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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

MMED RESEARCH REPORT

A DESCRIPTIVE STUDY OF NEONATES BORN TO MOTHERS WITH TUBERCULOSIS IN A LOW MIDDLE INCOME COUNTRY

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20th of July 2021

Declaration

I, Sonia Mariza Neves da Silva declare that this Research Report is my own, unaided work. It is being submitted for the Degree of MMED Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



_____ 20th of July 2021

Dedication

I dedicate this work to my mother,

who has always believed in my dreams and remained a pillar of strength through it all

Acknowledgements

I would like to give heartfelt thanks to my supervisors Prof Ballot and Dr Ramdin for their guidance and unwavering support. Many thanks are also extended to the staff at Charlotte Maxeke Johannesburg Academic Hospital involved in the data collection for the neonatal unit.

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List of abbreviations

TB	Tuberculosis
SA	South Africa
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
HIV	Human immunodeficiency virus
ARV	Antiretroviral
VL	Viral load
CD4	Cluster of differentiation 4
EOS	Early-onset sepsis
LOS	Late-onset sepsis
RDS	Respiratory distress syndrome
CLD	Chronic lung disease
LMIC	Low middle income country
LTB	Latent tuberculosis
ATB	Active tuberculosis
MDR TB	Multidrug-resistant tuberculosis
CTB	Congenital tuberculosis
PTB	Postnatal tuberculosis
REDCap	Research electronic data capture
WITS	The University of the Witwatersrand
CXR	Chest radiograph
AFB	Acid fast bacilli
GXP	Gene Xpert
INH	Isoniazid
RIF	Rifampicin
XDR TB	Extensively drug-resistant tuberculosis
JHB	Johannesburg
BCG	Bacillus Calmette-Guérin
PCR	Polymerase chain reaction
NCPAP	Nasal continuous positive airway pressure
IPPV	Intermittent positive pressure ventilation

A Descriptive Study of Neonates born to Mothers with Tuberculosis in a low income country

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ABSTRACT.

Background. Tuberculosis (TB) in pregnancy is associated with unfavourable maternal and neonatal outcomes. A paucity of South African (SA) data exists regarding the impact of maternal TB on neonates.

Objectives. To describe demographical and clinical characteristics and outcomes of mothers diagnosed with TB and their neonates and compare it to TB negative mothers and their neonates.

Methods. This was a retrospective unmatched case-control study of sick and premature neonates admitted to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 1 January 2013 and 31 December 2017. Cases were identified as neonates born to mothers with TB. Controls included the next two inborn neonates delivered to TB negative mothers.

Results. Maternal TB prevalence in this study was 0.9%. The majority of mothers confirmed human immunodeficiency virus (HIV) positive had TB and few were on antiretroviral (ARV) therapy. If taking ARVs, these mothers commonly defaulted treatment, had a higher viral load (VL) and a lower cluster of differentiation 4 (CD4) compared to the control group. Likewise, TB exposed neonates were more likely to be HIV positive. Mothers with TB were at higher risk for spontaneous abortions, pre-eclampsia, maternal anaemia, chorioamnionitis, pneumonia and more likely to require ventilation. Tuberculosis exposed neonates had higher rates of early-onset sepsis (EOS), late-onset sepsis (LOS), respiratory distress syndrome (RDS), chronic lung disease (CLD) and need for ventilation. The only factor associated with a high risk of TB in mothers was CD4.

Conclusion. Unfavourable neonatal and maternal outcomes associated with TB found at CMJAH were consistent with that reported globally.

Background

Tuberculosis (TB) is widely prevalent today, maintaining its status as one of the leading deadliest communicable diseases.[1,2] Tuberculosis has evaded eradication rendering it a global public health problem with a high burden of disease.[1-3] The incidence of TB in pregnancy is unknown but thought to be higher in low middle income countries (LMIC).[4,5] Pregnant women diagnosed with latent TB (LTB) are more likely to progress to active TB (ATB).[1,6] Active TB is associated with a higher incidence of unfavourable maternal outcomes such as death, chorioamnionitis, spontaneous abortion, postpartum anaemia, pre-eclampsia, pneumonia and ventilatory support.[4-9] Tuberculosis is a common opportunistic infection present in individuals with human immunodeficiency virus (HIV).[5] High morbidity and mortality rates are affiliated with HIV-associated TB during pregnancy.[9-11] Pregnancy-related multidrug-resistant (MDR) TB and late initiation of anti-TB treatment have also been correlated with less favourable outcomes.[5,6,9]

The disease burden associated with neonatal TB is difficult to quantify.[2] Despite classifying congenital TB (CTB) as rare, a South African study reported the transmission rate of Mycobacterium Tuberculosis in neonates as 16%.[2,3,5,7,10] Tuberculosis in the neonatal period is subdivided into CTB and postnatal TB (PTB).[1] Postnatal TB is contracted within the first weeks of life from a contagious adult in the form of airborne particles.[1,2] In comparison, CTB is acquired in utero or during delivery.[1-3,5,7,12-14] Distinguishing between CTB and PTB for the purpose of a diagnosis can be challenging due to vague signs and symptoms.[1,3,5]

Neonates born to mothers with ATB have a higher incidence of poor outcomes namely an increased risk of premature birth, low birth weight, intrauterine growth retardation, small for gestational age, RDS and a six-fold increase in perinatal death.[1,4-7,9,11,15] Neonates born to mothers with TB were also more likely to have a congenital abnormality.[6] South Africa (SA) has one of the highest-burden of TB and HIV worldwide.[10] Multidrug-resistant TB is a persistent threat in SA as evidenced by the increasing number of cases reported.[16,17] The impact of MDR TB and HIV on mothers and their offspring is difficult to quantify due to limited data available.[18] Despite the high prevalence of HIV and its association with TB, there is a paucity of research on the effects of maternal TB on neonatal outcomes internationally and in SA. Our aim was to describe the outcomes of mothers diagnosed with TB and their neonates and compare it to mothers unexposed to TB and their offspring, therefore contributing to the local and regional evidence base which would enhance our understanding of the burden of TB disease in neonates.

Methods

This was a retrospective unmatched case-control study using data from the CMJAH neonatal database. The study population included sick and premature neonates born to mothers with documented TB admitted to the neonatal unit at CMJAH between 1 January 2013 and 31 December 2017. Neonates for whom files could not be retrieved, were excluded as well as infants born to mothers with unknown TB status. The control group comprised of sick and premature neonates born to mothers without TB.

Data collection

Data was collected on discharge of patients from clinician completed hospital records for the purpose of a clinical audit. Research Electronic Data Capture (REDCap) hosted by the University of the Witwatersrand (WITS) was used to capture and manage the data.[19] Neonatal and maternal outcome to hospital discharge, obstetric information, neonatal and maternal clinical and demographic details were retrieved from the database for statistical analyses. Patients were identified from the database reviewed records.

Maternal TB was defined as a diagnosis of TB in the labour room notes as documented either by chest radiograph (CXR) or positive sputum for acid-fast bacilli (AFB) and Gene Xpert (GXP). Based on the results of the GXP, mothers were classified as either having rifampicin sensitive or resistant TB. Multidrug-resistant TB was defined as TB that did not respond to two anti-TB drugs namely isoniazid (INH) and rifampicin (RIF) as detected on GXP.[20] Extensively drug-resistant TB (XDR TB) is resistant to INH and RIF, plus any fluoroquinolone and at least one of the three injectable second-line drugs.[20] Respiratory distress syndrome, a disease of prematurity is characterised by a deficiency of surfactant leading to signs of respiratory distress necessitating oxygen.[21] Chronic lung disease was defined as requiring supplemental oxygen for more than 28 days.[22] Early-onset sepsis constituted a positive blood culture within 72 hours from birth and late-onset sepsis was defined as a positive blood culture > 72 hours after birth.

In this study, we combined the two disease entities namely CTB and PTB using the term ‘perinatal TB’. Perinatal TB was defined as TB present in the first month of life as diagnosed by positive GXP obtained from the neonate or histology suggestive of TB detected in the placenta.

Study site and routine care

Charlotte Maxeke Johannesburg Academic Hospital is a quaternary hospital in Johannesburg (JHB) that functions as a referral centre for surrounding clinics and district hospitals.

Mothers suspected of TB had a CXR ordered and sputum tested for AFB and GXP done. When TB is suspected in the neonate, gastric aspirate specimens are sent for TB microscopy, culture and GXP.[2,13,14] Gastric lavage is positive in 70% of cases and is the preferred method of testing in infants because they swallow their sputum and cannot expectorate.[14] Ziehl-Neelsen staining, culture and histopathological examination of the placenta remains the gold standard for diagnosing CTB.[23]

Neonates born to mothers diagnosed with TB were admitted for TB workup. For both asymptomatic and symptomatic neonates exposed to TB, no Bacillus Calmette-Guérin (BCG) vaccine was administered at birth. Gastric aspirates for AFB and TB culture was done as well as a CXR. Asymptomatic neonates were started on prophylactic INH for 3 months and reviewed at follow up clinic 3 months later. Symptomatic infants were notified and initiated on anti-TB treatment. Neonates born to mothers with MDR or XDR TB were managed on an individual basis in consultation with a paediatric infectious disease specialist. Placentas belonging to TB confirmed mothers were examined and sent off for histology.

All pregnant women who presented at CMJAH were offered an HIV test with pre and post-test counselling. Mothers testing positive for HIV were initiated on antiretroviral (ARV) therapy and had their viral loads (VL) and cluster of differentiation 4 (CD4) counts monitored. Similarly, all neonates that were born to HIV positive mothers were tested for HIV using a polymerase chain reaction (PCR) test. Neonatal HIV prophylaxis prescribed was dependent on the mother's VL and the duration of ARV therapy before delivery. [24]

Statistical methods

Controls for this study were not matched to the study population and were taken from the database by systematically selecting the next two sick or premature inborn neonates delivered to TB negative mothers. Statistical analysis was done using SPSS Statistics (IBM) version 25. Categorical variables were described using frequencies and percentages. Continuous variables were described as means and standard deviations where data were distributed normally or median and range if skewed. Demographic and clinical characteristics for control and case groups were compared. Independent t-test was used to compare differences in means across cases and controls for normally distributed continuous variables. Pearson Chi-square or Fischer exact tests were used to determine if there was a statistically significant difference in frequency between cases and controls. A p-value of less than 0.05 was considered significant. For all variables found to be significantly different, a logistic regression model was used to calculate adjusted odds ratios for associations with TB.

Ethics

The study was approved by the Human Research Ethics Committee at WITS, JHB (Clearance Certificate No. M180614).

Results

A total of 8684 sick and premature neonates were admitted to CMJAH between 1 January 2013 and 31 of December 2017. Four hundred and twenty-one of these neonates were excluded as they were born to mothers with unknown TB results. Seventy-four files were retrieved and one file was excluded, resulting in a final case sample of 74. The control group was comprised of 148 neonates born to mothers without TB.

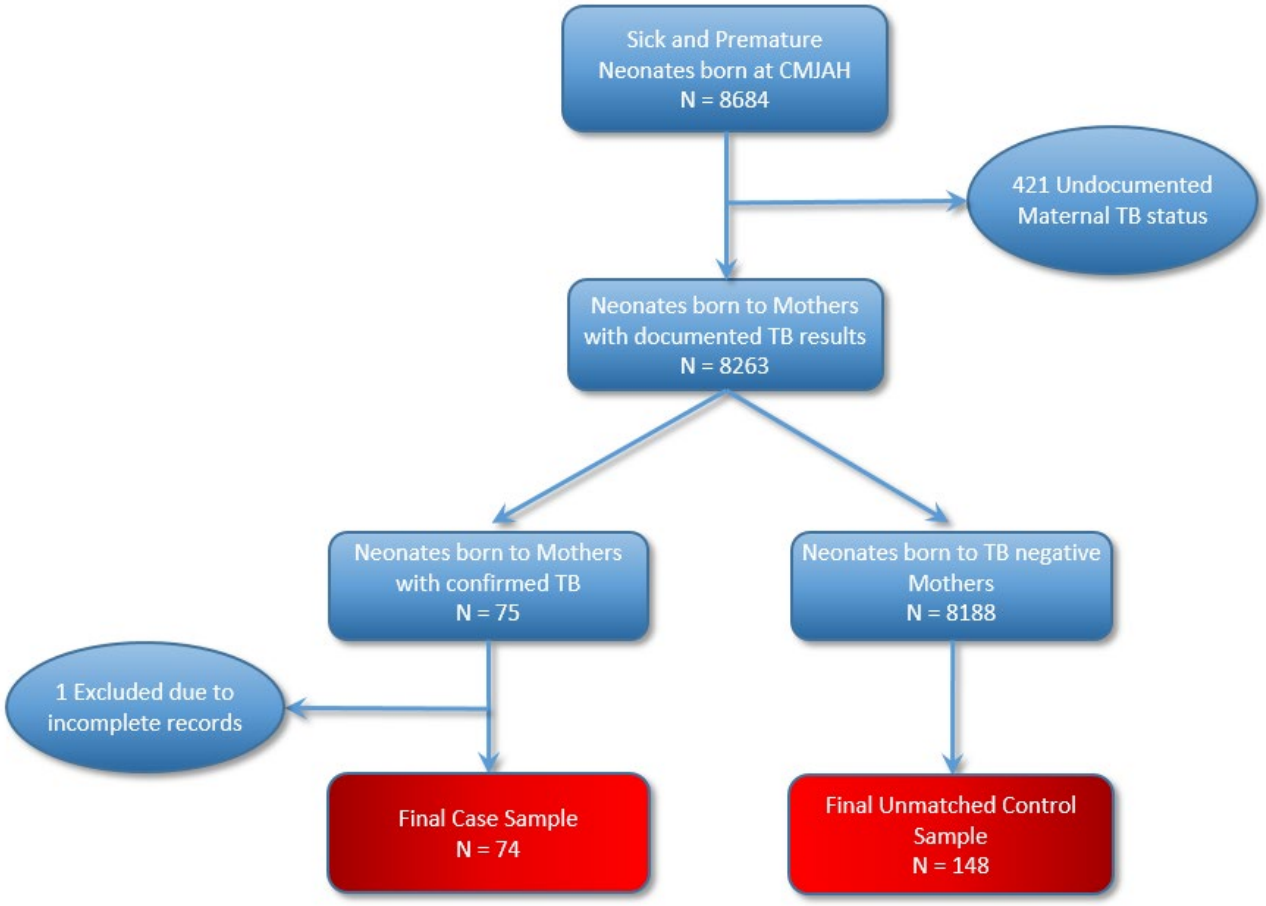


Figure 1. Flow diagram describing sample selection

Maternal characteristics

The following description of maternal clinical and demographical data is summarised in Table 1. The prevalence of maternal TB in this study was 0.9%, of which MDR TB accounted for 15% (11/74). Most of the TB positive mothers were initiated on first-line compared to second-line TB treatment (63/74, 85% vs 11/74, 15%) and (7/74) 10% of mothers defaulted TB treatment. The majority of mothers were initiated on TB treatment during pregnancy (47/74, 64%), followed by those started at delivery (15/74, 20%), with the minority of mothers being initiated before the pregnancy (12/74, 16%). The presence of maternal TB was found in the following sites namely pulmonary 81% (60/74), abdomen 5% (4/74), meningeal 4% 3/74), spinal 3% (2/74), cardiac 3% (2/74), thyroid 1% (1/74) , lymphatic 1% (1/74) and cryptococcal 1% (1/74). Tuberculosis was not detected in any of the thirteen placentas sent for histopathological examination.

When comparing maternal clinical characteristics for cases and controls, there was no significant difference in the mode of delivery and antenatal care. The majority of mothers confirmed HIV positive were from the case group. TB negative mothers were more likely to be on ARVs than TB positive mothers. Thirty-five percent (19/55) of HIV positive mothers in the case group defaulted ARV therapy versus only 8% (3/38) in the control group. On average, mothers with TB had higher VL than the control group (111 203.38 count +/- 205 848.713 vs 488.13 +/- 1025.085) $p = 0.044$ and lower CD4 than the control group (225.51 +/- 259.863 vs 494.90 +/- 217.202) $p < 0.001$.
Results showed that mothers with TB were more likely to have pregnancy related complications including spontaneous abortion (15/74, 21% vs 12/148, 8%) $p = 0.006$, pre-eclampsia (18/74, 24% vs 17/148, 11%) $p = 0.008$, maternal anaemia (38/74, 51% vs 27/148, 18%) $p < 0.001$, chorioamnionitis (9/74, 12% vs 3/148, 2%) $p = 0.002$ and pneumonia (5/74, 7% vs 0/148, 0%) $p < 0.001$. Significantly more mothers were ventilated in the case group compared to the control group $p < 0.001$, with many mothers requiring ventilation and facemask oxygen if confirmed TB positive. The mortality for mothers with TB (6/74, 8%) was higher than that for mothers without TB (1/148, 0.5%).

Neonatal characteristics

The following description of neonatal clinical and demographical data is summarised in Table 2. Perinatal TB was not diagnosed in the neonates born to TB confirmed mothers. The incidence of HIV amongst the neonates was 3%. All of the TB exposed neonates received TB prophylaxis. There was no significant difference in the sex and neonatal HIV prophylaxis between cases and controls. Similarly no significant difference in birth weight or gestational age was found between the two groups

(2070.47 grams +/- 845.802 vs 2150.70 grams +/- 936.376)) p = 0.523 (34.03 weeks +/- 4.14 vs 34.39 weeks +/- 4.82) p = 0.565. More TB exposed neonates were confirmed HIV PCR positive than TB unexposed neonates (2/74, 3% vs 0/38, 0%) p = 0.04.

Tuberculosis exposed neonates commonly developed EOS and LOS more often than TB unexposed neonates. The organisms causing EOS and LOS included *C. parapsilosis*, *A. baumannii*, *C. glabrata* and *C. krusei*. Tuberculosis exposed neonates were significantly more likely to have neonatal related complications including RDS and CLD and less likely to have congenital infections and congenital abnormalities.

Fifty-nine percent of neonates were ventilated in the case group compared to the neonates in the control group with more TB exposed neonates requiring nasal continuous positive airway pressure (NCPAP) than intermittent positive pressure ventilation (IPPV). Tuberculosis exposed neonates were ventilated on average for longer than non-exposed TB neonates. Receiving postnatal steroids was not found to be significant. Neonates from both groups were admitted to hospital for a similar duration of time (15.73 +/- 16.261 vs 13.92 +/- 17.845) p = 0.45. No significant difference in neonatal mortality was found between the two groups (p = 0.3).

Table 1: Maternal clinical and demographic characteristics

Characteristics	**Case n/N (%) (74)**	**Control n/N (%) (148)**	**p-value**
Maternal factors:			
Mode of delivery Vaginal Caesarean	 36/74 (49) 38/74 (51)	 72/148 (48) 76/148 (51)	1.0
Antenatal Care	61/74 (82)	125/148 (84)	0.7
HIV status	55/74 (74)	38/148 (26)	<0.001
ARV	49/55 (89)	38/38 (100)	0.01
Defaulted ARV	19/55 (35)	3/38 (8)	0.02
Ventilation	11/74 (15)	1/148 (0.7)	<0.001
Type of ventilation Facemask Intubation	 6/74 (8) 5/74 (7)	 0/148 (0) 1/148 (0.5)	<0.001
Deaths	6/74 (8)	1/148 (0.7)	<0.001

Table 2: Neonatal clinical and demographic characteristics

Characteristics	Case n/N (%) (74)	Control n/N (%) (148)	p-value
Neonatal factors:			
Sex Female Male	 36/74 (49) 38/74 (51)	 67/148 (45) 81/148 (55)	0.63
HIV prophylaxis	54/55 (98)	38/38 (100)	0.3
Congenital infections	1/74 (1)	0/148 (0)	0.1
EOS	2/74 (3)	0/148 (0)	0.025
LOS	11/74 (15)	17/148 (11)	0.4
Congenital abnormalities	6/74 (8)	15/148 (10)	0.7
RDS	39/74 (53)	52/148 (35)	0.012
Ventilation	44/74 (59)	65/148 (44)	0.018
Type of ventilation NCPAP IPPV	 38/74 (51) 6/74 (8)	 62/148 (42) 3/148 (2)	0.04
CLD	9/74 (12)	8/148 (5)	0.037
Postnatal steroids	19/74 (26)	44/148 (29)	0.5
Deaths	7/74 (9)	21/148 (14)	0.3

On multivariable logistic regression, the only factor associated with a high risk of TB in mothers was CD4.

Discussion

This study shows that ATB during pregnancy is associated with poor neonatal and maternal outcomes. Mothers with TB were more likely to have a spontaneous abortion, pre-eclampsia, maternal anaemia, chorioamnionitis, pneumonia and require ventilatory support. Likewise, neonates exposed to TB had higher rates of EOS and LOS, RDS, CLD, the need for ventilatory support and a longer duration of ventilation. Despite perinatal TB being associated with a higher neonatal mortality in the literature, the mortality rate for both case and control groups in the study was similar. This could be in part due to more neonates being initiated on TB prophylaxis and that maternal TB is being diagnosed and treated earlier in pregnancy.

In our retrospective unmatched case-control study, none of the neonates born to TB positive mothers were diagnosed with perinatal TB. The prevalence of perinatal TB was therefore in keeping with the literature but significantly lower than reported in a Durban based SA study.[2,3,5,7,10] Of note, only 13 placentas belonging to TB positive mothers were sent for TB testing. Furthermore, the placentas underwent histopathological examination alone, without TB culture testing or Ziehl-Neelsen staining.

This along with the low number of placentas submitted for testing could account for the lack of perinatal TB diagnosed.

The prevalence of TB in pregnant women in the study was 0.9%. Africa is said to have the highest case burden of TB in pregnant women and the burden is thought to be higher than that of the general population.[3,5,17] This is as a result of many cases remaining undiagnosed due to a low threshold of suspicion and similarity of TB symptoms with the physiological symptoms of pregnancy.[3,5,17] As a result, the prevalence of pregnancy-related TB could be higher than reported in the study.
On the grounds of a high burden of disease, the World Health Organisation (WHO) has implemented the Sustainable Development Goals with the aim of ending the global TB epidemic by 2035.[25] To this end, despite the challenge of distinguishing between TB and the physiological symptoms of pregnancy, 64% (47/74) women diagnosed with TB were initiated on anti-TB treatment during the course of their pregnancy, highlighting physician's efforts to recognise and treat TB.

Tuberculosis rates in Africa are said to be 10 times higher in HIV positive pregnant women than in those pregnant who are HIV negative.[18] In the study, more mothers with TB were diagnosed HIV positive than those mothers without, confirming this relationship. The late initiation of anti-TB treatment correlates with unfavourable maternal outcomes. Mothers with TB who were diagnosed HIV positive were more likely to not be on ARV treatment despite being aware of their HIV status. Once diagnosed and initiated on ARV and anti-TB treatment, mothers with TB commonly defaulted both treatments compared to the control group. As a result, TB exposed mothers with HIV had higher VL and lower CD4 counts.
Fifteen percent of TB confirmed mothers had MDR TB. Up to 20% of TB associated maternal deaths in South Africa were caused by HIV.[6] Human immunodeficiency virus-associated TB during pregnancy coupled with the pregnancy-related MDR TB where mothers didn't seek treatment or defaulted treatment in the face of high VL and low CD4 explains the higher mortality seen in TB confirmed mothers compared to mothers without TB. Cluster of differentiation 4 was the only factor identified by multivariable logistic regression with an association to maternal TB. This can be explained by the fact that low CD4 counts act as an indicator of disease pointing to a higher likelihood of developing or acquiring TB if diagnosed HIV positive.

Limitations

Mothers with undiagnosed TB may have been missed, so the prevalence of neonatal or maternal TB cannot be accurately determined from this study. One of the neonatal records were excluded due to incompleteness which would also negatively impact our ability to confidently comment on the prevalence of neonatal TB. Placentas for TB confirmed mothers were not always sent for TB detection. Furthermore, if placentas were sent for testing, only histopathological examination was done which would impact on the reporting of prevalence of neonatal TB. The long term outcome of all neonates post-discharge was unknown. Information pertaining to the mother's TB status was obtained from the labour ward nursery notes and as a result if it is not stated that the mother was TB positive we assumed that the mother was TB negative which is a limitation as it may not reflect the true number of women presenting with TB during pregnancy to CMJAH.

Conclusion

This study showed that perinatal TB is a rare disease in SA and that high morbidity and mortality rates correspond to HIV-associated TB during pregnancy. Pregnancy-related MDR TB and late initiation of anti-TB treatment also correlated with poorer outcomes which are consistent with data published in developed countries. It also confirmed that the unfavourable neonatal and maternal outcomes associated with TB found at CMJAH were consistent with those reported globally.

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- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

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- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

  National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

  In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

  Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

  South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

  South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

  South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

  South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

  Rex v Jopp and Another 1949 (4) SA 11 (N)

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  SA: SA Law Reports

  11: Page or section number

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MMED RESEARCH PROPOSAL

April 2018

A DESCRIPTIVE STUDY OF NEONATES BORN TO MOTHERS WITH TUBERCULOSIS IN A LOW MIDDLE-INCOME COUNTRY

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Paediatric Neonatologist at Charlotte Maxeke Johannesburg Academic Hospital

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GLOSSARY OF TERMS

TB	Tuberculosis
WW	World war
HIV	Human immunodeficiency virus
AIDS	Acquired immunodeficiency syndrome
WHO	World health organisation
PDA	Patent ductus arteriosus
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
REDCap	Research Electronic data capture
VON	Vermont Oxford Network

INTRODUCTION

Tuberculosis (TB) is widely prevalent today despite being a disease of antiquity.[1] Scientific documentation of TB dates back to as early as 8000 BC.[1,2] TB has plagued human history for millennia as evidenced by its presence in the bony remains of ancient Egyptian mummies to its affliction of soldiers in World War (WW)1 and WW2.[1,2] Tuberculosis has maintained the status as one of the leading deadliest communicable diseases, ranking ninth above human immunodeficiency virus (HIV) / acquired immunodeficiency syndrome (AIDS).[3,4] It has evaded eradication despite medical advances rendering it a largely curable and preventable disease.[2,5] Tuberculosis is, therefore a global public health problem that has resulted from the scientific, medical, social and political failures in society.[2] On the grounds of a high burden of disease the World Health Organisation (WHO) has implemented the Sustainable Development Goals with the aim of ending the global TB epidemic by 2035.[3,6]

According to the WHO, in 2016 there were approximately 10.4 million new cases of TB of which 3.7 million were women and 1 million were children with the majority of these cases occurring in Asia and Africa.[6] Women of childbearing age (15-45) carry seventy-five percent of the TB burden and the prevalence of TB in pregnant women is thought to be higher than that of the general population.[7,8] This has a crippling effect on socio-economic development as it disempowers women therefore encouraging the cycle of poverty.[7] It is estimated that active TB affects 216 500 pregnant women globally.[14] Africa is said to have the highest case burden of TB in pregnant women at around 41.3% but many cases remain undiagnosed due to a low threshold of suspicion and similarity of TB symptoms with physiological symptoms of pregnancy.[5,7,12] As a result, the full extent of the burden of disease amongst pregnant women is unknown but it is expected to be higher than currently reported especially in developing countries.[7,8]

Pregnant and postpartum women are at an increased risk for contracting TB due to the physiologic, hormonal, and immunologic changes that occur during pregnancy.[11,12] The physiological immunosuppression associated with pregnancy, resulting in a dampened T-helper 1 pro-inflammatory response may mask disease symptoms leaving these women susceptible to new mycobacterial infection or reactivation of TB.[4,13,14,15] Women diagnosed with latent pattern TB in pregnancy are more likely to progress to an active pattern TB.[4,13] Active TB during pregnancy is known to have unfavourable maternal and infant outcomes.[13,16]

In 2013, 1.5 million people worldwide died from TB of which 510 000 were women, one-third of these women were co-infected with HIV and roughly 15–35% of these deaths occurred during pregnancy.[9,13,14,17] Tuberculosis is the third leading cause of death worldwide among women of child-bearing age.[6,7,9,12,13] It is one of the most common opportunistic infections present in individuals with HIV.[7] There is a 16-27 times higher risk of developing TB if diagnosed HIV positive.[6] Human immunodeficiency virus-associated TB is linked to higher morbidity and mortality rates during pregnancy and postpartum.[15,19] Over 50% of the TB associated maternal mortality in pregnancy is due to coinfection with HIV, therefore maternal mortality is increased in women who are co-infected with HIV and TB.[7,13] Up to 20% of TB associated maternal deaths in South Africa were caused by HIV.[16] Pregnancy-associated multidrug-resistant (MDR) TB and late initiation of anti-TB treatment have even less favourable outcomes.[7,13,14] Other poor maternal outcomes documented in women diagnosed with TB include chorioamnionitis, spontaneous abortion, postpartum anaemia, vaginal bleeding, preeclampsia, the need for transfusions, pneumonia and mechanical ventilation.[7,9,14]

The disease burden associated with neonatal TB is difficult to accurately quantify.[18] Although around 350 cases of congenital TB have been reported in the literature classifying it as a rare infection, the prevalence in a Durban based South African study was estimated to be around 16% TB.[5,19] Tuberculosis in the neonatal period can be subdivided into two types: congenital and postnatally acquired TB.[4]

Postnatally acquired TB, which is more common, differs from congenital TB in that the infant is often infected after birth by a contagious adult (mother or undiagnosed family member) suffering from pulmonary TB.[4,18] These neonates acquire TB within the first weeks of life from adults harbouring *M. tuberculosis* which is transmitted by respiratory aerosol to them in the form of infective airborne particles called droplet nuclei.[17]

Neonates contract congenital TB caused by the bacterium *M. tuberculosis* either in utero through the haematogenous placental transmission of the organism via the umbilical vein from the mother to the liver of the foetus, at delivery via the ingestion or aspiration of infected amniotic fluid or by direct contact with an infected birth canal during delivery.[4,20,21,22] The liver and lungs are commonly affected with a primary focus developing in the liver and tubercle bacilli infecting the lungs.[10,18,21,22] Congenital TB can be distinguished from postnatal TB based on Cantwell's revision of Beitzki's criteria which includes the presence of a primary hepatic complex/ caseating granuloma on percutaneous liver biopsy at birth, TB infection of the

placenta or maternal genital tract TB, and the demonstration of lesions during the first week of life.[5,16,18,20,,21]

It can become challenging to differentiate congenital TB from other neonatal or congenital infections due to nonspecific signs and symptoms like hepatosplenomegaly, respiratory distress, fever, lymphadenopathy, abdominal distension, lethargy, irritability, ear discharge, and papular skin lesions which result in the gross underreporting of the disease.[4,7,16,17,19,21] Tuberculosis is known to mimic common premature conditions such as chronic lung disease, patent ductus arteriosus (PDA), pneumonia and sepsis.[16] Most infected neonates are asymptomatic at birth with many manifesting TB around 2-3 weeks of age although some develop symptoms of congenital TB during the first days of life. [22] Distinguishing clinically between congenital and postnatally acquired TB in order to make a diagnosis can be difficult as signs and symptoms may be vague.[4,5] For the purpose of this study, we are going to combine the two disease entities using the term 'perinatal TB'. If perinatal TB is suspected gastric aspirate specimens can be obtained from the neonate for TB microscopy and culture.[17,21,22] Gastric lavage is positive in 70% of case and is the preferred method in infants who swallow their sputum and cannot expectorate.[22] The Ziehl-Neelsen staining together with histopathological examination of the placenta remains the gold standard for diagnosing TB.[23]

Neonates born to mothers with active TB have a higher incidence of poor outcomes.[13] These include a nine-fold increased risk of premature birth, low birth weight, intrauterine growth retardation, small for gestational age, respiratory distress syndrome and a six-fold increase in perinatal death.[4,7,9,12,13,14] Babies born to mothers with TB were more likely to have a congenital abnormality.[8] The mortality rate due to perinatal TB is nearly 50% which is as a result of delayed diagnosis and treatment.[4]

South Africa is one of the countries with the highest burden of TB and HIV.[19] Multidrug-resistant TB is a persistent threat in South Africa.[24] There is an increasing number of multidrug-resistant cases of TB reported in South Africa.[6,24] The impact of multidrug-resistant TB and HIV in mothers and their offspring is difficult to quantify due to limited data available.[25] Despite the high prevalence of HIV and its association with TB, there is a paucity of information on the impact of maternal TB on neonates in South Africa. The aim of this study is to describe the maternal and neonatal characteristics of infants presenting at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) who were born to mothers with TB.

OBJECTIVES

OBJECTIVES

- To describe the demographic and clinical characteristics, as well as the short term outcomes of the neonates with or without TB born to mothers with TB
- To compare the two group of neonates born to mothers with or without TB
- To document the number of neonates with perinatal TB
- To describe the demographic and clinic characteristics of mothers with TB.

METHOD

STUDY DESIGN

This study is a retrospective case-control record review of neonates presenting to CMJAH between 1 January 2013 and 31 December 2017 born to mothers with TB. Cases will be classified as neonates born to mothers with TB, a control group will be comprised of neonates born to mothers without TB.

SITE OF STUDY

The study will be conducted in the neonatal section of the Paediatric department at CMJAH in Parktown, Gauteng Province.

STUDY POPULATION

The study population will include all neonatal patients with or without TB born to mothers with documented TB who were admitted within 72 hours of birth to CMJAH between 1 January 2013 and 31 December 2017. The sample size will be made up of 75 neonates born to mother with TB and 75 neonates born to mothers without TB.

INCLUSION CRITERIA

Cases: All neonates born to mothers with TB.

Controls: All the next consecutive inborn neonates born to mothers without TB.

EXCLUSION CRITERIA

Neonates for whom files could not be retrieved or are lost will be excluded from the study.

Neonates born to mothers with undocumented TB status will be excluded.

DEFINITIONS

Maternal TB is defined as a diagnosis of TB in the labour room notes.
Perinatal TB is defined as TB present in the first month of life as diagnosed by positive TB GeneXpert on gastric washing or histology of placenta.

CMJAH NEONATAL UNIT

The CMJAH neonatal unit consists of 14 ventilator beds, 35 high care, 30 low care and 10 kangaroo mother care beds. All neonates below 1750 grams are admitted to the neonatal unit. Neonates who are exposed to TB are admitted and investigated by the neonatal staff. These neonates are notified and followed up by the District clinical specialist team.

In all cases of maternal TB, the placenta is sent for histology and culture and gastric washings are sent from the neonates for acid-fast bacilli and GeneXpert. All TB exposed neonates who are admitted to the neonatal unit are treated with prophylactic INH. Neonates born to mothers with MDR or XDR TB are managed on an individual basis in consultation with an infectious diseases specialist.

DATA VARIABLES

The following maternal and neonatal variables will be looked at:

Maternal demographics and characteristics: antenatal care, HIV status: positive or negative, chorioamnionitis, type of ventilatory support and duration, pneumonia, postpartum anaemia, outcome: died or survived, spontaneous abortion, preeclampsia, whether treated for TB or not and time of initiation of treatment.

Neonatal demographics and characteristics:

- Gestational age, birth weight and head circumference
- Sex
- Mode of delivery
- Outcome: died or survived and duration of admission
- Whether or not diagnosed with perinatal TB
- HIV status: exposed or PCR positive/ negative
- Presence of congenital infections, indicating the type
- Early and late-onset sepsis
- Presence of congenital abnormalities, indicating the type based on the system involved

- Ventilatory support including type and duration
- Respiratory distress syndrome
- Chronic lung disease (supplementary oxygen at 28 days chronological and at 36 weeks post-conceptional age)
- Use of postnatal steroids
- TB prophylaxis given

PROCEDURES

Data on admitted neonates will be extracted from the existing CMJAH neonatal database in paediatric department. This data which is part of a continuing clinical audit is collected from clinician-completed hospital records. Data is managed using Research Electronic Data Capture (REDcap), hosted by the University of the Witwatersrand.[26] Definitions in the database are derived from the Vermont Oxford Network (VON) (www.vtoxford.org). The data collected for this database is rigorously checked and verified before being entered electronically. A data sheet with the relevant variables to be captured for this study will be attached (appendix A). Additional information, such as TB treatment will be obtained from retrieving hospital records.

DATA ANALYSIS

Data will be described using standard statistical methods. Categorical variables will be described using frequencies and percentages and continuous variables as means and standard deviations where data is distributed normally or median range if skewed. The two groups of neonates (TB exposed and TB unexposed) will be compared. Independent t-test or Mann-Whitney u-test will be used to compare differences in means across cases and controls for normally distributed continuous variables. Pearson chi-square tests will be used to determine if there is a statistically significant difference in frequency between cases and controls. A p-value of less than 0.05 will be considered significant. For all variables found to be significantly different, a univariant analysis will be entered into a logistic regression model to calculate adjusted odds ratios.

ETHICS

The protocol will be submitted for approval to the Human Research Ethics Committee (medical) of the University of the Witwatersrand. Permission to conduct the study will be requested from the department of paediatrics and the Chief Executive officer at CMJAH.
As this is a retrospective study, a waiver for informed consent will be requested. The Neonatal Database REDCap is confidential and has limited accessibility as it is password protected. No identifiable demographics like name, surname, hospital number or date of birth will be used. Study numbers will be allocated to the patients as a means to create anonymity and ensure confidentiality which will only be available to the student and supervisors.

TIME LINES

	April 2018	May 2018	June 2018	July 2018	Aug 2018	Sept 2018	Oct 2018	Nov 2018	Dec 2018
Literature review									
Protocol write up									
Protocol submission									
Ethical clearance									
Post grad committee clearance									
Data collection									
Data analysis and write up									

FUNDING

An estimated R300 will be required to fund the cost of stationary, binding and printing related to the study which will be borne by the investigator.

LIMITATIONS

Due to the retrospective nature of this study, records and data may be incomplete and information limited by what was previously captured which may affect the data set and weaken the result obtained. Undiagnosed mothers with TB may be missed, so the prevalence of

neonatal or maternal TB cannot be determined from this study. The long term outcome of neonates post discharge will be unknown. The information pertaining to the mother's TB status is obtained from the labour ward nursery notes and as a result if it is not stated that the mother is TB positive we assume that the mother is TB negative which is a limitation as it may not reflect the true number of women presenting with TB in pregnancy.

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Appendix A

DATASHEET

STUDY NUMBER			
Gestational age			
Birthweight			
Sex	M	F	
Mode of delivery	Normal vaginal	Caesarian section	
Maternal Data			
Antenatal care	Yes	No	Unknown
HIV status	Positive	Negative	Unknown
If HIV positive:	VL:	CD4:	
ARV treatment	Yes	No	Unknown
Defaulted ARV treatment	Yes	No	Unknown
Spontaneous abortions	Yes	No	Unknown
Preeclampsia	Yes	No	Unknown
Postpartum anaemia	Yes	No	Unknown
Chorioamnionitis	Yes	No	Unknown
Ventilatory support	Yes	No	Unknown
If yes:	Type:	Duration:	
Pneumonia	Yes	No	Unknown
Diagnosed with TB	Yes	No	Unknown
Type of TB diagnosed			
TB treatment	Yes	No	Unknown
Time to initiation of treatment			

TB treatment type	First line	MDR TB	XDR TB
Defaulted TB treatment	Yes	No	Unknown
Outcome	Demised	Survived	
Neonatal Data			
Perinatal TB	Yes	No	
Placenta tested for TB	Yes	No	
If yes, result:	Positive	Negative	Unknown
HIV status	Positive	Negative	Unknown
Received HIV prophylaxis	Yes	No	Unknown
Congenital infections	Yes	No	Unknown
Early-onset sepsis	Yes	No	Unknown
If yes, organism isolated:			
Late-onset sepsis	Yes	No	Unknown
If yes, organism isolated:			
Congenital abnormalities	Yes	No	Unknown
If yes, system involved:			
RDS	Yes	No	Unknown
Chronic lung disease	Yes	No	Unknown
Use of postnatal steroids	Yes	No	Unknown
Ventilatory support	Type:	Duration:	
Duration of admission			
TB prophylaxis	Yes	No	Unknown
Outcome	Survived	Demised	

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Sonia Mariza Neves da Silva et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180614

NAME: (Principal Investigator)	Dr Sonia Mariza Neves da Silva et al
DEPARTMENT:	Paediatrics Charlotte Maxeke Johannesburg Academic Hospital Neonatal department
PROJECT TITLE:	A descriptive study of neonates born to mothers with Tuberculosis in a middle income country
DATE CONSIDERED:	29/06/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Daynia Ballot
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/09/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore be due in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 04/09/2018

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

00820433:MMED_RESEARCH_REPORT_Nov_2020.docx

by Daynia Ballot

Submission date: 13-Nov-2020 09:30AM (UTC+0200)
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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

MMED RESEARCH REPORT

A DESCRIPTIVE STUDY OF NEONATES BORN TO MOTHERS WITH TUBERCULOSIS IN A LOW MIDDLE INCOME COUNTRY

INVESTIGATOR: Sonia Mariza Neves da Silva MBBCh (Wits), BSc (NWU), BPsych (NWU)
STUDENT NUMBER: 0102093V
DEGREE: MMED (Paediatrics)

SUPERVISORS:

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MBBCh (Wits), FCPaed (SA), MMED, DCH Cert
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Declaration

I, Sonia Mariza Neves da Silva declare that this Research Report is my own, unaided work. It is being submitted for the Degree of MMED Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Acknowledgements

I would like to give a heartfelt thanks to my supervisors Prof Ballot and Dr Rambin for their guidance and unwavering support. Many thanks is also extended to the staff at Charlotte Maxeke Johannesburg Academic Hospital involved in the data collection for the neonatal unit.

Dedication

I dedicate this work to my mother,

who has always believed in my dreams and remained a pillar of strength through it all

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List of abbreviations

TB	Tuberculosis
SA	South Africa
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
HIV	Human immunodeficiency virus
ARV	Anti-retroviral
VL	Viral load
CD4	Cluster of differentiation 4
EOS	Early onset sepsis
LOS	Late onset sepsis
RDS	Respiratory distress syndrome
CLD	Chronic lung disease
LMIC	Low middle income country
LTB	Latent tuberculosis
ATB	Active tuberculosis
MDR TB	Multidrug resistant tuberculosis
CTB	Congenital tuberculosis
PTB	Postnatal tuberculosis
REDCap	Research electronic data capture
WITS	The University of the Witwatersrand
CXR	Chest radiograph
GXP	Gene Xpert
INH	Isoniazid
XDR TB	Extensively drug resistant tuberculosis
JHB	Johannesburg
AFB	Acid fast bacilli
BCG	Bacillus Calmette-Guérin
PCR	Polymerase chain reaction
NCPAP	Nasal continuous positive airway pressure
IPPV	Intermittent positive pressure ventilation

A Descriptive Study of Neonates born to Mothers with Tuberculosis in a low income country

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ABSTRACT.

Background. Tuberculosis (TB) in pregnancy is associated with unfavourable maternal and neonatal outcomes. A paucity of South African (SA) data exists regarding the impact of maternal TB on neonates.

Objectives. To describe demographical and clinical characteristics and outcomes of mothers diagnosed with TB and their neonates and compare it to TB negative mothers and their neonates.

Methods. This was a retrospective unmatched case-control study of neonates admitted to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 1 January 2013 and 31 December 2017. Cases were identified as neonates born to mothers with TB. Controls included the next two inborn neonates delivered to TB negative mothers.

Results. Maternal TB prevalence in this study was 0.9%. Majority of mothers confirmed human immunodeficiency virus (HIV) positive had TB and few were on anti-retroviral (ARV) therapy. If taking ARVs, these mothers commonly defaulted treatment, had higher viral load (VL) and lower cluster of differentiation 4 (CD4) compared to the control group. Likewise TB exposed neonates were more likely to be HIV positive. Mothers with TB were at higher risk for spontaneous abortions, pre-eclampsia, maternal anaemia, chorioamnionitis, pneumonia and more likely to require ventilation. Tuberculosis exposed neonates had higher rates of early onset sepsis (EOS), late onset sepsis (LOS), respiratory distress syndrome (RDS), chronic lung disease (CLD) and need for ventilation. The only factor associated with a high risk of TB in mothers was CD4.

Conclusion. Unfavourable neonatal and maternal outcomes associated with TB found at CMJAH were consistent with that reported globally.

Background

Tuberculosis is widely prevalent today, maintaining its status as one of the leading deadliest communicable diseases.[1,2] Tuberculosis has evaded eradication rendering it a global public health problem with a high burden of disease.[1,2,3]

The incidence of TB in pregnancy is unknown but thought to be higher in low middle income countries (LMIC).[4,5] Pregnant women diagnosed with latent TB (LTB) are more likely to progress to active (ATB).[1,7] In SA, 11 and 49 percent of pregnant women had ATB and LTB respectively.[10] Active TB is associated with a higher incidence of unfavourable maternal outcomes such as death, chorioamnionitis, spontaneous abortion, postpartum anaemia, pre-eclampsia, pneumonia and ventilatory support.[4,5,7,8,9] Tuberculosis is a common opportunistic infection present in individuals with HIV.[5] High morbidity and mortality rates are affiliated with HIV-associated TB during pregnancy.[10,11] Pregnancy related multidrug resistant (MDR) TB and late initiation of anti-TB treatment has also been correlated with less favourable outcomes.[5,7,9]

The disease burden associated with neonatal TB is difficult to quantify.[2] Despite classifying congenital TB (CTB) as rare, a South African study reported the transmission rate of Mycobacterium Tuberculosis in neonates as 16%.[2,3,5,7,8,11] Tuberculosis in the neonatal period is subdivided into CTB and postnatal TB (PTB).[1] Postnatal TB is contracted within the first weeks of life from a contagious adult in the form of airborne particles.[1,11,12] In comparison, CTB is acquired in utero or during delivery.[1,13,14,15] Distinguishing between CTB and PTB for the purpose of a diagnosis can be challenging due to vague signs and symptoms.[1,2]
Neonates born to mothers with ATB have a higher incidence of poor outcomes namely an increased risk of premature birth, low birth weight, intrauterine growth retardation, small for gestational age, RDS and a six-fold increase in perinatal death.[1,4,5,7,9,17] Neonates born to mothers with TB were also more likely to have a congenital abnormality.[5]

South Africa has one of the highest burden of TB and HIV worldwide.[11] Multidrug resistant TB is a persistent threat in SA as evidenced by the increasing number of cases reported.[18,19] The impact of MDR TB and HIV on mothers and their offspring is difficult to quantify due to limited data available.[20] Despite the high prevalence of HIV and its association with TB, there is a paucity of research on the effects of maternal TB on neonatal outcomes internationally and in SA. Our aim was to describe the outcomes of mothers diagnosed with TB and their neonates and compare it to mothers unexposed to TB and their offspring, therefore contributing to the local and regional evidence base which would enhance our understanding of the burden of TB disease in neonates.

Methods

This was a retrospective unmatched case-control study using data from the CMJAH neonatal database. The study population included neonates born to mothers with documented TB admitted to the neonatal unit at CMJAH between 1 January 2013 and 31 December 2017. Neonates for whom files could not be retrieved, were excluded as well as infants born to mothers with unknown TB status. The control group comprised of neonates born to mothers without TB.

Data collection

Data was collected on discharge of patients from clinician completed hospital records for the purpose of a clinical audit. Research Electronic Data Capture (REDCap) hosted by the University of the Witwatersrand (WITS) was used to capture and manage the data.[21] Neonatal and maternal outcome to hospital discharge, obstetric information, neonatal and maternal clinical and demographic details were retrieved from the database for statistical analyses. Patients were identified from the database reviewed records.

Maternal TB was defined as a diagnosis of TB in the labour room notes as documented either by chest radiograph (CXR) or positive sputum for acid fast bacilli and Gene Xpert (GXP). Based on the results of the GXP, mothers were classified as either having rifampicin sensitive or resistant TB. Multidrug resistant TB was defined as TB that did not respond to two anti-TB drugs namely isoniazid (INH) and rifampicin as detected on GXP.[22] Extensively drug resistant TB (XDR TB) is resistant to INH and rifampicin, plus any fluoroquinolone and at least one of the three injectable second-line drugs.[22] Respiratory distress syndrome, a disease of prematurity is characterised by a deficiency of surfactant leading to signs of respiratory distress necessitating oxygen.[23] Chronic lung disease was defined as requiring supplemental oxygen for more than 28 days.[24] Early onset sepsis constituted a positive blood culture within 72 hours from birth and late onset sepsis was defined as a positive blood culture > 72 hours after birth.

In this study, we combined the two disease entities namely CTB and PTB using the term 'perinatal TB'. Perinatal TB was defined as TB present in the first month of life as diagnosed by positive GXP obtained from the neonate or histology suggestive of TB detected in the placenta.

Study site and routine care

Charlotte Maxeke Johannesburg Academic Hospital is a quaternary hospital in Johannesburg (JHB) that functions as a referral centre for surrounding clinics and district hospitals.

Mothers suspected of TB had a CXR ordered and sputum tested for acid fast bacilli (AFB) and GXP. When TB is suspected in the neonate, gastric aspirate specimens are sent for TB microscopy, culture and GXP.[12,14,15] Gastric lavage is positive in 70% of case and is the preferred method of testing in infants because they swallow their sputum and cannot expectorate.[15] Ziehl-Neelsen staining, culture and histopathological examination of the placenta remains the gold standard for diagnosing CTB.[16] Neonates born to mothers diagnosed with TB were admitted for TB workup. For both asymptomatic and symptomatic neonates exposed to TB, no Bacillus Calmette-Guérin (BCG) vaccine was administered at birth. Gastric aspirates for AFB and TB culture was done as well as a CXR. Asymptomatic neonates were started on prophylactic INH for 3 months and reviewed at follow up clinic 3 months later. Symptomatic infants were notified and initiated on anti-TB treatment. Neonates born to mothers with MDR or XDR TB were managed on an individual basis in consultation with a paediatric infectious disease specialist. Placentas belonging to TB confirmed mothers were examined and sent off for histology.

All pregnant women who presented at CMJAH were offered an HIV test with pre and post-test counselling. Mothers testing positive for HIV were initiated on ARV therapy and had their VL and CD4 counts monitored. Similarly all neonates that were born to HIV positive mothers were tested for HIV using polymerase chain reaction (PCR) test. Neonatal HIV prophylaxis prescribed was dependent on the mother's VL and duration of ARV therapy before delivery.[25]

Statistical methods

Controls for this study were not matched to the study population and were taken from the database by systematically selecting the next two inborn neonates delivered to TB negative mothers. Statistical analysis was done using SPSS Statistics (IBM) version 25. Categorical variables were described using frequencies and percentages. Continuous variables were described as means and standard deviations where data was distributed normally or median and range if skewed. Demographic and clinical characteristics for control and case groups were compared. Independent t-test was used to compare differences in means across cases and controls for normally distributed continuous variables. Pearson Chi-square or Fischer exact tests were used to determine if there was a statistically significant difference in frequency between cases and controls. A p-value less than 0.05 was considered significant. For all variables found to be significantly different, a logistic regression model was used to calculate adjusted odds ratios for associations with TB.

Ethics

The study was approved by the Human Research Ethics Committee at WITS, JHB (Clearance certificate No. M180614).

Results

A total of 8684 neonates were admitted to CMJAH between 1 January 2013 and 31 of December 2017. Four hundred and twenty one of these neonates were excluded as they were born to mothers with unknown TB results. Seventy four files were retrieved and one file was excluded due to incomplete data. The control group was comprised of 148 neonates born to mothers without TB.

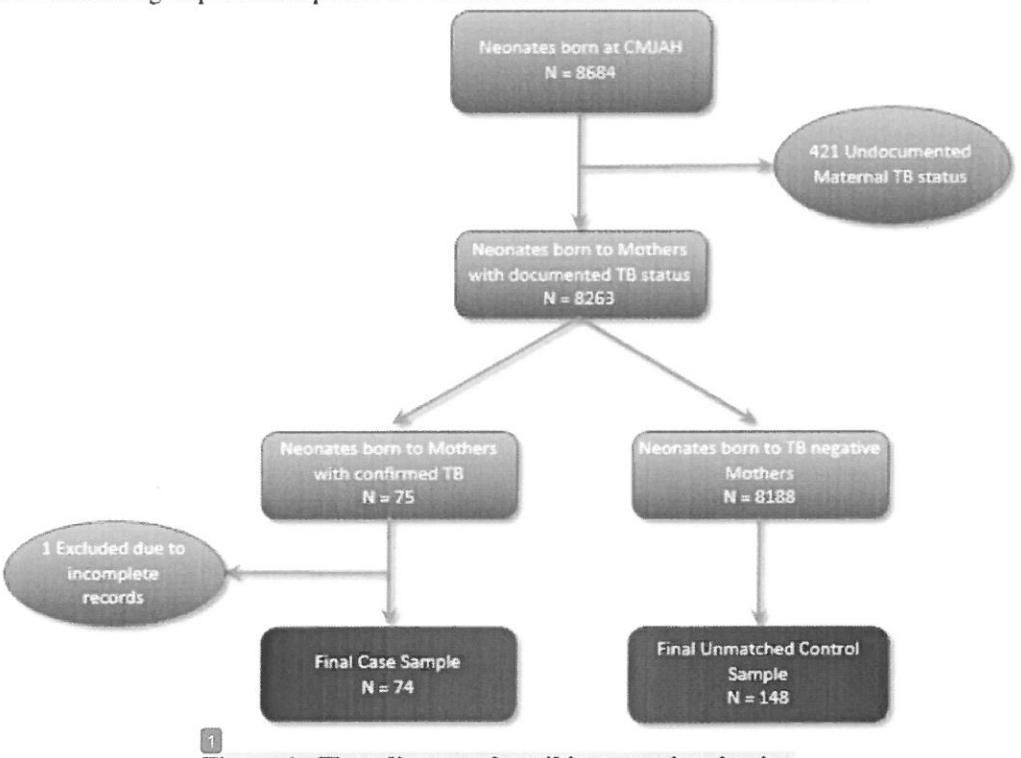


Figure 1. Flow diagram describing sample selection

Maternal characteristics

The prevalence of maternal TB in this study was 0.9%, of which MDR TB accounted for 15% (11/74). Most of the TB positive mothers were initiated on first line compared to second line TB treatment (63/74, 85% vs 11/74, 15%) and (7/74) 10% of mothers defaulted TB treatment. The majority of mothers were initiated on TB treatment during pregnancy (47/74, 64%), followed by those started at delivery (15/74, 20%), with the minority of mothers being initiated before the pregnancy (12/74, 16%). The presence of maternal TB was found in the following sites namely pulmonary 81% (60/74), abdomen 5% (4/74), meningeal 4% 3/74), spinal 3% (2/74), cardiac 3% (2/74), thyroid 1% (1/74) , lymphatic 1% (1/74) and cryptococcal 1% (1/74). Tuberculosis was not detected in any of the thirteen placentas sent for histopathological examination.

When comparing maternal clinical characteristics for cases and controls, there was no significant difference in the mode of delivery and antenatal care. The majority of mothers confirmed HIV positive were from the case group. TB negative mothers were more likely to be on ARVs than TB positive mothers. Thirty five percent (19/55) of HIV positive mothers in the case group defaulted ARV therapy versus only 8% (3/38) in the control group. On average, mothers with TB had higher VL than the control group (111 203.38 count +/- 205 848.713 vs 488.13 +/- 1025.085) p = 0.044 and lower CD4 than the control group (225.51 /- 259.863 vs 494.90 +/- 217.202) p < 0.001.

Results showed that mothers with TB were more likely to have pregnancy related complications including spontaneous abortion (15/74, 21% vs 12/148, 8%) p = 0.006, pre-eclampsia (18/74, 24% vs 17/148, 11%) p = 0.008, maternal anaemia (38/74, 51% vs 27/148, 18%) p = 0.00, chorioamnionitis (9/74, 12% vs 3/148, 2%) p = 0.02 and pneumonia (5/74, 7% vs 0/148, 0%) p = 0.00. Significantly more mothers were ventilated in the case group compared to the control group p = 0.00, with many mothers requiring ventilation and facemask oxygen if confirmed TB positive as shown in Table 1. The mortality for mothers with TB (6/74, 8%) was higher than that for mothers without TB (1/148, 0.5%).

Neonatal characteristics

Perinatal TB was not diagnosed in the neonates born to TB confirmed mothers. The incidence of HIV amongst the neonates was 0.03%. All of the TB exposed neonates received TB prophylaxis. There was no significant difference in the sex and neonatal HIV prophylaxis between cases and controls. Similarly no significant difference in birth weight or gestational age was found between the two groups (2070.47 grams +/- 845.802 vs 2150.70 grams +/- 936.376)) p = 0.523 (34.03 weeks +/- 4.14 vs 34.39 weeks +/- 4.82) p = 0.565.

More TB exposed neonates were confirmed HIV PCR positive than TB unexposed neonates (2/74, 3% vs 0/38, 0%) p = 0.04. TB exposed neonates commonly developed EOS and LOS more often than TB unexposed neonates. The organisms causing EOS and LOS inculded Candida parapsilosis, Acinebactor baumannii, Candida glabrata, Candida krusei and Coagulase negative stapholococcus. TB exposed neonates were significantly more likely to have neonatal related complications including RDS and CLD and less likely to have congenital infections and congenital abnormalities.

Fifty nine percent of neonates were ventilated in the case group compared to the neonates in the control group with more TB exposed neonates requiring nasal continuous positive airway pressure (NCPAP) than intermittent positive pressure ventilation (IPPV). TB exposed neonates were ventilated on average for longer than non-exposed TB neonates. Receiving postnatal steroids was not found to be significant. Neonates from both groups were admitted to hospital for a similar duration of time (15.73 +/- 16.261 vs 13.92 +/- 17.845) p = 0.45. No significant difference in neonatal mortality was found between the two groups (p = 0.3).

Table 1: Maternal clinical and demographic characteristics

Characteristics	**Case n/N (%) (74)**	**Control n/N (%) (148)**	**p-value**
Maternal factors:			
Mode of delivery Vaginal Caesarean	 36/74 (48) 38/74 (51)	 72/148 (48) 76/148 (51)	1.0
Antenatal Care	61/74 (82)	125/148 (84)	0.7
HIV status	55/74 (74)	38/148 (26)	<0.001
ARV	49/55 (89)	38/38 (100)	0.01
Defaulted ARV	19/55 (34)	3/38 (8)	0.02
Ventilation	11/74 (15)	2/148 (1)	<0.001
Type of ventilation Facemask Intubation	 6/74 (8) 5/74 (7)	 0/148 (0) 1/148 (0.5)	<0.001
Deaths	6/74 (8)	1/148 (0.5)	0.001

Table 2: Neonatal clinical and demographic characteristics

Neonatal factors:			
Sex Female Male	 36/74 (48) 38/74 (52)	 67/148 (45) 81/148 (55)	0.63
HIV prophylaxis	54/55 (98)	38/38 (100)	0.3
Congenital infections	1/74 (1)	0/148 (0)	0.1
EOS	2/74 (3)	0/148 (0)	0.025
LOS	11/74 (15)	17/148 (11)	0.4
Congenital abnormalities	6/74 (8)	15/148 (10)	0.7
RDS	39/74 (53)	52/148 (35)	0.012
Ventilation	44/74 (59)	65/148 (44)	0.018
Type of ventilation NCPAP IPPV	 38/74 (86) 6/74 (14)	 87/148 (58) 62/148 (42)	<0.001
CLD	9/74 (7)	8/148 (5)	0.037
Postnatal steroids	19/74 (26)	44/148 (29)	0.5
Deaths	7/74 (9)	21/148 (14)	0.3

On multivariable logistic regression, the only factor associated with a high risk of TB in mothers was CD4 (OR: 4.635; 95% CI: 0.995 – 1.00).

Discussion

This study shows that ATB during pregnancy is associated with poor neonatal and maternal outcomes. Mothers with TB were more likely to have a spontaneous abortions, pre-eclampsia, maternal anaemia, chorioamnionitis, pneumonia and require ventilatory support. Likewise neonates exposed to TB had higher rates of EOS and LOS, RDS, CLD, the need for ventilatory support and a longer duration of ventilation. Despite perinatal TB being associated with a higher neonatal mortality in the literature, the mortality rate for both case and control group in the study was similar. This could be in part due to

more neonates being initiated on TB prophylaxis and that maternal TB is being diagnosed and treated earlier in pregnancy.

In our retrospective unmatched case-control study, none of the neonates born to TB positive mothers were diagnosed with perinatal TB. The prevalence of perinatal TB was therefore in keeping with the literature but significantly lower than reported in a Durban based SA study. Of note, only 13 placentas belonging to TB positive mothers were sent for TB testing. Furthermore, the placentas underwent histopathological examination alone, without TB culture testing or Ziehl-Neelsen staining. This along with the low number of placentas submitted for testing could account for the lack of perinatal TB diagnosed.

The prevalence of TB in pregnant women in the study was 0.9%. Africa is said to have the highest case burden of TB in pregnant women and the burden is thought to be higher than that of the general population.[3,5,17] This is as a result of many cases remaining undiagnosed due to a low threshold of suspicion and similarity of TB symptoms with the physiological symptoms of pregnancy.[3,5,17] As a result, the prevalence of pregnancy related TB could actually be higher than reported in the study.

On the grounds of a high burden of disease, the World Health Organisation (WHO) has implemented the Sustainable Development Goals with the aim of ending the global TB epidemic by 2035. To this end, despite the challenge of distinguishing between TB and the physiological symptoms of pregnancy, 64% (47/74) women diagnosed with TB were initiated on anti-TB treatment during the course of their pregnancy, highlighting physician's efforts to recognise and treat TB.

Tuberculosis rates in Africa are said to be 10 times higher in HIV positive pregnant women than in those pregnant who are HIV negative.[18] In the study more mothers with TB were diagnosed HIV positive than those mothers without, confirming this relationship. The late initiation of anti-TB treatment correlates with unfavourable maternal outcomes. Mothers with TB who were diagnosed HIV positive were more likely to not be on ARV treatment despite being aware of their HIV status. Once diagnosed and initiated on ARV and anti-TB treatment, mothers with TB commonly defaulted both treatments compared to the control group. As a result, TB exposed mothers with HIV had higher VL and lower CD4 counts.

Fifteen percent of TB confirmed mothers had MDR TB. Up to 20% of TB associated maternal deaths in South Africa were caused by HIV. [8] Human immunodeficiency virus associated TB during pregnancy coupled with the pregnancy related MDR TB where mothers didn't seek treatment or defaulted treatment in the face of high VL and low CD4 explains the higher mortality seen in TB confirmed mothers compared to mothers without TB. Cluster of differentiation 4 was the only factor identified by multivariable logistic regression with an association to maternal TB. This can be explained by the fact that a low CD4 counts acts as an indicator of disease pointing to a higher likelihood of developing or acquiring TB if diagnosed HIV positive.

Limitations

Mothers with undiagnosed TB may have been missed, so the prevalence of neonatal or maternal TB cannot be accurately determined from this study. One of the neonatal records were excluded due to incompleteness which would also negatively impact our ability to confidently comment on the prevalence of neonatal TB. Placentas for TB confirmed mothers were not always sent for TB detection. Furthermore if placentas were sent for testing, only histopathological examination was done which would impact on the reporting of prevalence of neonatal TB. The long term outcome of all neonates post discharge was unknown. Information pertaining to the mother's TB status was obtained from the

labour ward nursery notes and as a result if it is not stated that the mother was TB positive we assumed that the mother was TB negative which is a limitation as it may not reflect the true number of women presenting with TB during pregnancy to CMJAH

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Conclusion

This study showed that perinatal TB is a rare disease in SA and that high morbidity and mortality rates correspond to HIV-associated TB during pregnancy. Pregnancy related MDR TB and late initiation of anti-TB treatment also correlated with poorer outcomes which is consistent with data published in developed countries. It also confirmed that the unfavourable neonatal and maternal outcomes associated with TB found at CMJAH were consistent with that reported globally.

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