

Adverse neonatal outcome associated with maternal tuberculosis in a public tertiary centre: a retrospective cohort study

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ABSTRACT

Introduction: The aim of this study was to evaluate a group of infants born to women with tuberculosis (TB) during pregnancy to determine the neonatal morbidities and its outcomes associated with tuberculosis in pregnancy.

Materials and Methods: Data from January 2007 to December 2021 was collected for analysis as part of a retrospective cohort study. This study was conducted in a tertiary public hospital in Malaysia, Hospital Sultan Idris Shah (HSIS). Cases were identified from the hospital's bacille Calmette-Guerin (BCG) vaccination notification forms and merged with records from the neonatal intensive care unit's census. Controls were infants born to mothers unaffected by TB within the same hospital and year as the index case (1:4 ratio). Descriptive statistics and logistic regression were used to analyse the data. The main outcome measures were the risk of congenital tuberculosis, premature birth, low birth weight, small for gestational age and low APGAR score.

Results: Infants born to mothers with TB exhibited a two-fold increased risk of low birth weight (Odds Ratio, OR: 2.51; 95% Confidence Interval, 95%CI: 1.31, 4.81), with an even higher risk (OR: 3.29; 95%CI: 1.637, 6.612) if active TB was diagnosed during the index pregnancy. These infants also had an elevated risk of being small for gestational age compared to infants born to healthy mothers (OR: 2.48; 95%CI: 1.15, 5.39). Furthermore, adverse outcomes were also more frequently detected among infants of mothers with pulmonary TB compared to those with extra-pulmonary TB. Infants born to mothers with PTB were more likely to be born with low birth weight (OR: 1.60; 95%CI: 1.095, 2.339). No cases of congenital TB were reported throughout the entire study period.

KEYWORDS:

Low birth weight, maternal, neonatal, respiratory failure, tuberculosis

INTRODUCTION

Tuberculosis (TB) remains one of the foremost infectious diseases worldwide, persisting as a significant health concern in many countries. According to the World Health

Organization (WHO), the global estimates place the number of individuals infected with TB were at 10 million, with the majority (45%) originating from Southeast Asian countries.¹ As per the latest statistics, Malaysia is categorised as a nation grappling with an intermediate TB burden.¹ In 2022, Malaysia recorded an estimated TB incidence rate of 113 per 100, 000 population, with female aged 15 and above constituting approximately 33% of those affected.²

The impact of TB on pregnancy outcomes is well-documented.³ A comprehensive analysis, involving 3384 pregnancies with TB, revealed that pregnant women with active TB were found to have increased odds of maternal morbidity, anaemia in pregnancy, caesarean birth and preterm birth compared to their healthy counterparts.³ In addition TB is also recognised as one of the primary causes of non-obstetric maternal mortality, particularly in countries with a high prevalence of human immunodeficiency virus (HIV) infection.⁴⁻⁶ Conversely, there is inconsistency in reports regarding the effect of TB on the unborn foetus. Some series have documented complications such as prematurity, low birth weight and increased neonatal mortality.⁷⁻¹¹ However, other studies have indicated no discernible difference in foetal outcomes between mothers with TB during pregnancy and unaffected mothers.¹²⁻¹⁴

Despite our status as an endemic country, there is still a lack of published data on tuberculosis infection among pregnant women and its impact on the unborn baby. This study was designed to assess the neonatal outcome of infants born to women with tuberculosis during pregnancy in our country.

MATERIALS AND METHODS

We conducted a retrospective analysis of the medical records for 30 consecutive infants born to mothers whose pregnancies were complicated with TB infection. These births occurred at a tertiary-level public hospital between January 2007 and December 2021. Cases were identified from the departmental records where infants of TB mothers were routinely admitted for evaluation and management. Inclusion criteria comprised of infants born to all mothers who either conceived while undergoing anti-tuberculosis therapy or were diagnosed with TB during pregnancy or the postpartum period. The diagnosis of TB was confirmed through clinical

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Table I: Neonatal outcome associated with TB infection in pregnancy compared to control (n = 150).

Neonatal outcome	Mother with TB (n=30) n (%)	Mother without TB (n=120) n (%)	p-value	OR (95%CI)
Birth weight (kg) median (IQR)	3.06 (0.8)	3.024 (0.5)	0.581 ^c	
Prematurity (<37 weeks)				
Yes	5 (16.7)	12 (10.0)	0.336 ^a	
No	25 (83.3)	108 (90.0)		
Birth weight				
low	8 (26.7)	11 (9.2)	0.026 ^a	2.51 (1.31 – 4.81)
normal	22 (73.3)	109 (90.8)		
Small for gestational age (SGA)				
Yes	6 (20.0)	11 (9.2)	0.110 ^a	
No	24 (80.0)	109 (90.8)		
APGAR score <7 at 1 minute of life				
Yes	1 (3.3)	6 (5.0)	1.000 ^b	
No	29 (96.7)	114 (95.0)		

a = Pearson Chi-square, b = Fisher exact test, c= Mann Whitney

Table II: Neonatal outcome associated with active TB infection during pregnancy compared to control (n=144).

Neonatal outcome	Mother with active TB (n=24) n (%)	Mother without TB (n=120) n (%)	p-value	OR (95% CI)
Birth weight (kg) median (IQR)	3.100 (1.0)	3.08 (0.5)	0.612 ^c	
Prematurity (<37 weeks)				
Yes	5 (20.8)	12(10.0)	0.163 ^b	
No	19 (79.2)	108 (90.0)		
Birth weight				
Low	8 (33.3)	11 (9.2)	0.004 ^a	3.29 (1.637-6.612)
Normal	16 (66.7)	109 (90.8)		
Small for gestational age (SGA)				
Yes	6 (25.0)	11 (9.2)	0.040 ^a	2.49 (1.15-5.39)
No	18 (75.0)	109 (90.8)		
APGAR score <7 at 1 minute of life				
Yes	1 (4.2)	6 (5.0)	1.000 ^b	
No	23 (95.8)	114 (95.0)		

a = Pearson Chi-squared , b = Fisher exact test, c = Mann Whitney

Table III: Neonatal outcome associated with PTB compared to EPTB infection in pregnancy (n = 24).

Neonatal outcome	Mother with PTB (n=18) n (%)	Mother EPTB (n=6) n (%)	p-value	OR (95% CI)
Birth weight (kg) median (IQR)	2.765 (1.0)	3.485 (0.6)	0.026 ^b	
Prematurity (< 37 weeks)				
Yes	5 (27.8)	0 (0.0)	0.147 ^a	
No	13 (72.2)	6 (100.0)		
Birth weight				
Low	8 (44.4)	0 (0.0)	0.046 ^a	1.60 (1.095-2.339)
Normal	10 (55.6)	6 (100.0)		
Small for gestational age (SGA)				
Yes	6 (33.3)	0 (0.0)	0.102 ^a	
No	12 (66.7)	6 (100.0)		
APGAR score < 7 at 1 minute of life				
Yes	1 (5.6)	0 (0.0)	0.550 ^a	
No	17 (94.4)	6 (100.0)		

a = Fisher exact test, b = Mann Whitney

manifestations of active infection, along with supporting evidence from acid-fast-bacilli (AFB) stains, Mycobacterium tuberculosis culture or histological studies. Cases with missing or irretrievable medical records were excluded from analysis.

We employed a purposive sampling strategy to select control, each infant born to a mother with a TB case was paired with four infants (1:4 ratio) born to mothers unaffected by TB within the same hospital and year as the index case. Subsequently, we randomly selected samples from the control group, and matched them to the cases based on maternal age and maternal morbidities, which included diabetes mellitus and/or gestational diabetes, as well as pre-existing hypertension and/or pregnancy-induced hypertension.

The medical records of both cases and controls were retrieved from the hospital's electronic medical records system. Subsequently data on primary neonatal outcomes or dependent variables including prematurity (defined as birth occurring before 37 completed weeks), birth weight, low birth weight (defined as birth weight less than 2,500 grams), small for gestational age (SGA) (defined as a birth weight below the 10th centile for age and gender), low APGAR score at 1 minute of life (defined as APGAR score less than 7 at 1 minute of life) and congenital TB were carefully identified, extracted and recorded into a standardised proforma. Additionally, maternal TB status, an independent variable, was also noted and recorded for further analysis. Congenital TB was defined as an infant presenting with a proven tuberculosis lesion associated with one of the following conditions: the lesion occurring in the first week of life, primary hepatic complex, maternal genital tract or placental tuberculosis or exclusion of postnatal transmission through a comprehensive investigation of contacts.¹⁵

The analysis of all data was carried out using IBM Statistical Package for the Social Sciences software, version 29.0 (SPSS Inc., Chicago, USA). Cohort comparability was assessed using the test of proportion, while descriptive analysis summarises the study population's demographics, with mean or median and standard deviation or interquartile range for continuous data, frequencies and percentages for categorical variables. We then compared the categorical variables between cases and controls using Pearson chi-squared test or Fisher exact test. Non-parametric test which is the Mann-Whitney test was performed to compare the birth weight between the two groups. Then multinomial logistic regression analysis was conducted with a power of 80% and a confidence level of 95% (95%CI). A p-value of <0.05 was considered statistically significant. Then, we computed the odd ratio and determined a 95% confidence interval to identify potential associations. Ethical approval was granted by the National Institute for Health (NIH) Malaysia (ref: NMRR ID-23-02386-ZNR).

RESULTS

During the study period, a total of 30 infants born to mothers diagnosed with TB infection were included. These mothers age ranged from 20-38 years, with a median age of 29 years. Out of the 30 mothers diagnosed with TB, 21 (70.0%) had pulmonary TB, while the remaining nine (30.0%) suffered from extrapulmonary infection: seven had lymph nodes

involvement, one had spinal TB and one had pleural TB. Among all cases of TB infection, six mothers (20%) conceived while undergoing anti-tuberculous therapy, while in 12 mothers (40%), treatment was initiated during the early stages of pregnancy. Anti-TB treatment was commenced during the second and third trimester in seven cases (23.3%) and five cases (16.7%) respectively.

A total of 120 healthy mothers constituted the control group, and they were comparable to the group of mothers with TB infection in terms of age, parity, nationality, ethnicity and pregnancy-related complications.

Neonatal outcome, including prematurity and small for gestational age, were observed as higher rates among infants born to mothers with TB compared to those born to healthy mothers (16.7 vs. 10.0% and 20.0 vs. 9.2% respectively) (Table I). However, bivariate analysis did not reveal any statistically significant difference ($p>0.05$). Infants born to mothers with TB exhibited a two-fold increased risk of low birth weight (OR 2.51; 95%CI: 1.31 – 4.81), with an even greater risk observed if active TB was diagnosed during pregnancy (OR 3.29; 95%CI: 1.637 – 6.612) (Table II). These infants also had an elevated risk of being small for gestational age compared to infants born to healthy mothers (OR 2.49; 95%CI: 1.15 – 5.39). Neonatal outcomes were more frequently observed among infants born to mothers with pulmonary TB compared to those with extra-pulmonary TB (Table III). While there were no significant statistical differences were found in the rates of premature birth, SGA and low APGAR score at 1 minute of life between the two groups, we found that infants born to mothers with PTB were more likely to be born with low birth weight (OR 1.60; 95% CI 1.095 – 2.339). Notably, no cases of congenital TB or neonatal mortality were reported throughout the study period.

DISCUSSION

As mentioned by several studies, maternal infection with Mycobacterium tuberculosis during pregnancy may pose a risk for foetal complications.^{7,8,11} In a study by Narayan Jana and colleagues from Northern India, infants born to mothers with pulmonary TB exhibited a two-fold increase in the risk of foetal distress (RR: 2.4; 95%CI: 1.2 – 4.7), low birth weight (RR: 2.1; 95%CI: 1.4 – 3.1), SGA (RR: 2.6; 95%CI 1.4 – 4.6), prematurity (RR: 2.1; 95%CI: 1.2 – 3.4) and a six-fold higher risk of perinatal mortality (RR: 6.4; 95%CI: 2.2 – 18.4) compared to healthy controls.⁷ Similar outcome were reported to be associated with extrapulmonary tuberculosis during pregnancy (except TB lymphadenitis).⁸ This finding is consistent with observations reported by Chopra et al.,¹¹ Our study aims to emphasise the effects of TB infection on newborns by comparing two cohorts from the study hospital.

The results from the current study revealed a significant relationship between TB infection during pregnancy and both low birth weight and being small for gestational age. The risk of being born with low birth weight or being small for gestational age was three to four times higher if active TB was diagnosed during pregnancy. This risk was even more pronounced when the diagnosis of infection was delayed, leading to a delay in the initiation of the anti-TB regimen.

Our findings align with the results obtained by other researchers who have documented similar neonatal outcomes.^{12,13,16} Lin et al., discovered significantly higher percentages of low birth weight and infants being small for gestational age among those born to mothers with TB infection during pregnancy, as compared to unaffected mothers.¹² In a recent population-based retrospective cohort study involving 243,682 deliveries in Israel, significantly higher rates of very low birth weight infants (birth weight <1500gm) were reported among mothers with TB compared to those born to healthy mothers (4.3 vs. 0.6%, p-value 0.03).¹⁵ Additionally, women with latent tuberculosis showed significantly higher rates of very low birth weight infants (5.6%), compared to women with active tuberculosis during pregnancy and those without tuberculosis (0.6% and 0.0%, respectively) (p<0.001).¹⁶ Conversely, Asuquo et al. analysed data from babies born to 24 mothers with TB in three hospitals in Birmingham, United Kingdom, in 2012, and they reported no differences in the rates of low birth weight and small for gestational age when compared to the healthy subjects.¹⁷ Likewise, a population-based survey that included 7.8 million births in the United States did not identify any adverse neonatal outcomes among infants born to mothers with TB during pregnancy.¹⁴ The inconsistencies in findings among these studies can be attributed to underlying differences in study design, patient selection, geographical variations, time periods and sample size. Furthermore, some investigators did not adequately control for certain confounding factors, such as common pregnancy-related complications like pregnancy-induced hypertension and gestational diabetes. The effects of TB on premature birth, low birth weight or small for gestational age could be indirectly influenced by placental insufficiency secondary to pregnancy-induced hypertension and gestational diabetes. In such cases, complication rates might be falsely high. To mitigate such issues, we matched the control subjects with the cases based on the presence of comorbidities.

Unfortunately, due to the nature of our study, our dataset did not allow for a detailed analysis of other potential confounding factors that may have adversely affected birth weight, such as socioeconomic factors, access to healthcare services and maternal nutritional status, as they were not routinely documented.

The in-utero growth of the foetus relies entirely on the functioning uteroplacental unit. TB infection or reactivation of latent TB may make pregnant women more susceptible to tuberculous bacillaemia. Consequently, the infection can disseminate to multiple organs, including the placenta and the maternal genital tract. Additionally, it can be vertically transmitted to the unborn foetus through the umbilical vein or by aspiration or ingestion of contaminated amniotic fluid. These transmissions can lead to the formation of primary complex in the liver, lung or gastrointestinal tract of the foetus.¹⁷ In our cohort of patients, no babies were born with congenital TB and there were no reported neonatal deaths among infants born to mothers with TB. These findings contrast with previous observations from studies conducted in India, Mexico and United Kingdom,^{7,19,20} where a three- to six-fold perinatal mortality rates was observed among infants

born to mothers with TB compared to unaffected mothers. However, it's important to note that all the perinatal deaths in those studies were attributable to complications of prematurity and small for gestational age.

Compared to earlier studies, both our study and more recent series have reported similarly improved outcomes. This can be attributed to significant advances in the healthcare system, as well as the improved socioeconomic and nutritional status of pregnant mothers. The majority (83.3%) of our cases were diagnosed rather early, either just prior to conception or during the first two trimesters. Only five cases were diagnosed late in the third trimester. Moreover, the early administration of the anti-TB regimen was effective in preventing or, if necessary, reducing the risk of adverse neonatal outcomes. Furthermore, advancements in obstetric and neonatal care have led to a lower incidence of premature birth, better overall prognosis and reduced morbidity and mortality for babies. Although concerns have been raised about the teratogenic effects of anti-TB medication, no congenital anomaly were observed among the infants in our study. Since this was a single-centre study, the results may not directly reflect the true disease burden. It is important to mention that the presence of latent tuberculosis infection (LTBI) among mothers has not been established which might impact the accuracy of the data about the prevalence of TB in the population under study. However, it has provided valuable information to stakeholders regarding the incidence rate of active TB among the population of interest, namely pregnant women in Malaysia. Given that universal screening for TB infection is not a routine practice and is typically performed only when women present with symptoms, highlighting the neonatal outcomes is crucial. This information can serve to educate and encourage pregnant women to undergo TB testing.

CONCLUSION

In conclusion, we find that tuberculous infection in pregnancy is strongly associated with low birth weight and small for gestational age infants. This underscores the importance of early diagnosis and treatment of TB infection during pregnancy to mitigate neonatal outcome. Moreover, it emphasises the need for continued efforts to improve healthcare and socioeconomic conditions for pregnant mothers. Healthcare providers should consider screening women presenting for prenatal and peripartum care for tuberculosis.

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CONFLICTS OF INTEREST

The authors declared no conflict of interest.

DECLARATIONS

This study was approved by the medical research and ethics committee, Ministry of Health Malaysia NMRR ID-23-02386-ZNR.

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