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Tuberculosis in pregnancy: The challenges for South Asian countries

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Abstract

Aim: Despite tuberculosis (TB) being a global problem, maternal TB remains an unrecognized and underestimated tragedy, especially in South Asian countries. Therefore, we performed a non-systematic review regarding implications of maternal TB on obstetric and perinatal outcomes in the South Asian context.

Material and Methods: We reviewed original studies, both descriptive and analytical, that originated from South Asian countries following an electronic search supplemented by a manual search. Although relevant studies from developed countries were reviewed, they were not included in the tabulation process because those studies had different socioeconomic/epidemiological background.

Results: Diagnosis of TB is often delayed during pregnancy, because of its non-specific symptoms, and overlapping presentation with other infectious diseases. Poverty, undernutrition, lack of social support and poor health infrastructure along with complications of TB and need for prolonged medications lead to increased maternal morbidity and mortality. Maternal TB in general (except lymphadenitis), is associated with an increased risk of small-for-gestational age, preterm and low-birthweight neonates, and high perinatal mortality. These adverse perinatal outcomes are even more pronounced in women with advanced disease, late diagnosis, and incomplete or irregular drug treatment. There could be a synergy of TB, socioeconomic and nutritional factors, which might have contributed to adverse perinatal effects, especially in low-income countries.

Conclusions: As active TB poses grave maternal and perinatal risks, early, appropriate and adequate anti-TB treatment is a mainstay for successful pregnancy outcome. The current knowledge gaps in perinatal implications of maternal TB can be addressed by a multicenter comparative cohort study.

Key words: infectious, perinatal mortality, pregnancy complications, pregnancy outcome, tuberculosis.

Introduction

Tuberculosis (TB), a dreadful infectious disease, remains a global public health threat.[1] The South Asian countries, which contribute to approximately 20% of the world's population, and half of the world's poor, have born its burden more acutely and persistently over the centuries.[1,2] Globally, there were an estimated 9.27 million new cases of TB in 2007. Most of these cases were in Asia (55%) and Africa (31%). Sadly, three Asian countries topped the list, namely India (2.0 million), China (1.3 million) and Indonesia (0.53 million).[1] Each year approximately 2 million people die from TB worldwide. A large proportion of deaths occur in the low-income countries of Asia and Africa.[1,3] Unfortunately, women in these countries are most

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profoundly affected by TB, which is the third leading cause of death among women of reproductive age.[4] As TB mostly occurs in young women, many infected women are diagnosed having the disease during pregnancy, while others become pregnant during TB medication; and more importantly, a proportion remains undiagnosed and suffers worse maternal and perinatal consequences.[5–17] A recent postmortem analysis of maternal deaths highlights that infection, including TB, is an important contributor to maternal death in India.[17]

Current literature on the prevalence of TB among pregnant women in developing countries like India is not available. Only a few studies, mostly from the large urban teaching hospitals in India, reported effects of TB during pregnancy.[7–10] Considering the current incidence of TB among women of reproductive age (around 100 cases per 100 000 population) and a total of 26 million births annually, our conservative estimate suggests that approximately 20 000–40 000 women in India are likely to have active TB during pregnancy each year.[18,19] Therefore, not only is there a knowledge gap, but also the true impact of this problem on the community is not known. Several descriptive studies, both old and new, often underestimated the maternal and perinatal complications of TB.[9,14,20,21] Therefore, there is a sense of complacency among obstetricians regarding the benign course of both disease and pregnancy among these women suffering from TB. However, several recent reports from diverse countries have tempered this false notion, and suggested that TB remains a potential danger for mother, fetus and newborn.[7–13,21,22] Furthermore, resurgence of TB in immunocompromised mothers with HIV infection, and multidrug-resistant TB and extreme-drug-resistant TB have added new dimensions to an already complex issue.[23,24] In this review, we plan to assemble current evidence regarding implications and management of maternal TB, especially in the context of South Asian countries.

Methods

This is a non-systematic review, which deals with maternal and perinatal outcomes among pregnant women who suffered from TB during pregnancy or immediately prior to pregnancy or during the postpartum period. For this review, we carried out an electronic search supplemented by a manual search. PubMed was searched using 'Pregnancy and tuberculosis' and 'Tuberculosis in pregnancy' as key words with no limit for language or timespan. Both searches yielded 2783 articles. A similar process with the search term 'Tuberculosis in pregnancy in South Asia' and 'Congenital Tuberculosis' returned seven and 1042 articles, respectively. We reviewed original studies – both descriptive and analytical – originated worldwide, with special emphasis on those from South Asian countries (as per the World Bank report, 'South Asia' included eight countries – Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka).[2] The manual search, especially from non-indexed (Index Medicus/Medline) journals, has been a long process for the last 20 years since our first original study in the early 1990s.[7] Only relevant articles which provide reasonable information regarding diagnosis, prognosis, obstetric and perinatal outcomes in maternal TB were considered for inclusion. Non-Asian studies (e.g., two from Mexico[12,13]) were also included in the discussion if study outcomes/results were generalizable to the South Asian context. Data were tabulated under six main headings (Table 1) with emphasis on characteristics of the cohorts and controls (if any), and maternal and perinatal outcomes. No meta-analysis was attempted as cohorts and outcomes were widely heterogeneous. Main outcomes are tabulated, and findings were further discussed in the text under several subheadings. Although relevant studies from developed countries were reviewed, they were not included in the tabulation process because those studies had different socioeconomic and epidemiological background.

Results and Discussion

Diagnosis of TB in pregnancy

TB is a great mimic. Diagnosis during pregnancy can be extremely challenging even to an astute clinician because of its insidious onset, protean manifestation, non-specific nature of symptoms, and overlapping presentation with other infectious diseases commonly prevalent in South Asian countries.[5–8] Furthermore, loss of appetite, tiredness, fatigue, shortness of breath and sweating, all common symptoms of TB, can be due to pregnancy.[5,14,25] Even in symptomatic patients, often diagnosis is delayed because of clinicians' reluctance to order a chest X-ray during pregnancy to avoid fetal exposure to radiation. Furthermore, bacteriological confirmation and other radiological evaluation are more difficult for extrapulmonary cases in pregnancy.[8] Surgical or endoscopic biopsy for extrapulmonary TB may not be possible in pregnant women because of technical difficulties, non-accessibility of the lesions,

Table 1 Maternal and perinatal effects of tuberculosis during pregnancy among Asian women

Authors (year)	Country	No. of patients	Characteristic of cohort and control	Maternal outcomes	Perinatal outcomes
Jana *et al.*[7] (1994)	India	79	Women with active pulmonary tuberculosis; 316 controls matched for age, parity and timing of delivery	No maternal death	Approximately twofold increase in prematurity, SGA (IUGR), and LBW neonates, and sixfold increase in PNM.
Jana *et al.*[8] (1998)	India	33	Women with extrapulmonary tuberculosis; 132 controls matched for age, parity and timing of delivery	No maternal death. Non-nodal extrapulmonary tuberculosis had more morbidity and hospital admission.	Tuberculous lymphadenitis has no perinatal effect; other extrapulmonary involvement causes LBW neonates and low Apgar scores at birth.
Tripathy and Tripathy[9] (2003)	India	111	101 pulmonary and 10 lymph node tuberculosis; 51 controls matched for age, parity and socioeconomic status	1 maternal death due to massive pulmonary embolism	Extreme prematurity, LBW and neonatal mortality were significantly higher among women with tuberculosis, who started treatment late in pregnancy
Khadilkar *et al.*[10] (2003)	India	153	133 pulmonary and 20 extrapulmonary tuberculosis; no controls.	3 maternal deaths	High rate of LBW neonates, primarily attributed to IUGR.
Lin *et al.*[22] (2010)	Taiwan	761	Both pulmonary and extrapulmonary tuberculosis diagnosed before index pregnancy; 3805 controls matched for age and year of delivery	Maternal morbidity and mortality not reported	Increased SGA and LBW neonates.

IUGR, intrauterine growth restriction; LBW, low-birthweight; PNM, perinatal mortality; SGA, small-for-gestational-age.

and risk of preterm labor and anesthetic hazards to the fetus.[8,26] The revised national TB control program of India adopts a uniform diagnostic procedure primarily based on sputum microscopy, supplemented by chest X-ray.[25] Although, this community-based widely tested national program yields good results, its scope and limitations among pregnant women are not specifically examined.[27–29]

In high-prevalence countries, tuberculin skin test is not used as a case-finding technique, as it cannot differentiate between past infection and active disease.[25] The value of γ-interferon-based *in vitro* test (Quantiferon Gold) is yet to be explored in pregnant women. New diagnostic techniques, such as liquid-based microculture methods and nucleic acid amplification techniques (DNA and RNA polymerase chain reaction), involve prohibitive expenditure in terms of instrumentation and expertise, putting them out of reach of most laboratories in South Asian countries.[30,31]

In addition to delay in diagnosis, there is delay due to lack of access to health-care service. Women in general, especially women in rural India, often have limited access to existing health care because of multiple social, economic and cultural barriers.[32–34] This problem of accessibility remains a major barrier to tuberculous mothers, who have to spend considerable time attending the directly observed treatment – short-course (DOTS) program as well as antenatal care. Domestic inconvenience, loss of daily wages, and transport problems in rural areas make TB treatment a big hurdle for mothers with TB. This undue delay has many deleterious effects on both the mother and the growing fetus.[7,8]

TB and maternal effects

TB has multiple implications on maternal health. Prolonged debility, nutritional deficiency, lack of social support, complications of TB and need for prolonged anti-TB medications put an enormous pressure on maternal physical and mental health.[5,8,10,11,32] Although most studies suggest that pregnancy does not alter the course and outcome of TB,[35–40] the quality of controls in these studies is questionable because of the practical difficulties of finding non-pregnant controls, who could be adequately matched for the severity of disease. Progress of TB is rare during pregnancy provided the women are compliant to drug therapy.[7,20,40] In our experience, many indigent pregnant women often fail to attend both the chest clinic and the antenatal clinic because of the dual burden of pregnancy and TB.

These factors perhaps make the disease progress and prognosis worse.[7,8]

There are conflicting reports regarding effects of pulmonary TB on maternal and obstetric outcomes. According to some studies, pulmonary TB is associated with major maternal/obstetric problems[7,12,13] while others consider it as less problematic.[9] Our experience showed that high-grade fever and maternal debility could lead to antenatal hospital admission of pregnant women with pulmonary TB.[7] Although most of these women responded well to anti-TB treatment, preterm delivery rate was doubled in pulmonary TB.[7] Maternal and obstetrical complications are more common if TB is diagnosed late in pregnancy, especially in the third trimester.[7,9] Similar results were also observed in a comparative study, in which obstetric complications were increased fourfold and preterm labor was increased by ninefold if diagnosis of TB was late in pregnancy.[12] If pregnant women were compliant to anti-TB drug treatment, maternal mortality due to pulmonary TB was rare.[7,9,12–14]

Women with extrapulmonary diseases except tuberculous lymphadenitis are the worst sufferers.[7,8] Spinal/vertebral TB, although rare among pregnant women, is associated with serious morbidity. Because of non-specific symptoms, such as back pain (a common symptom in pregnancy), and reluctance to perform radiography in pregnant women, the diagnosis is often delayed, which can lead to early onset paraplegia.[8,41] Paraplegia in pregnant women is associated with higher risk of urinary tract infection, decubitus ulcers, preterm labor, and autonomic hyperreflexia – a rare, but potentially fatal complication.[41] Transportation of a paraplegic woman with TB is extremely difficult, as public transport in many developing countries is not patient-friendly, and private transportation is often not affordable. Therefore, as a compromise, these women often skip antenatal care, what they need the most. Furthermore, surgical intervention for spinal TB during pregnancy is very challenging, and the expertise is limited to only a few super-specialty hospitals. Tuberculous kyphoscoliosis can also complicate maternal health and obstetric management. Spinal deformity and reduced cardiopulmonary reserve associated with kyphoscoliosis can complicate the use of regional and general anesthesia, respectively, during delivery.[42] In addition, surgical risk because of non-accessibility of lower segment can further complicate cesarean delivery.

Extrapulmonary TB, especially tuberculous meningitis, is rare in pregnancy.[11,43–45] Although it constitutes about 1% of all TB cases, only 55 cases of tuberculous meningitis affecting pregnancy were identified up to 1999.[43] Only a few cases have been reported from South Asian countries.[11] However, an alarmingly high maternal mortality (38.2%), and fetal or neonatal deaths (36.6%) among these women remains a major concern.[43] In our experience, misinterpretation of initial symptoms of meningitis with other infectious diseases can cause diagnostic delay resulting in dangerous complications, such as cranial nerve palsies and paraplegia. In these women, prolonged debility due to paraplegia and concurrent infections can also adversely affect the course of pregnancy and perinatal outcome.[11]

Similarly, abdominal TB is exceedingly difficult to diagnose during pregnancy. Women may present with pyrexia of unknown origin. Tuberculous ascites, often masked by an enlarged uterus, rarely draws the attention of the clinician towards TB. Ascitic fluid studies (cytological, biochemical, and bacteriological) may provide evidence for TB, but with inordinate delay. Intestinal TB can present with subacute intestinal obstruction, and is mostly diagnosed by laparotomy.[26] In certain cases, we find endoscopic biopsy or ultrasound-guided fine-needle aspiration biopsy to be very useful in pregnant women.[8,26] However, such expertise is mostly limited to apex hospitals, and unfortunately, many women may not have access to such service on an urgent basis. Therefore, both debility and delay adversely affect the maternal and perinatal prognosis in abdominal TB.

TB and perinatal effects

Maternal TB is potentially dangerous for the fetus and newborn. Only five well-matched comparative studies detailing perinatal effects of maternal TB could be identified worldwide. These comparative studies from India,[7,8] Mexico[12,13] and Taiwan[22] clearly suggested that infants born to tuberculous mothers are smaller than in healthy controls (Table 1). This is evident by higher risks of low-birthweight (LBW) and small-for-gestational-age (SGA) babies in tuberculous mothers.[46] The risks for prematurity, though inconsistent (a twofold rise in Indian[7] and Mexican[13] cohorts, but no change in Taiwan[22]), alone cannot explain birthweight reduction in women with TB. A significant birthweight reduction (215 g in pulmonary TB and 277 g in extrapulmonary TB in India, and 240 g in a combined group in Mexico) is most likely due to fetal growth restriction, which might have been superimposed on a higher prematurity rate.[7,13]

In our experience from northern India, pulmonary TB is associated with an approximately twofold increase in fetal distress during labor (relative risk [RR] 2.4; 95% confidence interval [CI] 1.2–4.7), and SGA (RR 2.6; 95%CI 1.4–4.6), preterm (RR 2.1; 95%CI 1.2–3.4), and LBW (RR 2.1; 95%CI 1.4–3.1) neonates when compared with the healthy controls.[7] Similarly, extrapulmonary TB (except tuberculous lymphadenitis) is also associated with adverse perinatal outcomes.[8] More importantly, perinatal mortality is approximately fivefold higher in both pulmonary and extrapulmonary TB.[7,8,46] These perinatal effects were even more pronounced in cases with late diagnosis, incomplete or irregular drug treatment, and in those with advanced pulmonary lesions.[7] Therefore, antenatal and intrapartum care may be modified according to severity of disease, and associated obstetric complications. As incomplete and irregular treatment of TB remains a major challenge in pregnant women, any strategy to promote adherence to TB treatment requires overcoming barriers at three levels – health system, social and family, and personal levels.[47] Removal of these barriers for pregnant women with TB remains a daunting task.

In contrast, Tripathy and Tripathy reported overall good perinatal outcome among 111 women with pulmonary/extrapulmonary TB over a period of 16 years (1986–2001) from eastern India.[9] Unfortunately, this study only had a 41% follow-up rate (original cohort of 271 patients). This might have introduced a bias, because the defaulters in the TB cohort could represent a relatively worse/severe spectrum of the disease and outcome. Furthermore, lack of follow up in the study was mostly attributed to non-compliance to medication and regular check-up, which has remained a major concern in South Asian countries.[18] In this study, extreme prematurity, LBW, and neonatal mortality were more common among pregnant women with TB, who started treatment late in pregnancy. The study also reiterated the importance of diagnosis and treatment of TB early in pregnancy to avoid perinatal complications.[9]

A prospective observational study over a period of 10 years (1991–2000) from Mumbai, western India, included 153 pregnant women with TB (133 pulmonary and 20 extrapulmonary cases).[10] This study revealed that maternal TB was associated with a high incidence of LBW neonates, which was primarily attributed to fetal growth restriction. Although there was some improvement of perinatal outcomes in the latter half of the study, the problems of LBW and late fetal death remained unabated.

Because of sparse literature on perinatal effects of maternal TB, it may be worthwhile extrapolating the experience from a comparative study carried out in Mexico, which also showed increased risk of perinatal morbidity and mortality among 35 women with pulmonary or extrapulmonary TB: prematurity (RR 2.1; 95%CI 1–4.3), LBW neonates (RR 2.2; 95%CI 1.1–4.9), neonatal complications (RR 2.1; 95%CI 1.1–3.9) and perinatal death (RR 3.1; 95%CI 1.6–6).[13] Approximately twofold increase in prematurity and fetal growth restriction was responsible for most neonatal complications.[13] In this study, pulmonary localization of TB and late start of treatment were two major factors which determined poor perinatal outcome in maternal TB.[12,13] Furthermore, by stratified analysis, the authors inferred that anti-TB treatment early in pregnancy can reverse these complications.[12] This is in contrast to a recent comparative study from Taiwan, which showed an increased risk of LBW (odds ratio [OR] 1.35; 95%CI 1.01–1.81) and SGA (OR 1.22; 95%CI 1.00–1.49) babies born to mothers who started anti-TB drugs even before conception.[22] Although several case series from developed countries reaffirmed potential perinatal dangers of maternal TB,[14,21,48] the others reported satisfactory pregnancy outcomes.[49–51]

Maternal TB and socioeconomic dimensions

Pregnancy outcome among women with TB is often influenced by poverty, which is a multidimensional phenomenon.[32,52,53] In South Asian countries, poverty, hunger and undernutrition are widespread.[2] There is a close link between TB and poverty.[32,52] It is very important to understand the potential effects of this combination on maternal and perinatal health, especially in low-income South Asian countries, where the health-care system is relatively dysfunctional and barriers to care are substantial.[27] Pervasive poverty, inequitable economic growth, political instability and widespread corruption are major roadblocks to most public health measures in the South Asian region.[2,54]

It is well known that nutritional status, chronic disease like TB and pregnancy events are influenced by each other.[7,8,32,52] These factors are synergistically modulated by the socioeconomic factors that include education, income and occupation of couples, demographic features of home, access to quality food and health-care practices.[32,52] Dynamics of socioeconomic and cultural realities affect the pregnancy outcomes among tuberculous mothers in different communities. Unfortunately, combined influences of maternal TB and co-existing undernutrition are not explored

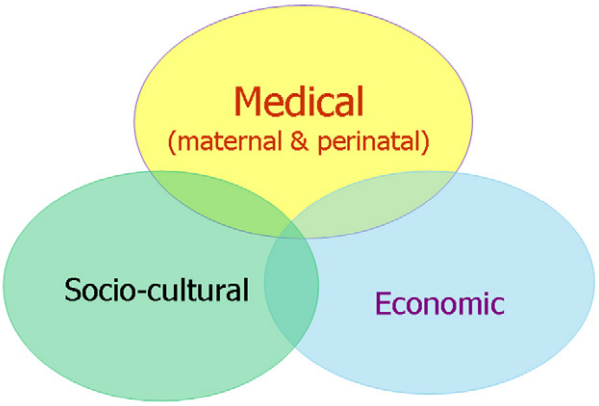

Figure 1 Effects of tuberculosis during pregnancy.

systematically in clinical studies. The potential role of socioeconomic factors[55] and maternal impoverished nutrition[56] has been suggested in earlier studies from developed countries. A recent study from India also showed that multiparity, anemia, undernutrition and overcrowding, all added to the problem of maternal TB.[10] The risk factors for TB also adversely affect perinatal outcome. It is very difficult, if not impossible to dismantle the potential effects of those risk factors on pregnancy outcome from that of TB.

In addition, TB being a chronic debilitating disease requiring long-term care and medication, often consumes enormous financial and non-financial resources of the family. Furthermore, simultaneously attending maternity care and the TB clinic can be a very daunting task for an indigent family. As a consequence, irregular treatment and advanced tuberculous disease can adversely affect both maternal and perinatal health and survival, especially for women in South Asian countries and ethnic minorities in the UK.[7,8,14] Therefore, it is important to consider the problem of TB not as a medical problem alone, but to consider it holistically in the context of socioeconomic background (Fig. 1).[57] Anti-TB drug therapy is only a part of the solution to a more complex issue with medical-social-economic-cultural factors, which need a multidimensional approach from several agencies.

Education and emotional support of the affected women and their family members emphasizing the twin need of TB treatment and pregnancy care are two vital issues,[29] which can affect successful obstetric outcome. These require the concerted efforts of the public health system and maternity service, which remain suboptimal in most South Asian countries.[27] Advocacy, communication and social mobilization are three key factors, which can effectively bridge pre-existing gaps between the health system and the community by enhancing TB knowledge, attitude and practice.[58] It is a sad irony that despite TB largely affecting young women of reproductive age, only piecemeal information about its effects in pregnancy is available, and this incomplete knowledge has clouded our understanding regarding management of TB in pregnant women, and its effect on perinatal outcomes.

TB in pregnancy and HIV infection

TB and HIV are inextricably related.[23,59] The negative impacts of each on the other have been widely documented.[59–62] Both infections occur in women of the reproductive age group.[60] HIV infection and TB during pregnancy are considered a 'deadly combination' and are independent risk factors for maternal mortality.[63] Although Africa is worst affected by this dual disease,[23,59] HIV co-infection affects approximately 4–5% of all TB incidence cases in India in 2008 and to a lesser extent, other South Asian countries.[64] However, recent data from surveillance sites indicate that HIV prevalence is stable or declining among pregnant women in the high-prevalence states in India.[65]

The curse of dual disease during pregnancy is widely studied in the African region.[23,59] Recent reports from India also explored the intricate correlation between HIV infection and TB in the context of pregnancy and the post-partum period.[61,62] Among HIV-infected Indian women, Gupta *et al*. found a high incidence of post-partum TB (five cases per 100 person-years).[62] Furthermore, co-infection of TB has substantially increased post-partum maternal death (2.2-fold; 95%CI 0.6–3.8) and death of their infants (3.4-fold; 95%CI 1.22–10.59). This raised a serious concern regarding the strategy of screening and managing latent TB during pregnancy in the context of India, and other South Asian countries, where isoniazid prophylaxis is not advocated at present in latent TB. The authors suggested that active screening and targeted use of isoniazid preventive therapy among HIV-infected women in India should be considered to prevent post-partum maternal TB. In a subsequent article, Gupta *et al*.[61] also reported that maternal TB, mostly detected after delivery, is associated with increased mother-to-child transmission of HIV (30% vs 12%). Therefore, prevention of TB among HIV-infected mothers should be a high priority for communities with significant HIV/TB burden.

Dual infection of TB and HIV-infection poses several unique challenges. Its management during pregnancy demands special expertise, judicial sequential combination of anti-TB drugs and anti-retroviral drugs, which is beyond purview of this current review.[23,59] This issue was recently addressed elsewhere.[59] It is increasingly evident that TB has many adverse effects on maternal and child health in high-prevalent countries, with HIV-infected mothers and their infants being particularly vulnerable.[66] These include not only direct effects, such as morbidity and mortality, but also multiple indirect effects that trap the woman in a vicious circle of perpetual poverty and vulnerability.[67]

Anti-TB drugs during pregnancy and lactation: maternal, fetal and neonatal considerations

As untreated or incompletely treated TB poses a great risk to pregnant women and their fetuses, all women with TB irrespective of sites involved must receive a full course of anti-TB drugs.[68] According to the recent World Health Organization (WHO) recommendation, 'A pregnant woman should be advised that successful treatment of TB with standard regimen is important for successful outcome of pregnancy.'[69] Management of active TB during pregnancy is similar to that in non-pregnant women. With the exception of streptomycin, all first-line anti-TB drugs (isoniazid [H], rifampicin [R], ethambutol [E], and pyrazinamide [P]) are considered safe for use in pregnancy, and have no proven teratogenic effects.[69–76] Streptomycin-induced fetal ototoxicity leading to hearing impairment and irreversible congenital deafness affects one in six neonates; therefore, it should not be used throughout pregnancy.[5,68] The dosage and the duration of therapy are not modified due to pregnancy. Pyridoxine, 10 mg/day (other guidelines recommended 25 mg/day[68]), should always be given with isoniazid during pregnancy because of increased requirement of this vitamin in pregnant women and to prevent potential neurotoxicity in the fetus.[69,72,76] The women should be monitored for compliance to and toxicity of the drugs. Hepatotoxicity of isoniazid remains a major concern especially during the peripartum period.[68]

Short-course chemotherapy for 6 months (2HRZE, 4HR given daily) is effective in pregnancy. An intermittent regimen (three times a week, on alternate days) under the directly observed treatment – short-course (DOTS) strategy of the Revised National Tuberculosis Programme is also used for pregnant women.[25,69] Multidrug-resistant TB (resistant to both isoniazid and rifampicin) requires second-line anti-TB drugs, which may not be safe during pregnancy because of teratogenic effects (especially aminoglycosides and quinolones).[5] In this situation, detailed counseling is necessary regarding potential maternal-fetal hazards and scope for therapeutic abortion. Although overall evidence is scanty and contradictory, a recent report suggested favorable perinatal outcome in a group of 38 women with multidrug-resistant TB.[24] Treatment must be initiated and closely monitored by an expert in TB management.

All first-line anti-TB drugs cross into breast milk in variable amounts.[71,77,78] The drug level in milk is less than 1% of the maternal dose except for isoniazid, where it ranges between 0.75% and 2.3%.[71,78] Although streptomycin is excreted into breast milk, no significant effect on the infant is seen, as it is very poorly absorbed from the gut.[71] The risk of toxic reactions to anti-TB drugs in breast-fed infants is low, and it can be further minimized if the mother takes her medication just after breast-feeding.[5] All the first-line drugs are considered to be compatible with breast-feeding by several national and international organizations.[69,74,79] Despite the safety of breast-feeding, there is a common tendency to avoid breast-feeding because of ignorance.[34] The WHO reinforces that the women with TB should breast-feed normally while taking anti-TB drugs, and the mother and baby should stay together.[69]

Perinatal TB

TB in the neonate can be either congenital (i.e., acquired *in utero*) or neonatal (i.e., acquired early in life from the mother or other persons). Sources of fetal infection can be hematogenous spread from placenta, or aspiration/ingestion of infected amniotic fluid. Hematogenous spread leads to formation of a primary complex in the liver or a caseating hepatic granuloma, whereas aspiration or ingestion of infected amniotic fluid results in primary complex in lungs or gastrointestinal tract, respectively.[5,15,80] Sometimes, ingested tubercle bacilli enter the Eustachian tubes, leading to TB of the middle ear. Endometrial TB can be an important cause of congenital TB in India and other low-resource countries.[81–85] More often the newborn acquires infection after birth from the untreated mother or other adult reservoirs in the family or surroundings. In clinical practice, it is difficult to identify the exact route of transmission of TB from mother to baby, so as to establish the diagnosis as congenital or neonatal.[85] Therefore, the term 'perinatal TB' is preferred to 'congenital' or 'neonatal TB'. Differentiation of

congenital TB from neonatal TB is of more epidemiological importance, as clinical management and prognosis does not differ significantly.[16,86] Early treatment of maternal TB during pregnancy is the best way of preventing perinatal TB.[5]

There is lack of information to clearly understand congenital or neonatal TB. Only 300 cases of congenital TB have been reported in the medical literature up to the 1990s, and only a few cases were reported from South Asian countries.[15,85–88] This is in contrast to the disproportionately high number of cases of TB among pregnant women in this region. Signs and symptoms of TB in the newborn are non-specific and may mimic bacterial or other congenital infections.[86,88,89] Symptoms of perinatal TB may be present at birth, but more commonly begin by the second or third week after delivery.[88,89] The most frequent signs and symptoms of congenital TB are hepatomegaly (76%), respiratory distress (72%), fever (48%) and lymphadenopathy (38%).[15] History of maternal TB may be lacking, especially in cases of extrapulmonary TB. In more than 50% of congenital TB cases, maternal TB was diagnosed only after it was diagnosed in the neonates.[80,85,88] Therefore, the current approach to investigate only those neonates born to the mothers with known TB would miss a large proportion of perinatal TB, who may otherwise be treated as neonatal sepsis.[86,88,89] If index of suspicion for TB in the neonates is high, it would be appropriate to initiate maternal investigations for TB.[85]

In perinatal TB, tuberculin skin test is usually negative, and it usually takes 1–3 months to be positive. Most infants have abnormal chest radiographic findings, such as adenopathy, consolidation with cavitation, and diffuse parenchymal infiltrates.[80,85,86,88] In most of the cases, the infants are put on empirical antibiotics, and diagnosis of TB is delayed. If the infant does not improve with empirical antibiotics, further investigations for TB are carried out.[88]

Positive smear and/or culture results can often be obtained from gastric washings, endotracheal aspirate, ear discharge, spinal fluid, or bone marrow aspirates. Therefore, one should at least test gastric and endotracheal aspirates for acid-fast bacilli for infants born to mothers with TB.[86,89,90] Placental studies for TB are essential in this situation.[5] The baby should be observed for signs and symptoms of TB.

If the baby is symptomatic, a chest X-ray is needed along with cerebrospinal fluid study. The second line of investigations would be ultrasonography of abdomen, and a liver biopsy. If these tests confirm/indicate TB, anti-TB drugs should be started without delay to prevent high fatality associated with this condition. Children on treatment with anti-TB drugs should have serial blood counts, liver function test, serum creatinine and hearing assessment periodically.

Mother and baby should stay together and the baby should continue to breast-feed regardless of the mother's status of TB.[25,78] If the mother is smear-negative for acid-fast bacilli before delivery, and active TB in the infant is ruled out, the baby is vaccinated with Bacillus Calmette-Guérin (BCG). If the mother is smear-positive for acid-fast bacilli shortly before delivery, this is considered to be a high-risk perinatal condition for the baby acquiring TB infection.[5] The baby should be screened for congenital TB, and development of TB in infancy. The placenta must be thoroughly examined for TB.[5] Regardless of the severity of active disease, the patients usually become non-infectious within 2 weeks of starting anti-TB therapy, and numbers of viable bacilli are greatly reduced after only 24 h.[91] Modern chemotherapy is so effective that separation of baby from the mother is no longer considered mandatory.[92] However, separation may be considered only if the mother has been or is likely to be non-compliant to drug treatment, or organisms are resistant strains of *Mycobacterium tuberculosis*.[92] In smear-positive maternal TB, the WHO recommendations include: (i) immediate maternal treatment for TB; (ii) the child to be breast-fed normally (a barrier mask for the mother may be advised); (iii) the child should be given isoniazid chemoprophylaxis for 6 months; and (iv) immunization of the infant with BCG after stopping chemotherapy.[93,94] An alternative policy is to give isoniazid preventive therapy for 3 months, and then the infant is tested with a tuberculin test. BCG vaccination is administered if the tuberculin test remains negative.[94] However, if the tuberculin test is positive at the end of 3 months, chemoprophylaxis is continued for another 3 months, and BCG is given after stopping isoniazid[94] (Indian national guidelines do not recommend BCG in this situation, if the tuberculin test is positive).[25] Practice regarding perinatal prophylaxis of TB varies widely and it remains an unresolved issue.[91]

Limitations of the review

Although comprehensive, this review has several limitations: non-systematic nature of the review, limited availability TB-related data among pregnant women from South Asian countries (data mostly available from India),[7–11] and sparse evidence for maternal and perinatal outcomes from a very few analytical studies worldwide.[7,8,12,13,22] Some clinical evidences were taken from

studies outside the geographical boundaries of South Asian countries. Extrapolation of some relevant information was done from immigrants to non-Asian developed countries.[14] We have also shared some concepts and ideas from African nations, which were burdened with the problems of dual infection (HIV and TB).[59,60] TB and HIV co-infection was only briefly touched in this review.[61,62] Several recommendations are based on expert opinions from several national and international organizations with limited support from primary research.[68,69,72–74] As these limitations are unavoidable, we adopted a pragmatic approach of combining current evidences with our long experience of managing such cases.

Conclusions

In South Asian countries, maternal TB remains an unrecognized and underestimated tragedy. TB in South Asia is related to pervasive undernutrition compounded with overcrowding and inequity in healthcare service. The disease was less driven by HIV infection compared to Africa.[59,95,96] Diagnosis of TB during pregnancy is often delayed because of overlapping signs and symptoms of TB and pregnancy; reluctance of clinicians to perform radiological investigation in pregnant women; and relative difficulties in accessing affected organs/sites for biopsy, especially in extrapulmonary diseases. Sometimes, the dysfunctional and inaccessible health system of South Asian countries adds to the inordinate delay. Integrating screening TB symptoms during antenatal visits[95,96] while keeping a high index of suspicion, and early recourse to the investigations for TB during pregnancy might yield better detection of TB in South Asian countries.

TB in general (except lymphadenitis) predisposes pregnant women to a higher risk of having SGA, premature and LBW neonates. Furthermore, perinatal mortality is increased approximately fivefold among women with TB. These adverse perinatal outcomes are even more pronounced in women with advanced disease, late diagnosis, and incomplete or irregular drug treatment, which are more common in South Asian countries. There could be a synergy of TB, socioeconomic and nutritional factors, which might have contributed to adverse perinatal effects, especially in these low-income countries.

Undiagnosed maternal TB remains a curse for the South Asian region. As active TB poses a great risk to pregnant women and their fetuses, TB in pregnancy must be treated with a full course of anti-TB drugs. Barring streptomycin, all first-line anti-TB drugs are considered safe during pregnancy. Perinatal TB is difficult to diagnose and can be fatal. Diagnosis of congenital/perinatal TB is less frequent, especially in low-resource South Asian countries, as most of these affected infants are often treated as having sepsis or pneumonia. All neonates born to tuberculous mothers should be screened for TB, and the placenta should be studied for evidence of TB. Women with TB can breastfeed normally while taking anti-TB drugs. Modern chemotherapy is so effective that separation of the mother and infant is not advocated, especially in low-income South Asian countries, where artificial feeding poses a big health hazard for the infants.[78]

Early diagnosis of maternal TB and perinatal TB is the biggest hurdle in the management of TB during pregnancy. Co-ordination between two health-care providers – maternal and child health-care services, and the national TB control program – is very urgent to break many barriers of maternal TB management. In addition, a coherent system of co-operation between the hospital and community services is also essential. Advocacy, communication and social mobilization are vital issues to bridge pre-existing gaps between the health system and the community by enhancing knowledge, attitude and practice related to TB, especially in pregnant women.

There remain several major knowledge gaps in the management of TB during pregnancy. Interaction between poverty and undernutrition on one hand, and combination of pregnancy and TB, on the other, deserve thorough exploration by a large-scale analytical study in South Asian countries. A multicenter comparative cohort study could also overcome the current knowledge gaps in the perinatal implications of maternal TB, which remains a widely deserted and neglected area.

Contribution of Authorship

N.J. conceived the idea of this article and provided the framework. All authors collected and analyzed the relevant information. N.J. wrote the first draft, and A.K.S. added perinatal management. Initial draft was modified by S.B., N.A. and A.K.S. with critical inputs. All authors read and approved the final manuscript.

Details of Ethics Approval

None required.

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