

Correlation of Clinical Features, Laboratory Finding, and Pelvic Ultrasonography of Pulmonary Tuberculosis Women with Infertility

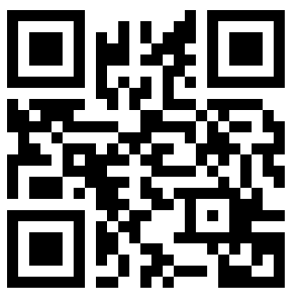
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Background and purpose: The prevalence of tuberculosis (TB) in Indonesia is still high, whereas the prevalence of extra pulmonary tuberculosis such as female genital tuberculosis (FGTB) affecting infertility is unknown. FGTB caused irreversible severe damaged of tubes and endometrium, resulting in tubal occlusion and partial or total obliteration of the uterine cavity. Diagnosis of FGTB is difficult. Therefore, a prompt diagnosis and treatment of pulmonary TB in women can prevent fertility complications. This study aims to analyze the correlation of clinical features taken from the history, physical examination, investigation of blood laboratory and gynecological ultrasound of pulmonary tuberculosis women with infertility.

Patients and methods: This was an observational analytic study with cross-sectional method. Subjects were women with pulmonary TB treated in TB-DOTS (tuberculosis-directly observed treatment, short-course) services at Dr Hasan Sadikin Hospital Bandung during December 2016 until March 2017. Subjects were divided into two groups consist of 32 TB patients with infertility, and 35 TB patients without infertility.

Results: The results showed that clinical features such as intermenstrual bleeding, endometrial synechiae, hydrosalpinx and endometritis appearance were the difference between two groups ($p < 0.001$), those clinical features had a moderate correlation with the incidence of pulmonary tuberculosis women.

Conclusion: Clinical features like endometrial synechia and ultrasound imaging such as hydrosalpinx and endometritis encountered in pulmonary and extra pulmonary tuberculosis patients with infertility can be used as a basis for the diagnosis of alleged genital TB.

Keywords: infertility, genital tuberculosis, ultrasonography

Introduction

In 1993 the World Health Organization (WHO) declared tuberculosis (TB) as a major health problem in the developing countries.¹⁻⁴ According to a survey conducted by WHO in 2004, while TB patients visit to hospital in Indonesia reached 60%, the treatment success is still below 50% due to high dropout rate (50–80%). According to data obtained from the Indonesian Ministry of Health's Data and Information Center, the prevalence of pulmonary and extra pulmonary TB in Indonesia in 2014 was 224 cases per 100000 population.⁴⁻⁶

Extrapulmonary TB, for example genital TB, has various prevalences worldwide. The lowest incidence was in Australia (0.69%) while the highest is in India (19%). No data from Indonesia was available.³⁻⁵

Female genital TB occurs primarily by hematogenous spread from focus in the lungs.^{6–8} Focal infection in the fallopian tube causes tubal obstruction, tubal dilatation and thickening of the fallopian tubes. Focal infection in the endometrium causes endometritis. Genital TB could result in infertility.

Infertility is defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. Infertility could be caused by female factors involving the uterine factor, fallopian tube factor, and ovarian reserve.^{9–12} Male factors are responsible in 20% cases while 10% is due to unexplained infertility. Direct infection is responsible in only 1% of genital TB through sexual contact with genital TB patients, and TB orchitis causes oligospermia to azoospermia.

The constitutional symptoms of genital tuberculosis are not different from the constitutional symptoms of pulmonary TB such as weakness, weight loss, and history of contact with TB patients. Infertility is the most common disorder in genital TB cases. Reported history of menstrual disorders such as intermenstrual bleeding and amenorrhea, along with clinical findings of endometrial synechiae accompanying infertility in patients with TB constitutional symptoms can be used in establishing the diagnosis of alleged genital TB.^{6,11,13}

Ultrasound is used to confirm the diagnosis of genital tuberculosis. Focal infection of the fallopian tube causing obstruction at ultrasound examination is described as hydrosalpinx. Hydrosalpinx appears as tubal dilatation with septae due to tubal mucosa thickening (cogwheel appearance). The focus of infection on the endometrium is described as endometritis, i.e., thin, diffuse endometrial images, with irregular borders, and accompanied by fluid accumulation in the uterine cavity. Hysterosalpingography (HSG) can diagnose genital TB by finding a hydrosalpinx image resembling a tobacco leaf, and a uterus resembling a honeycomb image caused by multiple diverticuli.

Based on several existing literatures, the diagnosis of genital tuberculosis is generally established by surgery such as laparoscopy or laparoscopic biopsy and endometrial curettage to find *Mycobacterium tuberculosis* on microbiological, or histopathological features of granuloma and *Langerhans* cells. This method is difficult to perform due to its invasive nature and not being covered under the national health insurance.^{4,6,12,14,15} The high index of suspicion method by combining and analyzing the relationship between clinical findings on physical examination and simple daily additional examination

with infertility incidence is expected to facilitate the diagnosis of alleged cases of genital TB.^{1–3}

Thoroughly treating all pulmonary and extrapulmonary tuberculosis patients serves an important role. It can prevent hematogenous spread to the internal genitalia, thus avoiding irreversible damage brought by tubal obstruction and tuberculous endometritis. This may improve the likelihood of spontaneous pregnancy prior to resorting to assisted reproductive technologies.^{8,9}

Materials and Methods

This research was an analytic observational research with cross-sectional research design. It was conducted at Dr. Hasan Sadikin Hospital between December 2016 and March 2017. Subjects were taken by consecutive sampling of reproductive age women presenting to DOTS outpatient clinic, having previously been diagnosed with pulmonary and/or extra-pulmonary TB.

The patients were given informed consent before the study. Patient history including parity, marital history, history of menstruation, and history of infertility was collected. Physical examination was performed with findings confirmed using gynaecological ultrasound. Patient's hematological lab results were also collected.

Analytical statistics to assess the differences between the patient groups and measure the correlation of clinical and ultrasound findings with infertility was performed using the software Statistical Package for Social Sciences (SPSS) version 21.0 for Windows. Database spreadsheets were generated using Microsoft Excel.

Results

There were 67 patients included and divided into two groups: 32 infertile tuberculosis patients and 35 patients with fertile tuberculosis (Table 1). The subjects were between 20 and 45 years old. Most infertile patients were between 20 and 29 years old while most fertile patients were between 30–39 years old. Pulmonary tuberculosis and tuberculous lymphadenitis were the most common types of tuberculosis among infertile and fertile TB patients, respectively.

Infertile TB patients had significantly more intermenstrual bleeding and endometrial synechiae than fertile TB patients ($p < 0.05$ and $p < 0.001$, respectively) (Table 2). Infertile TB patients also had significantly more hydrosalpinx and endometritis ($p < 0.001$) (Table 3).

There was a moderate correlation with infertility among patients with endometrial synechiae ($r = 0.562$);

Table 1 Characteristics of Research Subjects

Characteristics	Group	
	Infertile (n=32) N (%)	Fertile (n=35) N (%)
Age		
20–29	20 (62.5)	10 (28.5)
30–39	12 (37.5)	17 (48.6)
≥40	0 (0)	8 (22.9)
Contraceptive Use		
No	0 (0)	13 (37.1)
Yes	32 (100)	22 (62.9)
Tuberculosis Type		
Pulmonary tuberculosis	14 (43.8)	11 (31.4)
Tuberculous lymphadenitis	8 (25)	15 (42.9)
Abdominal tuberculosis	7 (21.8)	4 (11.4)
Tuberculous spondylitis	1 (3.1)	3 (8.5)
Tuberculous meningitis	1 (3.1)	1 (2.9)
Other type of tuberculosis	1 (3.1)	1 (2.9)

ultrasonographic features of hydrosalpinx ($r=0.604$), and endometriosis ($r=0.583$) (Table 4).

Discussion

Most infertile TB patients (62.5%) were between 20 and 29 years old (Table 1). Another study had the same demographics, with most subjects between the age of 20 and 40 years with 47.8% infertility rate.

The highest infertility incidence was found among pulmonary TB patients (43.8%) followed by tuberculous lymphadenitis (25%) and abdominal TB (21.8%) (Table 1). This suggests that having been established in the lungs, tuberculosis spread hematogenously to the reproductive organs.^{10,11}

Table 2 The Clinical Findings of Genital Leucorrhoea, Intermenstrual Bleeding, Amenorrhoea, and Endometrial Synechia in Infertile and Fertile TB Patients

Clinical Features	Group		p* Value
	Infertile (n=32) N (%)	Fertile (n=35) N (%)	
Leucorrhoea	3 (9.4)	4 (11.4)	1.000
Intermenstrual bleeding	13 (40.6)	5 (14.3)	0.015
Amenorrhoea	11 (34.4)	5 (14.3)	0.054
Endometrial synechia	15 (46.9)	0 (0.0)	<0.001

Note: *Based on Chi-Square test.

Table 3 The Difference Between Ultrasonographic Imaging in the Form of Hydrosalpinx and Endometritis Between Infertile and Fertile TB Patients

Ultrasonography Imaging	Group		p* Value
	Infertile (n= 32) N (%)	Fertile (n= 35) N (%)	
Hydrosalpinx	20 (62.5)	2 (5.7)	<0.001
Endometritis	17 (53.1)	1 (2.9)	<0.001

Note: *Based on Chi-Square test.

Table 4 The Relationship Between Clinical Features, Laboratory, and Ultrasound in Tuberculosis Patients with Infertility

Correlation of Risk Factors with Infertility Incidence	Correlation Coefficient Phi	P value
Clinical Features		
Intermenstrual bleeding	0.297	0.015
Amenorrhoea	0.235	0.054
Leucorrhoea	-0.034	1.0
Endometrial synechia	0.562	<0.001
Laboratory Finding		
Anemia	0.112	0.361
Elevated ESR	0.182	0.137
Ultrasonography Imaging		
Hydrosalpinx	0.604	<0.001
Endometritis	0.583	<0.001

Abbreviation: ESR, erythrocyte sedimentation rate.

Then, tuberculous foci in the ovaries, tubes and endometrium disrupts sperm passage and destroys ovarian reserve, hampering fertilization.⁸ Such foci also led to menstrual abnormalities, affecting 20–50% infertile TB patients.⁹

Menstrual disorders are associated with weight loss, possible anti-gonadotropic effects and increased enzymatic catabolism of estrogen as a result of the focal infection in the ovaries and endometrium. The edematous endometrial layer is very susceptible to bleeding and present clinically as intermenstrual bleedings.¹¹ If this condition persists, it can lead to endometrial adhesion and obliteration. This is reflected by the higher rates of both intermenstrual bleeding and endometrial synechia among infertile TB patients.

By ultrasonography, 90.9% of infertile subjects had hydrosalpinx and 94.4% had endometritis. Tuberculous hydrosalpinx is described as dilatation of the tube with septa caused by the thickening of the tubal mucosa, known as cogwheel appearance, whereas endometritis is described when there is a presence of a thin layer of endometrium, with irregular

edges, with discontinuity or even absence of endometrial line, and occasional fluid collection in the uterine cavity.¹⁰⁻¹² Hydrosalpinx and endometritis confirms tuberculosis infection in the reproductive organs. This study found that genital TB could be suggested on the basis of finding ultrasound features of hydrosalpinx and endometritis in TB patients presenting with infertility.

This study showed the positive correlation between infertility among tuberculosis patients and the presence of endometrial synechia, hydrosalpinx and endometritis on ultrasound. Previous research also reported a number of clinical and ultrasonographic features of the genitalia that may indicate TB influence on a patient's fertility.¹² The presence of such clinical findings may aid in the diagnosis of genital TB.

Conclusion

Clinical features like endometrial synechia and ultrasound imaging such as hydrosalpinx and endometritis encountered in pulmonary and extrapulmonary tuberculosis patients with infertility can be used as a basis for the diagnosis of alleged genital TB.

Ethics Statement

This study protocol was approved by the Ethics Committee Review Board of Dr. Hasan Sadikin General Hospital – Faculty of Medicine, Universitas Padjadjaran. All study participants gave written consents to participate. All authors declare that all patients were examined in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki.

Consent for Publication

All authors declare that written informed consent was obtained from every patient, regarding detail information and images to be described in this publication.

Data Sharing Statement

The authors declare that the personal data from any patients involved in this study will not be shared as they are patients' confidentialities.

Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of version to be pub-

lished, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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