Prevalence of infertility in women with genital tuberculosis: a systematic review and meta-analysis

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ABSTRACT

Infertility is a worldwide concern which has a variety of causes. This study was aimed to investigate the prevalence of infertility in women with genital tuberculosis. A search of PubMed, Science Direct, Scopus, Google Scholar and Cochrane databases (from 1990 to the present, date of last search February 2016) was performed using the keywords tuberculosis, genital tuberculosis, female genital, bacteriological, histological, infertility, primary infertility, secondary infertility, fallopian tube diseases, Asherman syndrome, women genital tract, fertility outcome, reproductive outcome, prevalence, rate, percent in order to identify the studies which have reported the prevalence of infertility in women with genital tuberculosis. Data were extracted, and a meta-analysis was done. Seven studies were identified. The prevalence of infertility among women with genital TB with 95% confidence interval was 70.67% (58.30-83.03). Also, the prevalence of primary infertility and secondary infertility among genital tuberculosis cases were 75.70% (69.03-82.36) and 24.30% (17.64-30.97), respectively. The prevalence of infertility in women with genital tuberculosis is high. Therefore, prevention and treatment of genital tuberculosis can be considered as a way to reduce the infertility rate.

Keywords: Infertility, Primary infertility, Secondary infertility, Tuberculosis, Genital tuberculosis

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INTRODUCTION

Infertility is defined as the inability to achieve conceive after one year or two years of regular and unprotected intercourse in women under 35 years old or inability to conceive after 6 months unprotected regular intercourse in 35 years and older women (1,2). Some demographers also define infertility as the inability of a woman to carry a pregnancy to live birth after one year active and unprotected intercourse (2). According to the World Health Organization (WHO), infertility can be described as the inability to become pregnant, maintain a pregnancy, or carry a pregnancy to live birth. Infertility can be broken down into 2 categories called primary and secondary infertility. Primary infertility refers to the inability to give birth either because of not being able to become pregnant or carry a child to live birth which may include miscarriage or a stillborn child. Secondary infertility refers to the inability to conceive or give birth when there was a previous pregnancy or live birth (1). Infertility is a common problem worldwide. Reports indicate that 10 to 20% of couples of reproductive ages around the world are affected by this condition (1,3-8). Also, there are some reports of 35% prevalence of infertility from some countries (3). Indeed, the trends show that women’s infertility rate has increased in recent decades which could be due to a variety of causes such as the changing role of women in social activities, increase of marriage age and the use of contraceptive methods (3,5,9). However, the prevalence of infertility varies widely between countries. This diversity can also be seen within countries. For example, in Iran, reports indicate that the prevalence of infertility varies between 13 to 25 percent in different regions of the country (1). Also, based on the current evidence, infertility could be occurred due to a variety of causes (10). It seems that the most effective approach to solving the infertility problem is training and prevention approach. In order to carry this approach, identification of the main causes of infertility could be a great help which can guide the health decision-makers to choose the best practices for the prevention of infertility. Therefore, further
studies are needed to understand these causes (1,4). Existing documents say that infertility has a very broad etiology including various cultural, economic, environmental and social factors (1). In general, causes of infertility can be divided into 2 categories including physiological factors which could be due to different originate such as genetic and non-physiological factors such as acquired or environmental factors including the geographical location, marriage age, environmental pollution, overweight, alcohol consumption and smoking, infectious disease and so on (4). Genital tuberculosis (genital TB) is a kind of infectious diseases which is among the important causes of infertility, especially in women (4,5). The actual prevalence of genital tract tuberculosis is unknown, but studies have reported up to 20% prevalence of genital tuberculosis from different countries (11). However, epidemiological studies from some countries have reported up to 40% prevalence of this condition (12).

As noted earlier due to the growing rate of infertility and it’s various adverse economic, social and emotional consequences for families and societies, this problem and its causes must be addressed by health systems of countries. Given that genital tuberculosis has been identified as an important cause of infertility, in this meta-analysis, we attempted to estimate the prevalence rate of infertility in women with genital tuberculosis.

**METHODS**

**Search strategies for the identification of studies**

We searched PubMed, Science Direct, Scopus, Google Scholar and Cochrane databases using the free text search terms tuberculosis, genital tuberculosis, female genital, bacteriological, histological, infertility, primary infertility, secondary infertility, fallopian tube diseases, Asherman syndrome, women genital tract, fertility outcome, reproductive outcome, prevalence, rate, percent with “Or” and “And” operations in the title and abstract. The reference list of retrieved studies was searched by hand to find publications which may not be retrieved through the databases’ search and to increase the sensitivity of study. No language restrictions were placed, but only articles which their publication date was from 1990 till now were included in the study. Search was conducted from 13 to 22 February. 2016 by 2 researchers independently and the third researcher checked the agreement of retrieved results with these 2 researchers.

**Study selection**

All published articles which had reported the prevalence of infertility in a sample of women with genital tuberculosis were considered. After retrieving the publications from databases, the duplicates were removed. Also, the unrelated articles were identified through the reviewing of title, abstract and full text of publications and were removed from the study. The remaining results were entered into the quality assessment. It should be noted that to prevent bias caused by reprint (publication bias of transverse and longitudinal), the investigation of results for identification and removing of duplicate studies was done with researchers.

**Quality assessment**

All relevant studies were considered to quality assessment using a quality assessment checklist (Moosazadeh et al., 2014) (13) which has been designed based on the STROBE (Strengthening the reporting of observational studies in epidemiology) checklist (Von Elm et al., 2007) (14). This checklist contains questions related to different aspects of a study including the study design, type of study, sample size, objectives, study population, inclusion and exclusion criteria, samples matching method, analyzing method and appropriate reporting of results based on the objectives in which for each question a score has been considered and any study that obtains at least 8 score is selected for including in meta-analysis.

**Data Extraction**

The required data from qualified studies including the title, name of first author, publication year, sample size (number of women with genital TB), the location of study, the type of study, the prevalence of infertility among samples, the prevalence of primary infertility among samples and the prevalence of secondary infertility among samples were extracted.

**Inclusion criteria**

All studies which passed the quality assessment process and which had reported the sample size and the prevalence of infertility were included in the study.

**Exclusion criteria**

All studies which have not reported the prevalence of infertility, studies which have not reported the sample size, the abstracts of seminars
without full text, old studies which their publication date was before 1990, case reports and studies which didn’t obtain the minimum required score were excluded from the study.

Data analysis

Data analysis was done using Stata ver.11 software (StataCorp, 2009, College Station, Texas, USA). The standard error of infertility prevalence, primary infertility prevalence and secondary infertility prevalence in each study was calculated using binomial distribution formula. The index of heterogeneity between studies was determined using Cochrans (Q) and I²-squared tests. Random effect model was used for estimating the prevalence of infertility due to the existing heterogeneity. The point prevalence of the infertility prevalence among the women with genital TB was calculated using forest plot and 95% confidence interval. In this plot, the size of the square represents the weight of each study, and its booth sidelines represent 95% confidence interval.

RESULTS

In the initial search a total number of 21600 studies were found from them, 19809 studies were removed after limiting the search. Then, 1223 studies were removed because of overlapping of searched databases. The reviewing of titles and abstracts of 568 studies indicated 448 studies as unrelated. The remaining 123 studies were selected to investigating the full text after that 113 studies were removed from study due to their irrelevancy. The remaining 10 studies and one article which was found in hand search were entered to be assessed based on the quality assessment checklist and inclusion and exclusion criteria from them 7 studies were found to be appropriate for our meta-analysis (Fig.1). From these studies, in 6 cases the type of study has been reported from them 3 were retrospective, one was prospective, one was cross-sectional, and one was descriptive study. Sampling method has been specified in 5 studies. In all of these 5 studies, the sampling method was consensus. The publication date of included studies was from 1990 to 2015. According to the location of study, from 7 included studies, 2 have been done in Iran, 2 in India, one in Mexico, one in Tunisia and one in Thailand. In 7 studies which were entered into a meta-analysis, infertility prevalence has been investigated among a total of 448 women with genital TB which varies between 27.2% in Weerakiet et al. (1999, Thailand) to 90.6% in Shrame et al. (2008, India). Also, the prevalence of primary infertility has been reported in 3 studies which vary from 67.8% in Sharma et al. (2008, India) to 85% in Hatami et al. (2005, Iran), (Table1)

Using meta-analysis, the results of 7 studies were combined. The random effect model was used to estimating of prevalence due to the high values of heterogeneity indices (I²-squared: 94%, Q = 117.2, P-value <0.001). Based on this model, the prevalence of infertility among women with genital TB with 95% confidence interval was calculated as 70.67% (58.30-83.03) (Figure2). Also, the prevalence of primary infertility and secondary infertility among genital TB cases were estimated as 75.70% (69.03-82.36) and 24.30% (17.64-38.97), respectively. (Fig.3 & Fig.4).

<table>
<thead>
<tr>
<th>No.</th>
<th>First Author</th>
<th>Publication year</th>
<th>Study area</th>
<th>Women with genital TB (n)</th>
<th>Infertility prevalence (%)</th>
<th>Primary infertility (%)</th>
<th>Secondary infertility (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Figueroa-Damian (16)</td>
<td>1996</td>
<td>Mexico</td>
<td>25</td>
<td>84</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Hatami (17)</td>
<td>2005</td>
<td>Iran</td>
<td>51</td>
<td>52</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Sfar (18)</td>
<td>1990</td>
<td>Tunis</td>
<td>118</td>
<td>81</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Sharifi-Mood (19)</td>
<td>2006</td>
<td>Iran</td>
<td>61</td>
<td>83.6</td>
<td>78.4</td>
<td>21.6</td>
</tr>
<tr>
<td>5</td>
<td>Sharma (20)</td>
<td>2008</td>
<td>India</td>
<td>85</td>
<td>90.6</td>
<td>67.8</td>
<td>32.2</td>
</tr>
<tr>
<td>6</td>
<td>Tripathy (21)</td>
<td>2002</td>
<td>India</td>
<td>97</td>
<td>58</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Weerakiet (22)</td>
<td>1999</td>
<td>Thailand</td>
<td>11</td>
<td>27.2</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table1. Characteristics of primary studies which were included into the meta-analysis
**Figure 1.**
Literature search and review flowchart for selection of primary studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study Name</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Figueroa-Damian (1996)</td>
<td>84.00 (69.63, 98.37)</td>
<td>13.73</td>
<td></td>
</tr>
<tr>
<td>Hatami (2005)</td>
<td>52.00 (38.29, 65.71)</td>
<td>13.96</td>
<td></td>
</tr>
<tr>
<td>Sfar (1990)</td>
<td>81.00 (73.92, 88.08)</td>
<td>15.97</td>
<td></td>
</tr>
<tr>
<td>Sharifi-Mood (2006)</td>
<td>83.60 (74.31, 92.89)</td>
<td>15.39</td>
<td></td>
</tr>
<tr>
<td>Sharma (2008)</td>
<td>90.60 (84.40, 96.80)</td>
<td>16.17</td>
<td></td>
</tr>
<tr>
<td>Tripathy (2002)</td>
<td>58.00 (48.18, 67.82)</td>
<td>15.23</td>
<td></td>
</tr>
<tr>
<td>Weerakiet (1999)</td>
<td>27.20 (0.90, 53.50)</td>
<td>9.56</td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 90.4%, p = 0.000)</td>
<td>70.67 (58.30, 83.03)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

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**Fig 2.**
Infertility prevalence among the genital TB patients in primary studies included in the meta-analysis and the total estimation
Fig 3.
Primary infertility prevalence among the genital TB patients in primary studies included in the meta-analysis and the total estimation

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hatami (2005)</td>
<td>85.00 (71.53, 98.47)</td>
<td>24.46</td>
</tr>
<tr>
<td>Sharifi-Mood (2006)</td>
<td>78.40 (67.11, 89.69)</td>
<td>34.79</td>
</tr>
<tr>
<td>Sharma (2008)</td>
<td>67.80 (57.36, 78.24)</td>
<td>40.75</td>
</tr>
<tr>
<td>Overall (I-squared = 53.0%, p = 0.119)</td>
<td>75.70 (69.03, 82.36)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Fig 4.
Secondary infertility prevalence among the genital TB patients in primary studies included in the meta-analysis and the total estimation

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hatami (2005)</td>
<td>15.00 (1.53, 28.47)</td>
<td>24.46</td>
</tr>
<tr>
<td>Sharifi-Mood (2006)</td>
<td>21.60 (10.31, 32.89)</td>
<td>34.79</td>
</tr>
<tr>
<td>Sharma (2008)</td>
<td>32.20 (21.76, 42.64)</td>
<td>40.75</td>
</tr>
<tr>
<td>Overall (I-squared = 53.0%, p = 0.119)</td>
<td>24.30 (17.64, 30.97)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
DISCUSSION
Infertility is a growing global concern that has many negative consequences. Studies show that despite recent technological advancements, the prevalence of infertility has been increased in the world for reasons such as changing the lifestyle of young couples (23). Although the prevalence of infertility varies between countries but studies show that generally, about 10 to 20 percent of couples experience a kind of primary or secondary infertility in their life worldwide. So, infertility is an important challenge of health systems around the world (2,3). Also, the population age pyramid of many countries makes the challenge of infertility more complex. Population age pyramid of nations shows that the population of many countries is aging and population growth rate has decreased in many countries in recent years. Thus, the growing rate of young couples’ infertility leads to the continuing decline in population growth and intensifies aging of the world population. Infertility has various causes. In general, theses cause can be divided into 2 categories called male and female factors (5-8). Based on previous research, some diseases can cause infertility in couples. One of these diseases is genital tuberculosis. Genital tuberculosis is an infectious disease with a high prevalence rate especially in developing countries (5). Given that previous studies have shown that genital tuberculosis related to infertility, the aim this meta-analysis was to analyze the results of existing studies on the prevalence of infertility among women with genital tuberculosis. For this purpose, an extensive search was conducted on various databases. A large number of studies have been retrieved and considered for quality assessment using a valid checklist. Finally, 7 studies were identified appropriate to be included in the meta-analysis. All of these studies have been done in developing countries, in which a total of 448 women with genital tuberculosis have been studied. The rate of prevalence of infertility in women with genital tuberculosis was ranged from about 27 percent to 90 percent. 4 studies, also have reported the rates of primary and secondary infertility. In these 4 studies, primary and secondary infertility rates in women with genital tuberculosis varies from 60 to 85% and from 15 to 32 percent. Analysis of the meta-analysis showed that the overall prevalence of infertility in women with genital tuberculosis is 70.67 percent. Also, primary and secondary infertilities account 75.70 and 24.30 percent of infertility of genital tuberculosis patients, respectively. Therefore, it seems that the majority of women with genital tuberculosis are experiencing a kind of infertility. As noted earlier, infertility is a major global concern which can cause disruptions in global development trend with widespread negative emotional, social and economic consequences (2-8). Therefore, prevention and treatment of infertility should be considered as a global priority. For this, the identification of infertility causes would be the first step of planning in order to reduce its prevalence. Our meta-analysis showed that the majority of women with genital tuberculosis are subject to a kind of infertility. Therefore, the prevention and treatment of genital tuberculosis can reduce the infertility rate and its negative consequences in addition to reduce the consequences of the disease itself.

CONCLUSION
This meta-analysis showed that 70.67 percent of women with genital tuberculosis experience a kind of infertility. Therefore, prevention and treatment of genital tuberculosis can be considered as a way to reduce the prevalence of infertility.

There is no conflict of interests.

REFERENCES
5) Mansoori A, Tara F, Poorjavad M, Farazmand T. The report of 4 cases of genital tuberculosis in...


