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Fetal-maternal complications due to pregnancy-acquired tuberculosis: a narrative review of the literature

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Abstract

Tuberculosis (TB) during pregnancy can cause certain deleterious effects to both the mother and the fetus, leading to significant morbidity and mortality. The risk of TB rises significantly during pregnancy due to dampening of the immune response in females and certain factors yet to be studied. Since pregnant females are ruled out of clinical trials due to their pregnancy status, not much clinical data is available on how to combat TB in them or about the clinical safety and efficacy of certain drugs. Hence, not only is it important to make pregnant females vital study participants of clinical trials, but also to enhance their knowledge regarding the disease so that they may timely access quality care. It is also important to facilitate these TB-positive pregnant females through the introduction of gender-sensitive policies that are more exclusive and allow access to quality TB control programs that provide timely care, nutritional support, and quality and supportive management.

Key words: tuberculosis, HIV, pregnancy, co-infection, immune response, lack of knowledge.

Introduction

Among infectious diseases, tuberculosis (TB) is the leading cause of death globally affecting more than 2 million people as reported by the World Health O rganisation (WHO) in 2018 [1]. As per the latest report by WHO, Europe has the lowest incidence of 231, 000 followed by America. A staggering 4,37 million cases have been reported in Southeast Asia causing it to have the highest incidence [1]. Globally, of the 9.9 million cases of TB, 2.5 million have been reported from Africa alone [1]. The following eight countries totaled two-thirds of the incidence worldwide in 2020, namely India (26%), China (8,5%), Indonesia (8.4%), the Philippines (6.0%), Pakistan (5.8%), Nigeria (4.6%), Bangladesh (3.6%) and South Africa (3.3%) [1]. In the year 2020, women made up 33% of the prevalence of TB, while men and children accounted for 56% and 11% , respectively. An addition of 150,000 cases of TB in 2019 among pregnant females worldwide has further added to the disease burden.

As per WHO reports, 67,500 cases were reported from pregnant women from the Southeast Asian region which is an alarming figure for the future in terms of the global impact of the disease [2]. TB has a detrimental impact on pregnancy outcomes, both for the mother and the fetus. This is predominantly governed by the site and severity of the disease, response to antituberculous drug therapy, TB complications, gestational age of the fetus at diagnosis, and if the patient has a co-infection with HIV. As a condition itself, pregnancy does not exacerbate the disease susceptibility nor does it influence the progression of the disease from latent to active form [3]. The epidemiological data regarding TB during pregnancy is scarce [4]. Unfortunately, pregnant women are underrepresented as a part of clinical research data since the status of pregnancy is not stored in any surveillance database. Additionally, pregnant women are routinely excluded from trials [5]. As per estimates by global modeling studies TB has an incidence of 200,000 cases each year during pregnancy [4].

Etiology of tuberculosis during pregnancy

Limited studies are available that explain the immunological mechanism by which the risk of TB increases during pregnancy. O f what is known, as pregnancy progresses, cells that are part of the cell-mediated immunity (e.g., CD4+/CD8+-T cells) diminish. In contrast, the cells that decrease the immune response (e.g., Treg) tend to rise in number [4]. At the time of pregnancy the function of CD4+ and CD8+ T-cells also decreases [4]. This immune suppression continues to decrease until it reaches the last point at the time nearing delivery [4]. Such collective changes in the immune response increase the susceptibility to some infections (e.g., Listeria) and exacerbate other infections (e.g., influenza). Research conducted in Kenya and India demonstrated that the amount of interferon-gamma (IFN-γ) produced after stimulation with Mycobacterium tuberculosis (Mtb)-specific antigens decreases at the time of pregnancy

compared to post-birth [4]. Pregnant females demonstrate such patterns both in the presence or absence of HIV. Though HIV decreases the production of IFN-γ throughout pregnancy, even in the presence of sufficient CD4+ T-cells [4]. In a study conducted comprising pregnant women from Kenya and Uganda, the Mtb-specific CD4+ polyfunctional response was diminished in late pregnancy irrespective of the HIV status [4]. A study with Indian pregnant female subjects was conducted who had gestational diabetes (GD M). The patients demonstrated an impaired IFN-γ response to Mtb-specific antigens. O f note, pregnant women with coexisting GD M and HIV had the highest level of impairment [4]. Such an explanation suggests that during pregnancy an impaired cell-mediated immune response may worsen because of underlying co-morbidities like HIV and GD M. This eventually will permit TB to thrive. This warrants further research consisting of pregnant females who have coexisting HIV, GD M, and TB.

Epidemiological data

As per recent epidemiologic data concerning pregnancy, women are more prone to developing TB disease within the first 90 days of their pregnancy as opposed to any other time of their life [4]. A study from the UK followed 192,000 pregnant females who had an incidence rate of TB of 1.95 (95% CI 1.24–3.07) in their postpartum period as compared to the time when they were not pregnant [4]. Another study from Sweden analyzed 649,000 medical records of women who were in their reproductive years. The researchers observed an escalating incidence of TB during pregnancy (IRR 1.4, 95% CI 1.1–1.7) and 6 months after delivery (IRR 1.9, 95% CI 1.5–2.5) as compared to the times the females were not pregnant [4]. A further higher incidence of TB along with mortality is reported in females having a history of HIV [4]. Through their study, Miele et al. report that TB kills around 500,000 females yearly with a majority of them being in their reproductive years [6]. Hence, this further affirms that TB is common during females' reproductive years and is a significant contributor to maternal and childhood mortality.

The WHO provides statistics for South Africa that there was an estimated incidence of 360,00 cases of TB in 2019. As per the WHO, 360,000 cases of TB were reported in South Africa in 2019 with 14,000 individuals suffering from MDR-TB the exact year at the rate of 615 per 100,000 population. Despite the high burden of TB cases, the publicity given to TB cases in pregnant women was scarce [7]. Sobhy et al. conducted a meta-analysis on active TB. They reported an increasing incidence of maternal morbidity (O dd Ratio (O R) 2.8), antenatal admission (OR 9.6), miscarriage (OR 9.0), anemia (OR 3.9), and cesarean delivery (CD , O R 2.1). In pregnant females who received no treatment for TB, there was an increased rate of preterm delivery (PTD , O R 1.7), low birth weight (LBW, O R 1.7), fetal distress (OR 2.3), low

Apgar score at 1 min (OR 5.7), birth asphyxia (OR 4.6) and perinatal death (OR 4.2) [8]. A large-scale US national cohort study by D ennis et al. comprising 4053 pregnant females with TB reported alarmingly high rates of severe pre-eclampsia and eclampsia (Proportionality Ratio (PR) 1.7 and 3.9, respectively), postpartum hemorrhage (PR 1.8), placenta praevia (PR 1.9), and sepsis (PR 6.2). The study subjects had a 37 times higher in-hospital mortality rate, compared to females without TB. No racial or ethnic disparities were considered in this study [9], which might be a limitation and is a factor upcoming studies can shed light on.

Additionally, another study by El-Messidi et al. comprising US-based subjects reported an increasing incidence of concurrent HIV in females having TB [10]. Another study from India by Lewis et al. reported an escalating number of cases of anemia, and intrauterine growth restriction (IUGR) in pregnancies with active TB [11]. A study consisting of the Chinese population was reported by Sun et al. which demonstrated that TB both in mothers or their partners led to an increased risk of stillbirths (OR 1.89 and 2.13, respectively) as opposed to individuals without active TB [12].

Challenges in receiving healthcare

The aftermath TB has on a pregnant woman is governed by multiple factors, primarily, which organs of the body are affected, the disease's extent, the trimester of pregnancy, the mother's nutritional profile, immune status, and the presence or absence of HIV infection. Lastly, the availability of healthcare facilities for diagnosing and treating TB earlier during the disease course also plays a crucial role in the prognosis [13]. The interplay of social and cultural barriers also has a pivotal role [14] which can cause a delay in seeking care along with a lack of knowledge.

A study comprising infants from Durban, South Africa of mothers suffering from TB were at increasing risk of contracting the disease as their mothers either had presented late for their antenatal check-ups or did not receive adequate prenatal care [15]. Mulondo et al. conducted a study in the Limpopo province in South Africa to assess the status of knowledge in pregnant females suffering from TB regarding seeking timely care. The authors reported that the participants had a lack of knowledge regarding late presentation to antenatal care checkups, complications of TB, and its concurrent presentation with HIV [16].

Pregnant females are inadequately represented in medical research which is primarily because pregnancy is not reported as part of the surveillance data and secondly, during clinical trials, pregnant women are routinely excluded as study subjects [17]. The national and international management guidelines for TB management during pregnancy suffer from inconsistencies since the data regarding the clinical safety and efficacy of TB drugs during pregnancy has not been collected or reported systematically [18].

MDR-TB poses another threat during pregnancy since specific treatment options remain scarce. Key medications like aminoglycosides remain a potential threat due to their adverse clinical safety profile as they can lead to ototoxicity and nephrotoxicity in the fetus. Furthermore, 2nd line drugs such as ethionamide-prothionamide, can lead to teratogenicity. With recent advancements, oral drugs have been recently approved for managing MDR-TB in the US (bedaquiline) and Europe (bedaquiline and delamanid). However, the limited pharmacokinetics data and clinical safety during pregnancy greatly limit their use [18]. A significant proportion of pregnant females with TB face death due to coinfection with HIV. Of note, poor adherence to dual ATT and antiretroviral (ARV) therapy can be the root cause in this subset of the population. Though treatment options exist for managing these co-existing conditions in pregnancy, they can cause increased pill burden, increased adverse effects, and drug-drug interactions [18].

It is well documented and understood that barriers to accessing and utilizing can trigger gaps in treatment control for TB, particularly in countries of South Asia, like India. Such barriers and challenges can not only lead to treatment delay but there by increase the transmission of the disease [19]. Challenges at healthcare facilities providing treatment for TB [20], like ill treatment from healthcare workers, dishonest and corrupt system, lack of flexible timings of the healthcare facilities, and long queues in government hospitals [21] can lead to drug resistance in the longer run [20].

In many parts of the world, tradition spearheads the right to access quality care for women. For instance in India, women to date are deemed inferior to men, hence reducing their role in making healthcare-related decisions [22]. Women from these cultures are financially dependent to a great extent on their husbands causing them to acquire permission to seek quality healthcare, which causes delays in seeking treatment [23] and hence medication resistance in the time to follow. Additionally, for women to have TB in these regions is considered a stigma that also impacts and dampens their right to quality care [24].

With 40% emerging cases of TB in India among women and counting, there is an urgent need for stakeholders to develop more gender-sensitive measures for controlling TB with crucial gaps present in the existing program such as a lack of women healthcare workers, poor nutritional support, and lack of integration with other local bodies like the National Health Mission and Reproductive and Child Health Programme, particularly Maternal Health Services [25]. In light of the aforementioned factors, it is instrumental to mention the study by Mathad et al., where they observed the care given to rifampin-resistant TB-positive pregnant females in the KwaZulu-Natal Province, South Africa. In their findings, they document discrimination by healthcare workers toward this patient population [26].

Recommendations and future directions for better healthcare access

To better screen and treat pregnant women with TB, it is vital to design a TB control program that is gender sensitive enabling such patients to pave the way through help-seeking barriers [14]. This further mandates an urgent prioritization of TB research in this population to bring forth evidence-based tailor-made strategies [27]. Preventive strategies against TB in conjugation with early TB screening followed by rapid pharmaceutical therapy via supportive means can in a nutshell guide the path to healthy parent-child pairs [28]. To further supplement this approach, the primary prevention of HIV is another core step in preventing TB during pregnancy. Due to the co-existing nature of HIV and TB, it is imperative to screen all pregnant women positive for HIV for active TB even when the characteristic signs of the disease are not evident [29].

Another measure of the WHO is Isoniazid preventive therapy (IPT) which is focused on curtailing the rate of TB infection in HIV-positive pregnant females. Based on clinical data it has been concluded that pregnancy should not be a contraindication to receiving IPT. Nonetheless, the decision to administer IPT should be patient-specific based on need and the ideal time of administration based on the trimester and state of pregnancy [30]. Adding data related to pregnancy and the postpartum period into routine surveillance can enhance our understanding of TB prevalence, risk, management, and outcomes. Some other critical gaps in managing TB during pregnancy remain like the pregnancy-related immunologic changes that affect the susceptibility to TB progression [4].

Conclusions

A collective effort is needed from the healthcare stakeholders and patients to eradicate the global burden of TB during pregnancy. It can be vital to start by educating pregnant females to counter their lack of knowledge regarding the disease and how it can adversely impact them and their fetuses. Further research through large-scale trials with pregnant females with TB as study subjects can help us better understand the clinical efficacy and safety of certain drugs that may be safe and used for both the mother and the fetus.

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