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T-SPOT.TB in Detection of Active Tuberculosis During Pregnancy: A Retrospective Study in China

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Background: Interferon-gamma release assays have not been validated in active TB among pregnant women. Therefore, the objective of this retrospective study was to estimate the diagnostic value of T-SPOT.TB in active TB among pregnant women.

Material/Methods: Between May 2012 and May 2015, 26 consecutive pregnant women with suspected TB were enrolled in our study. The clinicopathological characteristics and T-SPOT.TB results were reviewed and analyzed.

Results: Pregnant patients were divided into a TB group (n=21) and a Non-TB group (n=5). In the TB group, 5 patients had pulmonary TB, 5 had pulmonary TB+ extrapulmonary TB, and 11 had exclusively extrapulmonary TB. The most common site of extrapulmonary TB was pleural (n=11). Statistical analysis showed that the lymphocyte count in the TB group was lower than in the Non-TB group ($P<0.05$). For detection of active TB during pregnancy, T-SPOT.TB had a high sensitivity of 100.0% (84.5%–100.0%) and a specificity of 80.0% (37.6–96.4%).

Conclusions: T-SPOT.TB shows good performance in detection of active tuberculosis during pregnancy. Interferon gamma release assay for TB screening of pregnant women is recommended in clinical practice because it may be a more appropriate diagnostic tool than the tuberculin skin test.

MeSH Keywords: Interferon-gamma Release Tests • Pregnancy • Sensitivity and Specificity • Tuberculosis

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1451 1 — 16

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Background

In 2013, 3.3 million tuberculosis (TB) cases and 510 000 TB deaths were estimated to occur in women globally [1]. In pregnant woman, Sugarman et al. estimated that 216 500 active TB cases existed in 2011 [2]. During pregnancy, untreated TB or TB treated late may lead to severe consequences affecting both mother and child [3,4]. However, pregnant women with pulmonary TB who are treated appropriately do not have increased rates of maternal or neonatal complications [3]. Therefore, rapid diagnosis of TB and timely initiation of appropriate treatment are critical measures that promote optimal clinical outcomes for pregnant woman.

Clinical diagnosis of TB in pregnant women can be difficult. Firstly, pregnancy suppresses the T-helper 1 (Th1) pro-inflammatory response, which may mask symptoms while increasing susceptibility to new infection and reactivation of TB [5]. Secondly, TB symptoms such as fatigue, shortness of breath, sweating, tiredness, cough, and mild fever are similar to normal physiological symptoms of pregnancy [6]. Currently available diagnostic tools for TB are acid-fast bacilli (AFB) microscopy, culture growth, and molecular DNA detection of *Mycobacterium tuberculosis* (M.TB) in specimens. These assays have several limitations, which were summarized by Nguyen et al. [6].

Interferon-gamma release assays (IGRAs), such as QuantiFERON Gold Test In-Tube (QGIT; Cellestis) and T-SPOT.TB (Oxford Immunotech), measure IFN-γ released from peripheral blood mononuclear cell (PBMC) exposed to TB-specific antigens. For detection of latent TB in pregnancy, IGRA showed good performance, while concordance and agreement were poor when comparing the tuberculin skin test (TST) and IGRA results [7,8]. To avoid false-positive interpretations, TST is discouraged and IGRA is recommended for TB screening and diagnosis in pregnant populations with high BCG vaccination coverage or uncertain vaccination status [8,9].

Until now, IGRAs have not been validated in active TB among pregnant women [5]. Therefore, the objective of this retrospective study was to estimate the diagnostic value of T-SPOT.TB in active TB among pregnant women.

Material and Methods

This retrospective study was conducted at the Department of Laboratory Medicine, Shandong Provincial Chest Hospital and was approved by the Ethics Committee of our institute. Because of the retrospective nature of the investigation, the requirement of written consent was waived. All patient records were de-identified to ensure anonymity and confidentiality.

Between May 2012 and May 2015, consecutive pregnant women with suspected TB were enrolled in our hospital. All patients were hospitalized and the results of T-SPOT.TB were reviewed and analyzed. Finally, 26 pregnant patients with certain diagnosis were included in the study. TB was diagnosed based on clinical and radiographic evidence and response to treatment. Patients were classified as control subjects when an alternative diagnosis was established.

Statistical analysis was carried out using SPSS 17.0 software. Data are expressed as mean ± standard deviation (SD) and all calculations were estimated at a 95% confidence interval (95% CI). The Mann-Whitney U test was used to compare the differences between the 2 groups. Sensitivity and specificity were calculated using proven and probable cases as the reference standard. $P<0.05$ was considered a statistically significant difference.

Results

Table 1 shows the clinicopathological characteristics of TB during pregnancy. In our study, 26 pregnant patients were enrolled and subsequently were divided into the TB group (n=21) and Non-TB group (n=5). The mean age was 27.2±3.1 years for the TB group (fetal age 17.5±9.4 weeks) and 30±4.1 years for the Non-TB group (fetal age 11.8±3.6 weeks). The patient delay was 25.7±32.5 days and 33.8±34.7 days (TB *vs.* Non-TB).

In the TB group, 5 patients had pulmonary TB (PTB), 5 had PTB+ extrapulmonary (EPTB), and 11 had exclusively EPTB. The most common site of EPTB was pleural (n=11). Miliary TB accounted for 14.3% of all cases of TB. The contact source was identified in 2 cases (9.5%). Two of 20 patients (10.0%) were positive on AFB smear, and 11 of 20 patients (55.0%) were confirmed by the isolation of M.TB. One of 5 TB patients (20.0%) was TST-positive. Two of 20 TB patients (10.0%) were real-time PCR-positive. The most common complaints of TB patients were fever (71.4%), cough (57.1%), and shortness of breath (42.9%).

In the Non-TB group, fever was found in 40% (n=2), cough in 60% (n=3), and shortness of breath in 40% (n=2). No contact history was obtained, and the results of TB assays (TST, AFB, culture, and RT-PCR) were all negative.

Blood cell counts were estimated and compared between groups using the Mann-Whitney U test. Statistical analysis showed that there was no statistically significant difference between groups in white blood cell count, neutrophil count, monocyte count, and ESR; the lymphocyte count in the TB group was lower than in the Non-TB group ($P<0.05$)

In the present study, all pregnant women with TB were T-SPOT.TB-positive, and 1 of 5 Non-TB pregnant patients was positive.

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Table 1. Characteristics of pregnant patients.

	Tuberculosis	Non-Tuberculosis
Number	21	5
Age (years)	27.2±3.1	30±4.1
Fetal age (weeks)	17.5±9.4	11.8±3.6
Patient delay (days)	25.7±32.5	33.8±34.7
Contact history	2	0
PTB	10	0
EPTB		
Pleural	11	0
Lymph node	2	0
Meningitis	2	0
Miliary TB	3	0
TST	1/5	0/1
Symptoms		
Fever	15	2
Cough	12	3
Shortness of breath	9	2
AFB	2/20	0/4
Culture	11/20	0/4
RT-PCR	2/20	0/2
WBC (10^9/L)	6.81±2.17	8.18±2.06
Neutrophil (10^9/L)	5.13±2.10	5.97±2.73
Lymphocyte (10^9/L)	1.03±0.43	1.64±0.55
Monocyte (10^9/L)	0.59±0.29	0.41±0.14
ESR (mm/1 h)	60.0±32.9	67.2±48.1

TB – tuberculosis; PTB – pulmonary tuberculosis; EPTB – extrapulmonary tuberculosis; TST – tuberculin skin test; AFB – acid fast bacilli; RT-PCR – real-time polymerase chain reaction; WBC – white blood cell; ESR – erythrocyte sedimentation rate.

Therefore, for diagnosis of active TB among pregnant women, T-SPOT.TB had a high sensitivity of 100.0% (84.5–100.0%) and a specificity of 80.0% (37.6–96.4%).

Discussion

Until a whole-blood assay such as IGRA is developed, the diagnosis of latent TB infection relies on the TST. Comparing the TST and IGRA results in pregnancy, concordance and agreement were poor [8]. Given that much is still unknown about the performance of IGRAs in pregnancy, further research is necessary to evaluate the accuracy, using active TB as a reference [8].

Our study is the first to evaluate the performance of IGRAs in pregnant women with active TB at a provincial referral hospital in China. The release of IFN-γ from T-cells in fresh heparinized whole-blood samples was tested using T-SPOT.TB. The data show that T-SPOT.TB has a high sensitivity and a moderate specificity for detection of active TB during pregnancy. Interestingly, the lymphocyte count in the TB group was lower than in the Non-TB group, suggesting that lymphocyte count may be a biomarker in discrimination between TB and non-TB diseases in pregnant women.

Active TB during pregnancy can have serious consequences. TB is a leading cause of morbidity and mortality among women of child-bearing age in developing countries [10]. Additionally, pregnancy is associated with a more prevalent onset of active TB and more rapid progression of TB disease compared with non-pregnant females [11]. The Centers for Disease Control and Prevention (CDC) states that IGRAs are the preferred diagnostic tests for pregnant women with risk factors for exposure to M.TB [12]. These recommendations were made because false-positive tuberculin test results occur in persons who have been infected with non-tuberculous mycobacteria and in persons who have received BCG vaccine. Moreover, patients must return to a health-care provider for test reading, and inaccuracies and bias exist in reading the test.

To the best of our knowledge, there are only 2 studies comparing TST and IGRA, and the agreement between the TST and IGRA was 77.39% and 88%, respectively [7,8]. The positivity of TST appeared to be higher than that of IGRA, and almost two-thirds of pregnant patients with positive skin test results had negative IGRAs [7], a finding that was also reported in another at-risk pregnant population [8]. Although the results may indicate increased IGRA specificity, it is also possible that the IGRA may be less sensitive than the TST in certain circumstances. Our study showed that IGRA has high sensitivity in detecting M.TB infection during pregnancy. The data support that TST specificity is compromised in pregnant women for detection of latent TB, so IGRA should be more accurate than TST.

In a recent meta-analyses, pooled IGRA sensitivity among persons with confirmed TB ranged from 60% to 88%, with the lowest sensitivity among those with human immunodeficiency virus (HIV) infection [13–15]. The rate of T-SPOT.TB-positive results in confirmed cases was about 90% in our hospital (data not published). Several factors were highly correlated with false-negative results in the IGRA: advanced age (age ≥65 years), bilateral disease as determined by chest radiography,

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malignancy, and lymphocytopenia (total lymphocyte count <1.0×10^9/L) [16]. Since our study found T-SPOT.TB had high sensitivity in detection of active TB among pregnant women, we conclude that pregnancy does not appear to influence the results of T-SPOT.TB.

This study has several limitations. Firstly, we lacked maternal TST results, which would have been useful to compare with the IGRA results. Secondly, the incidence rate of TB during pregnancy may be lower than the estimates [2], and the sample size was small. Thirdly, few pregnant patients were confirmed to have TB by mycobacterial culture; the majority was diagnosed clinically. Lastly, the results from this study may not be generalizable to other IGRAs (such as QGIT).

Conclusions

T-SPOT.TB shows good performance in detection of active TB during pregnancy. IGRA for TB screening of pregnant women is recommended in clinical practice because it may be a more appropriate diagnostic test than the TST.

Competing interests

We declare that we have no conflicts of interest.

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