Original Article

Oocyte quality and ICSI outcome in patients with tuberculosis

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Abstract

Objective: To evaluate the effects of tuberculosis on oocyte characteristics and ICSI outcome. **Study design:** Prospective comparative observational study. **Setting:** Tertiary level infertility care centre. **Materials and methods:** Study group: Women undergoing ICSI with h/o tuberculosis (1 clinical + I laboratory criteria). **Control group:** Women undergoing ICSI without h/o tuberculosis or tubal factor infertility. **Sample size:** 28 patients in study and 30 patients in control group. **Exclusion criteria:** Age >35 yrs. **Intervention:** ICSI(intracytoplasmic sperm insemination). **Statistical analysis method:** Statistical analysis was performed by the SPSS program for Windows, version 17.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analysed using either the chi square test or Fisher's exact test. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference. **Primary outcome measures:** no. of mature oocytes (oocyte retrieval rate); no. of other variants of oocytes (M1, dysmorphic, GV, small, large, or polar body). Secondary outcome measures: FSH, LH, AMH, and AFC values; no. of days of stimulation; fertilization rates; embryo morphology; implantation rates; ongoing pregnancy rates. **Results:** There was no statistically significant difference with regards to age, FSH and LH levels, AFC between the two groups. The mean AMH values in cases and controls were 1.51 ± 0.96and 2.6 ± 1.46 respectively ,the difference being statistically significant. (p value -0.021) mean days of stimulation in cases were 10 while in controls were 10.4, the difference being statisticallt insignificant. Retrieval rates of M2 oocytes in cases and controls were 33.3% and 93.3% respectively , the difference being statistically significant(p value- <0.001) Comparison of other variants of oocytes and the fertilization rates (cases-72.0 ± 29.0,controls-83.7 ± 17.0) didn't reveal any statistically significant difference between the two groups. There was statistically significant difference (p value -0.0001) between the cases and controls when compared for number of grade A embryos (cases:85.7%, controls: 93.1%). The clinical pregnancy rates in the cases and controls were 14.3 % and 36.7% respectively, the difference being statistically insignificant. However when cases and controls were compared for ongoing pregnancy rates (cases: 3.6% ,controls : 30.0%) the difference was statistically significant (p value-0.013). There was only 1 case of ectopic gestation which was in controls and incidence was statistically insignificant. **Conclusion:** ICSI cycles in patient with positive history of genital tuberculosis were associated with low AMH values, lesser M2 retrieval rates, lesser grade A embryo formation rates and lesser ongoing pregnancy rates. However the study results are limited because of the small sample size. More studies with greater sample size are needed to evaluate the oocyte quality in these patients undergoing ICSI cycles.

Keywords: ICSI, M2 oocytes, tuberculosis

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INTRODUCTION

Infertility has turned from mere disease to an epidemic in the modern era. Whereas in the developed nations major causative factors are attributed to changes in the lifestyle, social factors, the causes in developing nations are contributed to a large extent by infections in addition to other causes. Genital tuberculosis is one such factor which causes irrepairable damage to the reproductive organs, resulting in infertility which poses a great challenge to manage. Although the exact incidence of genital tuberculosis is not known owing to its subtle manifestations and diagnostic modalities having low sensitivity, the reported worldwide incidence of genital tuberculosis has been calculated to be is approximately 5% to 10% in women with infertility. It varies from as low as 0.69% in some developed countries to as high as 19% in India (3.5%).[1] It has been estimated that about 30% of world population (more than 2 billion people) are infected with *Mycobacterium tuberculosis*.[2,3]

Genitourinary tuberculosis, responsible for 30% to 40% of all extrapulmonary cases, is second only to lymphonodal involvement, thereby accounting for the third most common form of extrapulmonary tuberculosis.[4]

In infertility patients, incidence of female genital tuberculosis (FGTB) varies from 3% to 16% in India.[5]

The affection of genital organs by the tubercular bacilli is through haematogenous route (with lungs as the common primary focus), lymphatic spread, through direct contiguity with an intra-abdominal or peritoneal surface and rarely as primary infection of the genitalia through sexual transmission.[5] The genital organs affected by *M. tuberculosis* (in descending order of frequency) are as follows: fallopian tubes (95%–100%), uterine endometrium (50%–60%), ovaries (20%–30%), cervix (5%–15%), uterine myometrium (2.5%) and vagina/vulva (1%).[6]

Although genital tuberculosis can happen in any age, reproductive age group females are most commonly affected[7] with infertility being the most common manifestation. Other manifestations include from being totally asymptomatic to wide range of menstrual disturbances, persistent vaginal discharge, pelvic pain and so on.

Blocked fallopian tube is the most common cause of inability to conceive in such women; however, even those whose fallopian tube or endometrium are not affected have infertility. This observation emphasize the importance of studying the effects of tuberculosis on ovarian function. The present study was conducted to evaluate the effects of tuberculosis on oocyte quality and subsequent Intracytoplasmic sperm insemination (ICSI) outcome in such patients.

MATERIALS AND METHODS

The cases for the study were recruited from the Kuldeep Jain IVF and Laparoscopy Center, Gagan Vihar, Delhi. The infertile couples were worked up according to the World Health Organization protocol[8] and were thoroughly investigated for the aetiological factor for infertility that included semen analysis, hormonal evaluation [serum FSH (follicle stimulating hormone), LH (luteinizing hormone)], baseline ultrasound of the pelvis and tests for ovarian reserve and laparoscopy. A total of 58 women in the age group 21 to 40 years needing art (ICSI) were recruited in the study. These 28 women comprised the study group and fulfilled the desired criteria of having one clinical and one laboratory evidence of genital tuberculosis, whereas 30 women in the control group had no h/o tuberculosis or tubal infertility, thus ruling out the possibility of having genital tuberculosis.

Method

These women then underwent ovarian stimulation with gonadotropins, and when the leading oocyte was ≥18 mm, trigger for ovulation was given with either inj human chorionic gonadotrophin (HCG) 10,000 IU or inj triptorelin depending on the protocol used. OPU (oocyte pickup) was performed 34 h later. The oocytes were then graded post denudation according to the criteria given by Xia.[9]

- Grade 1: fragmented first polar body and large perivitelline space
- Grade 2: intact first polar body and large perivitelline space
- Grade 3: fragmented first polar body and normal perivitelline space
- Grade 4: intact first polar body and normal perivitelline space

ICSI was thereafter performed and fertilization was checked 24h later, and embryos were graded on the day of transfer: day 3 as follows:

SART grading: based on assessment of certain characteristics of the embryo, such as fragmentation,

symmetry, inner cell mass quality or trophectoderm quality. Stage-dependent grading involves determining the developmental stage of the embryo.[10]

Embryos are to be graded into one of three classes:

Sart grading system

Growth phase	Overall grade	Stage
Cleavage	Good, Fair, Poor	Cell #: 1 through >8; Fragmentation: 0%, <10%, 11–25%, >25%; Symmetry: Perfect, Moderately Asymmetric, Severely Asymmetric
Morula	Good, Fair, Poor	Compaction: Complete, Incomplete; Fragmentation: 0%, <10%, 11–25%, >25%
Blastocyst	Good, Fair, Poor	Expansion: Early, Expanding, Expanded, Hatched; Inner Cell Mass: Good, Fair, Poor; Trophectoderm: Good, Fair, Poor

The primary outcome was assessed in terms of number of mature oocytes (oocyte retrieval rate) and the number of other variants of oocytes [M1, dysmorphic, germinal vesicle (GV), small or large polar body], whereas the secondary outcome was calculated with regards to the FSH, LH, anti-Müllerian hormone (AMH) and Antral follicle count (AFC) values, number of days of stimulation, fertilization rates, embryo morphology, implantation rates and the ongoing pregnancy rate.

Statistical analysis

Sample size was calculated before the start of the study. The data were analysed using the statistical package SPSS for Windows 16.0 (SPSS, Chicago, Illinois, USA). Means, standard deviations, medians and ranges were calculated for descriptive purposes. Comparison of patient characteristics and response to stimulation regime in terms of oocytes retrieved were performed using Chi-square test and Student's *t* test, as the appropriate tests *P* values less than 0.05 were considered statistically significant [Tables 1 and 2]. The primary objective, that is number of mature oocytes and number of other variants in either group, was compared using Chi-square test, whereas the secondary objective that included all the continuous variables were compared using Student's *t* test and Wilcoxon rank-sum test.

RESULTS

The study was undertaken in 58 women with infertility who underwent ovarian stimulation followed by OPU – ICSI and ET (embryo transfer)/frozen ET.

Table 1: Comparison of patient characteristics

Age Groups	Cases		Controls		*P* value
	Frequency	%	Frequency	%	
21–30 yrs	16	57.1	16	53.3	
31–40 yrs	12	42.9	14	46.7	0.771
Total	28	100	30	100	
Mean±SD	30.3±4.1		31.13±3.8		0.439

Table 2: Oocytes retrieved

	Cases	Controls	*P* value
	Mean ± SD	Mean ± SD	
Oocytes retrieved	9.79± 4.68	1010± 4.21	0.716

The study group comprised patients with h/o of genital tuberculosis as satisfied by presence of one laboratory and one clinical criteria being met and consisted of 28 women, whereas the control group which comprised 30 patients didn't have any h/o genital tuberculosis.

There was no statistically significant difference between the basic hormonal profile of patients in either group with FSH value of 6.89 ± 1.9 in study group and 5.9 ± 1.7 in control group (*P* value: 0.354), LH value of 4.4 ± 2.5 in study group and 3.7 ± 1.5 in the control group (*P* value: 0.076). The AMH value of the two groups however showed statistically significant difference (*P* value: 0.021) with AMH being 1.5 ± 0.9 in the study group and 2.6 ± 1.46 in the control group. This difference in the ovarian reserve was however not reflected in the antral follicle count observed on baseline scan in either group with AFC value 11.2 ± 4.2 in the study group and 12.6 ± 3.6 in the control group (*P* value: 0.296).

The stimulation was needed for 10.44 ± 2.22 days in the study group, whereas in control group, patients were stimulated for 10.47 ± 1.01 days (*P* value: 0.956). The total number of oocytes retrieved in the study group was 9.79 ± 4.68, whereas in the control group, 10.10 ± 4.21 oocytes were retrieved (*P* value: 0.716).

The M2 oocytes retrieved in study group were 11 (39.3%), whereas in control group, this value was 28 (93.3%). Although all the M2 oocytes were grade 4 in either group, the difference in number of oocytes retrieved was highly statistically significant with *P* value of 0.001.

Other variants of oocytes seen post denudation consisted of only two abnormal oocytes in the study group (0.229), whereas the control group had all variants with one M1 (*P* value: 1.00), three GV (*P* value: 0.238), three with zero polar body (*P* value: 0.238), one with large polar body (*P*

value: 1.00), one with small polar body (*P* value: 1.00) and one dysmorphic (*P* value: 1.00).

The fertilization rate in study group was 72.07 ± 29.08 compared to 83.79 ± 17.02 in the control group (*P* value: 0.249). Embryo morphology in study group was good in 74.4% of the embryos, fair in 25.5% and poor in 0.01% embryos, whereas in the control group, 75.3% of embryos were good morphology, 24.7% were fair morphology and none of the embryo was graded poor in morphology.

The embryos were graded on the day of ET, and it was found that 85.7% of embryos were grade A in the study group, whereas in the control group, this value was 93.1%, the difference being highly statistically significant (*P* value: 0.0001). Grade B embryos were 14.3% in the study group, whereas in the control group, they were 3.4%; the difference was statistically not significant (*P* value: 0.605). None of the embryos in study group was grade C compared to 3.4% in the control group (*P* value: 1.000).

Four patients (14.3%) conceived in the study group, whereas this number was 11 (36.7%) in the control group (*P* value: 0.073); those who did not conceive amounted to 82.1% in the study group and 60% in the control group (*P* value: 0.064). ET got cancelled in one patient in each group (*P* value: 1.000).

Only one patient was fortunate enough to have an ongoing pregnancy in the study group as compared to nine patients in the study group, the difference being of high statistical significance (*P* value: 0.013). A total of 24 (85.7%) patients in the study group had negative result (biochemical pregnancy), as compared to 19 (63.3%) in the control group (*P* value: 0.073%).

Three (10.7%) patients in study group had abortion as compared to one (3.3%) in control group (*P* value: 0.345). No patient in the study group had an ectopic pregnancy, whereas three (3.3%) in the control group had an ectopic (*P* value: 1.000).

Implantation rates (% of the ET red) were 16.6 in the study group, whereas in the control group, they were 20.3.

DISCUSSION

Genital tuberculosis unarguably hampers a woman's fertility potential to a larger than obvious magnitude. The results of ART (assisted reproductive technologies) are further compromised if the organs affected are the ovaries. Although there is no particular test to label a woman with genital tuberculosis to have ovarian involvement when there is no alteration in morphology, the compromised ovarian function is exhibited by markers of ovarian reserve. In our study, the AMH levels were significantly lower in study group as compared to that in the control group (1.5 ± 0.9 vs. 2.6 ± 1.46; $P = 0.021$). Similar results have also been seen in the study conducted by Jirge *et al.*[11] where they concluded that the women with latent tuberculosis had low AMH [median Interquartile range (IQR): 2 (0.9, 4.1) vs. 2.8 (1.3, 5) ng/ml; $P = 0.01$] and low AFC values [median (IQR): 7 (5, 11) vs. 8 (5, 14); $P < 0.001$]. AFC values in our study however were not significantly different in the two groups (11.2 ± 4.2 vs. 12.6 ± 3.6) (*P* value: 0.296). This finding was also in contradiction to another study conducted by Malhotra *et al.*[12] where AFC count in the participants were lower in the women with genital tuberculosis. In addition, in their study, the mean FSH and LH value were significantly higher in the study group, whereas in our study, these values were comparable with no statistically significant difference between the two groups.If we compare the number of oocytes retrieved, there was no statistically significant difference between the two groups (9.79 ± 4.68 vs. 10.10 ± 4.21; *P* value: 0.716), but significantly higher number of M2 oocytes were retrieved in control group as compared to study group [11 (39.3%) vs. 28 (93.35%); *P* value: 0.001] indicating possibly the effect of tuberculosis on quality of oocytes. This was in contrast to the study by Jirge *et al.*[11] where women with latent tuberculosis yielded fewer oocytes (9.3 ± 7.6 vs. 10.9 ± 8.1; $P = 0.01$).

Jirge *et al.*[11] also found better embryo grades (1.1 ± 0.5 vs. 0.89 ± 1.0; $P = 0.001$) and better implantation rates (26.8% vs. 17.5%; $P = 0.004$) in the study group which was also reflected in the improved pregnancy rates (51.6% vs. 40.5%; $P = 0.001$). Our study on the contrary found significantly better embryo grades and implantation rates in the control group, which seems better justified as better oocytes were retrieved in the control group.

Lower ongoing pregnancy rates were observed in the study group in our study.

In our study, all the compromised parameters were observed in the study group which shows how strongly tuberculosis damages the reproductive potential of women even when grossly there is no evident abnormality in the morphology of tubes and endometrium. This also emphasize the need for further research and improvement in the diagnosis of genital tuberculosis particularly and ART technologies, so as to further improve the detection rate and treatment outcomes in patients with genital tuberculosis.

Conflicts of interest

There are no conflicts of interest.

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