Effect of antitubercular treatment on ovarian function in female genital tuberculosis with infertility

Jai Bhagwan Sharma, J. Sneha, U. B. Singh[1], Sunesh Kumar, K. K. Roy, Neeta Singh, Sona Dharmendra
Departments of Obstetrics and Gynaecology and [1]Microbiology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence:
Dr. Jai Bhagwan Sharma, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India.
E-mail: jbsharma2000@gmail.com

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ABSTRACT

AIM: To evaluate the effect of antitubercular therapy (ATT) on an ovarian function such as ovarian reserve, ovarian dimensions, and ovarian stromal blood flow. **SETTINGS AND DESIGN:** Prospective study design. **MATERIALS AND METHODS:** Fifty infertile women with female genital tuberculosis (FGTB) without tubo-ovarian masses diagnosed by positive acid-fast bacilli culture or epithelioid granuloma on endometrial aspirate or positive polymerase chain reaction with positive findings on laparoscopy or hysteroscopy were recruited. The ovarian function tests were performed on day 2/3 as follicle-stimulating hormone (FSH) levels and anti-Mullerian hormone (AMH) levels. Ovarian dimensions (length, width, and depth) were measured using a transvaginal ultrasound. Mean antral follicle count (AFC) and ovarian stromal blood flow (peak systolic velocity [PSV], pulsatility index (PI), and resistive index [RI]) were measured using a transvaginal ultrasound. All women were started on ATT for 6 months by directly observed treatment strategy. After completion of ATT, all the parameters were repeated. **RESULTS:** There was a significant increase in AMH (2.68 ± 0.97 ng/ml to 2.8 ± 1.03 ng/ml) pre- to post-ATT, nonsignificant increase in FSH (7.16 ± 2.34 mIU/ml to 7.26 ± 2.33 mIU/ml) post-ATT, significant increase in mean AFC (7.40 ± 2.12–8.14 ± 2.17), PSV in the right ovary (6.015–6.11 cm/s) and left ovary (6.05–6.08 cm/s), PI in the right ovary (0.935–0.951 cm/s) and left ovary (0.936–0.957 cm/s), and RI in the right ovary (0.62 ± 0.01–0.79 ± 0.02) and left ovary (0.65 ± 0.02–0.84 ± 0.01) with ATT. There was no significant change in mean ovarian dimensions (ovarian length, breadth, and width) and summed ovarian volume with ATT. On laparoscopy, tubercles were seen in 27 (54%) women. Caseous nodules and encysted ascites were seen in 8% cases each. **CONCLUSION:** ATT improves the ovarian function (AMH and AFC) and ovarian blood flow in women with FGTB.

KEY WORDS: Anti-Mullerian hormone, antral follicle count, female genital tuberculosis, laparoscopy, ovarian blood flow, ovarian function, ovarian reserve, tubo-ovarian mass

INTRODUCTION

Female genital tuberculosis (FGTB) is an important variety of extrapulmonary tuberculosis (TB) causing significant morbidity in women such as menstrual dysfunction, infertility, ectopic pregnancy, and tubo-ovarian mass.[1-4] The prevalence of FGTB in infertile women ranges from 7% to 15% in developing countries rising to 26% in tertiary referral hospitals and up to 48% in tubal factor infertility.[3,5] The infection spreads to genital organs normally by hematogenous route with the frequency of involvement of fallopian tubes (90%), endometrium (50–80%), ovaries (20–30%), cervix (5–10%), and rarely vulva and vagina.[1] FGTB is an important cause of intrauterine adhesions (Asherman's syndrome), pelvic adhesions, and perihepatic adhesions (Fitz–Hugh–Curtis syndrome).[6,7]

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Diagnosis of FGTB is usually made by endometrial sampling for acid-fast bacilli (AFB) microscopy, culture, histopathological epithelioid granuloma, positive polymerase chain reaction, diagnostic hysteroscopy, and/or laparoscopy for various TB findings.[8,9] Imaging modalities such as ultrasound, computerized axial tomography, magnetic resonance imaging (MRI), and positron-emission tomography (PET) have also been found to be useful in women with tubo-ovarian masses with FGTB.[10,11]

FGTB can involve ovaries directly causing tubo-ovarian masses. Even without a direct involvement of ovaries, the ovarian function, especially the ovarian reserve is affected in FGTB.[12] Malhotra *et al*.[12] reported a significantly higher value of follicle-stimulating hormone (FSH) in FGTB cases enrolled for *in vitro* fertilization and embryo transfer (IVF-ET) as compared to control. Other tests for ovarian reserve such as anti-Mullerian hormone (AMH) and antral follicle count (AFC) have also shown reduced ovarian reserve in women with FGTB.[12,13] Ovarian dimensions observed by length, width and depth, and mean summed ovarian volume have been observed to be significantly lower in women with FGTB as compared to controls.[12] Ovarian stromal blood flow as measured by ultrasound Doppler was observed to be lower (lower peak systolic velocity [PSV]) in genital TB. Similarly, resistive index (RI) was also found to be lower in FGTB women.[12] Marcus *et al*.[14] found term oocyte, poor pregnancy rate and higher abortion rate with IVF-ET in patients with genital TB. Other authors have observed the antigonadotropic effect of *Mycobacterium tuberculosis*.[15] Adequate and timely treatment of TB should improve the ovarian response to gonadotropins along with increased ovarian stromal blood flow and ovarian responsiveness. This study observed the ovarian involvement in FGTB cases by laparoscopy, and ovarian function was assessed before and after antitubercular therapy (ATT).

MATERIALS AND METHODS

It was a prospective observational study conducted on a total of fifty infertile patients with genital TB, to assess the effect of tuberculosis on ovarian function, and to see the effect of ATT on ovarian dimension and ovarian function. Hence, women with tubo-ovarian masses were excluded from the study. The patient's ovarian function was assessed pre and post the ATT. The patients willing to participate with proven and/or possible diagnosis of genital TB by endometrial aspirate positive for *M. tuberculosis* by culture or AFB on microscopy or histopathological evidence of tuberculous granuloma on endometrial aspirate (definitive/proven diagnosis) or endometrial aspirate positive for DNA polymerase chain reaction (PCR) with hysteroscopic features suggestive of FGTB and/or laparoscopic examination suggestive of FGTB. DNA PCR was used in the study. RNA PCR was not used due to logistic and financial constraints as RNA PCR was very expensive.

All the patients recruited were aged between 20 and 45 years. Ethical approval was taken from the Institutional Ethical Committee, and an informed consent was taken from all the participants. A detailed history of the symptoms, menstrual history (amenorrhea, oligomenorrhea, menorrhagia; duration of cycles, amount of menstrual blood flow, with or without associated dysmenorrhea) was taken. The endometrial aspirate was taken in premenstrual phase and sent in saline for AFB microscopy, culture, PCR for *M. tuberculosis*, and in formaline for histopathological evidence of epithelioid granuloma.

Ovarian function was assessed by hormonal assays – day 2–3 follicular stimulating hormone and AMH, ultrasonic measurement on day 2/3 of the menstrual cycle of ovarian dimensions and volume by the formula, i.e., length × width × depth × pie/6; summed ovarian volume; AFC; and ovarian stromal blood flow (the PSV, pulsatility index [PI], and RI) were calculated. The ultrasound machine used was Siemens-Acuson Antares (Siemens Health Care, Germany) and the probe used was transvaginal probe (6.5 MHz) ovarian dimensions, volume, and AFC and endometrial thickness were checked and recorded. However, during the course of the study, the machine became dysfunctional and the second machine GE Voluson with 6.5 MHz transvaginal probe was used in the later part of the study. To avoid interobserver variability between different observers and different cycles, all the ultrasonic measurements were performed by only one sonologist.

Diagnostic laparoscopy was performed in all cases for findings of TB such as whitish, yellow, or opaque plaques surrounded by hyperemic areas over the fallopian tubes and uterus, presence of miliary granuloma, nodular salpingitis, patchy salpingitis, hydrosalpinx, caseosalpinx, adhesions, tubercles on ovarian surface, or tubo-ovarian mass.

ATT was started in all the patients. At the end of the course of ATT, the patient was reassessed for the effect of the therapy by a detailed history of the improvement in the symptoms with regard to the menstrual history, endometrial aspiration studies - the changes in histopathology findings, PCR, and AFB. The ovarian reserve - the improvement in the level of FSH and AMH, ovarian dimensions, summed ovarian volume, AFC and ovarian stromal blood flow by ultrasound, and Doppler. The laparoscopic changes were reassessed in all the cases excluding women who conceived during ATT. It was a thesis study in which fifty women with FGTB were enrolled. They underwent endometrial sampling, ultrasonic examination, and diagnostic laparohysteroscopy at the beginning of the study. They were given ATT for 6 months. As per protocol of the study, all the investigations were repeated in all the patients (except those who became pregnant during the study, lost to follow-up, or refused repeat testing). Repeat testing helped to confirm that tuberculosis was cured and for prognostication of the disease and for further planning for infertility treatment. Although PCR was performed twice, its positivity was not used either to start ATT or to stop the treatment. AMH was performed by the ELISA method.

Statistical analysis

Descriptive statistics such as mean, median, standard deviation, and range were calculated for study characteristics age, weight, and duration of infertility. Assumptions of normality for continuous primary outcome variables were tested using Kolmogrov-Smirnov-tests. Changes in outcome variables (continuous variables) were compared using student's t-test paired test from baseline to posttest. Similarly, changes in qualitative variables were compared using McNemar's chi-square test. Frequency variables across categories were compared using chi-square test or Fischer's exact test as appropriate. A probability level $P < 0.05$ Was considered for statistical significance. All data analysis was carried out using the SPSS software version 9.0, IBM Inc., USA).

RESULTS

The characteristics of women and their symptoms are shown in Table 1. The mean age was 28.7 ± 4.4 years, mean body mass index was 23.6 kg/m^2, and mean duration of infertility was 6.06 years. Primary infertility was seen in 33 (66%) women, while secondary infertility was seen in 17 (34%) women. The menstrual pattern is also shown in Table 1. Normal cycles were seen in 26 (52%) women, menorrhagia in 5 (10%), hypomenorrhea in 15 (30%), oligomenorrhea in 2 (4%), primary amenorrhea in 1 (2%), and secondary amenorrhea in 1 (2%) women. The method of diagnosis of FGTB is shown in Table 2. There were positive endometrial aspirate AFB culture in 2 (4%), epithelioid tuberculous granuloma on endometrial aspirate in 4 (8%), TB granuloma on histopathology of biopsy from peritoneal tubercle in 4 (8%), and positive PCR in 47 (94%) cases. There were findings of FGTB on laparoscopy in 47 (94%) women. Laparoscopic findings in the patients are shown in Table 3. The various findings before ATT

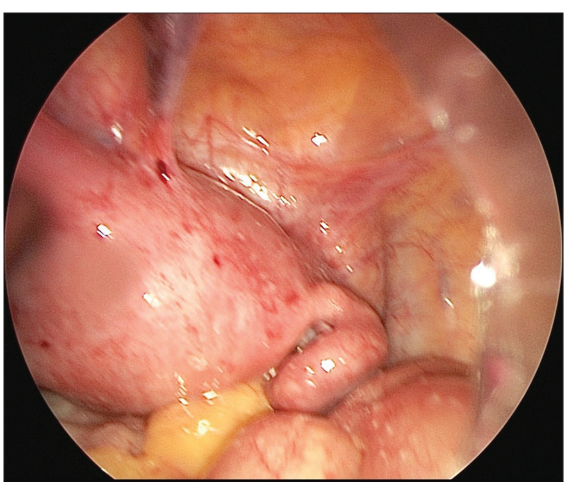

Figure 1: Laparoscopic findings showing tubercles on ovary before antitubercular therapy in one of the cases. Few pelvic adhesions are also seen

Table 1: Characteristics and menstrual pattern of women (*n*=50)

Characteristic	Range	Mean
Age (years)	21–37	28.7
Body mass index (kg/m²)	18.3–32.4	23.6
Parity	0–4	0.9
Duration of infertility (years)	2–14	6.06±2.8
Type of infertility (%)		
Primary	33 women (66)	
Secondary	17 women (34)	
Menstrual pattern	***n* (%)**	
Normal cycle	26 (52)	
Hypomenorrhea	15 (30)	
Menorrhagia	5 (10)	
Oligomenorrhea	2 (4)	
Primary amenorrhea	1 (2)	
Secondary amenorrhea	1 (2)	

Table 2: Diagnosis of female genital tuberculosis

Diagnostic method	*n* (%)
Positive acid-fast bacilli on endometrial aspirate	2 (4)
Tuberculous granuloma on histopathology of endometrial tissue	3 (6)
Tuberculous granuloma on histopathology of biopsy from peritoneal tubercles	4 (8)
Positive DNA polymerase chain reaction on endometrial aspirate	50 (100)
Definite findings of tuberculosis on laparoscopy	43 (86)

Note: Some women had more than one finding

Table 3: Laparoscopic findings in study patients

Laparoscopy findings (*n*=50)	*n* (%) (*n*=50)
Normal findings	2 (4)
Tubercles	
Pelvic peritoneum	21 (42)
Fallopian tubes	4 (8)
Ovaries	2 (4)
Caseous nodules	4 (8)
Encysted ascites	4 (8)
Pelvic adhesions	21 (42)
Mild	2 (4)
Moderate	9 (18)
Severe	10 (20)
Perihepatic adhesions	28 (56)

Table 4: Effects of antitubercular therapy on ovarian dimensions

Parameter	Pre-ATT (cm) mean (n=50)	Post-ATT (cm) mean (n=48)	P	Significance
Right ovary length	2.25	2.27	0.634	NS
Right ovary width	1.78	1.83	0.672	NS
Right ovary depth	2.39	2.79	0.320	NS
Left ovary length	2.37	2.35	0.185	NS
Left ovary width	1.84	1.89	0.772	NS
Left ovary depth	2.47	2.46	0.815	NS
Summed ovarian volume (cc)	10.9	11.1	0.55	NS

NS=Not significant, ATT=Antitubercular therapy

Table 5: Effects of antitubercular therapy on antral follicular count and ovarian stromal blood flow

Parameter	Pre-ATT (n=50)	Post-ATT (n=48)	P	Significance
Mean antral follicular count	7.40	8.14	<0.001	S
Standard deviation	2.12	2.17		
Ovarian stromal blood flow				
Peak systolic velocity (cm/s)				
Right ovary	6.015	6.11	<0.001	S
Left ovary	6.05	6.08	0.768	NS
Pulsatility index				
Right ovary	0.935	0.951	<0.001	S
Left ovary	0.936	0.957	<0.001	S
Resistive index				
Right ovary	0.62	0.79	<0.001	S
Left ovary	0.65	0.84	<0.001	S

S=Significant, NS=Not significant, ATT=Antitubercular therapy

were tubercles on pelvic peritoneum 21 (42%), fallopian tube 4 (8%), ovaries 2 (4%) [Figure 1], caseous nodules 4 (8%) [Figure 2], encysted ascites 4 (8%), pelvic adhesions 21 (42%), and perihepatic adhesions 28 (56%) in women.

Table 4 shows the ovarian reserve before and after ATT. On day 2–3, FSH levels raised from 7.16 ± 2.36 mIU/ml before ATT to 7.26 ± 2.33 mIU/ml, but the rise was not significant (P = 0.628). However, there was a significant increase in AMH levels from 2.68 ± 0.97 ng/ml before ATT to 2.8 ± 1.03 ng/ml after ATT (P = 0.046). Effects of ATT on mean ovarian dimensions as measured by transvaginal ultrasound are shown in Table 4. Although there was some improvement and increase in ovarian dimensions with ATT it is not statistically significant.

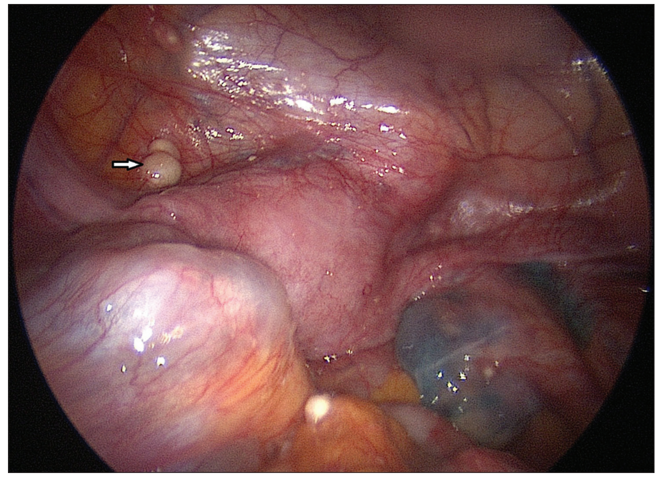

Figure 2: Laparoscopic findings showing caseous nodule in a case of female genital tuberculosis

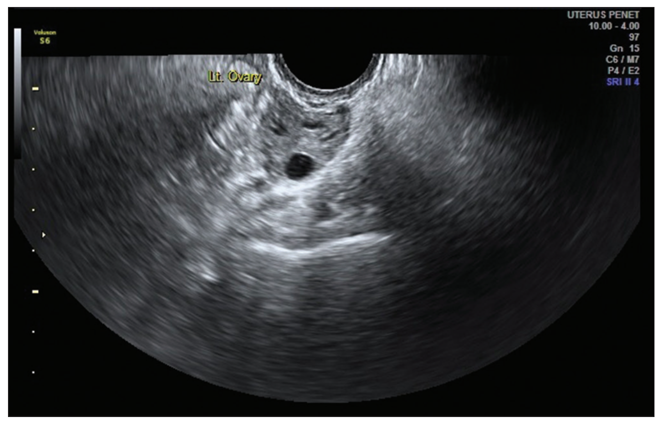

Figure 3: Day 2 scan showing three follicles in the right ovary before antitubercular therapy

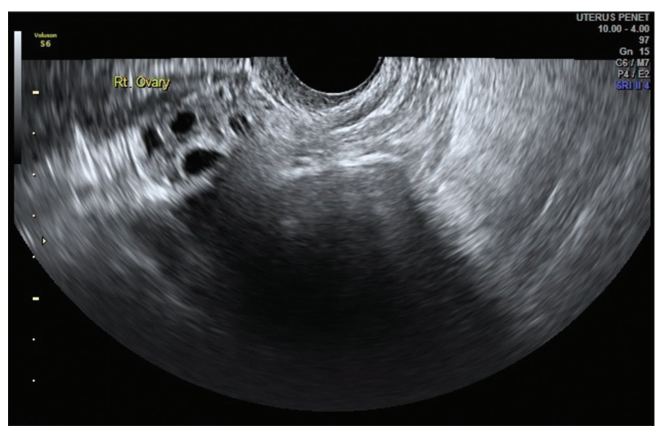

Figure 4: Day 2 scan showing four follicles in the right ovary after antitubercular therapy

The summed ovarian volume was increased significantly from 10.9cc to 11.1 cc after ATT (P = 0.55). Table 5 shows ultrasonic measurement of mean AFC and ovarian stromal blood flow before and after ATT. There was a significant improvement in most of the parameters. The mean AFC increased significantly from 7.40 ± 2.12 to 8.14 ± 2.17 with ATT (P < 0.001) PSV increased significantly in the right ovary and nonsignificantly in the left ovary with ATT [Figure 3 and 4]. PI increased from 0.935 to 0.951 (P < 0.001) in the right ovary and from 0.936 to 0.957 (P < 0.001) in the left ovary. RI also increased significantly from 0.62 ± 0.01 to 0.79 ± 0.02 in the right ovary (P < 0.001) and from 0.65 ± 0.02 to 0.84 ± 0.01 in the left ovary (P < 0.001). While the patients were getting ATT, no active treatment for infertility was performed. However, two women (4%) conceived during ATT and another four women (6%), total (10%) conceived during the 1-year follow-up after ATT.

Hence, there was a significant improvement in ovarian function and ovarian stromal blood flow with ATT in FGTB cases though ovarian dimensions did not change significantly.

Statistical analysis

Descriptive statistics such as mean, median, standard deviation, and range were calculated for study characteristics age, weight, and duration of infertility. Assumptions of normality for continuous primary outcome variables were tested using Kolmogrov-Smirnov-tests. Changes in outcome variables (continuous variables) were compared using student's *t*-test paired test from baseline to posttest. Similarly, changes in qualitative variables were compared using Mcmear chi-square test. Frequency variables across categories were compared using chi-square test or Fischer's exact test as appropriate. A probability level P < 0.05 Was considered for statistical significance. All data analysis was carried out using the SPSS, IBM Inc. (spss software version 9.0, IBM Inc., USA).

DISCUSSION

FGTB is a common disease in developing countries causing significant morbidity, especially infertility.[1-5] Being paucibacillary disease, its diagnosis, especially in the early stage, is a diagnostic challenge. Combinations of tests are performed to reach a diagnosis.[16,17] These include endometrial sampling for AFB on microscopy or culture, PCR for *M. tuberculosis*, histopathological evidence of epithelioid granuloma, laparoscopic, and/or hysteroscopic evidence of FGTB.[8,16,18] Ultrasound, CT scan, MRI, and PET scan are more useful for FGTB with tubo-ovarian mass, especially when the differential diagnosis is ovarian cancer as FGTB is known to masquerade as ovarian cancer.[1,10,11,19] Some authors have made an algorithm by combining various tests for early diagnosis of FGTB.[17]

Direct ovarian involvement in FGTB occurs less commonly (20–30%). However, even in the absence of direct ovarian involvement, FGTB affects ovarian function, especially ovarian reserve as observed by other authors in their study.[12-14] Adequate follicular development in response to gonadotrophins is dependent on the ovarian reserve at that period of time. Various tests of ovarian reserve such as AMH, FSH, and AFC have become a part of the routine diagnostic procedure for infertility patients. Recent studies have shown decreased ovarian reserve in FGTB patients.[12-14]

Poor ovarian blood flow has also been observed in infertile women with FGTB undergoing assisted reproduction.[20] Although many studies have observed the effect of FGTB on ovarian function, no study in our knowledge has observed the effect of ATT on ovarian function in FGTB. In the present study, performed in FGTB patients without obvious ovarian involvement (cases with tubo-ovarian mass were excluded) diagnosed by endometrial aspiration studies showing evidence of AFB on culture or microscopy, histopathological evidence of epithelioid granuloma, positive PCR along with findings on laparoscopy and/or hysteroscopy, and ovarian function was assessed at enrolment. The women were then given 6 months course of ATT. Ovarian function was then reassessed after completion of ATT in all women (except two women who conceived during treatment). We observed a significant increase in AMH levels with ATT and a nonsignificant increase in FSH levels with ATT.

The rise in FSH in FGTB could be due to the antigonadotropic effect of *M. tuberculosis* as has been observed by Kumar and Rattan in their study.[15] AMH has been observed to be a superior marker for predicting both oocyte number and quality.[21,22] However, there is no literature on AMH levels in FGTB patients. In the present study, there was an increase in AMH levels, nonsignificant increase in FSH levels, and significant increase in AFC using ATT. *M. tuberculosis* has an antigonadotropic effect. After ATT, toxins disappeared improving gonadotropic levels. There is an increase in ovarian blood flow with ATT improving ovarian function including AFC.

Ovarian dimensions, especially mean summed ovarian volume as measured by ultrasound has been observed to be decreased significantly in women with FGTB.[12] Malhotra *et al*.[12] showed that mean summed ovarian volume was significantly lower among women with genital TB in contrast to nontuberculous patients (10.8 mm vs. 11.9 mm, P = 0.004). They also observed significantly higher levels of FSH in FGTB cases compared to controls enrolled for IVF program (6.7 mIU/ml vs. 5.3 mIU/ml).[12] They also observed mean AFC to be significantly lower in women with FGTB in contrast to controls in women enrolled for IVF program (10.8 vs. 11.9, P = 0.001). They also observed significantly lower PSV, PI, and RI in women with FGTB in a contrast to nontubercular controls.[12] Small ovarian size on ultrasound has fewer basal follicles and may respond poorly to subsequent controlled ovarian stimulation.[23] In the present study, mean summed ovarian volume increased nonsignificantly from 10.9 to 11.1 mm^3 with ATT. There was, however, a significant increase in mean AFC from 7.4 to 8.14 ($P < 0.001$) after ATT in the present study which may enhance pregnancy rate, especially if treated on time. Zaidi *et al*.[24] observed a relationship between ovarian stromal blood flow and ovarian follicular response and showed that poor responders had a low stromal PSV. Ebner *et al*.[21] found that in patients with normal basal FSH, the mean ovarian stromal PSV on the day of pituitary suppression was a better predictor of ovarian response than age. Deficient intra-ovarian vascularity may serve as the initial marker of decreased ovarian reserve which precedes an increased FSH level and reduction of ovarian reserve.[21] In the present study, there was a significant increase in PSV in the right ovary and nonsignificant increase in PSV in the left ovary with ATT. An increase in RI was also noted in both ovaries with ATT.

CONCLUSION

FGTB causes a reduction in ovarian function and ovarian reserve and ovarian blood flow. Timely diagnosis and early start of ATT improve the ovarian function as evidenced by significant increase in AMH, AFC, and RI with ATT.

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Conflicts of interest

There are no conflicts of interest.

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