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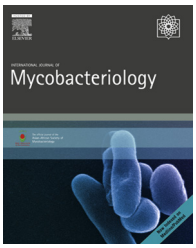

Full Length Article

Extrapulmonary tuberculosis among females in South Asia—gap analysis

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ABSTRACT

The percentage of extrapulmonary tuberculosis (EPTB) among new and relapse tuberculosis cases in South Asia (Afghanistan, Pakistan, India, and Bangladesh) ranged from 19% to 23% in 2014. While tuberculosis was reportedly more prevalent in males, a higher preponderance of EPTB was observed in females. National tuberculosis control programs are highly focused on pulmonary tuberculosis. This creates gaps in the surveillance, diagnosis, and study of EPTB among females, which is especially pronounced in the South Asian setting. We have reviewed recently published literatures from January 2010 to June 2016 reporting EPTB in females with a view to evaluate the current epidemiology, risk factors, diagnostic modalities, and treatment outcomes. We report significant gaps in the surveillance of EPTB among women in South Asia, emphasizing the need for greater focus on EPTB in females to overcome current surveillance and knowledge gaps.

Introduction

Globally, tuberculosis (TB) is among the top five killers of women aged 20–59 years [1]. While the proportion of pulmonary TB (PTB) notifications is higher among males worldwide, TB in females remains a major threat to control due to the impact felt by households, particularly children. It has been argued that the higher case notifications among males may reflect the barriers faced by the female population in accessing health care [2]. Extrapulmonary tuberculosis (EPTB) accounted for 15% of the new and relapse TB cases in 2014 [3]. In contrast to PTB, preponderance for EPTB is reportedly higher among females [4–6]. Irrespective of whether the underlying mechanism is biological, socioeconomic, or cultural, a deeper understanding of the risk factors, impact, access to directly observed therapy (DOT), as well as

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diagnosis of all forms of TB among females is necessary to devise effective control strategies. This is imperative as the millennium development goals, despite achieving progress, faltered in addressing gender disparity, in assessing impact of TB on maternal mortality, and/or indeed in TB control, especially in South Asia [5].

Among the South Asian countries, Pakistan, India, and Bangladesh are included in the category of high-burden countries for TB and MDR (Multidrug resistant) TB [6]. Although post 2015, Afghanistan is not included in high-burden countries; it has the second highest TB burden in World Health Organization's Eastern Mediterranean Region [3].

In keeping with the stalled progress of Millennium Development Goals 3, 5, and 6 (i.e., reducing gender disparity, decreasing maternal mortality, and decreasing the TB burden), efforts to control EPTB among women in South Asia need to be reassessed to identify the gaps in knowledge and/or services. In this review, we aimed at assessing the extent of gender disparity in EPTB in Afghanistan, Pakistan, India, and Bangladesh through researching published literatures over the past 6 years. We further sought to determine the organ systems affected and assess outcome data for EPTB in women available from South Asia, as well as evaluate the utility of diagnostic modalities used for EPTB in high-TB-burden countries of South Asian region. The search results are presented, and the resulting information gaps are highlighted.

Methods

Search strategy

A PubMed systematic literature search was performed for English-language articles related to EPTB among females in South Asia, published between January 2010 and June 2016. Unpublished and ongoing studies could not be explored in this review. We used the following terms in our search, individually as well as in various combinations: tuberculosis women, females, Pakistan, Afghanistan, India, Bangladesh, extrapulmonary, genitourinary, infertility, postpartum, placenta, Asherman syndrome, peritoneal, tubo-ovarian, and endometrium. Two independent reviewers (J.M. and Z.Y.K.) reviewed the titles, abstracts, and full-text articles, and selected potentially relevant studies based on inclusion criteria established prior to the literature search. Discrepancies arising between the reviewers were resolved by consensus in consultation with a third reviewer (R.H.).

Inclusion criteria

We included observational studies including case series, surveys, and descriptive cross-sectional studies focusing on EPTB and PTB among females in specified South Asian countries.

Exclusion criteria

We excluded all studies focusing only on diagnostic criteria, clinical trials on drugs, case reports or case series without details of EPTB and PTB, and articles focusing only on genetic analysis and nonhuman studies. Studies that were conducted in countries other than the specified countries of the Asian region were also excluded.

Outcomes of interest

Reported cases of EPTB among males and females, female:-male ratio (FMR) in reported studies, site of EPTB in females, and diagnostic modalities used for diagnosis of different types of EPTB were evaluated as outcomes in the review. We also reviewed studies on PTB published in the same time period, in order to compare between FMRs of EPTB and PTB.

Results

Search results and studies selected for review

A total of 31 studies on PTB and EPTB (published during 2010–2016) were selected for review. Among these studies, 11 presented data on PTB, 13 presented data on EPTB, while seven reported data on both PTB and EPTB. All seven studies provided proportions for both EPTB and PTB, but only two studies reported separate data on EPTB and PTB for both males and females [9,10]. Among the 20 EPTB studies reviewed, 19 studies reported on EPTB in females; 12 were from India, five from Pakistan, and one each from Afghanistan and Bangladesh. Among 18 studies reporting on PTB, one was from Bangladesh, eight were from India, and nine were from Pakistan.

The overall selection process and characteristics of the excluded studies are summarized in Fig. S1. Excluded studies are listed together with the reason for exclusion in the Table S1.

Study sample characteristics

All 19 studies on EPTB were conducted in health care settings (hospitals, clinics, diagnostic centers, etc.), and in 10 studies data were extracted from hospital records. Age ranges for patients in these studies varied from 15 years to 70 years. The total numbers of patients were 8,829 (ranging from a minimum of 37 to a maximum of 1,994) in these studies. Characteristics of the studies included in this review are summarized in Table 1.

Table S2 presents details of studies reporting on PTB, which were also reviewed for comparison of FMRs in PTB with EPTB. Compared with PTB studies, sample sizes were smaller for EPTB studies.

Types of EPTB among females

Six studies reported distribution of EPTB according to disease sites among females. Among these, only two studies reported various types of EPTB [20,11], while the other four [9,19–21] were based on gender-specific cohorts of women tested for or diagnosed with infertility. Of the two studies reporting on distribution by site, TB adenitis was the commonest form, followed by pleural TB, central nervous system TB, musculoskeletal (bone) TB, and abdominal TB.

Table 1 – Summary of characteristics of the studies included in the review and proportion of extrapulmonary tuberculosis among participants in South Asia (Afghanistan, Bangladesh, India, and Pakistan).

Author & year of publication	Country	Type of study	Study population & settings	Sample size (no. of EPTB)	Types of EPTB (%)	FMR[a]
Fader et al., 2010 [8]	Afghanistan	Retrospective review of records	EPTB patients diagnosed at local hospital	118 (118)	Lymph node (37.3%), CNS (20.3%), skeletal (11.9%), pleural (8.5%), abdominal (6.8%), genitourinary (5.1%), others (10.1%)	2
Miah et al., 2011 [9]	Bangladesh	Cross-sectional study	Abdominal TB patients	53 (53)	Abdominal TB	0.6
Sharma et al., 2010 [10]	India	Retrospective review of the records	Women who underwent laparoscopy for infertility	313 (87)	Genital TB	—
Mukherjee et al., 2012 [11]	India	Retrospective record review	TB patients registered under RNTCP in Nadia, West Bengal	3,605 (335)	—	0.8
Rana et al., 2011 [12]	India	Cross-sectional study	Women presenting to infertility clinics	143 (34)	Genital TB	—
Sharma et al., 2011 [13]	India	Retrospective case series	Women undergoing vaginal hysterectomy	70 (7)	Genital TB	—
Kohli et al., 2011 [14]	India	Cross sectional study	Women attending infertility clinic of hospital	100 (13)	Genital TB	—
Maurya et al., 2012 [15]	India	Prospective observational study	Specimen of EPTB patients submitted from two tertiary care centers	756 (165)	Not specified	0.8
Banerjee et al., 2012 [16]	India	Prospective case–control study	Women with ectopic pregnancy or spontaneous miscarriage	37 (7)	Genital TB	—
Prakasha et al., 2013 [17]	India	Retrospective record-based study	Registered TB patients for DOTs treatment in hospital	1,267 (528)	Pleural TB (28.03%), lymph node (24.81%), abdomen (9.66%), CNS (12.50%), bones and joints (12.31%), others (12.69%)	0.9
Das et al., 2014 [18]	India	Retrospective cohort study	TB patients of all age groups in Nagaland hospitals	238 (29)	Not specified	—
Samant et al., 2014 [19]	India	Retrospective review of records	Patients of diagnosed with abdominal TB in a hospital	61 (61)	Abdominal TB	1.7
Awasthi, 2015 [20]	India	Retrospective review of records	Patients diagnosed with abdominal TB in a hospital	48 (48)	Abdominal TB	0.7
Sarpal et al., 2015 [7]	India	Cohort study	Patients registered under RNTCP category II	545 (115)	Not specified	0.95
Singh et al., 2016 [21]	India	Prospective study	All patients with tuberculous peripheral lymphadenitis at a diagnostic center	255 (204)	Tuberculous lymphadenopathy	1.4
Dusthackeer et al., 2015 [22]	India	Review of laboratory records	Samples submitted for culture	1,295 (189)	CSF (5.3%), renal (9%), endometrial (1.6%), lymph node (30.7%), unknown (53.4)	—
Chandir et al., 2010 [23]	Pakistan	Retrospective case series	All patients diagnosed or treated for EPTB	194 (194)	Pleural TB (1.0%), lymph node (35.6%), abdomen (9.3%), CNS (9.3%), musculoskeletal and others (9.3%)	2.9

Batra et al., 2012 [24]	Pakistan	Retrospective analysis	TB cases among child contacts of adult TB patients presenting to nine clinics in Karachi	121 (32)	Not specified	—
Saleem et al., 2013 [25]	Pakistan	Cross-sectional study	TB patients from eight TB national centers in Kotli district of Azad Kashmir	752 (173)	Bone TB (8.09%), lymph node (11.56%), abdomen (24.85%), meningitis (2.31%), spinal (8.67%), pleural (42.77%), skin (1.73)	—
Miandad et al., 2016 [26]	Pakistan	Cross-sectional survey	Patients in TB diagnostic centers in Karachi	1,260 (188)	Not specified	1.9
Kamal et al., 2015 [27]	Pakistan	Retrospective review of records	Patients registered with DTO office Mansehra	625 (159)	Not specified	—

Note: CNS = central nervous system; CSF = cerebrospinal fluid; DOTs = directly observed treatment short course; DTO = district tuberculosis control officer; EPTB = extrapulmonary tuberculosis; FMR = female to male ratio; RNTCP = Revised National Tuberculosis Control Program; TB = tuberculosis.
a FMR is shown only for EPTB where data are available.

FMR in EPTB and PTB

The proportion of women with EPTB in the studies reviewed was in the range of 10–74.7%. The FMR was 0.6–2.9. Of the 19 studies included, 10 provided data on FMRs in EPTB. These studies suggest that FMR varies with higher ratios toward the western part of the region: 1.9–2.9 in Afghanistan and Pakistan versus 0.6–1.7 in India and Bangladesh.

The analysis also aimed at evaluating whether there were any reported gender-associated differences among sites of EPTB. FMR in EPTB by site of involvement of organs is presented in Table S3. Most studies showed a slightly greater incidence of abdominal TB in males as compared with females, while central nervous system, pleural, and cutaneous TB were present in an equal proportion among both genders. The literature reviewed reported more dominance of lymph node, bone, pericardial, breast, genitourinary, and miliary TB in females as compared with males.

In contrast, PTB was more common in males than in females. However, the FMR varied by study and geographical location (Fig. S2).

Risk factors

Although a number of studies documented socioeconomic factors in EPTB cases, none explored risk factors for TB and/or for EPTB in women. Where presented, a history of contact or Mantoux test results were not analyzed separately for females or those affected by TB among a cohort, or for EPTB.

Diagnostic modalities

Diagnostic modalities most relied upon for diagnosis of EPTB were histopathology followed by microscopy. In histopathology, presence of granuloma was frequently taken as evidence of TB. Extent of testing to exclude other etiologies presenting as granulomas was discussed in only one instance where the authors cited insufficient facilities to exclude other etiologies [8]. Table 2 presents the combinations of various diagnostic modalities used in reviewed studies.

The use of adenine deaminase activity was reported in one study [9], whereas the use of radiological evidence was included in five studies.

DOT coverage

Although seven of 18 studies reporting EPTB were from program-related sites [9,10,20,21,27–29], they did not report on DOT coverage among females affected by EPTB. The majority of the remaining 11 studies were from tertiary care facilities or advanced diagnostic centers (mainly for infertility) that did not reveal links with DOT programs.

Treatment outcome

Outcome data on EPTB were scanty, although poorer outcomes for EPTB as compared with PTB were reported in one study albeit without gender disaggregated rates [18], while another reported no difference by gender in EPTB outcomes

Table 2 – Investigative modalities used in research studies to diagnose EPTB in females, 2010–2016.

Reference	Presentation	Diagnostic modality used					
		Clinical	TST	Radiological	Histopathology	Bacteriological	Others
Sharma et al. [10]	Women undergoing laparoscopy	Laparoscopic findings	–	–	+	Microscopy/culture	
Chandir et al. [23]	EPTB (mixed)	+	–	X-ray	+	Microscopy/culture	CSF analysis
Fader et al. [8]	EPTB (n = 118)	+	–	X-ray	+ (granulomas)	–	Body fluid analysis
Kohli et al. [14]	Infertility with endometritis		–	–	+ (granulomas)	Microscopy/ culture PCR	IgG to 38 kDa Ag
Miah et al. [9]	Abdominal TB	Endoscopy, laparoscopy, laparotomy	+	X-ray, ultrasound/ barium/CT scans	FNA/biopsy	Microscopy	ADA Ascitic fluid examination
Sharma et al. [13]	Vaginal hysterectomy	–	–	–	+	–	–
Rana et al. [12]	Infertility	–	–	–	+	Microscopy/culture	
Maurya et al. [15]	MTB isolates from EPTB patients	–	–	–	–	Culture	
Banerjee et al. [16]	Ectopic pregnancy	–	–	–	+	Culture	
Batra et al. [24]	EPTB in children		+	X-ray			
Samant et al. [19]	Abdominal TB	Response to therapy	–	–	+ (granuloma)	Microscopy/culture	
Awasthi [20]	Abdominal TB	Response to ATT	+	X-ray	+ (granuloma)	Microscopy/culture	
Dusthackeer et al. [22]	EPTB suspects	–				Culture	
Singh and Tiwari [21]	Lymphadenitis	Response to treatment			FNAC/biopsy (granuloma/necrosis)	Microscopy	

Note: ADA = adenine deaminase activity; ATT = antitubercular treatment; CSF = cerebrospinal fluid; CT = computed tomography; CSF = cerebrospinal fluid; EPTB = extrapulmonary tuberculosis; FNA = fine needle aspiration; FNAC = fine needle aspiration cytology; PCR = polymerase chain reaction; TB = tuberculosis; TST = tuberculin skin test; + = positive; – = negative.

Table 3 – Based on publications of 2010–2016, surveillance, information, and knowledge gaps identified in EPTB studies on females in South Asia.

	EPTB in females			
	Epidemiology	Risk factors	Diagnostics	Treatment outcomes and sequelae
Data available	FMRs	Limited data on contact history among females with EPTB	Percent studies using culture, histopathological, radiological, or clinical criteria for diagnosis	Limited data on FMR for "cure," percent females cured in EPTB cohorts
Gaps	Prevalence data, mortality data, EPTB in pregnant women, age disaggregated rates among females, prevalence of multidrug-resistant TB	Diabetes prevalence and associated EPTB rates, HIV with EPTB among females, genetic susceptibility, ethnic variation in rates, correlation with malnutrition and wealth index, role of environmental factors	Diagnostic algorithm evaluation studies for EPTB (by type) among females, test predictive values and likelihood ratios	DOT coverage in EPTB among females, default rates, outcome by resistance rates, sequelae of renal or genital tuberculosis (e.g., incidence of infertility)

Note: DOT = directly observed treatment; EPTB = extrapulmonary tuberculosis; FMR = female to male ratio; HIV = human immunodeficiency virus.

[23]. Higher postsurgical complications were reported in females with genital TB [10,13].

Gap analysis

From the body of literature published during 2010–2016, gaps were identified in a number of areas in EPTB among females. Table 3 presents gap analysis results comparing available data with gaps in the information, knowledge, or surveillance required to inform epidemiology of, risk factors for, diagnostic needs for, and treatment outcomes for EPTB among females in South Asia.

Discussion

From 2010 to mid-2016, research into EPTB among females in the South Asian countries of Afghanistan, Pakistan, India, and Bangladesh has not informed current epidemiology of TB. While several factors may be responsible for research studies falling short of this requirement (including funding, research capacity, and infrastructure), gender- and age-disaggregated data by site have also not been provided by the world TB reports published annually by the World Health Organization. This surveillance gap comprises the first of the many hurdles in understanding EPTB among females. The lack of robust diagnostic modalities for EPTB further widens these surveillance gaps. The advent of Xpert MTB/RIF (Cepheid, Sunnyvale, California, USA) test as an effective diagnostic test for EPTB [28] is expected to improve the diagnostic landscape. Future assessments of EPTB among females should, therefore, use advanced molecular tests as part of the algorithm used to establish the diagnosis of EPTB. Although significant progress has been made in strengthening the national TB program surveillance systems in case notifications and recording treatment outcomes in all four countries [3], gender stratified treatment outcome data on EPTB are not routinely recorded or presented. What follows is an unmet information gap in the factors associated (including resistance rates) with treatment failures among females with EPTB. These are important, as sequelae of EPTB among women of reproductive age group (except in TB adenitis) are associated with significant morbidity and even more seriously felt in maternal EPTB through impact on perinatal morbidity and mortality [29].

Other notable gaps include the lack of knowledge regarding EPTB risk factors among females. This is especially significant in view of the high FMRs in Afghanistan and western Pakistan, suggesting genetic predisposition to EPTB among indigenous ethnic populations. Moreover, diabetes and malnutrition, which are known risk factors for TB [30,31], are also highly prevalent among females in South Asia [32,33], but have not been analyzed as risk factors for EPTB.

Finally, the overarching gap is in the engagement of multisite health care providers in South Asia, as observed by limited integration of public private partnerships in study designs. The surveillance and knowledge gaps reinforce the importance of overcoming these gaps thorough collaboration with private health care providers to enhance surveillance and develop well-designed and large-scale research studies.

Conclusion

There is a need to focus on EPTB among female populations to document the epidemiology in South Asia, and examine the risk factors, diagnostic modalities, treatment strategies, and outcomes to carry out preventive and control measures.

Conflicts of interest

None to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijmyco.2016.09.054.

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