale for evaluating the drug in pregnancy?	The rationale should be clear, scientifically defensible to clinicians/regulators, and take into account the potential scope and risk/benefit ratio of the drug's intended use in pregnancy.
2. Are segments 1, 2, and 3 testing completed?	Results of Segments 1, 2, and 3 testing (animal fertility, reproductive, and developmental toxicity) should be evaluated for evidence of risk in pregnancy.
3. Have signals been identified in <i>in vitro</i> or animal testing?	Any toxicity signal should be evaluated for potential relevance to humans. ⁵⁰
4. Have any drugs of the same class been evaluated in preclinical or clinical testing during pregnancy?	There is increased concern for reproductive or developmental toxicity in humans when the drug is from a class with known adverse effects in humans and animals, and vice-versa. There may also be decreased concern if adverse effects detected in animal studies were not confirmed in humans.
5. Are there known or potential risks to the mother or fetus?	The study protocol and informed consent documents must include a clear description of the drug's potential risk profile articulated appropriately for participants, clinicians, and regulators. Safety monitoring must carefully evaluate participants for adverse events anticipated from the risk profile.
6. Are there known or potential benefits to the mother or fetus?	The study protocol and informed consent documents must include a clear description of the drug's potential benefits articulated appropriately for participants, clinicians, and regulators.
7. Can a case be made for the prospect of direct benefit to the mother or fetus?	The U.S. Code of Federal Regulations outlines conditions for research involving pregnant women or fetuses. Without prospect of benefit, risk to a fetus must not exceed minimal and the purpose of the research must be the development of important biomedical knowledge that cannot be obtained by any other means. ⁵¹
8. Do alternatives exist to use of this drug in pregnancy?	Having few or no known effective alternatives for the indication (whether treatment or prevention of a condition) may support study during pregnancy.
9. Which trimester(s) would be exposed with use?	Trimester of exposure impacts the type of developmental and/or functional risk(s) that may be associated with drug exposure.
10. How is the drug eliminated?	Drug elimination is impacted by physiologic changes of pregnancy, and may be impacted by pathophysiology of condition to be treated.
11. Are clinical data available on pregnancy outcomes following exposure, and what is the quality of this evidence?	These data, if available (such as from pregnancy registries), should inform the study design, safety monitoring and informed consent documents.

large societal cost from the lack of safety data and the resulting reticence to use indicated therapies during pregnancy. Previous tragedies related to detrimental drugs used in pregnancy occurred because research in pregnancy did not occur prior to release into market, not because research had been done.

A strong case for research involving HIV prevention agents during pregnancy can be made, because the science strongly suggests that pregnant and lactating women represent a key target group for HIV prevention efforts and because subsequent drug exposure during unrecognized pregnancy will occur given the target population. Studies of HIV prevention agents in pregnancy and lactation are ethically justifiable based on the concept of “prospect of direct benefit” to the mother, without a requirement for statistical power to detect this benefit.

Candidate HIV Prevention Drug Research as a Template For Research in Pregnancy and Lactation

Meeting deliberations centered on a general conceptual template and featured specific protocol examples for each step of the template. What follows is a step-by-step paradigm, with tenofovir gel being used as the case example, potentially applicable to many current and new pharmaceuticals.

The first step entails a review of reproductive toxicity studies and existing human data for safety in pregnancy. Prior to the development of the first tenofovir-based microbicide study in pregnancy, all available data were reviewed. The preclinical toxicity studies, available data from clinical trials for HIV treatment, and data from the Antiretroviral Pregnancy Registry (APR) failed to identify signals of toxicity, suggesting that controlled investigation for prevention was a reasonable step forward.⁴⁹

Additional information can be obtained by collecting outcomes from inadvertent exposure in early pregnancy during extended safety and efficacy trials. Despite recommendations to use effective contraception, pregnancies are common and drug exposures often occur during organogenesis, before pregnancy detection. Use of a registry-like research protocol can assist with standardized collection of these data.⁶ In the example of tenofovir gel and oral antiretrovirals studied for HIV prophylaxis, these data are being collected from a research pregnancy registry (microbicide trials network [MTN]-016).

After fulfilling the initial step of safety review, a second step is testing a limited exposure at term gestation with collection of safety and pharmacokinetic information. This provides for a term fetus with more mature physiology for drug excretion, should drug cross the placenta. For tenofovir gel, a phase 1 study (MTN-002) enrolled 16 women with uncomplicated term pregnancies planning cesarean delivery. Each participant received a single vaginal dose of tenofovir vaginal gel within 8 hours of delivery, and samples for drug concentrations were collected over 24 hours. Amniotic fluid, cord blood, and placental tissue were collected at delivery. Cesarean delivery offers the advantage of collection of uterine tissue to assess endometrial drug levels. Having intact membranes is also an important consideration for vaginally applied drugs and for potential collection of amniotic fluid. Adverse events were tabulated to identify any safety signals. In this example, the findings were reassuring and supported additional research.¹⁷

The proposed third step is a multiday dosing protocol conducted at term, followed by near-term exposures, enrolling enough participants to have power to detect clinically significant increases in important outcomes. The tenofovir gel example for this step is the study MTN-008, which was designed to enroll women with uncomplicated pregnancies above 36 weeks to receive either tenofovir vaginal or placebo gel daily for 7 consecutive days. After completion of the first cohort of 45 term women, an interim safety evaluation occurred. As no safety signals were identified, a second cohort of 45 women at 34–37 weeks (near-term) gestation will be enrolled. If after thorough review of safety data from both cohorts, no safety signals are identified, further investigations can be undertaken.

Further investigations in pregnancy (fourth step) would plan for a progression to earlier gestational ages with more extended dosing, depending on the drug-specific planned dosing pattern. In the case of tenofovir gel, a phase 2 study (MTN-019) was designed to enroll women with uncomplicated pregnancies at progressively lower gestational ages based on interim safety reviews. Women would be enrolled in three cohorts between 28 and 33 weeks, 20 and 25 weeks, and 12 and 17 weeks' gestation, respectively. Participants would receive 28 consecutive daily doses of either tenofovir or placebo gel and would then be followed off product until delivery with analysis of maternal and fetal adverse events.

The last proposed investigation is evaluation of drug use before conception and continued throughout pregnancy with assessment of maternal and fetal safety. Based on the extent of information collected through inadvertent exposure in early pregnancy (step 1) and the purposeful studies in pregnancy (steps 2–4), additional data on exposure throughout organogenesis and the remainder of pregnancy is often needed. Once all of the steps above have been completed and no safety signals have been identified, consideration should be given to allowing women in whom the drug has been initiated to stay on the drug after becoming pregnant with careful collection of pregnancy outcomes. This surveillance can occur through demonstration projects to expand delivery of the drug after establishment of efficacy for non-pregnant women. Such investigations could also serve to potentially identify uncommon adverse effects that were not previously identified in earlier stage studies (partly due to relatively smaller sample size).

Safety and pharmacokinetics in lactating women and their infants can be assessed in parallel to the steps described in pregnancy. Timing of dosing in lactation studies may be dependent on the timing of infant weaning as well as the route of drug delivery. Pharmacokinetics for both mother and infant will be impacted by exclusive versus nonexclusive breastfeeding. Hence, studies are typically conducted prior to introduction of other foods. For a drug applied intravaginally, consideration must also be given to time required for involution of the uterus/cervix and healing of lacerations or episiotomy. With both considerations in mind, a lactation safety and pharmacokinetic component for tenofovir gel was incorporated into the MTN-008 protocol, enrolling lactating women one to six months postpartum. Women will insert tenofovir vaginal gel daily for 7 consecutive days with pharmacokinetics measured in both blood and breast milk samples. Adverse events in women and their infants will be assessed.

Summary and Conclusions

Drug safety during pregnancy and lactation is understudied and a framework for such research may facilitate filling this knowledge gap. The HIV prevention field presents an opportunity to perform such research and also has provided an ethically and scientifically justified model for future investigations that may be applicable to a broad range of pharmaceutical products.

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