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Original Research Article

Deficient Ovarian Reserve in Genital Tuberculosis

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Conflict of interest: Nil

Abstract:

Objective: To assess ovarian reserve (OR) in infertile women with GTB and compare with women with proven fertility by Hormonal and Ultrasound markers of ovarian reserve

Methods: A cross-sectional study was conducted at an outpatient DMCH, DARBHANGA, India with 50 women with Gestational Tuberculosis (GTB) and 50 healthy controls. Ovarian reserve tests were done by estimating serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), on day 3 of a natural menstrual cycle and anti-Mullerian hormone (AMH) in any day of cycle. On D3 Antral Follicles Count (AFC) were also estimated on Ultrasound.

Result: The median FSH was 8.91 (5.60-11.07) mIU/ml, LH 6 (4.65-8.55) mIU/ml and the mean E2 61.30□15.23 pg/ml which were significantly higher than controls (FSH-5.50, LH-3.80, and E2-41.53). The median AMH levels 1.23 ng/ml was significantly lower in GTB than controls (AMH-2.50). And, the median AFC 6.0(4.0-8.0) was significantly lower in GTB than control 11.0 (8.25-12.0).

Conclusion: The median FSH, LH and the mean E2 on day-3 of cycle and AMH on any day of cycle along with AFC are good predictors of Ovarian reserve and found to be low in GTB.

Keywords: Ovarian reserve, Gestational tuberculosis, Antral Follicles Count.

Introduction

Ovarian reserve (OR) determine the physiological age of ovary, it is a major predictor of a women's reproductive capacity regardless of her chronological age. Reproductive potential depends on OR.OR refers to a women's current supply of eggs.

Every womanis born with a fixed no. of primordial follicle(6-8 millions)1and many of these are lost during childhood so that she has only about 300,000-500,0002eggs left by time of beginning of periods and this number decline each year passing until menopause when only few follicle remains. This normal decrease in the number of primordial follicle eventually results in a low OR which has a direct effect on the quality of eggs. OR is defined as quantity and quality of eggs that women have in their ovaries that could result in pregnancy. The greater number of remaining eggs, the better will be the chance for conception. Conversely, deficient OR diminishes chances for conception. The probable theoretical causes of decline in reproductive potential in women beginning at the third decade of life may be diminished ovarian reserve, Quantitative decrease in oocytes, Qualitative changes in oocytes and diminished uterine receptivity for implantation. This study was conducted to look ovarian reserve (OR) in infertile women with Gestational tuberculosis (GTB) and compare with women with proven fertility by Hormonal and Ultrasound markers of ovarian reserve.

Materials and Methods

The present cross-sectional study was conducted from July 2020 to July 2022, at the outpatient clinic of Department of Obstetrics and Gynecology, Darbhanga Medical College and Hospital, Lahariasarai, Darbhanga, Bihar, India. The study group consisted of 50 women with genital tuberculosis and the control group of 50 women who had been delivered in the previous 2 years.

Ethical 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 40 years were excluded. 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.

Diagnosis of genital tuberculosis - was made by any of test because it is not necessary that all tests were positive. GTB is very difficult to diagnose. Although Histopathology is gold standard. Techniques used were ultrasound abdominal and pelvis, laparoscopy, hysteroscopy, endometrial PCR (polymerase chain reaction), Hysterosalpingography (HSG), Histopathology and Positive culture (BACTEC, Lowenstein jenson culture). All cases with proven diagnosis of genital tuberculosis was underwent test of ovarian reserve. Hormonal assays-Day 2-3 FSH, LH, E2 assessed by chemiluminescence immunoassay method performed on atumated multianalyser-(ADVIA Centaur RXP immunoassay system, Siemens Healthcare Diagnostic Inc. USA).Serum AMH was measured by enzyme-linked immunosorbent assay (ELISA) using the MIS/AMH ELISA kit (DRG instruments GmbH, Germany. ULTRASONIC measurement of AFC On the same day as blood sampling, ultrasonography was performed employing a two dimensional transvaginal 6.5Hz probe with pulsed Doppler and color Doppler facilities using Siemens-ACUSON Antares System (Siemens Healthcare Diagnosis Inc. USA), to estimate ovarian volume, antral follicle counts.

Data are presented as mean and median. Correlations were established by means of the Pearson or the Spearman rank correlation procedure. Analysis was done using SPSS version 12.0 (SPSS, Chicago, Illinois, USA). $P<0.05$ was considered to be statistically significant.

Results

In our study, we have taken patients and controls between ages 20 -39 yrs. Majority of patient (69.3%) were in age group of 25-34 years. (Table 1)

Table 1: Age Distribution

Age group	Genital TB	
	No. of cases	% of cases
20-24	9	18
25-29	18	36
30-34	13	26
35-39	10	20
Total	50	100

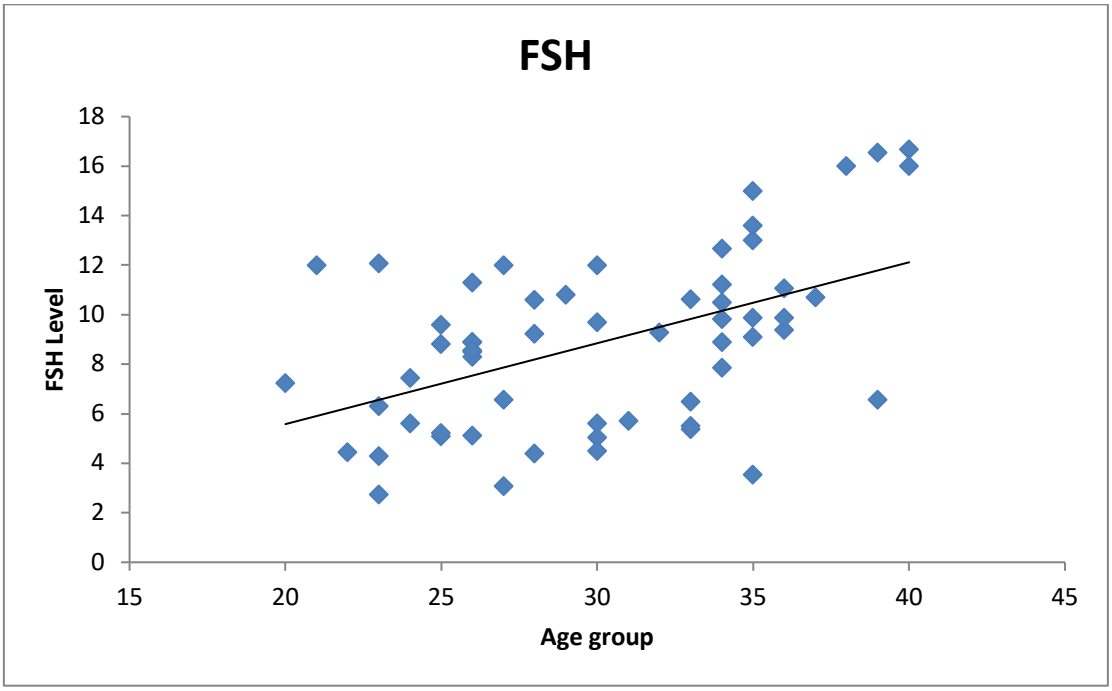

Figure 1: FSH level in various age groups

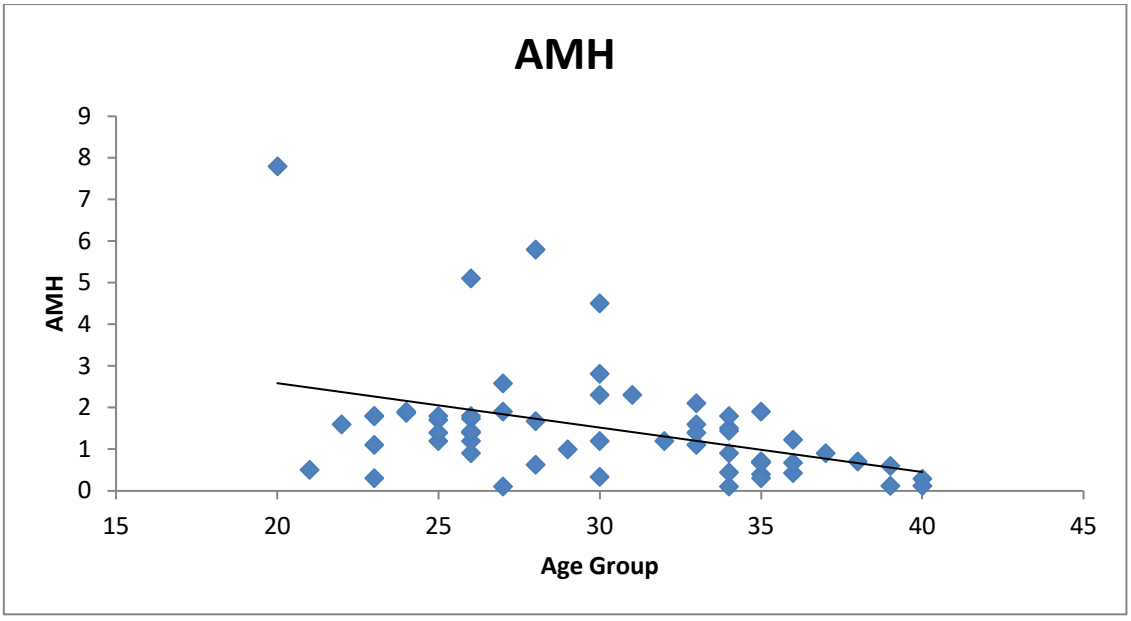

Figure 2: AMH level in various age groups

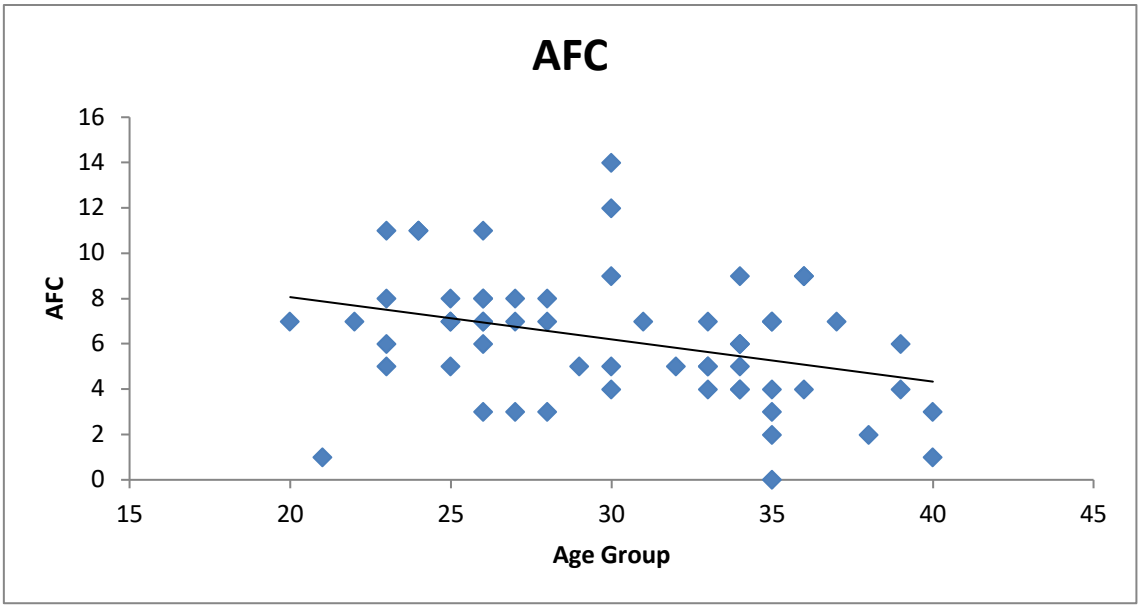

Figure 3: Antral Follicle count in various age groups

Ovarian reserve was assessed by means of hormonal assays and ultrasound markers. Median value of day 2-3 Serum FSH was 8.90mIU/ml is significantly higher in GTB ($p<0.001$) than median value of day 2-3 serum FSH in control group (5.50mIU/ml). The median value of LH was 6.0 IU/L was significantly higher in GTB ($p<0.001$) than control group (3.80IU/L). The Mean estradiol was 61.30pg/ml was significantly higher ($p<0.001$) than controls (41.53pg/ml).The Median was 1.23ng/ml was significantly lower ($p<0.001$) than controls (2.50ng/ml).The Median AFC was 6.00 in GTB and 11.0 in controls which was clearly demonstrated that AFC is significantly($p<0.001$) low in case as compared to that in controls. So AMH and AFC are more sensitive markers of DOR (deficient ovarian reserve).

FSH was found high in cases and controls and FSH value increasing in different age group of 20-24, 25-29, 30-34 and 35-39, and it was found significant in all age group. LH was slightly higher in age group30-39 as compared to controls and also in young age group and found significant.

Estradiol level was showing higher levels in cases as compared to controls and found significant. AMH and AFC were found to be low in cases as compared to controls and their levels decreases with increasing age and found significant in all age group as compared to cases. (Table 2)

Table 2: Comparison of various parameters between gtb patients and controls

	TB	Control	p-value
FSH (mIU/ml)#	8.90 (5.60-11.07)	5.50 (4.80-6.92)	<0.001
LH(IU/L)#	6.0 (4.65-8.55)	3.80 (2.97-4.42)	<0.001
Estradiol(pg/ml)*	61.30□15.23	41.53□17.57	<0.001
AMH(ng/ml)#	1.23 (0.67-1.80)	2.50 (1.60-2.97)	<0.001
AFC #	6.0 (4.0-8.0)	11.0 (8.25-12.0)	<0.001

*Mean□SD, #Median (Inter quartile range – IQR).

In this study, we found a positive correlation between age and FSH(r-0.47, p<0.001) and negative correlation between age and AMH(r-0.43, p<0.001) and AFC(r-0.347.p0.007) in genital tuberculosis. We found correlation between age and LH, estradiol but that was not significant. (Table 3 and 4).We found a positive correlation between age and FSH(r-0.47, p<0.001) and negative correlation between age and AMH(r-0.43, p<0.001) and AFC(r-0.347.p0.007) in genital tuberculosis.

We found correlation between age and LH, estradiol but that was not significant.

Table 3: Mean values of various parameters in different age groups in TB patients

	Age group	Case	Control	p-value
FSH(mIU/ml)#	20-24	6.32 (4.38-9.72)	4.20 (4.05-5.70)	0.025
	25-29	8.69 (5.20-9.85)	4.85 (4.80-6.70)	<0.001
	30-35	9.29(5.60-11.22)	5.50 (4.90-6.70)	<0.001
	36-40	11.07 (9.63-16.28)	7.0 (6.20-7.30)	<0.001
LH(IU/L)#	20-24	6.31 (5.02-7.70)	3.90 (3.46-4.60)	<0.001
	25-29	6.13 (4.68-7.36)	3.60 (3.20-3.80)	<0.001
	30-35	5.74 (4.40-8.0)	3.35 (2.80-4.20)	<0.001
	36-40	8.60 (5.36-9.79)	4.20 (3.70-5.40)	0.005
Estradiol* (pg/ml)	20-24	59.66□14.60	32.85□16.44	0.001
	25-29	60.46□18.33	43.85□14.17	0.001
	30-35	61.72□12.88	45.02□16.46	<0.001
	36-40	63.55□16.94	39.75□21.75	0.006
AMH(ng/ml)#	20-24	1.80 (0.80-1.88)	2.70 (1.90-3.30)	0.005
	25-29	1.75 (1.50-1.90)	2.30 (1.70-2.90)	0.007
	30-35	1.55 (1.15-1.82)	2.0 (1.60-2.10)	0.007
	36-40	0.60 (0.20-0.80)	1.60 (1.50-1.80)	<0.001
AFC#	20-24	8.0 (5.50-11.0)	11.0 (9.0-12.0)	0.005
	25-29	7.0 (5.0-8.0)	10.50 (8.0-11.00)	<0.001
	30-35	5.0 (4.0-7.0)	9.50 (9.0-10.50)	<0.001
	36-40	4.0 (2.50-8.0)	8.0 (8.0-9.0)	0.005

*Mean□SD, #Median (Inter quartile range – IQR)

Table 4: Correlation between various parameters with age in TB patients

	AGE	LH	FSH	ESTRADIOL	AMH	AFC
Correlation Coefficient (R)	1.000	.078	.470**	.129	-.431**	-0.347
p-value	.	.557	<0.001	.331	0.001	0.007
N	59	59	59	59	59	59

**.Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

Discussion

There are several ways to estimate the ovarian reserve in individual women. There are several predictors of ovarian reserve. Numerous tests have been used to predict ovarian reserve. These are broadly grouped into: a. Clinical details (age, previous history), b. Passive tests (hormonal assays, ultrasound), c. Dynamic test (clomiphene citrate challenge test, gonadotropin analogue stimulation test, exogenous FSH ovarian reserve test) and histology (ovarian biopsy). One can estimate markers for ovarian reserve. (Table 5)

Table 5: Spectrums of prognostic markers of ovarian reserve are validated to varying degrees:

Static tests	Dynamic tests
Baseline hormone FSH FSH:LH ratio Estradiol Inhibin B Anti-mullerian Hormone Ultrasound parameters Antral follicle count	Challenge tests Clomiphene citrate challenge test(CCCT) Exogenous FSH ovarian response test(EFORT) GnRH Analogue Stimulation test(GAST)

Genital tuberculosis is one of the common cause of female infertility. Incidence of genital tuberculosis in infertility clinics worldwide is 5-10% and varies from 0.69% in Australia to 17.4% in India [5].Tuberculosis is chronic bacterial infection affecting almost any organ of body(most frequently lung) with few exception like thyroid , skeletal muscle. Nearly 2 billion people all over the world are infected with tuberculosis, genital tuberculosis having a global prevalence of 8-10 million. In India subcontinent, 40% of population is exposed to tuberculosis. India is an endemic country for tuberculosis (TB) with prevalence rates of genital tuberculosis in tubal factor infertility being reported to be as high as 41 % [6]. Genital TB occurs mostly secondary to pulmonary TB, commonly by haematogenous route in a manner similar to spread to other extra-pulmonary site like genital organ' urinary tract, bones, and joints etc. The fallopian tube are affected in almost 100% of the cases followed by endometrium in 50%,ovaries in 20%, cervix in 5% and vagina and vulva in <1%.Among various cause of infertility tubal factors are responsible in about 20 -25% cases of infertility.

Ovarian reserve declines with age and is therefore an important determinant of the success of any fertility treatment. OR testing not only predicts fertility but also helps clinicians determine the best doses or protocols to help their patients achieve pregnancy. The present results were similar to those published in a study by Malhotra et al (2012) [7], Anupama Bahadur et al (2013) [8]. The mean value of FSH was 6.7±1.7 in Malhotra et al. 2012 et al series and 6.3±1.9 in Anupama Bahadur et al. 2013 series and in our study we found slightly higher median FSH (8.90) which is age depended. Mean valve of LH was found higher in Malhotra et al. 2012 (4.0), Anupama Bahadur et al 2013(4.9) and our study (6.0) but it was significant in our study and Malhotra et al 2012 and not significant in Anupama Bahadur et al.2013. Estradiol was slightly high in our study, it may be due slightly higher level of FSH and found significant. Malhotra et al 2012, had higher estradiol than control but not significant. The mean value of AFC was 10.27±2.5 in Malhotra et al.2012, and 6.5(3-24) p-0.85(Anupama Bahadur et. al.2013) and in our study 6.0 (4.0-8.0), but non-significant only in Anupama Bahadur otherwise it found significant in Malhotra et. al 2012 and our study.

We have done AMH which was found significantly lower in our study as compared to Anupama Bahadur et.al.2013. [8] AMH and AFC was found most sensitive marker than other marker as they have definite co-relation with age and inversely proportional with age. (Table 7)

Table 6: Comparison of various factors in different series

	Malhotra et al (2012) [7]	**Anupama Bahadur et al(2013) [8]**	**Our study(2014)**
FSH(mIU/ml)	6.7±1.7(p-0.000)	6.3±1.9(p-0.62)	8.90(5.60-11.07) p-0.001
LH(IU/L)	4.0(p-0.01)	4.9(1.6-19.5)p-0.31	6.0(4.65-8.55)p-0.001
Estradiol(pg/ml)	55.3±13.2(p-0.22)	Not done	61.30±15.23p-0.001
AFC	10.27±2.5(p-0.000)	6.5(3-24)p-0.85	6.0(4.0-8.0)p-0.001
AMH(ng/ml)	Not done	4.8(2.6-7.7)p-0.21	1.23(0.67-1.80)p-0.001
Inhibin(pg/ml)	54.9±21.1(p-0.001)	36.2(5.2-103.8)p-0.04	Not done

Gnoth et.al [9]. Determined an AMH of less than 1.26 ng/ml denotes a diminished ovarian reserve regardless of age. Ebner et al. [10] Determined that an AMH between 1.7 and 4.5 ng/ml results in maximal egg quality. Tremellen et al. [11] Defined diminished ovarian reserve as an AMH less than 0.8 ng/ml, which they specify is comparable to an FSH of 11 mIU/ml.

Conclusion

Estimation of FSH, LH and E2 on Day2/3 of cycle and AMH any day of cycle along with AFC are good predictors of Ovarian reserve are found to be low in GTB. Early diagnosis of GTB and its treatment and if no conception then timely intervention by ART may be required to have a successful pregnancy.

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