

Comments for Federal Task Force August 23, 2017 by Amita Gupta, MD, MHS

Good Morning. My name is Amita Gupta and I am an infectious diseases physician and clinical researcher at Johns Hopkins University who conducts studies on HIV and TB in pregnant and lactating women internationally. Active tuberculosis (TB) is a leading cause of maternal mortality, including in HIV-infected women. Infants born to mothers with TB have a higher rate of prematurity, low birth weight and stillbirth. Maternal TB more than doubles the risk of mother-to-child transmission of HIV, and significantly increases the risk of mortality for the newborn and other young children living in the household. Women of childbearing age are more likely than men to progress from latent TB infection (LTBI) to active TB, possibly owing to immune changes associated with pregnancy. In fact, the risk of developing TB is the highest within the first 90 days postpartum than any other time in a woman's life.

However, TB prevention and treatment during pregnancy pose challenges. Physiologic adaptations occur throughout pregnancy and peak in the third trimester. These changes are dynamic and can significantly affect drug disposition. The safety and efficacy of individual or multidrug regimens for pregnant women cannot be adequately predicted without clinical trials, yet safety and pharmacokinetic (PK) data during pregnancy are lacking for most TB drugs, including first line drugs that we have been using since the 1950s. Because of the lack of data regarding safety, tolerability, and the pharmacokinetics of TB drugs during pregnancy, inconsistencies in national and international treatment guidelines exist. The World Health Organization, for example, recommends the use of pyrazinamide during pregnancy in first-line TB treatment, but the US CDC does not, owing to inadequate data on potential adverse fetal effects. Thus, the type and duration of regimen that a pregnant woman with TB receives literally depends on what country she is in and what guidelines her doctor chooses to follow.

Multidrug-resistant (MDR) TB presents a bigger challenge, because treatment options remain extremely limited during pregnancy. Most aminoglycosides, key in MDR TB treatment, are potentially ototoxic and nephrotoxic for the fetus. Reproductive toxicity studies suggest that other second-line drugs for MDR TB, such as ethionamide-prothionamide, may also have teratogenic potential. Although new compounds are in development and new oral drugs have been recently approved such as bedaquiline and delamanid, lack of safety or PK data during pregnancy severely limits their use in this population.

Guidelines for prevention of TB progression has also suffered from lack of adequate data in pregnancy. The standard regimen (daily isoniazid for ≥ 6 months) has never been systematically assessed for safety and PK data in pregnancy, and there are some data to suggest there is increased risk of drug-induced liver injury. After exclusion from 13 trials of LTBI treatment in HIV-infected adults and the critical need to advance prevention for HIV-infected pregnant women, a NIH-funded Phase IV clinical trial was designed to study INH in pregnancy and is near completion. Why did it take so long to study a drug used since the 1950s in pregnant women? Furthermore, newer, shorter preventive regimens (e.g., 12 once-weekly doses of isoniazid plus rifapentine; 1 month of daily isoniazid plus rifapentine) are now available or under study in non-pregnant populations, but again pregnant women have been excluded from clinical trials of these regimens. Pregnant women should be allowed access to and benefit from advances in TB treatment. Pregnancy provides an important healthcare system entry point, at which women can be screened and treated for both TB and LTBI. But we urgently need the development of evidence-based treatment standards for pregnant women, which will require inclusion of this special population into studies of newly approved and investigational drugs for MDR TB or dedicated studies of these drugs in pregnant and lactating women.

Potential benefit of research on TB drugs would be significant, and consideration must also be given to the consequences of off-label use in the absence of evidence-based guidance. It is safer to administer TB drugs during pregnancy in a research setting, given the rigorous safety monitoring, requisite informed consent requirements, and ability to confirm correct dosing. Access to the benefits of research is an essential component of the ethical principle of justice in clinical research, and pregnant women have not benefited fairly from research given their under-representation in past trials.

Based on a NIH convened expert consensus meeting, we have outlined a set of recommendations for earlier inclusion of pregnant and lactating women in clinical trials and published these in *Clinical Infectious Diseases* in 2016. In summary, despite substantial TB-related morbidity and mortality in pregnant/lactating women and their infants, drug-sensitive TB, MDR TB and LTBI care is currently being provided without sufficient clinical trial data on drug safety and dosing. Studies in pregnant or lactating women with TB are needed to provide accurate data to improve clinical treatment decisions.