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CLINICAL ARTICLE

The effect of tuberculosis on ovarian reserve among women undergoing IVF in India

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ABSTRACT

Objective: To assess ovarian reserve in infertile women with genital tuberculosis planning to undergo in vitro fertilization and in women of proven fertility, and compare the findings. *Methods:* A cross-sectional study was conducted at an outpatient gynecology unit with 104 women with genital tuberculosis and 104 healthy controls. In each group, ovarian reserve tests consisted in estimating serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and inhibin B on day 3 of a natural menstrual cycle. On the same day ovarian volume, number of antral follicles, and ovarian stromal blood flow were also estimated. *Results:* The mean FSH and LH levels were significantly higher, and the mean inhibin B levels were significantly lower, among the participants with genital tuberculosis than among the controls. Conversely, the mean ovarian volume and the mean number of antral follicles were significantly lower among the participants with genital tuberculosis, as were the mean peak systolic velocity and pulsatility index for each ovary. *Conclusion:* There is no single absolute predictor of ovarian reserve, but combining the current assessment methods provides a close estimation of a woman's reproductive capability. Values for the studied markers showed that ovarian reserve was compromised in women with genital tuberculosis.

1. Introduction

The phrase ovarian reserve refers to the number of competent oocytes, within follicles of competent granulosa cells, that the ovary has the capacity to release at any given time [1]. The ovarian reserve determining the physiologic age of the ovary, it is a major predictor of a woman's reproductive capacity regardless of her chronologic age. Every woman is born with a fixed number of primordial ovarian follicles and this number declines with each passing year until menopause, when only a few follicles remain. This normal decrease in the number of primordial follicles eventually results in a low ovarian reserve, which has a direct bearing on the quality of oocytes [2]. Although the processes that control ovarian aging remain unclear, it is known that women do not respond well to ovarian stimulation when these processes are accelerated. Hormonal markers are used to predict ovarian response, however, if an infertile women has high levels of follicle stimulating hormone (FSH) and estradiol and low levels of inhibin B and anti-Müllerian hormone on day 2 or 3 of a natural cycle, her ovarian reserve is considered low. Ovarian volume, ovarian blood flow, and number of small antral follicles as assessed on ultrasound are also considered predictive of reproductive potential [3–6]. As the woman's age advances her ovarian volume and antral follicle count gradually decline, though this decline is more gradual for the latter [7–9]. There is no clear consensus on the best marker for ovarian reserve.

In India, the burden of genital tuberculosis is extremely high among infertile women, with an incidence as high as 19% [10]. The first genital organs to be affected are the fallopian tubes (about 90%), followed by the endometrium (50%–60%), the ovaries (10%–30%), and rarely the cervix, vagina, and vulva (5% for all combined) [11], which leads to tubal blockage and pelvic, abdominal, and perihepatic adhesions (Fitz-Hugh–Curtis syndrome). Women with tuberculosis have higher basal FSH levels, lower peak estradiol levels, and fewer oocytes than women who do not have the disease. They require higher doses of exogenous gonadotropins for ovulation induction but in vitro (IVF) fertilization results in fewer embryos [12]. Whereas tubal and endometrial involvement of tuberculosis is apparent at laparoscopy and hysteroscopy, little is known about ovarian involvement in women with genital tuberculosis. *Mycobacterium tuberculosis* may have toxic effects on ovarian reserve, which would explain the poor results observed during the intrauterine insemination or IVF cycle, particularly in response to ovulation induction. While it would be useful to verify this hypothesis, there is no consensus regarding the best test for assessing ovarian reserve in women undergoing assisted reproduction procedures.

The present study was carried out to study ovarian reserve in infertile women with genital tuberculosis who plan to undergo IVF, and compare findings with corresponding findings obtained with women of proven fertility.

2. Materials and methods

The present cross-sectional study was conducted from October 1, 2007, to September 30, 2009, at the outpatient unit of the Gynecology

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Department of the All India Institute of Medical Sciences, New Delhi, India. The study group consisted of 104 women with genital tuberculosis and the control group of 104 women who had been delivered in the previous 2 years. Ethics clearance was obtained from the institute's Ethics Committee and written informed consent was provided by all participants prior to enrollment in the study. Women younger than 20 years or older than 35 years were excluded, as were women with polycystic ovaries, a single ovary, a tubo-ovarian mass, an ovarian endometrioma, or a history of ovarian surgery. All participants were spontaneously menstruating and had no signs or symptoms suggestive of menopause.

The detailed medical history of each participant was taken, which included her menstrual and obstetric history, and a general medical examination was followed by an abdominal and vaginal evaluation. A diagnosis of genital tuberculosis was made based either on the results of tests performed from an endometrial aspiration sample (the tests were a polymerase chain reaction to detect *M. tuberculosis* DNA, acid-fast bacilli staining, or liquid culture by means of mycobacteria growth indicator tubes and the Lowenstein-Jensen medium) or on histopathologic, hysterosalpingography, hysteroscopy, or laparoscopy findings. Basal ovarian reserve studies included measuring serum levels of FSH, luteinizing hormone (LH), E_2, and inhibin B on day 3 of a natural cycle by the non-immunometric method. Double-antibody enzyme-linked immunosorbent assays were performed using kits from Serotech (Indianapolis, IN, USA) and an automated multi-analyzer permitting direct chemiluminescence visualization (ADVIA Centaur XP immunoassay system; Siemens Healthcare Diagnostics, Deerfield, IL, USA). On the same day, the participants underwent a transvaginal ultrasound examination by means of a 2-dimensional 6.5 MHz probe with color Doppler facility fitted to a Siemens-Acuson Antares System (Siemens Healthcare Diagnostics). Ovarian volume and number of antral follicles were estimated for each ovary and blood flow was assessed in the ovarian stroma, where areas of maximum blood vessel color intensity were noted. Peak systolic velocity (PSV) waveforms were detected and the optimal flow velocity waveforms were selected for analysis. The pulsatility index (PI), resistance index (RI), and PSV were measured over 3 cardiac cycles. Control participants underwent the same tests on day 2 or 3 of their menstrual cycle.

Data are presented as mean ± SD. Continuous variables such as age and body mass index (calculated as weight in kilograms divided by the square of height in meters) were compared using the *t* test. Correlations were established by means of the Pearson or the Spearman rank correlation procedure, as appropriate. Analysis was done using SPSS version 12.0 (SPSS, Chicago, Illinois, USA). $P<0.05$ was considered to be statistically significant.

3. Results

Of the 104 study patients, 88 (84.6%) had primary infertility and 16 (15.4%) had secondary infertility (Table 1). The diagnosis of genital tuberculosis was established on the basis of the following: positive results to a PCR (n = 45 [43.3%]) or an acid-fast bacilli culture (n = 5 [4.8%]); histologic studies revealing tuberculous granulation in the endometrial aspirate (n = 10 [9.6%]); or of observations during laparoscopy (n = 24 [23.1%]), hysteroscopy (n = 8 [7.7%]), or hysterosalpingography (n = 12 [11.5%]).

Table 1
Baseline demographic characteristics of participants with genital tuberculosis and controls.[a]

Characteristic	Study group (n = 104)	Control group (n = 104)
Age, y	28.7 ± 3.9 (20–35)	28.2 ± 3.1 (20–35)
Infertility duration, y	6.5 ± 3.4 (1–15)	6.7 ± 3.8 (2–12)
Primary infertility	88 (84.6)	70 (67.3)
Secondary infertility	16 (15.4)	34 (33.7)
BMI	26.4 ± 3.6 (18.9–35.6)	26.4 ± 3.7 (26–33.6)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).
[a] Values are given as mean ± SD (range) or number (percentage).

Table 2
Variables studied to assess ovarian reserve in participants with genital tuberculosis and controls.[a]

Variable	Study group (n = 104)	Control group (n = 104)	95% CI for the difference between the groups	*P* value
FSH, IU/L	6.7 ± 1.69	5.3 ± 0.95	−1.84 to −1.084	0.001
LH, IU/L	4.5 ± 1.52	4.1 ± 0.93	−0.79 to −0.10	0.01
Estradiol, pg/mL	55.4 ± 13.23	53.0 ± 14.13	−6.07 to 1.41	0.22
Inhibin B, pg/mL	54.9 ± 21.11	64.3 ± 19.79	3.72 to 14.90	0.001
No. of antral follicles counted	10.3 ± 2.47	11.8 ± 2.76	0.77 to 2.21	0.001
Ovarian length, mm	23.9 ± 3.35	25.3 ± 2.11	0.54 to 2.07	0.001
Ovarian width, mm	19.2 ± 1.96	20.7 ± 2.46	0.98 to 2.19	0.001
Ovarian depth, mm	22.2 ± 2.63	21.6 ± 1.71	−1.23 to −0.02	0.04
Ovarian volume, cm	10.8 ± 3.33	11.9 ± 2.11	0.37 to 1.89	0.004
Peak systolic velocity, cm/s	5.9 ± 0.92	6.6 ± 1.21	0.32 to 0.92	0.001
Pulsatility index	0.9 ± 0.15	0.9 ± 0.11	0.01 to 0.09	0.007
Resistive index	0.6 ± 0.08	0.6 ± 0.06	−0.03 to 0.01	0.37

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.
[a] Values are given as mean ± SD unless otherwise indicated.

Ovarian reserve was assessed by means of hormonal assays and ultrasound markers (Table 2). On day 3 of the menstrual cycle the mean ± SD values for FSH levels were significantly higher in the study than in the control group (6.7 ± 1.7 IU/L vs 5.3 ± 0.9 IU/L, $P<0.001$) (Fig. 1), as were mean values for LH (4.5 ± 1.4 IU/L vs 4.0 ± 0.7 IU/L, $P<0.001$) (Fig. 2) and the mean FSH:LH ratio (1.6 ± 0.4 vs 1.4 ± 0.3, $P<0.001$). The mean values for inhibin B, however, were significantly lower in the study group (54.9 ± 21.1 pg/mL vs 64.2 ± 19.8 pg/mL, $P<0.001$) (Fig. 3). Moreover, the ovarian lengths and widths were significantly less in the study than in the control group, as was the measure of interest, i.e., ovarian volume (10.8 ± 3.3 cm^3 vs 11.9 ± 2.1 cm^3, $P<0.004$) (Fig. 4). The antral follicle count was significantly lower in in the study than in the control group (10.3 ± 2.5 vs 11.8 ± 2.8, ($P<0.001$) (Fig. 5), as were the mean PSV and pulsatility index for both ovaries (Fig. 6).

4. Discussion

Ovarian reserve declines with age and is therefore an important determinant of the success of any fertility treatment. Ovarian reserve

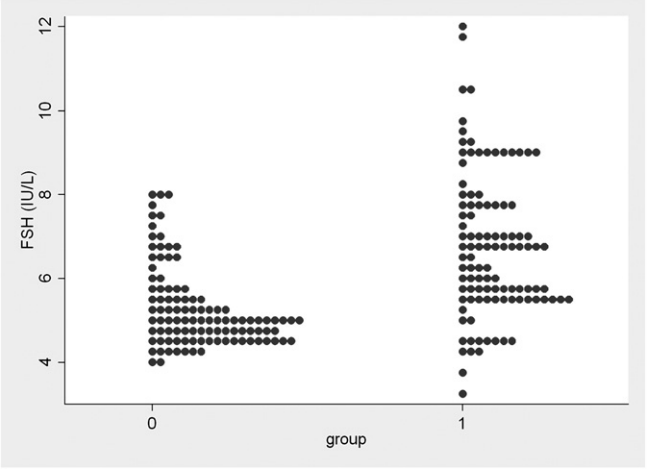

Fig. 1. Serum levels of follicle-stimulating hormone in a group of 104 fertile controls and 104 women with genital tuberculosis.