Clinical Infectious Diseases

VIEWPOINTS

A Community Perspective on the Inclusion of Pregnant Women in Tuberculosis Drug Trials

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Affecting both mother and the existing pregnancy, tuberculosis (TB) increases the likelihood of poor birth outcomes. Despite substantial clinical need for TB prevention and treatment, pregnant women remain neglected by research initiatives. As members of 3 community advisory boards that provide input into TB drug trials, we offer a community perspective on the inclusion of pregnant women in TB drug research and discuss (1) our perspective on the risk/benefit tradeoff of including pregnant women in research to address different forms of TB; (2) recent examples of progress in this area; (3) lessons learned from the human immunodeficiency virus research field, where pregnant women have enjoyed better—although imperfect—representation in research; and (4) recommendations for different stakeholders, including researchers, regulatory authorities, ethics committees, and policymakers.

Keywords. tuberculosis; pregnancy; pregnant women; research ethics; drug development.

Pregnancy-associated tuberculosis (TB) has been largely overlooked in past global health and development agendas. Adoption of the 2030 Agenda for Sustainable Development provides a chance to address this longstanding oversight. Reducing the burden of pregnancy-associated TB would drive progress toward achieving sustainable development goal (SDG) 3, which aims to ensure healthy lives and promote well-being for all people. The challenges of addressing TB and pregnancy epitomize the health disparities that SDG 3 seeks to overcome through its targets to reduce maternal mortality, end preventable newborn deaths, end the global TB epidemic, ensure universal access to sexual and reproductive health services, and support the development of new medicines and vaccines. For this reason, pregnancy-associated TB deserves a more explicit focus in global health research, policy, and practice.

TB is one of the leading nonobstetric causes of death in pregnant women, which now account for an estimated 28% of maternal deaths globally [1]. If left untreated, TB in pregnancy can result in mortality rates up to 40% [2]; in human immunodeficiency virus (HIV)–infected pregnant women, TB increases the risk of mortality by nearly 300% [3]. There is limited specific information on the effects of pregnancy on drug metabolism and achieved drug exposures to guide treatment of TB during pregnancy. Pregnant women are systematically excluded from TB research, even when the ratio of potential benefit to harm may favor inclusion. In the absence of research, clinicians must treat TB in pregnant women using regimens of both old and newer TB drugs without adequate guidance on safety, efficacy, or dose adjustments.

In 2015, an expert panel convened by the US National Institutes of Health (NIH) published a consensus statement advocating for the earlier inclusion of pregnant and postpartum women in TB drug trials and outlining priority research needs [4]. Foremost among these priorities are studies that address safety, drug pharmacokinetics by stage of pregnancy, and drug–drug interactions between TB drugs and antiretroviral medications for pregnant and postpartum women.

As members of 3 community advisory boards (CABs) that provide community input into TB drug trials conducted by public and private sponsors, we echo the expert panel's call for earlier inclusion and urge TB investigators to take up these recommendations. We represent the Community Research Advisors Group (CRAG) to the Centers for Disease Control and Prevention's Tuberculosis Trials Consortium (TBTC), Community Partners (the community advisory structure for the NIH Division of AIDS research networks), and the Global TB Community Advisory Board. Our CABs work to facilitate effective communication between TB researchers and TB-affected communities and seek to ensure that individual studies and the overall TB research agenda respond to community needs

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and priorities. Pregnancy-associated TB is an urgent issue for the communities we represent, and our CABs agree that pregnant women are one of the patient groups for which the lack of research to date now constitutes a major barrier to preventing, treating, and curing TB.

Reviewing clinical trials protocols is one of the primary ways our CABs convey community input to researchers. When reviewing protocols, we pay close attention to whether a rationale for excluding pregnant women is presented and, where the benefits to pregnant women might outweigh the risks, advocate for inclusion. In addition, we advocate for women who become pregnant during the course of a trial to be given the option to continue therapy and, when this is not possible, for study teams to follow up exposed mothers and infants for long-term birth outcomes. We often observe nearly identical boilerplate language about the exclusion of pregnant women in the protocols we review. In our view, this demonstrates that the majority of TB researchers are not critically assessing the risk/benefit tradeoff in the context of particular study designs, settling instead for a norm that presumes pregnant women to be ineligible. The commonality of this position across trials and research networks does not make it defensible. To the contrary, in 1994, the Institute of Medicine recommended that pregnant women be "presumed eligible for participation in clinical studies." [5] The TB research community has not embraced this recommendation, despite the development of expert consensus statements, regulatory frameworks, and guidance to facilitate the appropriate and earlier inclusion of pregnant women in research [4, 6, 7].

Below, we offer a community perspective on the inclusion of pregnant women in TB drug research as impetus for implementing the recommendations of the 1994 Institute of Medicine report and 2015 TB expert consensus. We first provide our perspective on the tradeoffs of including pregnant women in research to address different forms of TB before discussing recent examples of progress in this area and reviewing lessons learned from HIV research, where pregnant women have enjoyed better—although imperfect—representation. We close with recommendations for different stakeholders, including researchers, regulatory authorities, ethics committees, and policymakers.

WEIGHING THE RISKS AND BENEFITS OF INCLUSION IN RESEARCH FOR DIFFERENT FORMS OF TUBERCULOSIS

Pregnancy increases the risk of active TB in women, and as such, pregnant women constitute a group with substantial clinical need for TB prevention and treatment [2, 8]. Affecting both mother and the existing pregnancy, active TB increases the likelihood of spontaneous abortion, suboptimal weight gain, preterm labor, transmission of congenital TB, neonatal and perinatal mortality, low birth weight, and postnatal TB [9, 10]. The risk of these poor outcomes must be carefully weighed against the potential risks and benefits of TB treatment in the context of research. The balance may shift depending on the type of TB (TB infection, drug-sensitive TB [DS-TB], or drug-resistant TB [DR-TB]) and existing evidence or lack thereof.

Tuberculosis Infection

Pregnant women with TB infection (sometimes called latent TB) have an increased risk of developing active TB; this risk is further elevated by HIV coinfection [2]. Existing regimens to treat TB infection have undergone evaluation in >40 clinical trials, including 8 phase 3 trials and 13 that focused on HIV-infected adults, all of which excluded pregnant women [11]. Ending this decades-long lag in evidence, the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) network is currently evaluating the safety and efficacy of antepartum vs postpartum isoniazid for HIV-infected pregnant women on antiretroviral therapy and the pharmacokinetics and safety of a shorter rifapentine-based regimen for treating TB infection in pregnant women [12, 13].

Although pregnant women with TB infection are not sick, their increased risk of progression to active disease justifies earlier inclusion in research, especially among pregnant women with HIV infection and/or recent TB exposure or documented infection. This justification is even stronger when the contact is a person confirmed to have DR-TB. In our view, pregnant women with infection likely due to DR-TB should be included in efficacy studies when safety has been demonstrated in nonpregnant populations and there is no evidence of teratogenicity in animals at recommended human drug levels.

The development of the protecting households on exposure to newly diagnosed index MDR-TB patients (PHOENIx) trial, a phase 3 study sponsored by IMPAACT and the AIDS Clinical Trials Group (ACTG), provides an illustrative example. The PHOENIx protocol originally proposed treating household contacts of DR-TB patients with levofloxacin and planned to include pregnant women given that levofloxacin has not shown evidence of teratogenicity in rats or rabbits at the highest recommended human dose [14]. However, PHOENIx was later redesigned to evaluate delamanid, a new drug for which there are limited safety data and observed embryo-fetal toxicities at maternally toxic doses in rabbit reproductive studies [15]. Plans for a future substudy of delamanid for the prevention of DR-TB in pregnant women are under discussion.

Active Tuberculosis Disease

Pregnant women with active TB disease, especially those untreated, are at increased risk of adverse outcomes; maternal, fetal, and infant complications, including transmission of TB to the infant; and maternal and infant mortality [2]. Although the benefits of treatment during pregnancy far outweigh risks, adequate data regarding dosing and toxicity for some first- and most second-line TB drugs in pregnant women, especially those coinfected with HIV and taking antiretroviral medications, are lacking.

Table 2. Planned or Ongoing Tuberculosis Prevention and Treatment Studies in Pregnant Women

Trial[a]	Phase	TB Type	Study Purpose
IMPAACT P1078 NCT01494038	4	DS-TBI	To evaluate antepartum vs postpartum isoniazid preventive therapy in pregnant women with HIV
IMPAACT P2001 NCT02651259	1/2	DS-TBI	To evaluate the pharmacokinetics and safety of rifapentine and isoniazid preventive therapy in pregnant women with and without HIV
IMPAACT P1026s NCT00042289	4	DS-/DR-TB	To evaluate the pharmacokinetics of first- and second-line TB drugs in pregnant women with and without HIV

Abbreviations: DR-TB, drug-resistant tuberculosis; DS-TBI, drug-sensitive tuberculosis infection; HIV, human immunodeficiency virus; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials Network.

[a]National Institutes of Health clinical trial identifiers are shown; for more information, go to ClinicalTrials.gov.

The close monitoring afforded to participants in clinical trials may offer pregnant women with TB enrolled in research programs more safety measures and monitoring than they would receive under routine clinical care. While the experimental nature of research carries inherent risks, the absence of research also engenders risk. In the absence of research, each pregnant woman treated for TB becomes an individual experiment. Approaching each pregnant woman with TB as an experiment with a sample size of 1 precludes conducting the systematic research needed to produce the generalizable knowledge necessary to improve clinical care for all pregnant women with TB. The current practice of physicians treating each case of pregnancy-associated TB individually can at best produce case series data, not the more robust evidence of randomized, controlled clinical trials or the long-term follow-up data of observational cohort studies. Additionally, in the absence of research to better inform the risks and benefits under consideration, clinicians may deny pregnant women new treatments, or in some cases, treatment in general, increasing the potential for poor outcomes in pregnant women in routine clinical care.

The current research agenda for improving DS-TB treatment is focused on evaluating whether different combinations of existing and/or new TB drugs can shorten treatment from 6 to as few as 2 months [16]. The increased risk of TB drug-related hepatotoxicity in the third trimester and postpartum period [17] and potential to reduce the risk of postpartum TB and transmission to the infant make the ability to complete treatment earlier and before delivery an important aspiration. However, given that the existing standard of care for DS-TB is safe and efficacious, the inclusion of pregnant women in treatment-shortening trials without evidence of efficacy in nonpregnant populations might be premature, especially when considering the potential risk of relapse in the postpartum period and possibility of TB transmission to the newborn child.

The inclusion of pregnant women in DR-TB treatment-shortening trials may be more easily justified. The drug combinations proposed for evaluation will need to be carefully considered

Table 1. Lack of Inclusion of Pregnant Women in Ongoing and Planned Phase 3/4 Treatment-Shortening Trials for Active Tuberculosis

Trial[a]	TB Type	Drugs in Regimens Under Study	Pregnant Women
NIX-TB (NCT02333799)	XDR	BDQ, LZD, Pa	No
NEXT (NCT02454205)	MDR	BDQ, LZD, LFX, PYZ, ± HD INH or ETO	No
TB-PRACTECAL (NCT02589782)	MDR/XDR	BDQ, LZD, Pa, ± MFX or CFZ	No
STREAM II (NCT02409290)	MDR	CFZ, ETO, MFX, PYZ, INH, KAN, PTO, CFZ, ETO, MFX, PYZ, INH, PTO, BDQ, CFZ, ETO, MFX, PYZ, INH, KAN, PTO, BDQ	No
STAND (NCT02342886)	DS	Pa, MFX, PYZ	No
TBTC Study 31 (NCT02410772)	DS	INH, PYZ, HD RPT, ± MFX or ETO	No
TRUNCATE-TB	DS	INH, PYZ, HD RIF, E, ± CFZ or LZD, INH, PYZ, RPT, LZD, LFX, INH, PYZ, ETO, LZD, BDQ, INH, PYZ, LZD, LFX, DLM	No
endTB	MDR	CFZ, DLM, MFX, PYZ, CFZ, BDQ, LFX, LZD, PYZ, CFZ, DLM, LFX, LZD, PYZ, BDQ, LZD, MFX, PYZ, BDQ, DLM, LZD, LFX, PYZ	No

Abbreviations: BDQ, bedaquiline; CFZ, clofazimine; DLM, delamanid; DS-TB, drug-sensitive tuberculosis; E, ethambutol; ETO, ethionamide; HD, high dose; INH, isoniazid; KAN, kanamycin; LFX, levofloxacin; LZD, linezolid; MDR-TB, multidrug-resistant tuberculosis; MFX, moxifloxacin; Pa, pretomanid; PTO, protionamide; PYZ, pyrazinamide, RIF, rifampin; RPT, rifapentine; TBTC, Tuberculosis Trials Consortium; XDR-TB, extensively drug-resistant tuberculosis.

[a]National Institutes of Health clinical trial identifiers are shown; for more information, go to ClinicalTrials.gov.

with respect to pregnancy, but without urgent action to change the way the TB field approaches the inclusion of pregnant women in research, the same types of knowledge gaps that have persisted for decades for existing TB drugs will be replicated for new drugs (Table 1).

Novel drugs bedaquiline and delamanid, conditionally approved by the US Food and Drug Administration in 2012 and the European Medicines Agency in 2014 for multidrug-resistant TB, respectively, have not yet been evaluated in pregnant women. In situations where pregnant women with DR-TB are unable to tolerate existing second- or third-line TB drugs or have few treatment options, the use of new drugs in routine clinical care is justified with careful articulation of the potential risks and benefits to the individual and free and informed consent. Bedaquiline has been given to a handful of pregnant women under programmatic conditions in South Africa (personal communication, J. Furin, Harvard University, December 2016), and Otsuka Pharmaceutical opened its compassionate use program for delamanid to pregnant women in 2016 [18].

The inclusion of pregnant women in investigational plans and clinical trials (where appropriate) for novel drugs and regimens is the preferred approach and one that we encourage. However, programmatic or compassionate use of novel drugs during pregnancy is sometimes indicated. When this occurs, every effort should be made to evaluate pharmacokinetics as well as safety and tolerability outcomes to help inform future use. Data generated in clinical practice—while no substitute for clinical trials—is an important resource that can help bridge the evidence gap until the results of formal clinical trials including pregnant women become available.

PROGRESS FOR PREGNANT WOMEN IN TUBERCULOSIS DRUG RESEARCH

Recently, there has been a modest improvement in the representation of pregnant women in TB trials. Planned and ongoing IMPAACT and ACTG studies point toward the formation of a research agenda intentionally focused on questions of pregnancy-associated TB (Table 2). Furthermore, efforts are under way to establish a registry for TB medicines similar to the Antiretroviral Pregnancy Registry created in 1989. If established, this registry would collect data on the incidence of adverse events among pregnant women treated for TB infection and disease and their infants. In December 2015, our CABs wrote an open letter to the NIH Division of AIDS encouraging it to support the establishment of such a registry [19]. Advocacy and efforts to identify potential sources of funding are ongoing.

Resulting from the CRAG's advocacy, the TBTC recently established a cross-network TB and pregnancy research working group (TBPWG). The TBPWG has already fostered collaborations among researchers to enable data sharing and identify funds to better characterize the pharmacokinetics of first-line TB drugs in pregnant and postpartum women. The TBPWG continues to push researchers to follow up and analyze pharmacokinetics, safety, tolerability, drug–drug interaction, and outcomes data in women who become pregnant during clinical trials, and to explore opportunities to collaborate with other research networks to help fill data gaps for pregnant women with TB.

LEARNING FROM HUMAN IMMUNODEFICIENCY VIRUS

The TB field is not the first to tackle the inclusion of pregnant women in clinical research. In many ways, recent progress in TB follows a path paved by the HIV research community, which succeeded in building a robust evidence base for the prevention of mother-to-child transmission (PMTCT). Before the evidence base for PMTCT was established, the decision to use antiretroviral agents for HIV-infected women during pregnancy had to take into account 2 related issues: antiretroviral treatment of maternal HIV infection, and antiretroviral chemoprophylaxis to reduce the risk for perinatal HIV transmission. Researchers had to weigh the benefits of therapy for pregnant women against the risk of adverse events to the woman, fetus, and newborn [12].

The HIV research community continues to face several barriers mirroring those encountered by the TB community. These shared challenges range from legal and ethical uncertainties, to financial and professional disincentives, to analytical and logistical complexities [20]. Together, they point to the importance of using expert consensus statements, regulatory frameworks, and guidance documents to facilitate the appropriate and earlier inclusion of pregnant women in research.

CONCLUSIONS AND RECOMMENDATIONS

TB research has an informal but entrenched policy of excluding pregnant women from TB drug trials. To counter this, we believe TB researchers should begin from a position of presuming pregnant women eligible for research and then, based on the specific characteristics of particular clinical trials, carefully consider safety and whether the balance of risks and benefit warrants the exclusion of this population. These considerations will depend on the type of TB, the safety and efficacy of the prevailing standard of care, and availability of existing evidence. While the ethical dimensions of research involving vulnerable groups require special consideration, the routine exclusion of vulnerable participants from research can extend marginalization and deny pregnant women access to the benefits of scientific progress. In studies where the benefits may outweigh the risks, pregnant women deserve an opportunity to make an informed choice about their participation.

To support the earlier inclusion of pregnant women in TB drug research, as outlined in the aforementioned NIH-convened

expert panel's consensus statement, we make the following recommendations:

For Researchers

Research networks and institutions should create a standing protocol to, where appropriate, allow for the enrollment of pregnant women in the studies they conduct. They should consider joining the TBPWG and participate in efforts to establish a TB registry for pregnant women.

For Regulatory Authorities

Regulatory authorities should require developers to submit an investigational plan for pregnant and postpartum women alongside any new drug application. A regulatory mandate would facilitate a necessary shift in the mindset of researchers from one of presumed ineligibility to carefully considered inclusion. Similar regulatory requirements have effectively promoted the inclusion of children in research, for example, the European Medicines Agency's requirement that sponsors submit a Pediatric Investigational Plan alongside new drug applications [21].

For Policymakers and Advocates

Policymakers should consider legislative pathways to codify assessments in pregnant women under law that can be enforced by regulatory authorities. For example, through the Pediatric Research Equity Act, sponsors and developers must implement their pediatric study plan or file a waiver that justifies not pursuing pediatric investigations [22].

For Ethics Committees and International Review Boards

In our experience, many researchers presume that ethics committees will object to studies that include pregnant women. Ethics committees and internal review boards should build their members' capacity to assess the scientific merits and ethical issues of including pregnant women in TB research in conversation with researchers, regulators, and community representatives.

Notes

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