Tuberculosis in pregnancy: an estimate of the global burden of disease

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Summary

Background The estimated number of maternal deaths in 2013 worldwide was 289 000, a 45% reduction from 1990. Non-obstetric causes such as infectious diseases including tuberculosis now account for 28% of maternal deaths. In 2013, 3·3 million cases of tuberculosis were estimated to occur in women globally. During pregnancy, tuberculosis is associated with poor outcomes, including increased mortality in both the neonate and the pregnant woman. The aim of our study was to estimate the burden of tuberculosis disease among pregnant women, and to describe how maternal care services could be used as a platform to improve case detection.

Methods We used publicly accessible country-level estimates of the total population, distribution of the total population by age and sex, crude birth rate, estimated prevalence of active tuberculosis, and case notification data by age and sex to estimate the number of pregnant women with active tuberculosis for 217 countries. We then used indicators of health system access and tuberculosis diagnostic test performance obtained from published literature to determine how many of these cases could ultimately be detected.

Findings We estimated that 216 500 (95% uncertainty range 192 100–247 000) active tuberculosis cases existed in pregnant women globally in 2011. The greatest burdens were in the WHO African region with 89 400 cases and the WHO South East Asian region with 67 500 cases in pregnant women. Chest radiography or Xpert RIF/MTB, delivered through maternal care services, were estimated to detect as many as 114 100 and 120 300 tuberculosis cases, respectively.

Interpretation The burden of tuberculosis disease in pregnant women is substantial. Maternal care services could provide an important platform for tuberculosis detection, treatment initiation, and subsequent follow-up.

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Introduction

In the past two decades, there have been major declines in maternal mortality. The estimated number of maternal deaths in 2013 worldwide was 289 000, a 45% reduction from 1990.[1] Globally, the leading causes of maternal death include direct obstetric causes, such as haemorrhage and hypertensive disorders; however, other non-obstetric causes including infectious diseases are now responsible for 28% of maternal mortality worldwide.[2] Despite widespread implementation of the DOTS strategy and progress towards the tuberculosis-specific targets articulated in the Millennium Development Goals, tuberculosis remains a significant global public health challenge. In 2013, 3·3 million tuberculosis cases and 510 000 tuberculosis deaths were estimated to occur in women globally.[3]

The presence of tuberculosis disease during pregnancy, delivery, and post partum is known to result in unfavorable outcomes for both pregnant women and infants.[4,5] These outcomes include a roughly two-fold increased risk of premature birth, low birthweight, intrauterine growth retardation, and a six-fold increase in perinatal death,[6,7] especially in women who are co-infected with HIV.[4,8–11] Tuberculosis disease in the infant is also an outcome of concern. In the high tuberculosis and HIV prevalence setting of Durban, South Africa, 15% of mothers with active tuberculosis transmitted the infection to their newborns within the first 3 weeks of life.[6]

Clinical diagnosis of tuberculosis in pregnant women can be difficult due to non-specific symptoms related to the physiological response to pregnancy.[4] For pregnant women in most countries with a high tuberculosis burden, the current standard practice of care for tuberculosis screening and diagnosis is the same as that used to detect disease in the general population. Recommended diagnostic tests may include smear microscopy, culture, and molecular DNA detection methods such as Xpert MTB/RIF.[4] Shielded chest radiography, which poses minimal risk to the fetus, is also recommended in women with a recent tuberculosis contact.[4–6] In settings of high HIV burden, the WHO symptom screen and Xpert MTB/RIF are recommended. Once diagnosis is confirmed, the WHO recommendation for tuberculosis treatment in pregnant women is the same as for non-pregnant women,[12] even for HIV-positive women on antiretroviral therapy (ART).[5,12]

The burden of tuberculosis disease among pregnant women is not known. Consequently, there are few data to guide efforts to reduce the tuberculosis burden in this population. Therefore, the objectives of this paper were to

(1) estimate the global and country-level burden of tuberculosis disease among pregnant women; (2) determine how many pregnant women could benefit from tuberculosis diagnosis integrated with maternity care; and (3) estimate the number of cases that could be detected using three different diagnostic tests.

Methods

Estimating the burden of tuberculosis in pregnant women

We derived an estimate of the number of pregnant women with active tuberculosis in 217 countries using publicly accessible country-level estimates of the following parameters: total population,[13] distribution of the total population by age and sex,[13] crude birth rate,[14] estimated prevalence of active tuberculosis,[15] and case notification data by age and sex.[15] In each country, the estimated tuberculosis prevalence rate was adjusted to reflect more accurately the prevalence of tuberculosis among women of childbearing age (15–44 years) by using the ratio of smear-positive cases notified in women of childbearing age relative to the smear positive notification rate in the full population. The calculated adjusted tuberculosis prevalence rates by region are shown in table 1 together with case notification rates in women aged 15–44 years, and in the full population (as reported by WHO).[16] The point estimate of tuberculosis cases in pregnant woman was obtained using the following formulae:

Formula 1·1:

$$\textit{Case notification rate women (age 15–44 years) smear positive} = \frac{\textit{Total N new smear positive cases notified woman (15–44 years)}}{\textit{Full country population} \times \textit{proportion of population women age 15–44 years}}$$

Formula 1·2:

$$\textit{Estimated tuberculosis prevalence rate women (age 15–44 years)} = \frac{\textit{Case notification rate woman (age 15–44 years) smear positive}}{\textit{Full country case notification rate smear positive} \times \textit{Full country tuberculosis prevalence rate}}$$

Formula 1·3:

$$\textit{Estimated number of tuberculosis cases in pregnant women} = \textit{Total population} \times \textit{crude birth rate} \times \frac{\textit{280 days per pregnancy}}{\textit{365 days per year}} \times \textit{Estimated tuberculosis prevalence rate women (age 15–44 years)}$$

We multiplied the total population by the crude birth rate, and then by the average gestational period (280 days), to calculate the number of pregnant days, per country, in 2011. By dividing this number by 365 days, we estimated the number of women pregnant on any given day during the year. Finally, by multiplying this number by the age-specific and sex-specific tuberculosis prevalence, we calculated a point estimate of the number of pregnant women with active tuberculosis in each country in 2011. In summary, formula 1·1 was used to calculate the case notification rate in women aged 15–44 years. This rate was used to estimate the total prevalence in women aged 15–44 years (formula 1·2). Formula 1·3 was then used to estimate the total number of tuberculosis cases in pregnant women. Country-level estimates were added together to generate regional and global estimates of tuberculosis burden.

Monte Carlo simulations were used to define the uncertainty ranges (UR; 2·5 and 97·5 percentiles) around point estimates. To calculate ranges, we used formulas 1·1 to 1·3, and randomly and individually sampled three key parameters (crude birth rate, total population, and estimated prevalence of tuberculosis) 1000 times. Reported maxima and minima for each key input informed the variability of the distributions, which were assumed to be Gaussian based on best fit in comparison to other two-tailed distributions. For each distribution, the mean was selected as the medium-level estimate of the primary data.[12,13] The variance was defined as three standard deviations from the mean, as the primary data sources provided high-level and low-level data that represented the highest and lowest possible data points.[12,13]

Estimating the burden of tuberculosis in pregnant women among those who access maternal health services

We estimated the proportion of tuberculosis cases with access to antenatal and labour or delivery care in each country by multiplying the country-level estimate of tuberculosis cases by two different indicators of access: at least one antenatal care visit (antenatal care services),[17,18] and birth attended by skilled health professional (labour and delivery services).[18] The WHO regional averages for these statistics are shown in table 1.

Estimating the burden of tuberculosis detected in pregnant women

We present three hypothetical diagnostic scenarios, each using a different single test that could be implemented in the maternal care setting. Tests considered include: (1) the present standard of care for tuberculosis diagnosis in most settings (sputum smear microscopy); (2) a test that is currently recommended in pregnant women with high sensitivity but only moderate specificity (chest radiography for detection of active tuberculosis); and (3) a recently recommended test with high sensitivity and excellent specificity (Xpert RIF/MTB). WHO symptom screen with subsequent Xpert RIF/MTB was not explicitly