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Perspectives on tuberculosis in pregnancy

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SUMMARY

Tuberculosis (TB) has been recognized as an important cause of morbidity and mortality in pregnancy for nearly a century, but research and efforts to roll out comprehensive TB screening and treatment in high-risk populations such as those with a high prevalence of HIV or other diseases of poverty, have lagged behind similar efforts to address HIV infection in pregnancy and the prevention of mother-to-child-transmission. Immunological changes during pregnancy make the activation of latent TB infection or *de novo* infection more likely than among non-pregnant women. TB treatment in pregnancy poses several problems that have been under-researched, such as contraindications to anti-TB and anti-HIV drugs and potential risks to the neonate, which are particularly important with respect to second-line TB treatment. Whilst congenital TB is thought to be rare, data from high HIV burden settings suggest this is not the case. There is a need for more studies screening for TB in neonates and observing outcomes, and testing preventative or curative actions. National tuberculosis control programmes (NTPs) should work with antenatal and national HIV programmes in high-burden populations to provide screening at antenatal clinics, or to establish functioning systems whereby pregnant women at high risk can drop in to routine NTP screening stations.

1. Introduction

Worldwide, an estimated 900 million women have a latent *Mycobacterium tuberculosis* infection (LTBI), and pregnant women with LTBI are more likely to progress to developing active tuberculous disease than men. It has long been observed by obstetricians that pregnancy is associated with a more prevalent onset of active tuberculosis (TB) and also more rapid progression of TB disease compared with the non-pregnant state. The earliest publications on this topic date back to 1922, when Dr David Stewart, a medical superintendent of a women's TB sanatorium, wrote two articles in the Canadian Medical Association Journal on TB in pregnancy.[1,2] Looking past the very archaic writing style of this early medical literature, from a time when pregnant women admitted to a sanatorium faced the prospect of forced abortion (or even hysterectomy) in addition to the regular tortures then accepted as soundly evidenced TB treatment, these early TB practitioners, with their extensive experience of seeing thousands of patients, made some valuable observations that are true to this day: (1) both pregnancy and TB can have adverse effects on each other and are linked with poor outcomes; (2) outcomes are variable and extremely difficult to predict early in pregnancy, and management decisions should be made on a case-by-case basis; and (3) for all populations, there should be special provision made for pregnant women with TB.

This last point seems to have been forgotten by many. Whilst there have been colossal investments in maternal HIV diagnosis and treatment at the epicentre of the modern day TB pandemic (Sub-Saharan Africa), with interventions rolled out across the region improving both maternal and neonatal health, the same attention has not been given to maternal TB, despite the well-established epidemiological links between TB and HIV. Only 44% of countries have World Health Organization (WHO)-compliant guidelines for antiretroviral therapy (ART) in pregnant women.[3]

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It is highly likely that there is even less clarity and unified mass action with respect to TB diagnosis and treatment during pregnancy. Treating TB in HIV-infected pregnant women poses huge challenges because of overlapping toxicities, side effects, pill burden, changes in tolerability, and the pharmacokinetics of drugs. Rifampicin, a first-line TB drug, induces liver enzymes and alters the metabolism of all antiretrovirals recommended for use during pregnancy. There is a lack of data on all these factors and their influence on the treatment outcomes of TB and HIV in pregnancy.

2. Prevalence of TB in pregnancy

The recently published WHO Tuberculosis Report for 2014 states that in 2013 there were an estimated 3.3 million cases among women, with 510 000 deaths; a third of these women were co-infected with HIV.[4] The report does not mention the word 'pregnancy' or 'pregnant', indicative of the fact that most countries do not screen routinely for TB in pregnancy nor do they report the pregnancy status of female TB cases.[5] The symptoms of TB overlap considerably with those of pregnancy, and one South African study has shown that the sensitivity of clinical screening for TB among pregnant women is as low as 28%.[6] This shows that without active screening and case finding programmes among pregnant women, we can never hope to reach sufficient numbers of cases diagnosed and treated.

A review of the available data suggested that the prevalence of active TB among pregnant women ranges from 0.06% to 0.25% in low-burden countries. In high-burden countries, rates of between 0.07% and 0.5% were found among HIV-negative women, and between 0.7% and 11% among HIV-positive women.[5] In a recent epidemiological modelling study, Sugarman et al. estimated that there may have been 216 500 (95% uncertainty range 192 000–247 000) active TB cases among pregnant women globally in 2011, with the highest case burden (41.3% of cases) in the WHO African region.[7]

Large birthing centres represent a great opportunity for active case finding. A recent evaluation of the Xpert MTB/RIF assay among both obstetric and gynaecological admissions with suspected TB found culture-proven TB in 27.7% of suspected cases.[8] This TB burden among maternal admissions with suspected TB was comparable to that among all adult admissions at the same centre, where active TB was diagnosed in 10% of adult admissions able to produce a sputum specimen in whom TB was not suspected on admission, making inpatients potentially a higher risk group for missed TB infections than prisoners, refugees, and other well-publicized groups.[9,10] In the context of maternal HIV infection, and also HIV-negative women from high TB burden communities, the WHO prudently recommends standardized TB screening in antenatal clinics.[11] However, there is a general consensus that the uptake of this guidance has been poor.[5,8,12]

3. Effects on immunity

Women are at increased risk of TB during pregnancy,[13,14] and it is commonly assumed that immunological changes associated with pregnancy present an opportunity for mycobacterial infection or re-activation. In the late stages of pregnancy, a whole range of modifications in immune correlates have been observed. With respect to cellular immunity, increased levels and activity of phagocytes and plasmacytoid dendritic cells have been reported, with down-regulated natural killer (NK) cell cytotoxicity by progesterone-induced blocking factor and interleukin (IL)-10, and also a decrease in interferon gamma (IFN-γ) production, indicting a generally suppressed innate cellular response.[15,16] Adaptive cellular responses have also been evaluated, showing that Th1 cytokines (IFN-γ and IL-12) are down-regulated; however, reports on whether Th2 responses are modulated in pregnancy have been conflicting.[15,16] Observed changes in humoral immunity include increased levels of complement proteins and acute phase reactants, and also increased T-cell-dependent immunoglobulin production.[15,16] Pregnant women who are HIV-positive and have LTBI are more likely to progress to active TB disease.

4. TB as a cause of maternal deaths

Maternal mortality is high among women co-infected with HIV and TB,[17] and TB is associated with increased mortality both during pregnancy and postpartum.[14] Over 50% of pregnant women who die of TB during pregnancy and postpartum are HIV-positive. A medical record review of maternal mortality in Zambia dating to the pre-nevirapine era, documented TB as a cause of death in 25% of HIV-negative versus 32% of HIV-positive mothers.[18–20] More recent reviews or verbal autopsies of maternal deaths in Kenya and South Africa have recorded death as being directly attributable to TB in up to 20% of HIV-positive pregnant women.[21,22] However, post-mortem studies among the general population have shown that medical record reviews and verbal autopsies grossly underestimate the burden of TB as a cause of death.[23,24]

There has been just one post-mortem study undertaken in Africa on maternal deaths, and this study identified TB as a cause of death in 12.9% of deaths overall and 27.7% of deaths among HIV-infected women.[25] Such studies are the exception not the rule, and so for the most part we must rely on comprehensive record reviews to monitor changes in the burden of TB deaths over time. In South Africa the prevalence of non-obstetric infectious causes of death has increased steadily over the last two decades, concurrently with the HIV pandemic, so that as of 2007, infections such as TB, pneumonia, meningitis, and malaria accounted for 47% of all maternal deaths as reviewed.[26] Many record reviews have highlighted serious shortcomings in how we record causes of death, with 'HIV/AIDS' often being treated as a mutually exclusive cause of death, with separate categories for TB and other opportunistic infections. Consistent recording of maternal deaths is challenging due to the varied obstetric and non-obstetric causes that may present as co-morbidities.

5. Effects of maternal TB infection and treatment on the neonate

It has long been known that a few neonates born to mothers who have active TB disease will contract TB congenitally. Congenital TB may be subclinical or associated with a range of birth defects.[27] This has been little studied at the centre of the HIV/TB pandemic in Sub-Saharan Africa, but one study of 107 pregnant South African women diagnosed with active TB (50% with extrapulmonary or disseminated infection) documented seven perinatal deaths, with an adjusted perinatal mortality rate attributable to TB of 65.2/1000 among HIV-infected women.[28] Sixty-six percent of neonates were of low birth weight, compared to a hospital population rate of 22%.

Another South African study detected TB in 9% of infants born to mothers with active TB, and found maternal TB to be strongly associated with both maternal and neonatal mortality.[14] Epidemiological methods suggest a lower rate of vertical transmission, but these rely on routine culture returns and it is highly likely that many neonates born to mothers with TB are either not screened or may develop symptoms after discharge.[29]

A Mexican study found maternal TB to be associated with increased morbidity, lower birth weight, and an increased risk of death.[30] Studies from South Asia have linked TB during pregnancy to poor perinatal outcomes, including low birth weight,

small-for-gestational age, and perinatal mortality,[31–34] and also maternal morbidity and mortality.[32,34] Even in low-burden countries such as the UK, where TB during pregnancy is much less prevalent (62/100 000 pregnancies), it is still associated with low birth weight.[35]

A recent South African study of 97 HIV-infected women, half of whom had TB, found just one case of mother-to-child-transmission of HIV, and so could not prove that in the context of HIV, maternal TB has any influence on mother-to-child transmission of HIV, although women with TB had a higher HIV viral load at birth and had on average initiated ART earlier.[36]

6. Multidrug-resistant TB and pregnancy

Whilst the use of rifampicin and isoniazid in pregnancy have not been associated with major toxic effects on the mother or neonate, treatment options for multidrug-resistant TB (MDR-TB) in pregnancy are limited. Second-line TB drugs carry greater risks to both mother and child. Most have proven foetal toxicity from animal studies and are also present in breast milk, posing a risk to the infant; nevertheless the potential benefits could justify treatment depending on the specific case.[5]

Case-controlled observational studies to assess maternal outcomes are logistically challenging for MDR-TB, since the case burden will be low and laboratory capacity to detect MDR-TB is poor. There have been several case studies published; some have documented no adverse perinatal outcomes,[37–39] while others have recorded growth restriction[40] and congenital defects.[41] Such case studies must be interpreted with extreme caution, however, as there are a range of potential risk factors for neonatal morbidity and mortality that might be epidemiologically linked with MDR-TB.

Second-line TB drugs used to treat MDR-TB, such as aminoglycosides, are ototoxic and nephrotoxic for both the mother and the foetus. Quinolones have teratogenic potential and cause skeletal deformities. There are no safety data from human studies for the new TB drugs bedaquiline and delamanid, limiting their usefulness in treating pregnant women with MDR-TB. The WHO now recommends isoniazid preventative therapy (IPT) in HIV-infected individuals. A study from Botswana found a 6–12-month course of IPT to be safe in pregnant women, and neither IPT nor ART was associated with poor outcomes.[42]

7. Extrapulmonary TB and pregnancy

The literature is abound with case series and individual reports of extrapulmonary TB (EPTB) in pregnancy, so much so that, taken with the proven burden of pulmonary TB in pregnancy, it is reasonable to suggest that EPTB will account for a significant minority of cases of TB in pregnancy. Reported outcomes are frequently better in high-income populations,[43,44] but many cases are diagnosed late, as the symptoms may be confused with those of other possible conditions; some cases may even be diagnosed retrospectively after identification of neonatal TB.[45,46]

Reported presentations include, but are not restricted to, papulonecrotic tuberculids,[47] TB spine,[48,49] meningitis,[50] primitive caeco-appendicular TB,[51] genital TB as a possible cause of ectopic pregnancy,[52,53] pericarditis,[54] hemoptysis,[55,56] and peritoneal TB.[57–59] Foetal outcomes range from being completely asymptomatic, to serious congenital abnormalities, and even a spontaneous abortion with TB histology in both placenta and foetus.[60]

8. Conclusions

The study of TB in pregnancy is confounded by overlapping clinical presentations of TB with normal pregnancy-related conditions. As per the WHO recommendations for microbiological screening of TB in pregnancy for high HIV and TB-burden antenatal clinics, National TB Programmes (NTPs) should make a concerted effort to capture pregnancy-associated TB and to follow-up on perinatal outcomes. Collected data should then be analysed and published to better inform guidelines for TB diagnosis and treatment in pregnancy. This is of particular importance with respect to EPTB and MDR-TB. Such cases should be reported to the NTP with immediate effect and efforts made to follow-up these cases, providing the best available care and also recording outcomes.

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