The Clinical Features and Prognosis Analysis of Pregnant Women with Tuberculosis After in Vitro Fertilization and Embryo Transfer and Natural Fertilization

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Research Article

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Abstract

Objective: To investigate the clinical characteristics and prognosis of women with tuberculosis after in vitro fertilization and embryo transfer (IVF-ET) and natural pregnancy.

Design/Methods: Ninety-five pregnant women with tuberculosis admitted to Shanghai Public Health Clinical Center between February 2013 and July 2020 were retrospectively analyzed. They were divided into 24 cases of IVF-ET with tuberculosis and 71 cases of natural pregnancy group with tuberculosis. Baseline demographic, medical history were collected. We used descriptive statistics to describe demographic, clinical features and prognosis of pregnant women with tuberculosis using Pearson chi-squared, Fisher's exact tests, or Kruskal-Wallis.

Results: The incidence of fever, hematogenous disseminated pulmonary, drug-induced liver injury and fetal adverse outcomes in IVF-ET group were higher than those in natural pregnancy group ($p<0.05$). The lymphocyte count, hemoglobin level, albumin level and the number of $CD4^+$T lymphocyte$CD8^+$ T lymphocyte in IVF-ET group were significantly lower than that in natural pregnancy group ($p<0.05$).

Conclusions: Pregnant women with tuberculosis after in vitro fertilization and embryo transfer have broader lung lesions, more prominent symptoms of systemic poisoning, larger proportion of severe tuberculosis, more prone to anti-tuberculosis drugs induced liver injury and higher proportion of spontaneous abortion and inevitable abortion, which calls for enough attentions.

Summary Of Article's Main Point

Among pregnant women with tuberculosis, patients after in vitro fertilization and embryo transfer need to pay enough attention. We report higher proportion of severe cases and abortion in IVF pregnant women. Early screening for tuberculosis and early intervention in pregant women after IVF may improve the prognosis of pregnant women and fetuses.

Background

Tuberculosis remains a global emergency and continues to poses a considerable threat to human health. In 2019, an estimated 10 million people fell ill with TB, women accounted for 32%; moreover, it was responsible for an estimated 1.2 million deaths globally[1]. Tuberculosis is one of the top causes of death in women of reproductive age and is a common non-obstetric cause of maternal mortality[2,3]. It has been estimated that, in 2011, 216 500 active tuberculosis cases existed in pregnant women globally and 9 500 active TB cases during pregnancy in China, which is equivalent to 0.7 per 1 000 pregnant women, accounting for 4.4% of global burden among pregnant women[4]. Indeed, Active TB in pregnancy is associated with adverse maternal and fetal outcome[5].

In contrast to normal pregnancy, more infertility patients prefer to get pregnant by in vitro fertilization and embryo transfer (IVF-ET) .In some patients, the use of progesterone and glucocorticoids is needed to

resist IVF-ET rejection, improve the intrauterine environment and guarantee normal embryonic growth, which may influence cell-mediated immunity and cause TB relapse and dissemination. However, there are only a few reported cased of tuberculosis in IVF pregnancy[6–10], and these literatures do not describe the difference in clinical characteristics between natural pregnancy and IVF pregnant women with tuberculosis.

In this study, we summarized the clinical characteristics and prognosis of pregnant Chinese women with TB. The purpose of this study is to raise awareness of TB diagnosis during pregnancy and improve the prognosis of tuberculosis in pregnant women.

Materials And Methods

Study design.

Pregnant patients with pulmonary tuberculosis, who were hospitalized in Shanghai Public Health Clinical Center from February 2013 to July 2020, were enrolled. The inclusion criteria were as follows: 1) Cases data were complete. 2) With conform to the diagnostic criteria for tuberculosis in pregnancy. Patient was diagnosed with TB during pregnancy and postpartum. To ensure that TB cases were not omitted during pregnancy, patients diagnosed with TB from pregnancy until 42 days after delivery were included. Women who suffered from TB before pregnancy and conceived during the period of anti-tubercular therapy (ATT) were excluded from this study.

Information such as age, TB history, history of BCG vaccination, contact history of TB, Education level, clinical symptom, laboratory-test results, radiographic features, therapeutic regimens, and the outcomes of pregnant women and neonates were reviewed in the medical records. Physician contacted the patients via a follow-up phone call.

This study was approved by the Ethics Committee of Shanghai Public Health Clinical Center [batch number:2020-S112-03]. And this study was approved by the Ethics Committee of Shanghai Public Health Clinical Center to exempt subjects from informed consent.

Diagnostic criteria and classification of TB.

Active TB was diagnosed based on the 2013 WHO guideline[11]. for example: A patient was diagnosed as having definite TB based on the identification of mycobacterium tuberculosis complex in the clinical sample (sputum, body tissue, or body fluid), either by culture or molecular method. In the absence of bacteriological confirmation of TB disease, a clinical diagnosis was based on clinical evaluation by a medical doctor, radiography and the clinician prescribed a full course of anti-tubercular therapy (ATT).

Contacts were defined as individuals who being in the same room as the index patients for more than 6h per week in the 2 weeks preceding the index patient's diagnosis[12].

In accordance with the WHO definitions for TB, Pulmonary Tuberculosis (PTB) was defined as TB involving lung parenchyma, which included military TB[13]; Extra-pulmonary Tuberculosis (EPTB) referred to presence of mycobacterium tuberculosis in organs, except the lung[13]. Both PTB and EPTB was defined as PTB not only involving lung parenchyma but also including other organs[13].

Clinical chemistry criteria for drug-induced liver injury(DILI)is any one of the following: 1) ALT≥ 5 ULN; 2) ALP≥2 ULN; 3) ALT≥3 ULN and TBil>2 ULN[14]. (ALT: alanine aminotransferase; ALP: alkaline phosphatase; TBil: bilirubin; ULN: upper limit of normal)

Data analysis.

The medical records were analyzed, with descriptive analysis conducted for clinical data. Statistical analysis data were analyzed using the Statistical Package for Social Sciences (SPSS) software (version 23.0). Data were presents as mean ± SD for continuous variables with normal distribution or median (IQR) for continuous variables with a skewed distribution. The ANOVA or Kruskal-Wallis H test was used to compare the difference among groups. Categorical variables were expressed as n(%) and Chi-square test or Fisher's exact test was used to compare the difference. All P-values were calculated with statistical significance set to $P < 0.05$.

Results

Baseline characteristics and onset time of pregnant women with tuberculosis on admission

The total number of pregnant women with tuberculosis in Shanghai Public Health Clinical Center between February 01, 2013 and July 31, 2020 was 134. After applying the exclusion criteria, the final cohort consisted of 95 pregnant women with tuberculosis. Among the 95 cases, there are 24 cases with IVF-ET and 71 cases with natural fertilization (figure 1). The baseline characteristics of pregnant women with tuberculosis after in vitro fertilization and embryo transfer (IVF-ET) and natural pregnancy are compared (Table 1).The average age of was 29.17±4.18 in IVF-ET group, while 27.08±5.27 in natural fertilization group (p=0.082). Indeed, the proportion of double embryos in IVF-ET group is significantly higher than that in natural group (37.5% vs. 1.4%, p<0.05), but the other elements such as TB history, contact history of TB, BCG vaccination status and education level did not reach statistical significance (p>0.05). The proportion of HBsAg positive in two groups was same (4.2% vs. 4.2%) and the HCV antibody of the two groups was negative. The onset period of patients with IVF-ET was at a median of 115th day of pregnancy (ranged 92th-141th day), while the onset period of patients with natural fertilization was at a median of 147th day of pregnancy (ranged 68th-219th day), there is no statistical significance (p>0.05) (figure 2).

Table 1
Baseline characteristics of pregnant women with tuberculosis after in vitro fertilization and embryo transfer (IVF-ET) and natural pregnancy.

	IVF-ET (n=24) (%)	**Natural fertilization (n=71) (%)**	**t/χ^2 value**	***P*-value**
Age [year, mean±SD]	29.17±4.177	27.08±5.269	-1.756	0.082
TB history	1(4.2%)	4(5.6%)		**1.000***
History of BCG vaccination	22(91.7%)	68(95.8%)		**0.598***
Contact history of TB	2(8.3%)	5(7%)		**1.000***
Education level				**0.334***
Less than high school	5(20.8%)	9(12.7%)		
High school or greater	19(79.2%)	62(87.3%)		
HBsAg positive(n.)	1(4.2%)	3(4.2%)		**1.000***
HCV antibody positive (n.)	0	0		
Embryo				**0.000***
n=1	15(62..5%)	71(98.6%)		
n≥2	9(37.5%)	1(1.4%)		

Categorical data was compared using the Chi-square test or Fisher's exact test. Statistical significance set to P < 0.05 and was emphasized in bold. *Fisher's exact test.

Symptoms of TB in pregnant women

The symptoms of TB in pregnant women with tuberculosis after in IVF-ET and natural pregnancy are shown in Table 2. The incidents of fever among pregnant women with IVF-ET was significantly higher than that among pregnant women with natural fertilization (79.2% vs. 35.2%, p<0.05). The ratio of respiratory symptom (cough, cough with phlegm, and shortness of breath), the incident of failure to gain weight, headache and night sweating was higher in IVF-ET group than those in natural fertilization, but the difference did not reach statistical significance (p>0.05). however, the ratio of cough with blood was lower in IVF-ET group than that in natural fertilization (0% vs. 12.7%, p>0.05).

Table 2
Symptoms of TB in pregnant women after IVF-ET and natural fertilization.

	IVF-ET (n=24) (%)	Natural fertilization (n=71) (%)	χ^2 value	*P*-value
Cough	14(58.3%)	44(62%)	0.1	0.752
Cough with phlegm	10(41.7%)	18(25.4%)	2.297	0.130
Cough with blood	0	9(12.7%)		**0.106***
Shortness of breath	3(12.5%)	4(5.6%)		**0.364***
Fever	19(79.2%)	25(35.2%)	13.938	0.000
Night sweating	1(4.2%)	1(1.4%)		**0.443***
Failure to gain weigh	1(4.2%)	1(1.4%)		**0.443***
Headache	1(4.2%)	2(2.8%)		**1.000***

Categorical data was compared using the Chi-square test or Fisher's exact test. Statistical significance set to P < 0.05 and was emphasized in bold. *Fisher's exact test.

Laboratory tests, Radiographic finding and Regimens to treat TB in pregnant women

Routine blood tests indicated lymphocyte count, hemoglobin level in IVF-ET group were significantly lower than that in natural pregnancy group at admission ($p<0.05$). Aspartate aminotransferase, Alanine aminotransferase level in IVF-ET group were higher than that in natural pregnancy group ($p<0.05$). while the albumin level, the number of $CD4^+$T lymphocyte (260.00 vs.390.50), $CD8^+$T lymphocyte (168.50 vs. 266.00) in IVF-ET group were significantly lower than that in natural pregnancy group ($p<0.05$) (Table 3). Chest X-ray or CT images from the IVF-ET group showed a higher proportion of diffuse military infiltration than those from the natural pregnancy group (87.5% vs. 12.7%, $p<0.05$). In addition, a higher proportion of pregnant women in the IVF-ET group had coexisting pulmonary tuberculosis with extrapulmonary tuberculosis (45.8% vs. 12.7%, $p<0.05$). Although the lymphocyte count of pregnant women in the IVF-ET group is low, the positive rate of T-spot/TST is higher than that in natural pregnancy group, and the difference did not reach statistical significance (91.7% vs. 83.1%, $p>0.05$). The proportion of pathogenic diagnosis and the proportion of treatment options are similar in two groups (Table 3, supplementary table 1).

Table 3
Laboratory tests, Radiographic finding and Regimens to treat TB in pregnant women after IVF-ET and natural fertilization.

	IVF-ET (n=24) (%)	Natural fertilization (n=71) (%)	Z/χ^2 value	*P*-value
White cell count, ⊆10^9/L	5.98 (4.50, 8.06)	6.04 (5.06, 7.80)	-0.368	0.713
Neutrophil count, ⊆10^9/L	4.54 (3.31, 6.93)	4.43 (3.68, 5.93)	-0.133	0.894
Lymphocyte count, ⊆10^9/L	0.77 (0.68, 1.01)	1.05 (0.82, 1.51)	-2.989	0.003
Monocyte count, ⊆10^9/L	0.38 (0.28, 0.60)	0.42 (0.30, 0.54)	-0.137	0.891
Hemoglobin, g/L	91.50 (83.50, 101.75)	105.00 (92.00, 114.00)	-3.158	0.002
Platelet count, ⊆10^9/L	243.50 (164.50, 299.00)	244.00 (193.00, 303.00)	-0.227	0.820
Aspartate aminotransferase(U/L)	59.00(27.25, 85.75)	12.00(9.00,25.00)	-4.864	0.000
Alanine aminotransferase(U/L)	58.00 (35.75, 121.50)	17.00(14.00,26.00)	-5.458	0.000
Total bilirubin(μmol/L)	7.45 (5.43, 10.00)	7.30 (5.00, 12.70)	-0.013	0.990
Alkaline phosphatase (U/L)	69.50 (53.25, 125.25)	96.00 (68.00, 127.00)	-1.1379	0.168
Albumin(g/L)	27.50 (25.43, 30.89)	33.60 (28.80, 38.10)	-3.238	0.001
Serum creatinine(μmol/L)	36.90 (32.08, 45.59)	39.94 (32.58,47.30)	-0.989	0.323
CD4+ count (cells/μl)	260.00 (237.75, 326.00); n=24	390.50 (257.00, 566.75); n=44	-2.554	0.011
CD8+count (cells/μl)	168.50 (134.00, 244.50);n=24	266.00 (191.75, 371.75); n=44	-2.984	0.003
T-SPOT/PPD positive	22 (91.7%)	59 (83.1%)		**0.506***
Chest X-ray or CT findings				
Military tuberculosis	21 (87.5%)	9 (12.7%)	46.477	0.000
Site of infection				
PTB	13(54.2%)	60(84.5%)	9.279	0.002
EPTB	0	2(2.8%)		**1.000***

Categorical data was compared using the Chi-square test or Fisher's exact test. Statistical significance set to P < 0.05 and was emphasized in bold. *Fisher's exact test.

	IVF-ET (n=24) (%)	Natural fertilization (n=71) (%)	Z/χ^2 value	*P* value
PTB and EPTB	11(45.8%)	9(12.7%)	11.865	0.001
Microbiologically confirmed TB	15(62.5%)	47 (66.2%)	0.108	0.742
Regimens to treat TB				**1.000***
DR-TB regimens	23(95.8)	68(95.8)		
RR-TB regimens	1(4.2%)	3(4.2%)		
Categorical data was compared using the Chi-square test or Fisher's exact test. Statistical significance set to P < 0.05 and was emphasized in bold. *Fisher's exact test.				

Outcomes following pregnancy-related TB

None of 95 pregnant women died. At the end of treatment, 92 (96.8%) patients were cured, the others are in stable condition and still receiving anti-tuberculosis treatment. All patients received anti-tuberculosis treatment for 6 months or more. Throughout the course of anti-tuberculosis treatment, frequency of anti-tuberculosis drugs induced liver injury was 62.5% (15/24) in IVF-ET group and 21.1% (15/71) among natural pregnancy group ($p<0.05$) (Table 4). There are 8 (33.3%) patients of spontaneous abortion, 5 (20.8%) patients of inevitable abortion in IVF-ET group, the proportion is significantly higher than those in natural fertilization (33.3% vs. 4.2%, $p<0.05$; 20.8% vs. 1.4%, $p<0.05$). 24 (33.8%) patients choose artificial abortion in natural fertilization group, while none of patients among the IVF-ET group selected artificial abortion. 43 (60.6%) cases delivered live births (premature birth/ term birth) in IVF-ET group, and 11 (45.8%) cases delivered live births in natural pregnancy group.

Table 4
Prognosis of women with tuberculosis after IVF-ET and natural fertilization

	IVF-ET (n=24) (%)	Natural fertilization (n=71) (%)	χ^2 value	*P*-value
DILI	15 (62.5%)	15 (21.1%)	14.210	0.000
Maternal Mortality	0	0		
Pregnant outcome				
Spontaneous abortion	8(33.3%)	3(4.2%)		**0.001***
Inevitable abortion	5(20.8%)	1(1.4%)		**0.004***
Artificial abortion	0	24(33.8%)	10.855	0.001
Premature birth/ term birth	11(45.8%)	43(60.6%)	1.586	0.208
Categorical data was compared using the Chi-square test or Fisher's exact test. Statistical significance set to P < 0.05 and was emphasized in bold. *Fisher's exact test.				
IVF-ET: in vitro fertilization and embryo transfer				
ATT: anti-tubercular therapy				
Days of Natural pregnancy: 147(68,219)				
Days of IVF-ET: 115(91.75,140.5)				

Discussion

To our knowledge, no other studies have compared the clinical features and TB treatment outcome among pregnant women after IVF-ET and naturally pregant women. In this study, we observed similar baseline characteristics (such as: age, TB history, history of BCG vaccination, contact history of TB, education level, HBsAg positive and HCV antibody positive) of pregnant women with tuberculosis after in vitro fertilization and embryo transfer (IVF-ET) and natural pregnancy. The onset period of patients with IVF-ET was earlier than the time of patients with natural fertilization (115th vs. 147th, p>0.05).

Generally speaking, TB symptoms during pregnancy were not much different from those of non-pregnancy TB. Cough, cough with phlegm and fever are still the main clinical manifestations. But we found the incidents of fever among pregnant women with IVF-ET was significantly higher than that among pregnant women with natural fertilization, which suggests that pregnant women with tuberculosis after IVF-ET are more likely to have systemic symptoms (tuberculosis toxemia).

During pregnancy, the mother uses a complex network of hormones, immune cells and cytokines to immunoregulate the various physiological processes of pregnancy. The specific and non-specific immune tolerance between the mother and the fetus are the main factors for maintaining the success of the

pregnancy. Hormones such as progesterone, estrogens and human chorionic gonadotropin have very important effect on early pregnancy which play essential roles in the immune crosstalk at the maternal-fetal interface[15,16]. Studies have shown specific immunity is suppressed in pregnant women, including the decrease in the number of T cells, the decline in T-cell functions and the change Th1/Th2 cytokine towards Th2 bias, which enhance the maternal-fetal immune tolerance but impair responses against some pathogens[17–19]. IVF is widely used to treat infertility. The clinical pregnancy rate and embryo growth rate are closely related to the receptivity of the endometrium, and are affected by ovarian steroid hormones, particularly estradiol and progesterone[20].In the process of controlled ovarian hyperstimulation (COH) and luteal phase, progesterone needs to be injected daily[21]. Glucocorticoids, acting as immunomodulators to influence cell-mediated immunity and reduce inflammation, have been used to improve folliculogenesis and the intrauterine environment[22]. Therefore, once a woman becomes pregnant, especially after IVF-ET, the changes in the immune function of the body are not conducive to the control and elimination of mycobacterium tuberculosis. Our study also shows the lymphocyte count, CD4 T cell count, CD8 T cell count of pregnant women in the IVF-ET group were significantly lower than those in natural pregnancy group and the proportion of military tuberculosis of pregnant women in the IVF-ET group at admission were higher than those in natural pregnancy group.

In the published literature, there are few studies on the side effects of tuberculosis treatment in pregnant women, especially liver toxicity. Our study showed severe hepatotoxicity was significantly more frequent in pregnant women after IVF-ET compared to those in natural pregnancy. It is speculated that it may be related to pregant women after IVF-ET who are mostly twin pregnancies leading to liver overload, and pregnant women are mostly hematological disseminated tuberculosis patients, with severe symptoms of infection and poisoning, and DILI is more likely to occur. Temporary drug withdrawal or change anti-tuberculosis treatment regimen due to DILI was more frequent in pregant women after IVF-ET than those in nature fertilization. The usual recommendation is restart with rifampin with or without ethambutol, then add isoniazid after 3-7 days, and to continue treatment, if liver function tests are normal. In case of prolonged or severe hepatotoxicity, add other second-line medication (Levofloxacin, Linezolid, Prothionamide, etc.) and discontinue pyzinamide[23].

A 2017 meta-analysis[5] showed tuberculosis in pregnancy has a greater impact on fetus than on pregnant women, compared with pregant women without TB, pregnant women with active TB tended to have a higher risk of death(OR 4.1, 95%CI 0.65-25.2), was associated with increased odds of preterm birth (OR 1.7, 95%CI 1.2-2.4) and perinatal death (OR 4.2, 95%CI 1.5-11.8). Pregnancy with hematogenous disseminated tuberculosis can cause chorioamnionitis due to severe tuberculosis toxemia and mycobacterium tuberculosis spreading along the blood to infect the placenta[24,25], leading to miscarriage (spontaneous abortion, inevitable abortion) and fetal death. We also found that the proportion of artificial abortion among naturally pregnant tuberculosis patients is higher, mainly because most of them have unplanned pregnancies, and the others were worried about the side effects of drugs, although there is evidence that the use of these first-line antituberculous drugs in pregnancy are considered safe for the mother and the foetus[26].

Our study had several limitations. First, the study is a retrospective study, and it is impossible to determine whether maternal tuberculosis was infected during pregnancy or caused by recurrence of old lesions in the body, and this may involve different interventions, especially for women who are about to undergo IVF-ET. If active tuberculosis is caused by re-infection, the measures taken are to protect pregnancy women during pregnancy. If it is caused by the reignition of old lesion, detailed tuberculosis screening work is required before IVF-ET. If infertility is caused by congenital tuberculosis, anti-tuberculosis treatment should be initiated immediately and if congenital tuberculosis and active tuberculosis in other parts are ruled out, women infected mycobacterium tuberculosis might need to receive preventive treatment. These measures may reduce the incidence of tuberculosis during pregnancy and abortion rate of pregnant women. We will do further research on these issues next.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shanghai Public Health Clinical Center [batch number:2020-S112-03] .The retrospective nature of the study resulted in a waiver regarding the signing of the informed consent form. And this study was approved by the Ethics Committee of Shanghai Public Health Clinical Center to exempt subjects from informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Wei Huang,Tao Li, Jinghua Liu, Xuhui Liu and Shuihua Lu contributed substantially to the conception and design of the study, acquisition of data, or analysis and interpretation of data. Yang Yang, Ping Liu, Linyun Dong, Xiuhong Xi and Lu Xia. contributed substantially to the analysis and interpretation of

data. Wei Huang drafted the initial version of the manuscript, which was subsequently revised and approved for submission by all authors.

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Figures

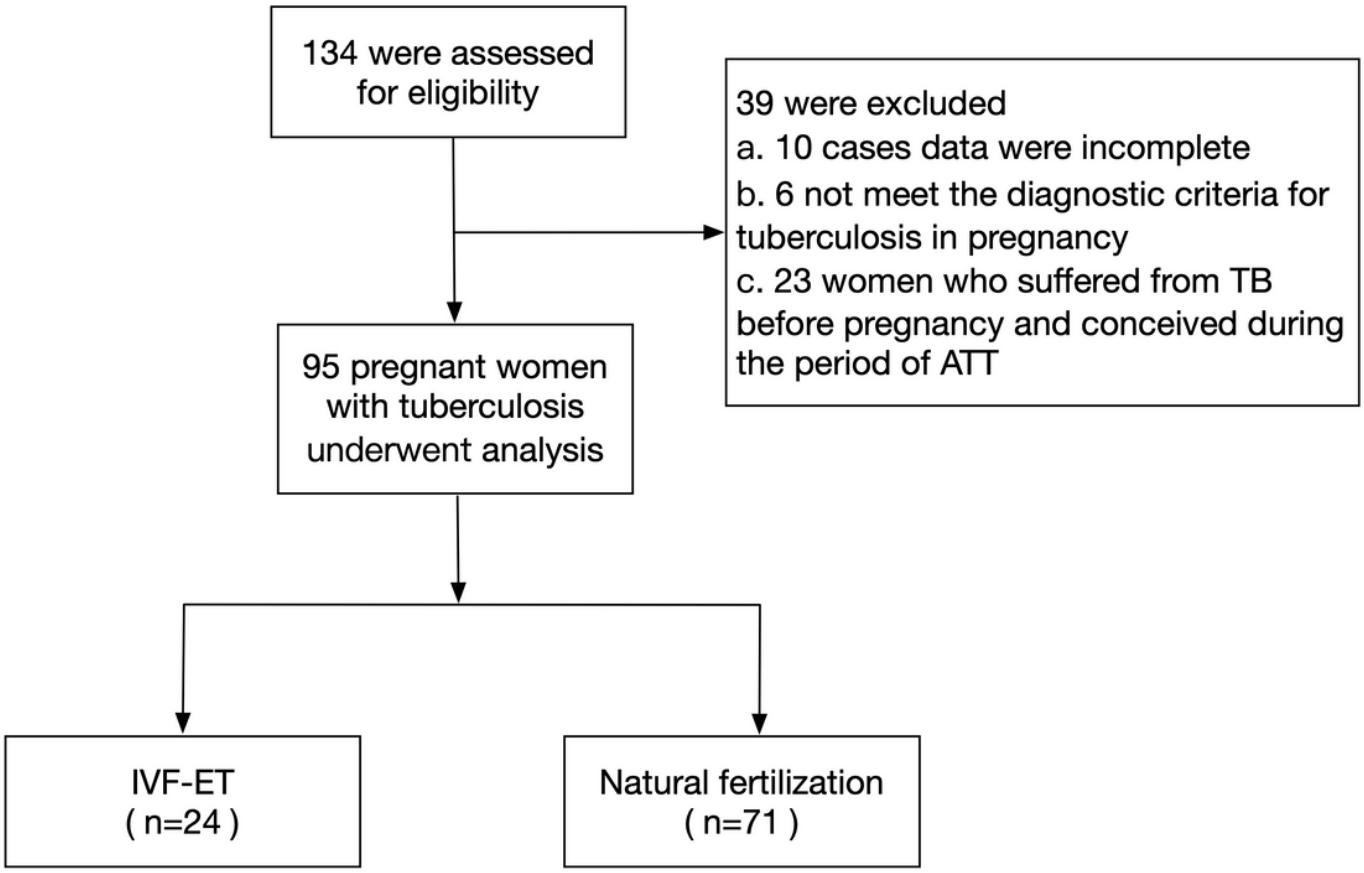
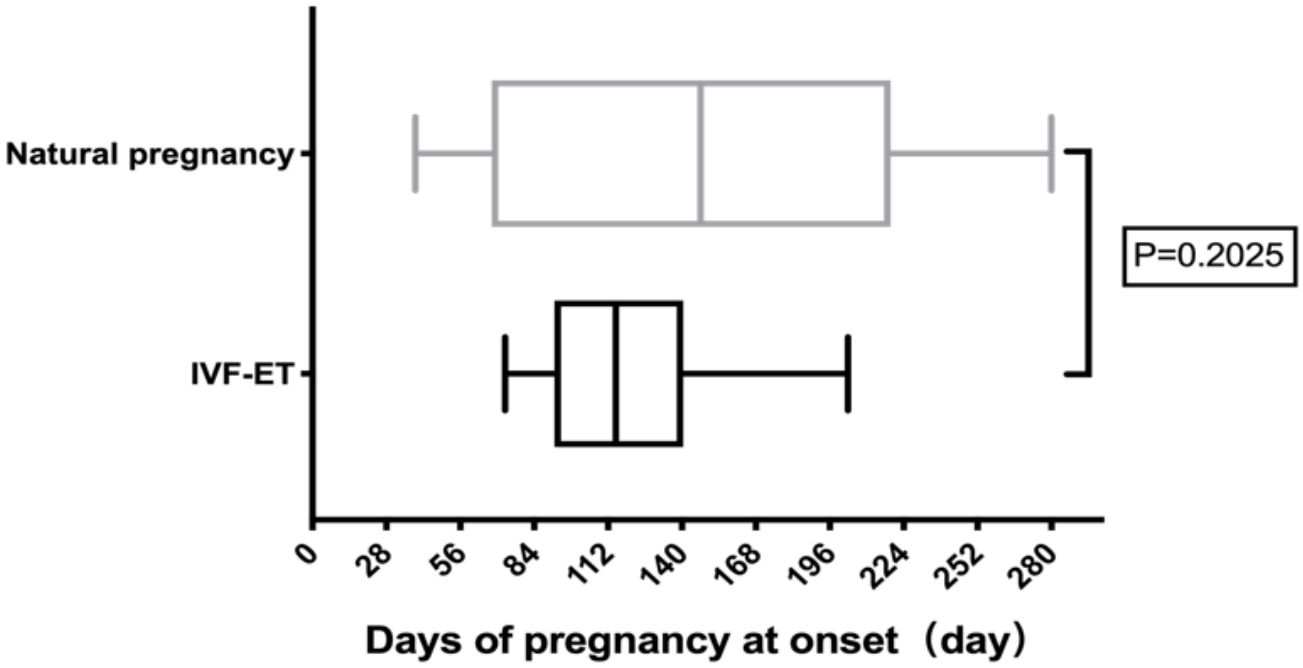


Figure 1

Flow diagram of patients with tuberculosis in pregnancy in the study IVF-ET: in vitro fertilization and embryo transfer ATT: anti-tubercular therapy



Days of Natural pregnancy：147（68，219）

Days of IVF-ET：115（91.75，140.5）

Group	IVF-ET (n=24)	Natural fertilization (n=71)	*p*-value
Onset time week^{+days}	16w3d (13w1d, 20w1d)	21w (9w5d, 31w2d)	0.2025

Figure 2

Days of Pregnancy at onset in pregnant women after IVF-ET and natural fertilization.

Supplementary Files

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- supplementarytable1.docx