Effect of antitubercular treatment on the pregnancy outcomes and prognoses of patients with genital tuberculosis

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Abstract **This retrospective study aims to demonstrate the effect of antitubercular treatment (ATT) on the pregnancy outcomes and prognoses of patients with genital tuberculosis (GTB) who had received laparoscopy and/ or hysteroscopy. This study included 78 patients with infertility and who were diagnosed with GTB through laparoscopy and/or hysteroscopy over the period of November 2005 to October 2015. The recruited patients were divided into ATT and nonATT groups on the basis of ATT duration. The GTB recurrence rates, menstrual patterns, and pregnancy outcomes of the patients were determined at follow-up. Among the 78 patients, 46 received ATT and 32 did not receive ATT. The menstrual volumes of patients in the ATT group significantly decreased relative to those of patients in the nonATT group. GTB did not recur among all patients regardless of treatment. A total of 11 pregnancies (36.7%) in the ATT group and 19 pregnancies (63.3%) in the nonATT group were observed. Pregnancy rates significantly differed ($P = 0.002$) between the two groups. ATT may decrease the menstrual volume and pregnancy rates of patients who were diagnosed with GTB through laparoscopy and/or hysteroscopy. In addition, ATT did not improve the prognosis of patients with chronic GTB.**

Keywords antitubercular treatment; pregnancy; prognosis; genital tuberculosis

Introduction

Genital tuberculosis (GTB) is highly prevalent in developing countries, such as China [1]. As first shown by Malkani, GTB infection may affect the Fallopian tubes, endometrium, and ovaries [2]. It is usually present as a primary to secondary infection in other sites and spreads through a hematogenous route from the initial source of infection to the Fallopian tubes. After the initial involvement of the Fallopian tubes, the infection spreads to the ovaries through direct extension. Thus, GTB may cause tubal blockage; pelvic, abdominal, and perihepatic adhesions; and frozen pelvis. GTB should be considered as a cause of menstrual irregularities, menstrual reduction, and infertility [3].

The clinical diagnosis of GTB is complicated. Laparoscopy and/or hysteroscopy are the most effective tools for the diagnosis of GTB [4,5]. These methods enable the observation of the disturbed structures of the Fallopian tubes, endometrial cavity, and pelvic cavity. These disturbances may be the cause of unexplained infertility. Laparoscopy and/or hysteroscopy can enable the collection of biopsy specimens, particularly from coarse and yellow nodules [6]. Tissue paraffin sections, which are the bases of histopathology diagnosis, can be used to confirm the presence of caseous necrosis.

Antitubercular treatment (ATT) is required after the surgical diagnosis of GTB. ATT consists of an initial treatment phase with isoniazid, rifampicin, ethambutol, and pyrazinamide, followed by treatment with isoniazid and rifampicin [7]. Given that these drugs have potentially teratogenic effects, women with GTB are advised to use contraception at least six months after receiving ATT. However, previous studies on the fertility-related effects of ATT were conducted on female patients with nonactive GTB. Some studies have shown that ATT does not alleviate pelvic or perihepatic adhesions, shrunken uterine cavity, and bilateral blocked tubes, which may cause infertility [8,9]. The necessity for ATT is a key problem for subsequent treatment. No literature about the effect of ATT

on the pregnancy outcomes and prognoses of patients with GTB is available.

Hence, the objective of the present study is to demonstrate the effect of ATT on the pregnancy outcomes and prognoses of patients with GTB who had received laparoscopy and/or hysteroscopy.

Methods and statistical analysis

This retrospective study was performed in the Reproductive Medical Center of Tongji Hospital, Huazhong University of Science and Technology, Hubei Province, over the period of November 2005 to October 2015. This study was performed with the approval and support of the Ethics Institutional Review Board of Tongji Hospital, Huazhong University of Science and Technology, Hubei Province. We recruited 78 patients with infertility and who were diagnosed with GTB through laparoscopy and/or hysteroscopy. GTB was diagnosed on the basis of a pathology and/or biopsy specimen collected from the endometrium or pelvic cavity of the participating patient. The relevant institutional ethics committee approved the research protocol. All participants provided informed consent. Patient characteristics, detailed symptom history, menstrual history, presurgical condition, laparoscopy and/or hysteroscopy findings, and pelvic adhesions were noted.

Some patients with GTB were treated with ATT using isoniazid after surgery. The patients then received rifampicin, ethambutol, and pyrazinamide for 2 months, followed by isoniazid and rifampicin for the next 4–10 months. ATT could last for 6–12 months. The patients were divided into two subgroups (ATT and nonATT group) in accordance with ATT duration. A total of 46 patients received ATT, and 32 patients did not receive ATT. All patients were followed up to determine GTB recurrence, menstrual pattern, and pregnancy outcome.

Statistical analysis was performed using SPSS version 19.0, and two-sided hypothesis tests were conducted. Categorical data were presented as number and percentages and compared through the χ^2-test. Given that all continuous variables were normally distributed, they were presented as mean ± standard deviation and compared through Student's t-test. $P < 0.05$ was considered statistically significant.

GTB in our center

We recruited 78 patients who were diagnosed with GTB through laparoscopy or hysteroscopy. The patients were divided into two subgroups (ATT and nonATT groups) in accordance with ATT duration. A total of 46 patients received ATT, and 32 patients did not receive ATT. The mean age of the ATT group was 27.8 ± 2.9 years and that of nonATT group was 28.4 ± 4.4 years.

The characteristics of the patients in each group are presented in Table 1. The baseline variables of patients in the two groups were comparable. The age range ($P = 0.515$), type of infertility ($P = 0.669$), number of patients with tuberculosis (TB)-positive endometrial biopsy ($P = 0.598$), number of patients with hydrosalpinx ($P = 0.696$), number of patients who underwent bilateral or unilateral salpingectomy ($P = 0.914$), number of patients with pelvic adhesions ($P = 0.682$), and number of patients with TB-positive chest X-ray results ($P = 0.074$) were similar and were not significantly different between the two groups.

The menstrual volumes and menstrual periods of patients in the two groups before and after ATT were compared (Table 2). Before ATT, the menstrual volume and menstrual period of patients in the ATT group were not significantly different from those of patients in the nonATT group ($P = 0.447$; $P = 0.114$). However, after ATT, the menstrual volumes of patients in the ATT group significantly decreased relative to those of patients in the nonATT group ($P = 0.007$). However, the menstrual periods of the patients in the two groups were similar ($P = 0.192$).

The prognoses and pregnancy outcomes of patients in the ATT and nonATT groups were compared (Table 3). GTB did not recur in all patients (46 patients in the ATT group and 32 patients in the nonATT group) regardless of treatment. A total of 11 pregnancies (36.7%) were recorded. Surprisingly, in the nonATT group, 19 patients (63.3%) became pregnant after laparoscopy or hysteroscopy. The pregnancy rates of the two groups were significantly different ($P = 0.002$). Only one patient in the ATT group (3.3%) reported spontaneous pregnancy, whereas 29 patients (96.7%) from the two groups became pregnant through *in vitro* fertilization or embryo transfer.

Conclusions

GTB is an important disease that is highly prevalent in developing countries, such as China. It may cause menstrual irregularities and infertility. More than 90% of female patients with GTB suffer from Fallopian tube blockage, calcification, hydrosalpinx, and adhesions. Furthermore, GTB infection results in the development of adhesions in the endometrial cavity, such as those observed in Asherman's syndrome [10,11]. GTB also induces the formation of thick and plastic adhesions between the ovaries and other pelvic organs. The presence of these adhesions may cause ovulation failure and hypoovarianism. Severe cases of GTB may lead to frozen pelvis as a result of the formation of multiple adhesions in the pelvic and peritoneal cavities. Such cases also exhibit nodular thickening, which can be attributed to epithelial proliferation [12].

Table 1 Patient characteristics

	Total	ATT		NonATT		P value
		No.	%	No.	%	
Total	78	46	59.0	32	41.0	
Age (year)						0.515
<30	55	32	58.2	23	41.8	
⩾30	23	14	60.9	9	39.1	
Infertility						0.669
Primary	73	43	58.9	30	41.1	
Secondary	5	3	60.0	2	40.0	
Endometrial biopsy						0.598
TB-positive	22	13	59.1	9	40.9	
TB-negative	56	33	58.9	23	41.1	
Hydrosalpinx						0.696
Yes	32	19	59.4	13	40.6	
No	46	27	57.8	19	42.2	
Salpingectomy						0.914
Bilateral	33	20	60.6	13	39.4	
Unilateral	13	7	53.8	6	46.2	
None	32	19	59.4	13	40.6	
Pelvic adhesions						0.682
Yes	76	45	58.7	31	41.3	
No	2	1	50.0	1	50.0	
Chest X-ray						0.074
Positive	28	13	46.4	15	53.6	
Negative	50	33	66.0	17	34.0	

Table 2 Comparison of the menstrual volumes and menstrual periods of patients in the two groups before and after ATT

	Before ATT			After ATT		
	ATT	NonATT	P value	ATT	NonATT	P value
Menstrual volume			0.447			0.007*
Normal	37	27		24	26	
Less	9	5		22	6	
Menstrual period			0.114			0.192
Regular	42	32		43	33	
Non-regular	4	0		2	0	

*P<0.050, statistically significant.

Table 3 Comparison of the prognoses and pregnancy outcomes of the two groups

	No.	ATT	NonATT	P value
Total	78	46	32	
Recurrence				
Yes	0	0 (0.0%)	0 (0.0%)	a
No	78	46 (100.0%)	32 (100.0%)	
Pregnant outcome				0.002*
Pregnancy	30	11 (36.7%)	19 (63.3%)	
Nonpregnancy	48	35 (72.9%)	13 (27.1%)	

*P<0.050, statistically significant. a, the statistic is a constant and cannot be estimated.

Even though ultrasonographic examination, chest X-ray, hysterosalpingograms, and DNA PCR assays have provided diagnostic clues for GTB, tissue sampling for histopathological examination remains the golden standard for the diagnosis of GTB [13,14]. This method could reveal the presence of caseous necrosis. However, tissue collection from the endometrium, Fallopian tubes, and pelvic cavity is difficult. Laparoscopy is the most reliable tool among all surgical methods for the diagnosis of GTB. It could show the morphological abnormalities of organs in the pelvic cavity. When performed with hysteroscopy, laparoscopy could directly show the status of the

endometrial cavity.

Our study obtained reliable diagnostic results given that laparoscopy and/or hysteroscopy was performed to diagnose GTB. The data presented in Table 1 show that the most significant characteristic of GTB is pelvic adhesion (75/78, 96.2%), followed by primary infertility (73/78, 93.6%). PCR assay confirmed that the biopsied endometrial tissue were TB-positive (22/78, 28.2%). Laparoscopy and/or hysteroscopy detected the involvement of one or two involved Fallopian tubes (46/78, 59.0%) and hydrosalpinx (32/78, 41.0%). Some patients also exhibited positive chest X-ray films (28/78, 35.9%). The ATT and nonATT groups were not significantly different ($P > 0.05$). This result showed that pelvic adhesion, which can be detected only through laparoscopy and/or hysteroscopy, may be the most important reason for GTB-associated infertility, especially primary infertility. Adhesion causes the formation of fibrotic lesions that may change the structure and function of organs in the pelvic cavity.

In our study, all patients with GTB did not exhibit obvious symptoms and were thus in the nonactive phase. We found that laparoscopy and/or hysteroscopy did not increase the risk of spreading *Mycobacterium tuberculosis*, especially in patients with chronic nonactive GTB.

The patients who were diagnosed with GTB through laparoscopy and/or hysteroscopy did not undergo ATT at our hospital. Instead, they were referred to special tuberculosis hospitals that can provide ATT for free. In China, different special tuberculosis hospitals are established in different provinces. Some hospitals believe that patients with nonactive GTB do not require ATT despite having positive biopsy results and that only patients in the active phase who exhibit symptoms, such as coughing, fever, and abdominal pain, should receive ATT. On the other hand, some patients who were diagnosed with GTB through laparoscopy and/or hysteroscopy at our hospital may not undergo ATT because they cannot afford treatment.

The initial clinical therapy for GTB is a multidrug approach that consists of isoniazid, rifampicin, streptomycin, pyrazinamide, and ethambutol. It is given for 6–12 months. ATT is necessary for patients with active GTB because it can relieve infection symptoms, such as coughing, fever, and abdominal pain and because it can block the spread of *M. tuberculosis* [15]. However, the necessity of ATT for patients with chronic nonactive GTB remains controversial. Based on literature reports, ATT has little effect on pelvic anatomy once sufficient agglutination or adhesion occurs. The poor tubal response to ATT can be attributed to the irreversible Fallopian tube damage caused by TB. ATT cannot alleviate advanced fibrotic lesions (pelvic adhesions and Fallopian tube blockage), which may be the most important reason for infertility in patients with GTB [7]. At the same time, a previous study showed

that ATT improves menstrual cycles and endometrial thicknesses and reduces the incidence of grade 1 adhesions in patients with early-stage GTB. However, ATT does not improve the symptoms of patients with advanced GTB [8]. Furthermore, ATT does not improve the prognosis of patients with chronic nonactive GTB. The data shown in Table 3 indicated that GTB did not recur in patients regardless of treatment.

In this study, the patients who underwent laparoscopy and/or hysteroscopy were suffering from chronic and advanced GTB and exhibited the formation of thick adhesions. ATT may affect endometrial tissue, as indicated by the reduced menstrual volumes of patients who received ATT. The menstrual volumes of patients in the ATT and nonATT groups were not significantly different prior to treatment ($P = 0.447$). Treatment, however, significantly decreased the menstrual volumes of 22 patients (47.8%) in the ATT group and of 6 patients (18.8%) in the nonATT group. The result of the ATT group was significantly different from that of the nonATT group ($P = 0.007$). ATT did not affect the menstrual periods of patients in both groups. No significant difference was found in the two groups regardless of treatment ($P = 0.114$, $P = 0.192$).

On the other hand, the effect of ATT on pregnancy outcomes remains uncertain. A previous study suggested that extending ATT would improve the pregnancy outcomes of women with GTB [16]. By contrast, our study showed that ATT may decrease pregnancy rates among women with GTB. Conception occurred in only 11 out of 46 patients (36.7%) who had received ATT and in 19 out of 31 patients (63.3%) who did not receive ATT. The pregnancy rates of the two groups were significantly different ($P = 0.002$). ATT may negatively affect the pregnancy outcomes of patients with GTB for reasons connected to the effects of ATT on endometrial lesions. In the context of traditional Chinese medicine, the multidrug approach for ATT may cause a deficiency of qi and blood. This deficiency further damages endometrial tissue. The damaging effect of ATT on endometrial tissue may need further medical research.

In conclusion, our results indicated that ATT, which is widely applied for the clinical treatment of patients diagnosed with GTB through laparoscopy and/or hysteroscopy, may reduce menstrual volume and decrease pregnancy rates. In addition, ATT does not improve the prognosis of patients with chronic GTB.

Compliance with ethics guidelines

References

1. Schaefer G. Female genital tuberculosis. Clin Obstet Gynecol 1976; 19(1): 223–239

2. Malkani PK, Rajani CK. Pelvic tuberculosis. Obstet Gynecol 1959; 14: 600–611

3. Tinelli A, Malvasi A, Vergara D, Martignago R, Nicolardi G, Tinelli R, Pellegrino M. Abdominopelvic tuberculosis in gynaecology: laparoscopical and new laboratory findings. Aust N Z J Obstet Gynaecol 2008; 48(1): 90–95

4. Jindal UN, Bala Y, Sodhi S, Verma S, Jindal S. Female genital tuberculosis: early diagnosis by laparoscopy and endometrial polymerase chain reaction. Int J Tuberc Lung Dis 2010; 14(12): 1629–1634

5. Eftekhar M, Pourmasumi S, Sabeti P, Aflatoonian A, Sheikhha MH. *Mycobacterium tuberculosis* infection in women with unexplained infertility. Int J Reprod Biomed (Yazd) 2015; 13(12): 749–754

6. Bhanothu V, Theophilus JP, Reddy PK, Rozati R. Occurrence of female genital tuberculosis among infertile women: a study from a tertiary maternal health care research centre in South India. Eur J Clin Microbiol Infect Dis 2014; 33(11): 1937–1949

7. Sharma JB, Sneha J, Singh UB, Kumar S, Roy KK, Singh N, Dharmendra S, Vanamail P. Comparative study of laparoscopic abdominopelvic and fallopian tube findings before and after antitubercular therapy in female genital tuberculosis with infertility. J Minim Invasive Gynecol 2016; 23(2): 215–222

8. Sharma JB, Sneha J, Singh UB, Kumar S, Roy KK, Singh N, Dharmendra S, Sharma E, Sharma A. Effect of antitubercular therapy on endometrial function in infertile women with female genital tuberculosis. Infect Disord Drug Targets 2016; 16(2):101–108

9. Neonakis IK, Spandidos DA, Petinaki E. Female genital tuberculosis: a review. Scand J Infect Dis 2011; 43(8): 564–572

10. Deans R, Abbott J. Review of intrauterine adhesions. J Minim Invasive Gynecol 2010; 17(5): 555–569

11. Jindal UN, Verma S, Bala Y. Favorable infertility outcomes following anti-tubercular treatment prescribed on the sole basis of a positive polymerase chain reaction test for endometrial tuberculosis. Hum Reprod 2012; 27(5): 1368–1374

12. Jindal UN, Bala Y, Sodhi S, Verma S, Jindal S. Female genital tuberculosis: early diagnosis by laparoscopy and endometrial polymerase chain reaction. Int J Tuberc Lung Dis 2010; 14(12): 1629–1634

13. Rana T, Singh UB, Kulshrestha V, Kaushik A, Porwal C, Agarwal N, Kriplani A. Utility of reverse transcriptase PCR and DNA-PCR in the diagnosis of female genital tuberculosis. J Med Microbiol 2011; 60(Pt 4): 486–491

14. Parikh FR, Nadkarni SG, Kamat SA, Naik N, Soonawala SB, Parikh RM. Genital tuberculosis — a major pelvic factor causing infertility in Indian women. Fertil Steril 1997; 67(3): 497–500

15. Kulshrestha V, Kriplani A, Agarwal N, Singh UB, Rana T. Genital tuberculosis among infertile women and fertility outcome after antitubercular therapy. Int J Gynaecol Obstet 2011; 113(3): 229–234

16. Caliskan E, Cakiroglu Y, Sofuoglu K, Doger E, Akar ME, Ozkan SO. Effects of salpingectomy and antituberculosis treatments on fertility results in patients with genital tuberculosis. J Obstet Gynaecol Res 2014; 40(10): 2104–2109