

# THE INCREASING BURDEN OF TUBERCULOSIS IN PREGNANT WOMEN, NEWBORNS AND INFANTS UNDER 6 MONTHS OF AGE IN DURBAN, KWAZULU-NATAL

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*Objectives.* In spite of the global epidemic of tuberculosis (TB) which has been exacerbated by HIV, the impact of these co-infections on maternal and perinatal health has been limited. We document new evidence from Durban, KwaZulu-Natal, on the increasing effects of TB in pregnant women, neonates and infants.

*Method.* Women with TB were prospectively studied at the antenatal clinics and obstetric and labour wards at King Edward VIII Hospital, Durban, between 1996 and 1998. The incidence of TB was calculated, and the population-attributable fraction of TB due to HIV infection in pregnancy was estimated. Concurrently, culture-confirmed cases of *Mycobacterium tuberculosis* in neonates and infants under 6 months of age at the hospital were documented.

*Results.* One hundred and forty-six cases of maternal TB were detected. TB occurred in 0.1% and 0.6% of maternities in 1996 and 1998 respectively. Overall, TB rates for HIV non-infected maternities was 72.9/10<sup>5</sup>, and for HIV-infected maternities, 774.5/10<sup>5</sup>. The attributable fraction of TB related to HIV in pregnancy was 71.7%; 10.3% of these mothers died. There was a 2.2-fold increase in the caseload of culture-confirmed TB in neonates and young infants at the hospital.

*Conclusion.* In regions where TB and HIV prevalence is high, efforts to improve maternal and perinatal health must include the detection of TB in pregnancy.

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Maternal diseases account for 2.2% of the disability-adjusted life years in the global burden of disease,<sup>1</sup> and the largest proportion of deaths in women of reproductive age occur in relation to pregnancy.<sup>2</sup> This burden of death and disease occurs mostly in developing countries and includes among its leading causes hypertension, haemorrhage and sepsis.<sup>3</sup> HIV and tuberculosis (TB) have been major causes of adult death and disease in the developing world,<sup>4</sup> but their joint contribution to maternal morbidity and mortality has been sparsely documented.<sup>5-9</sup> Neonatal and early infant TB are usually acquired through maternal TB and have also been poorly documented within the context of HIV infection. TB is infrequently detected among infants born to HIV-seropositive women,<sup>10</sup> and has rarely been described in HIV-infected neonates.<sup>11</sup> In this report from KwaZulu-Natal we describe the increasing burden of TB, in association with HIV, on maternal health in the region. In addition, we document neonatal and early infant TB under 6 months of age as surrogate indicators of latent, active or undetected maternal disease.

## PATIENTS

### Pregnant women

Pregnant women with TB, detected at the antenatal clinics and labour ward at King Edward VIII Hospital (KEH) in Durban, South Africa, between January 1996 and December 1998, were prospectively studied. All of the mothers recruited presented with clinical signs and symptoms of disease, and TB was diagnosed by: (i) detection of acid-fast bacilli on sputum-smear microscopy; (ii) culture of *Mycobacterium tuberculosis*; (iii) histological evidence of tuberculous disease; and/or (iv) radiological features supporting TB in the mother. A maternal endometrial sample for TB culture was submitted where congenital TB was suspected. HIV antibody status of the mothers was determined by HIV-1 ELISA (Abbot, Wiesbaden, Germany), following both pre- and post-test counselling conducted by a trained HIV counsellor. Maternal clinical profiles and deaths were documented.

### Neonates and infants

During the same time period, the number of neonates and infants under 6 months of age with culture-confirmed TB at the hospital was recorded. For neonates these data were collected prospectively, and for infants the data were obtained retrospectively from the hospital's microbiology database. These neonates and infants did not necessarily represent mother-baby pairs. Neonates were investigated for TB if: (i) the mother had TB during pregnancy; or (ii) the neonate had a progressive pneumonia, and/or unexplained visceromegaly.<sup>11</sup> For neonates and infants, investigation for TB included three early-morning gastric aspirates buffered in a 1% sodium bicarbonate solution and submitted for smear microscopy and

culture for *M. tuberculosis*, and chest radiography. Additional investigations, such as cerebrospinal fluid culture and biopsy samples, were undertaken when clinically indicated.

## METHODS

### HIV-1 seroprevalence rate

Some of the women who delivered at the hospital had received antenatal care at KEH, some had received antenatal care at other primary and secondary health care centres in the region and some had received no antenatal care before delivery. Although all mothers using the hospital's antenatal facilities were offered HIV testing with counselling, this service was not routinely available at other antenatal centres within the greater Durban area during this study period, and peripartum HIV screening was not standard practice at KEH labour ward. As a result, although the hospital recorded 50 518 maternities, it was not possible to determine the exact number of HIV-infected maternities during the study period. We therefore estimated the total number of HIV-infected maternities based on the following documented statistics: (i) the total number of deliveries per year studied in 1996, 1997 and 1998, namely 16 908, 16 811 and 16 799 respectively; (ii) 25%, 28% and 30% HIV-1 seroprevalence rates for 1996, 1997 and 1998 among antenatal attendees respectively (Department of Obstetrics and Gynaecology, and KEH Virology statistics — unpublished data); and (iii) a 10% unbooked rate — among these women HIV-1 seroprevalence rates were 45%.<sup>12</sup>

### Statistical calculations

The caseload of TB in pregnant women, neonates and infants at the hospital was estimated. Hospital-specific infection rates for TB in pregnancy were calculated. The attributable fraction (AF) of TB related to HIV infection in pregnancy was calculated using the formula:  $AF_{\text{exposure}} = 1 - 1/RR$ , and  $AF_{\text{population}} = AF_e \times PE$  (prevalence of exposure). RR was the relative risk of TB-HIV co-infection v. TB without HIV infection in pregnancy, and PE was the fraction of TB-HIV co-infected mothers of the total mothers with TB in pregnancy. Analysis was performed using Epi-Info Version 6.02 (Centers for Disease Control, Atlanta, Georgia); categorical data were analysed using the chi-square test, and exact binomial confidence intervals (CIs) were calculated for proportions.

## RESULTS

### TB in pregnancy

One hundred and forty-six women were diagnosed with TB during pregnancy; the overall hospital rate of TB was 289.0 per 100 000 maternities. TB accounted for 11 of 16 908 deliveries (0.1%) in 1996 and 94 of 16 799 deliveries (0.6%) in 1998 (Fig. 1). Of these mothers with TB, 115 (78.8%, 95% CI 71.2 -



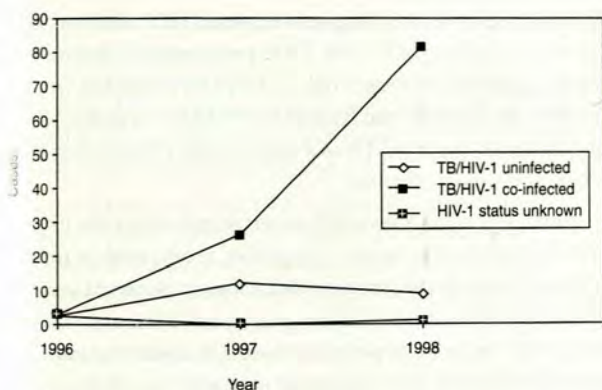


Fig. 1. Caseload of TB and TB-HIV co-infection in pregnant women attending King Edward VIII Hospital, 1996 - 1998.

8.1%) were HIV-infected, 26 (17.8%, 95% CI 12.0 - 25.0%) were HIV-non-infected, and in 5 mothers HIV status was not determined. Minimum TB-HIV co-infection rates increased from 36.4% in 1996 to 88.3% in 1998 ( $P < 0.001$ , Fig. 1).

Based on our calculations, 14 849 of the 50 518 parturients were HIV-infected. The TB prevalence rate for HIV-non-infected maternities at the hospital was 72.9/100 000, and for HIV-infected maternities, 774.5/100 000. The relative risk of TB due to HIV infection was  $774.5/72.9 = 10.62$  (95% CI 6.9 - 16.3). The  $AF_{\text{exposure}}$  was therefore  $1-1/10.62 = 0.91$  and the  $AF_{\text{population}} = 0.91 \times 78.8 = 71.7\%$ , i.e. the population-attributable fraction of TB related to HIV infection in pregnant women was 71.7%.

Diagnosis and type of TB in the mothers are described in Table I. Pulmonary TB (PTB) was the commonest form of TB, occurring in 115/146 (78.8%); there was no statistical difference between the rates of PTB among HIV-infected women and their

non-infected counterparts. Similarly, there was no difference between the rates of sputum smear microscopy positivity between the two groups. Sixty-three per cent of the mothers had TB detected within the last 3 months of pregnancy. No significant difference in the prevalence of extrapulmonary TB was detected between the HIV-infected and non-infected cohorts. Two mothers, one in each category, had multidrug-resistant TB. Fifteen mothers with TB died during the study period, resulting in a mortality rate of 103 deaths per 1 000 women with overt TB during pregnancy. Fourteen of these women (93.3%) were HIV-co-infected.<sup>13</sup>

### Neonatal and infant tuberculosis

Thirty-five neonates and 59 infants had culture-confirmed TB during this time period. In only 13 of the neonates (37.1%) was maternal TB diagnosed before detection in the neonate. Fig. 2 describes the progression in the number of culture-confirmed cases of TB in neonates and infants under 6 months of age at KEH. There was a 2.2-fold increase in TB detected in newborn babies and infants between 1996 and 1998, from 20 (21.2% of total cases) in 1996 to 43 (45.7% of total cases) in 1998. Most of the newborns (85.7%) and infants (83.1%) were smear-negative, with median time of culture confirmation 6 weeks. In 95.7% of cases the organism was susceptible to first-line anti-TB drugs; 4 babies had multidrug-resistant TB. Median age of detection of TB in infants in the 1 - 6-month age category was 2.5 months (standard deviation (SD) 1.8). HIV distribution in the infants was not calculated as this component was undertaken retrospectively and complete follow-up datasets were not available for these infants. HIV infection status in the neonates is currently being evaluated in a longitudinal follow-up study at the unit.

Table I. TB in HIV-infected and HIV-non-infected women at King Edward VIII Hospital, 1996 - 1998

	HIV-infected (%) (N = 115)	HIV-non-infected (%) (N = 26)	HIV status unknown (N = 5)	P-value
Pulmonary TB	90 (78.2)	20 (76.9)	5 (100)	0.88
AFB-positive	35 (38.9)	7 (26.9)	0	0.48
Culture-positive, smear-negative	4	2	-	
Clinical/radiological	50	11	-	0.89
Histology*	1	-	-	-
Extrapulmonary TB	25 (21.8)	6 (23.1)	0	0.88
Pleural effusion	14	2	-	0.32
Miliary TB	2	-	-	
CNS/spinal TB	3	2	-	0.23
Genital/abdominal TB	4	2	-	1.0
Lymph node TB	1	-	-	
Constrictive pericarditis	1	-	-	

\* Tuberculous granulomas on bronchoscopic biopsy sample.  
AFB = acid-fast bacilli; CNS = central nervous system.



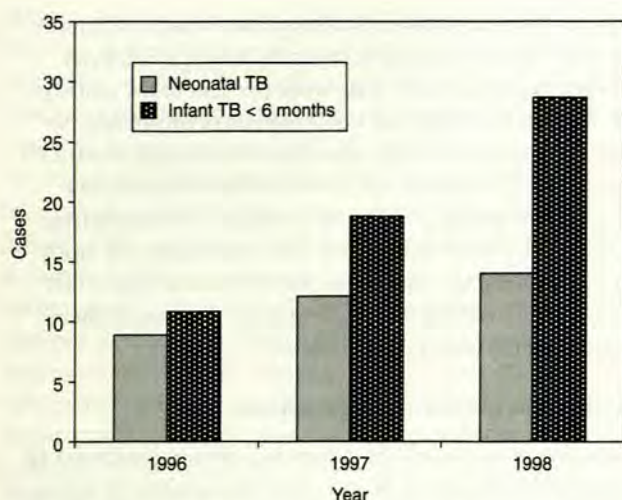


Fig. 2. Culture-confirmed TB in neonates and infants less than 6 months of age in the paediatric wards, neonatal and intensive care units, King Edward VIII Hospital, 1996 - 1998.

## DISCUSSION

In this study we draw attention to the major impact of TB, when it occurs together with HIV, on the reproductive health of women in South Africa. In the recent extensive literature on TB and HIV, with the latter fuelling the epidemic of the former, the impact of TB on pregnant women, their newborn babies and infants has not been adequately documented. In this study we have shown a dramatic increase in the caseload of TB in pregnancy between 1996 and 1998, 71.7% of which was attributable to HIV. This increase was paralleled by a rise in incidence of newborn and infant TB at the hospital.

Our findings parallel the global finding of increase in TB incidence over the last two decades,<sup>14</sup> and the increase in TB in women of childbearing age in our region. In rural KwaZulu-Natal, TB among women (mean age 33.4 years) increased from 28% to 37% between 1991 and 1995;<sup>15</sup> and a 157.5%<sup>16</sup> - 400%<sup>17</sup> increase in the number of TB-related deaths in women in their thirties was documented in conjunction with the escalating HIV epidemic in this province.<sup>18</sup>

HIV and TB target women in their prime childbearing years, and co-infection has been widely reported, reaching a peak of 65% in adults in our region.<sup>16</sup> Consequently, one would have anticipated an increase in reports of TB and HIV co-infection in pregnant women, especially in sub-Saharan Africa, since this region carries the brunt of TB and HIV infection in adults globally.<sup>4</sup> However, this has not been the case. TB has not been documented in major HIV cohort studies from Africa or the developed countries.<sup>10</sup> Only two studies in the USA have reported on maternal TB in relation to HIV infection: The Women and Infants Transmission Study in the USA<sup>19</sup> documented 11 of 52 pregnant women with a positive tuberculin skin test of more than 5 mm or medical history of

TB, and Margono and colleagues<sup>20</sup> reported HIV infection in 7 of 11 tested women (64%) with TB in pregnancy. In Africa, reports suggest an increased risk of TB in HIV-infected women post delivery (Nairobi and Rwanda).<sup>10,21,22</sup> More recently, Ahmed and colleagues<sup>9</sup> reported TB as a major cause of non-obstetric-related mortality in Zambia.

Historical data have revealed uncertainties about the impact of TB on reproductive health.<sup>23</sup> However, recent studies from the Third World detail consistently increased perinatal and obstetric complications: TB in pregnancy has been associated with a 6-fold increase in perinatal deaths, a 2-fold increase in perinatal morbidity and a maternal mortality rate of 66 per 1 000 pregnant women infected with TB.<sup>24-26</sup> Early treatment of TB in pregnancy improves obstetric and perinatal outcome.<sup>21</sup> However, routine antenatal care (ANC) services may not be sensitised to the early detection of TB in the Third World. Moreover, women often attend ANC services late in pregnancy in Africa. At KEH, the mean age of antenatal booking is 28 weeks; therefore the window of opportunity for the detection of TB disease before labour is small. Also, the presentation of TB in pregnancy may vary from asymptomatic to nonspecific mimicking the physiological signs of pregnancy. Our data failed to show an increase in extrapulmonary TB in HIV-infected pregnant women, and are similar to those from the pre-HIV era which noted a 10 - 24.4%<sup>27,28</sup> extrapulmonary TB rate in pregnancy. As the detection of genital TB requires detailed placental and endometrial tissue analysis, it is possible that our figures underrepresent the true extent of undetected extrapulmonary and genital TB in our region. Our cases of neonatal TB without concordance with maternal disease (62.9%) support this hypothesis.

Although there are adverse perinatal outcomes, and mortality, from whatever cause is high in pregnancies complicated by TB and HIV co-infection, it is difficult at this stage to recommend any specific antenatal prevention strategy without further study. Such interventions are most likely to be effective if they are coupled with programmes aimed at interruption of mother-to-child transmission of HIV. A method for determining women at greatest risk for developing TB during pregnancy needs to be established. Also, if it is true that pregnancy potentiates re-activation or re-infection with TB within the index pregnancy, prophylactic regimens including isoniazid for a fixed duration may be indicated in an attempt to reduce adverse maternal and perinatal outcomes.

This study represents only women with overt TB in pregnancy detected at KEH. These figures may not reflect the true prevalence in the general urban and semi-urban population around the greater Durban area. It is difficult to gauge the extent of missed cases in other health facilities in our region as pregnancy is not a recognised category on South African TB notification forms. Regardless, the combined escalation of TB incidence in pregnancy, newborns and young



infants requires heightened awareness from all health care workers in the region.

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