Screening for tuberculosis in pregnancy: do we need more than a symptom screen? Experience from western Kenya

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Reduction of tuberculosis (TB) transmission, morbidity and mortality relies largely on intensified case finding, with consequent early initiation of adequate treatment.1,2 This is particularly important among pregnant women in resource-limited settings where TB is a cause of non-obstetrical (indirect) maternal deaths.3,4 This burden is higher in settings with a high prevalence of human immunodeficiency virus (HIV) infection.5,6 Kenya has an adult HIV prevalence of 6.2%,7 with an unacceptably high maternal mortality ratio of 488 per 100000 live births; 25% of these deaths are attributed to indirect causes such as TB, anaemia, HIV and malaria.8

TB case notification data are not stratified for pregnancy, but women of reproductive age bear a heavier burden of TB in sub-Saharan Africa than their male counterparts.1,9 Data from Western Cape, South Africa, indicate that there is a 24.2-fold higher incidence of TB disease among infants born to HIV-infected mothers, diagnosed at a mean age of 6 months, than among those of HIV-negative mothers.10 This suggests probable underdiagnosis of active TB disease during the antenatal and postnatal periods. HIV and TB co-infection during pregnancy have a multiplier effect on maternal morbidity and mortality, and result in poorer pregnancy outcomes.1,11 In Pune, India, TB increased the probability of death by 2.2-fold among HIV-infected women who developed TB and by 3.4-fold for their infants compared to women who did not develop TB.11 In Johannesburg, South Africa, 70% of obstetric deaths in HIV-infected women were mainly attributed to TB.12 These figures suggest that routine screening of pregnant women for TB in endemic settings would be helpful, particularly those who are HIV-infected.

The World Health Organization (WHO) recommends ruling out active TB and identifying those in need of further testing among HIV-infected adults using specific symptoms (current cough of any duration, fever, weight loss or night sweats).13 Although these recommendations were not specific for pregnancy, Gupta et al. used this recommendation and found a 1.4% (11/799) prevalence of active TB among HIV-infected pregnant women who were part of a clinical trial in India.14 Another study of cough of ≥2 weeks, performed in Kenya by the same clinical team and by the same first author in a routine setting similar to the target population for this study, failed to identify those with TB disease (n = 187).15 The current study differs from the earlier one in its larger sample size and because it compares HIV-infected and non-infected pregnant women.

Data on the utilization of symptom screening among pregnant women in routine settings are scarce. This has been attributed to significant financial and logistical challenges in the implementation of screening in this group of patients.1 The objectives of the present study were 1) to explore the utility of TB symptom screening using symptoms of ≥2 weeks’ duration in a routine setting, and 2) to compare differences in diagnosis of TB among HIV-infected and non-infected pregnant women in western Kenya.

METHODS

Study design

This was a descriptive cohort study among HIV-infected and non-infected pregnant women.

Study site and setting

The study was conducted at the Moi Teaching and Referral Hospital (MTRH) antenatal care clinic and the AMPATH Prevention of Mother-To-Child Transmission
HIV-infected pregnant women were offered antenatal and HIV care in the AMPATH clinic, while their non-HIV-infected counterparts were offered antenatal care in the MTRH clinic. Both clinics are located on the MTHR grounds in separate buildings, about 200 m apart, and serve a similar patient population.

**TB screening and management**

Recommendations by the Kenya National AIDS and STI Control Programme were to screen for TB in all pregnant mothers at every visit. However, as no programme guidelines on how screening should be carried out were available, screening for TB in pregnancy was opportunistic. The AMPATH programme screened both HIV-infected and non-infected patients for TB using a routine six-question symptom screening questionnaire in its cough monitor programme (Table 1). Five years of experience among non-pregnant adult population demonstrated a 13% sputum smear-positive rate, with 8% of smear-negative adults positive on either culture or GeneXpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA; unpublished programme data). The Cough Monitor Programme for pregnant women was set up within the AMPATH programme with funding from the International Union Against Tuberculosis and Lung Disease, Paris, France, between October 2010 and July 2012, as part of standard routine care in the AMPATH and MTRH antenatal care clinics.

The symptom screen questionnaire was administered by cough monitors, who were lay staff trained for this purpose. A positive response to any of the questions was regarded as a positive symptom screen, and prompted sputum collection from those with productive cough for TB smear microscopy. The symptom screen questionnaire was administered to each patient only once. Patients whose microscopy and/or culture were positive for *Mycobacterium tuberculosis* were offered standard anti-tuberculosis treatment per national guidelines. The data from the symptom screen questionnaire were entered into an Excel database for programmatic use (Microsoft, Redmond, WA, USA).

When the attending clinician had a high clinical index of suspicion for TB disease, despite unproductive cough or sputum negative for *M. tuberculosis*, a shielded chest X-ray (CXR) was performed based on clinical opinion. Based on positive CXR results or suggestive clinical symptoms, presumptive anti-tuberculosis treatment was offered for these patients.

**HIV screening and management**

About 90% of pregnant women in Kenya were screened for HIV infection as standard of care, unless a woman opted out at the time of the study. Women at the MTRH were screened according to the national HIV screening protocol.

**Population**

The population included all pregnant women cared for at the AMPATH and MTRH antenatal care clinics from October 2010 to July 2012, who were screened for TB using the AMPATH symptom screen questionnaire and who had clinical data captured in the cough monitor database. Patients with unknown HIV status and those admitted to hospital were excluded from the analysis.

**Sample size**

During the study period, a total of 2983 pregnant women received antenatal services at the AMPATH and MTRH antenatal care clinics; these women formed the population of this study.

**Data collection and data variables**

Routine clinical data were collected retrospectively. There were three sources of data in this study: the symptom screening questionnaire database, the TB laboratory register and patient files. The following variables were collected from pregnant women attending the PMTCT and antenatal care clinics who were administered the symptom screening questionnaire: age, HIV status, CD4 counts if HIV-infected, TB symptoms per the symptom screening questionnaire, CXR patterns, sputum obtained (yes/no) and sputum microscopy results.

**Data analysis**

Data were retrieved from the cough monitor database and evaluated for inconsistencies and missing data. Where possible, data were corrected from source data. Descriptive data were reported, numbers and proportions were stratified by HIV status, and continuous data were given as median and interquartile range (IQR) for the various subcategories related to TB symptom screening in each group.

**Ethics**

This study was approved by both the Institutional and Research Ethics Committee of the MTRH, Moi University School of Medicine, Eldoret, Kenya, as well as the Institutional Review Board of Lifespan, Providence, RI, USA. Only de-identified data were analysed. No patient names were recorded, only patient numbers, to enable linkage with the laboratory and patient files. No extra data were collected outside of routine care, and confidentiality was observed at all levels of data collection. The study was classified as an audit, and hence of minimum risk to participants.

**TABLE 1** AMPATH symptom screening questionnaire

<table>
<thead>
<tr>
<th>Cough of ⩾ 2 weeks</th>
<th>Bloody cough in the past year</th>
<th>Fever of ⩾ 3 weeks</th>
<th>Past history of TB diagnosis</th>
<th>History of TB contact in the household</th>
<th>Weight loss/failure to gain weight if pregnant in the past year</th>
</tr>
</thead>
</table>
| TB = tuberculosis.
RESULTS

Of 2983 pregnant women enrolled in the study, 34 (1%) had unknown HIV status and were excluded from the analysis. Of the remaining 2949 pregnant women, 1488 (50.5%) were HIV-positive and 1461 (49.5%) were HIV-negative (Figure). The median age of the HIV-infected and non-HIV-infected women was respectively 30 (IQR 26–35) and 26 years (IQR 24–31). Of the HIV-infected women, 1101 had a CD4 count available; the median count at enrolment in the PMTCT programme was 377 cells/μl (IQR 244–530).

Of the 1488 HIV-infected women, 119 (8%) had a positive TB symptom screen, which was significantly higher than among the non-HIV-infected women (5%, 67/1461; \( P < 0.001 \)). As regards specific symptoms, 3% (43/1488) had a cough of \( \geq 2 \) weeks among the HIV-infected group vs. 1% (21/1461) among the non-HIV-infected group (\( P = 0.014 \); Table 2).

Only patients with a productive cough had sputum collected for microscopy. Of the HIV-infected and non-infected women who had cough of \( \geq 2 \) weeks, respectively 27/43 and 15/21 had productive cough. One non-HIV-infected patient (1/1461) was sputum-positive; none were positive in the HIV-infected group (Figure). The non-HIV-infected TB patient had cough, positive history of contact with an active TB case and weight loss.

During the study period, 1% (16/1488) of the women in the HIV-infected group were treated for TB presumptively; 14 underwent CXR and two did not. Table 3 shows the CXR features of patients treated presumptively for TB. Of the 14 patients with CXR, 10 had features suggestive of TB (pleural effusion, infiltrate and miliary pattern).

During the study period, 0.6% (17/2949) of the women were treated for TB: 16 presumptively in the HIV-infected group and one based on a positive smear microscopy result in the non-HIV-infected group. Table 4 shows the clinical characteristics of the patients treated for TB during the study period.

DISCUSSION

In this study in western Kenya, a symptom screening questionnaire did not produce a high yield of active TB disease among pregnant women, either HIV-infected or non-infected. Although some women were identified using screening, the majority did not have cough with sputum and could not be evaluated using microscopy. CXR in this group with non-productive cough might have revealed more positive TB cases; however, CXR was not performed systematically. Most of the cases treated were thus based on CXR findings, demonstrating a need for further evaluation of this test in pregnant women. Reliance on sputum microscopy did not seem to be useful given the low sputum availability. There seemed to be little difference in results for HIV-positive and -negative women.

These findings are similar to previous findings in the same target population, although the earlier study had a smaller sample size.

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TABLE 2  TB symptoms of pregnant women who were positive on TB symptom screen in western Kenya, 2010–2012

<table>
<thead>
<tr>
<th>HIV-infected (n = 1488)</th>
<th>Non-HIV-infected (n = 1461)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom screen-positive</td>
<td>119 (8)</td>
<td>67 (5)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough ( \geq 2 ) weeks</td>
<td>43 (3)</td>
<td>21 (1)</td>
</tr>
<tr>
<td>Coughed blood in the past year</td>
<td>2 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Fever ( \geq 3 ) weeks</td>
<td>19 (1)</td>
<td>31 (2)</td>
</tr>
<tr>
<td>Weight loss/failure to gain weight in the past year</td>
<td>19 (1)</td>
<td>18 (1)</td>
</tr>
<tr>
<td>Past history of TB contact in the household</td>
<td>36 (2)</td>
<td>15 (1)</td>
</tr>
<tr>
<td>Past history of TB diagnosis</td>
<td>40 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

TB = tuberculosis; HIV = human immunodeficiency virus.

TABLE 3  CXR patterns for HIV-infected pregnant women treated presumptively for tuberculosis in western Kenya, 2010–2013 (n = 14)

<table>
<thead>
<tr>
<th>CXR patterns</th>
<th>HIV-infected</th>
<th>Non-HIV-infected</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltrate</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miliary pattern</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other abnormalities</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CXR = chest X-ray; HIV = human immunodeficiency virus.

TABLE 4  Clinical characteristics of pregnant women treated for TB in western Kenya, 2010–2013 (n = 17)

<table>
<thead>
<tr>
<th>Age, years, median [IQR]</th>
<th>30 [27–33]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive symptom screen</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough ( \geq 2 ) weeks</td>
<td>4</td>
</tr>
<tr>
<td>Coughed blood in the past year</td>
<td>1</td>
</tr>
<tr>
<td>Productive cough</td>
<td>4</td>
</tr>
<tr>
<td>Fever ( \geq 3 ) weeks</td>
<td>1</td>
</tr>
<tr>
<td>Weight loss/failure to gain weight in past year</td>
<td>2</td>
</tr>
<tr>
<td>Past history of TB contact in the household</td>
<td>2</td>
</tr>
<tr>
<td>Past history of TB diagnosis</td>
<td>0</td>
</tr>
</tbody>
</table>

CD4 counts, cells/μl, median [IQR]* | 256 [106–302]

*1 non-HIV-infected patient.

TB = tuberculosis; IQR = interquartile range; HIV = human immunodeficiency virus.
size \( (n = 187) \).\(^{13}\) The findings are surprising, given the fact that Kenya is a high burden setting for HIV and TB, with an HIV prevalence of 6.2\%, and ranks thirteenth among the 22 high TB burden countries globally.\(^{2,22}\) Of the 17 pregnant women treated for TB, only one had a positive smear microscopy result. The large number of patients reporting unproductive cough, particularly in the HIV-infected group, raises concerns that TB diagnosis was perhaps being missed in this population, as sputum microscopy remains the major diagnostic testing strategy.

These findings could be attributed to the following five possibilities: 1) the TB symptom screening tool is not sensitive enough during pregnancy. In a study in South Africa that documented a high prevalence of TB among HIV-infected women (47/1415, 3.3\%), the majority (73\%) did not report any TB symptoms.\(^{23}\) 2) Symptoms may be attenuated in people living with HIV, often yielding negative results on smear microscopy.\(^{24}\) Participants in this study who were treated for TB had a lower CD4 count than those who were not treated for TB (256 cells/\( \mu \text{l, IQR} 106–302 \) vs. 377 cells/\( \mu \text{l, IQR} 244–530 \)). 3) Physiological changes associated with pregnancy may mask the symptoms of TB.\(^{23,4}\) There may be a low prevalence of TB in pregnancy—this is less plausible considering TB is a major cause of non-obstetrical maternal deaths.\(^3,5\) A combination of all of the above.

In our setting, the utility of shielded CXR in screening for TB in pregnancy among HIV-infected women needs to be evaluated. Of the 17 women treated for TB in this study, 10 had CXR features suggestive of TB. Of particular note are two cases who had a miliary pattern. This finding is consistent with previous findings in the same population, where 10/187 patients were presumptively treated for TB based on suggestive CXR, three of whom had a miliary pattern.\(^{13}\) However, a study in India demonstrated marginal to no added value of CXR in this group.\(^{14}\)

Our study had three major limitations. First, a gold standard for TB diagnosis was lacking, and not all patients underwent culture for TB, CXR or further evaluation other than clinical examination. Second, the WHO TB symptom screening protocol of current cough of any duration, fever, weight loss or night sweats was not used because the routine data analysed was from before implementation of the WHO recommendation. Third, data on antiretroviral use among HIV-positive participants were not collected. However, our large sample size, the fact that MTHR is a referral hospital, which meant that our study had an equal proportion of HIV-negative and -positive participants, and the fact that this was carried out under routine programme conditions, are of value.

**CONCLUSION**

This study does not seem to demonstrate the utility of TB symptom screening questionnaires in routine settings among pregnant women in Western Kenya. There may, however, be a role of CXR in screening for TB among HIV-infected pregnant women. More analytical hypothesis-driven studies need to be developed to determine the best screening tool for TB in pregnancy in high HIV-TB burden, low-resource settings.

**References**

Objective: 1) Explore the utility of screening for symptoms of tuberculosis (TB) in trained settings and identify patients with symptoms of at least 2 weeks in duration in a routine context, and 2) compare the differences in diagnostic test results for TB between pregnant women infected or not infected with the human immunodeficiency virus (HIV) in Western Kenya.

Schéma: A cross-sectional comparative study of pregnant women with known HIV status who were screened for TB symptoms between 2010 and 2012 in Eldoret, Western Kenya.

Results: Of 2983 participants, respectively 34 (1%), 1488 (50.5%) and 1461 (49.5%) had unknown HIV status, positive and negative status. The median age in years was 30 (IQR 26–35) and 26 (IQR 24–31), respectively, among infected and non-infected women. A positive TB screening was found respectively in 8% (119/1488) and 5% (67/1461) among infected and non-infected. The median CD4 count at the time of enrollment was 377 cells/μl (IQR 244–530) in women infected with HIV. In a woman not infected with HIV, a sputum smear test for TB was positive. In the group of women infected with HIV, treatment was done on suspicion of TB in 1% (16/1488) based on clinical symptoms and chest X-ray. Overall, treatment for TB was offered to 0.6% (17/2949) of participants.

Conclusion: This study does not seem to show the utility of a questionnaire on symptoms for the screening of TB in a routine context for pregnant women, whether or not they are infected with HIV in Western Kenya.

Objetivos: 1) Explorar la utilidad del cribado sistemático de los síntomas de tuberculosis (TB) en la práctica ordinaria, con base en los síntomas de ≥2 semanas de duración; y 2) comparar las diferencias en el diagnóstico de la TB entre las embarazadas que presentan infección por el virus de la inmunodeficiencia humana (VIH) y las embarazadas exentas de esta infección en Kenia occidental.

Métodos: Se realizó un estudio transversal comparativo de las embarazadas con situación conocida frente al VIH, a quienes se administró un cuestionario de cribado de síntomas de TB entre el 2010 y el 2012, en Eldoret en Kenia occidental.

Resultados: De las 2983 participantes, 34 mujeres desconocían su situación frente al VIH (1%), 1488 eran positivas al VIH (50.5%) y 1461 eran negativas (49.5%). La mediana de la edad fue 30 años (IQR 26–35) en las mujeres positivas al VIH y 26 años (IQR 24–31) en las mujeres sin infección por el virus. Se obtuvo un cribado positivo de síntomas en 8% de las mujeres infectadas por el VIH (IQR 119–1488) y en 5% de las mujeres sin infección (IQR 67–1461). La mediana del recuento de células CD4 en el momento del ingreso al estudio fue 377 células/μl en mujeres infectadas por el VIH (IQR 244–530). Una mujer negativa para el VIH presentó una baciloscopia de esputo positiva. En el grupo de mujeres infectadas por el VIH se practicó el tratamiento por presunción de TB en 1% de los casos (16/1488) con base en los síntomas clínicos y la radiografía de tórax. Durante el estudio se ofreció tratamiento antituberculoso a 0,6% de las participantes (17/2949).

Conclusión: Los resultados del presente estudio no parecen demostrar la utilidad del cuestionario de cribado de síntomas de TB en la práctica corriente de atención a las embarazadas, que presenten infección por el VIH o que estén exentas de la infección, en Kenia occidental.