

# Tuberculosis in Pregnancy: A Treacherous Yet Neglected Issue



G. Sulis



M. Pai

Giorgia Sulis, MD;<sup>1,2</sup> Madhukar Pai, MD, PhD<sup>1,2</sup>

<sup>1</sup>Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montréal, QC

<sup>2</sup>McGill International TB Centre, McGill University, Montréal, QC

Although tuberculosis (TB) is now the leading infectious killer, affecting nearly 10.4 million people each year and killing 1.7 million individuals, the precise number of pregnant women who have TB is unknown.<sup>1</sup> Available estimates are calculated on the basis of the proportion of cases among women in their child-bearing years combined with the crude birth rate for a given area. The most recent systematic assessment of TB in pregnancy revealed that as many as 192 100 to 247 000 cases occurred globally in 2011, mostly concentrated in the African region and in Southeast Asia.<sup>2</sup>

The clinical picture of TB in pregnancy is often non-specific and difficult to diagnose, especially for health professionals who are less familiar with the disease. Therefore, diagnostic delays are very common with important negative consequences on treatment outcome that are further worsened by the increased risk of complications resulting from the impaired immunologic response related to pregnancy.<sup>3</sup>

The peculiar biologic changes that occur in a woman's body during pregnancy lead to a reduced Th1 inflammatory activity, which increases the risk of TB by at least two-fold compared with non-pregnant women and makes the clinical presentation of TB particularly subtle.<sup>4</sup> In the immediate postpartum phase, a high degree of vulnerability still exists as a result of immune reconstitution, which is typically characterized by a strong exacerbation of any TB symptom and a less favourable evolution of the disease.<sup>3</sup>

Reactivation of latent TB infection (LTBI) is responsible for the largest proportion of incident TB cases in low-burden settings.<sup>5</sup> Approximately one-fourth of the global population is estimated to be infected, and the prevalence of LTBI among pregnant women likely reflects the prevalence observed in the general population.<sup>6</sup> However, the risk of experiencing reactivation is known to be greater in pregnant women,<sup>3</sup> a finding suggesting that a high level of vigilance is necessary to allow early detection of TB cases.

Systematic screening for LTBI with the tuberculin skin test or interferon-gamma release assay is not currently recommended for all pregnant women in both high- and low-burden settings, but it becomes crucial for pregnant women who belong to a high-risk category (e.g., concomitant HIV infection, contact with a contagious TB case). Preventive therapy should be seriously considered regardless of the pregnancy status in case of a positive yield.<sup>7</sup> An easy to use online calculator is available for health care providers to compute the risk of active TB in individuals with a positive tuberculin skin test or interferon-gamma release assay result (<http://www.tstin3d.com/index.html>).

Although prescribing reticence is common among antenatal care professionals in an attempt to cause the least possible harm to the unborn child, the benefits of LTBI treatment usually outweigh the potential risks in such a vulnerable group. In fact, the consequences of developing active TB would be much worse for both the mother and her child.

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Corresponding Author: Dr. Giorgia Sulis, Department of Epidemiology, Biostatistics and Occupational Health & McGill International TB Centre, McGill University, Montréal, QC. [giorgia.sulis@mail.mcgill.ca](mailto:giorgia.sulis@mail.mcgill.ca)

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Available evidence suggests that neither isoniazid nor rifampicin is associated with teratogenic effects, but, according to some studies, the risk of hepatotoxicity appears to be greater in pregnant women than in the general population.<sup>8</sup> For this reason, in the absence of high-risk conditions such as HIV infection, LTBI treatment should be deferred until 3 months after delivery.<sup>7,9</sup>

It should be highlighted that a delayed TB diagnosis is a common occurrence not only because of the more insidious onset of the disease but also because of physicians' widespread reluctance to order tests such as a chest radiograph. However, this common fear is largely unjustified because evidence suggests that the risk to the fetus is indeed minimal.<sup>10</sup>

If active TB is detected, it is of utmost importance to treat it promptly and properly without hesitation. The WHO recommends the same therapeutic regimen as advised for the general population in terms of both composition and dosage, and most national guidelines are now in line with this position.<sup>11</sup> Yet the use of pyrazinamide during pregnancy is still discouraged by the U.S. Centers for Disease Control and Prevention, the American Thoracic Society, and the Infectious Diseases Society of America. These organizations instead support the adoption of a 2-month intensive phase with isoniazid, rifampicin, and ethambutol, followed by isoniazid and rifampicin for 7 months, associated with daily pyridoxine supplementation for the whole duration of treatment.<sup>12</sup> Ensuring the correct therapeutic management and an optimal patient's adherence is key to avoid the development of drug resistances that would seriously undermine the outcome. Besides being poorly tolerated and less effective, most second-line drugs are known to be teratogenic, which would make treatment extremely challenging for all pregnant women.<sup>11,12</sup>

There are many reasons that starting treatment immediately in all pregnant women diagnosed with active TB is crucial. First, TB is associated with a considerably increased risk of obstetric complications and preterm labour that sum up to the higher probability of disease dissemination and progression to more severe forms that would be more difficult to treat at a later stage.<sup>13</sup> Second, maternal TB is a cause of low birth weight and of several birth defects, and it enhances perinatal mortality. Although rare, transplacental spread of TB bacteria and/or aspiration of contaminated amniotic fluid may also occur, leading to congenital infection, which is fatal in approximately one half of cases. Yet TB must not be considered an indication for pregnancy termination because available therapeutic options are safe and effective if they are rapidly adopted. Third,

contagious patients with TB who are left untreated, including pregnant women, can infect others in the community.

Despite its tremendous impact, TB remains a neglected issue in several contexts. Given the serious consequences of delayed diagnosis and lack of treatment during pregnancy and the puerperium, a greater awareness of this clinical and public health problem is required among antenatal care providers. Obstetricians and gynaecologists are often the only health professionals with whom women come into contact throughout their gestational period, and therefore these physicians play a key role in the prompt recognition of alarm signs and the subsequent diagnostic investigations. A few simple precautions such as actively searching for common manifestations (e.g., unexplained chronic cough, mild fever, loss of appetite, fatigue, or shortness of breath) may make a difference towards TB detection. Similar to what observed in the general population, TB can also affect extrapulmonary sites, leading to protean clinical presentations that make the diagnostic workup particularly complex. Socially marginalized women, those belonging to indigenous communities, and those who migrated from high-TB burden countries deserve special attention when it comes to TB suspicion and screening. Even more than for any other TB-affected patient, close monitoring and constant support during treatment are indispensable to achieve a successful outcome for both the mother and her child.

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