

Research Article

Latent Genital Tuberculosis – A Possible Explanation for Unexplained Infertility

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Abstract

Latent Genital Tuberculosis (LGTB) is commonly asymptomatic, and it is usually diagnosed during infertility investigations. The main objective of the present study was to establish the role of LGTB in causing unexplained infertility.

Material and method: 517 women, from January 2016- December 2018, at Calcutta Fertility Mission, had undergone DNA-PCR test (polymerase chain reaction) for screening of LGTB, then had had subsequent treatment with Anti-Tubercular Drugs (ATD) with or without laparoscopy. These patients were further classified as Group A and Group B based on their findings on laparoscopy to have early endometriosis or minor tubal defects or both. The Clinical pregnancy rate was calculated and analyzed among groups of women who were treated with ATD; treated with ATD and laparoscopy and those who were treated with estrogen-progestins for endometriosis.

Result: 28.6% of patients with apparently unexplained infertility were found to have LGTB and 31.76% of them had conceived following treatment with ATD. 71.4% of the patients who did not have LGTB had to be re-evaluated by laparoscopy. 35.64% patients in Group A and 34.15% patients in Group B, were diagnosed to have early endometriosis. Minor tubal defects on laparoscopy were found in as high as 43.56% of Group A patients and 29% in Group B. Hence the patients in Group A who had LGTB and had to be treated with ATD were seen to have quite higher prevalence of tubal defects compared to Group B and it has been seen to be statistically significant also (p value=0.003). 36.36% of Group A patients had conceived within 6 months of laparoscopy and 23.36% of women in Group B had achieved pregnancy.

Conclusion: LGTB is one of the major causes of apparently unexplained infertility and even the factors like early endometriosis or minor tubal defects are often associated with this condition and enhances the ill-effect causing infertility.

Keywords: Latent genital tuberculosis, Unexplained infertility, Laparoscopy, Pregnancy, Endometriosis, Tubal defect

Introduction

Unexplained infertility which amounts to about 30% of the infertile couple, can be defined as the lack of an obvious cause for a couple's infertility and the inability to conceive after at least 12 cycles of unprotected intercourse for whom all the standard evaluations are normal. The veracity of 'unexplained infertility' term has been challenged by many clinicians and researchers and it has been emphasized that the assignment of the title to an infertile couple is much dependent on the quality and nature of the diagnostic tests performed [1,2]. According to the NICE guidelines, necessary tests for unexplained infertility are semen analysis, assessment of ovulation and the luteal phase, and assessment of tubal patency by hysterosalpingogram or laparoscopy. However, there is controversy about the value of endometrial biopsy, ovarian reserve (Serum anti-mullerian hormone, antral follicle count), post-coital test and serum prolactin levels. The inability to find the specific cause of couples' infertility does not mean that there is absolutely no cause for the

disorder. Factors including lack of strong evidence, couples' impatience for completion of standard protocols and dominance of Artificial Reproductive Technique (ART) treatment compared to other options in infertility clinics lead to diversity of clinical practice regarding unexplained infertility. Extensive research should be conducted on other possible causes of failed conception such as ovarian and testicular dysfunctions, sperm and oocyte quality, minor fallopian tube defects, endometrial receptivity, implantation failure and endometriosis [3,4]. Latent Genital Tuberculosis (LGTB) is a major health problem in many developing countries in Asia and Africa and has been proved to be responsible for a significant proportion of female infertility. It is asymptomatic in majority of the affected women and is diagnosed only during infertility work-up [5]. The most involved genital organs (whether solely or with other organs) have been seen to be fallopian tubes (63.84%), ovaries (46.15%), endometrium (38.46%) and the cervix (23.07%) in female genital tuberculosis but the involvement has not been documented in LGTB [6]. However, a few authors have reported the endometrium to be involved the most with as high as

60% in cases of infertility [7]. The present study was conducted to determine the role of latent genital tuberculosis in couples diagnosed with apparently unexplained infertility.

Material and Methods

This retrospective study was conducted at Calcutta Fertility Mission in Kolkata, India, from January 2016 to December 2018. The data were collected from a total of 517 patients as cases between 25-35 years of age, who had primary infertility which was apparently unexplained. These patients had normal ovulatory function and normal ovarian reserve, fallopian tubes appeared normal on hysterosalpingogram, their partners had normal semen parameters. They had undergone routine tests along with the DNA-PCR test with an endometrial aspirate on day 21 to day 24 of respective menstrual cycles (Table 1).

517 patients were grouped initially as those who had LGTB (PCR positive) and who did not have LGTB (PCR negative). 148 (28.6%) patients were found to have LGTB and 369 (71.4%) of them were not affected (Table 2). These 148 patients were treated with Anti-tubercular drugs (ATD) for 6 months and subsequently 47 (31.76%) of them had conceived following the treatment.

Hence in the said cohort there were 101 patients who could not conceive after being treated with ATD and 369 patients were PCR negative and had to be further re-evaluated for infertility. These women

were grouped as Group A (101) (PCR negative after treatment with ATD) and Group B (369) (PCR negative). These patients were counselled for laparoscopy and based on the laparoscopy findings they were diagnosed to have either Stage 1 or Stage 2 endometriosis, or minor tubal defects and some had both early endometriosis and minor tubal defect.

On laparoscopy these patients with early endometriosis had one or two of the following features:

1. Endometriotic spots on pelvic organs and in POD
2. Flimsy adhesions in POD.
3. Pseudocavitations.
4. Peritoneal deficiency.

These patients were treated with estrogen and progesterone combination or with dienogest for 3-6 months for endometriosis and patients with minor tubal defects were corrected by laparoscopy. The post-treatment Clinical Pregnancy Rates (CPR) were calculated and analysed in all these groups (Table 3).

Statistical Analysis

Categorical variables will be expressed as Number of patients and percentage of patients and compared across the 2 groups Pearson's Chi Square test for Independence of Attributes. The statistical software

Table 1: Age of patients in groups.

		Age		Total	p Value	Significance
		25-30	31-35			
PCR	POSITIVE	58 (29.74)	90 (27.95)	148 (28.63)	0.662	Not Significant
	NEGATIVE	137 (70.26)	232 (72.05)	369 (71.37)		
Total		195 (100)	322 (100)	517 (100)		
Group A and B	Mild/Moderate Endometriosis	59 (33.52)	103 (35.03)	162 (34.47)	0.426	Not Significant
	Tubal Defects	52 (29.55)	99 (33.67)	151 (32.13)		
	Both	65 (36.93)	92 (31.29)	157 (33.4)		
Total		176 (100)	294 (100)	470 (100)		

Pearson's Chi Square test for Independence of Attributes.

Table 2: Patients of unexplained infertility with LGTB.

PCR	Frequency	Percent
Positive	148	28.6
Negative	369	71.4
Total	517	100.0

Table 3: Clinical Pregnancy in patients in Group A and B.

Clinical pregnancy			Group			Total	p Value	Significance
			Mild/Moderate Endometriosis	Tubal Defects	Both			
Group A	Pregnancy	No	26 (72.22)	28 (63.64)	16 (76.19)	70 (69.31)	0.528	Not Significant
		Yes	10 (27.78)	16 (36.36)	5 (23.81)	31 (30.69)		
	Total		36 (100)	44 (100)	21 (100)	101 (100)		
Group B	Pregnancy	No	94 (74.6)	82 (76.64)	108 (79.41)	284 (76.96)	0.650	Not Significant
		Yes	32 (25.4)	25 (23.36)	28 (20.59)	85 (23.04)		
	Total		126 (100)	107 (100)	136 (100)	369 (100)		

Pearson's Chi Square test for Independence of Attributes.

SPSS version 20 will be used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it will be considered as significant.

Ethical Consideration

The Ethical Committee of Calcutta Fertility Mission has given clearance for the retrospective study of a prospective database on 21/10/2019 (CFM/2019/029). Written informed consent has been obtained from all women who participated in the study.

Discussion

Management of infertile couples should always be individualized. The key variables like age, treatment history, costs and risks should be considered in selecting treatment plan of every couple. Over recent decades, the use of medically assisted reproduction (MAR) has increased enormously [8]. It is important to select couples who would actually benefit from MAR [9,10]. In couples with unexplained infertility the chance of a natural conception within 1 year is 30% or higher. MAR is no better than tailored expectant management (TEM) of 6–12months, except in those who have gradually diminishing ovarian reserve [11,12]. Most often TEM is underutilised either due to failure in identifying couples who are eligible for TEM, or couples do not undergo expectant management for lack of advice by medical professional or impatience of the couple concerned.

Latent genital tuberculosis is rare in developed countries but is an important cause of subclinical chronic pelvic inflammatory disease and infertility in underdeveloped and developing countries. Previous literature show genital tuberculosis as a cause of infertility in 3-16% of women, varying to about 20% in India [13,14]. In the present study 28.6% of patients with apparently unexplained infertility were found to have LGTB and 31.76% of them had conceived following treatment with ATD. 71.4% of the patients who did not have LGTB had to be re-evaluated by laparoscopy along with those who could not achieve pregnancy even after treatment with ATD.

The relationship between endometriosis and infertility has been debated since years. Women with endometriosis tend to have a 2-10% lower monthly fecundity [15,16]. 25-50% infertile women are likely to have endometriosis which results in about 6-8% of the total population [17]. Several mechanisms have been proposed to explain the association between endometriosis and infertility which include distorted pelvic anatomy, endocrine and ovulatory abnormalities and altered humoral and cell-mediated functions in the endometrium. Major pelvic adhesions or peritubal adhesions that alter the tubo-ovarian relation, impair oocyte release from the ovary, inhibit ovum pickup, or impede ovum transport [18]. In our study 35.64% patients with unexplained

infertility in Group A and 34.15% patients in Group B, were diagnosed to have early endometriosis. (Stage I and II). The overall prevalence of endometriosis in population-based studies varies from 0.8% to 6%; however, in case of associated infertility, the prevalence seems to be considerably higher, ranging from 20% to 50%, but with significant variation over time periods and the age of patients [19-22].

In our previous study it has been stated that 846 out of 1726 (49%) women with unexplained infertility, were diagnosed to have minor tubal defects and were treated for the same by laparoscopy. The clinical pregnancy rate was about 27% following the treatment [23].

Similarly in the present study, we had detected minor tubal defects on laparoscopy in as high as 43.56% of Group A patients and 29% in Group B. Hence the patients in Group A who had LGTB and had to be treated with ATD were seen to have quite higher prevalence of tubal defects compared to Group B and it has been seen to be statistically significant also (p value=0.003). 36.36% of Group A patients had conceived within 6 months of laparoscopy and 23.36% of women in Group B had achieved pregnancy.

In the present study we had also found 20.79% women in Group A and 36.86% in Group B had both minor tubal defects and early endometriosis. Early endometriosis, minor tubal defects or even both of these conditions have been seen to be associated with a substantial number of patients with apparently “unexplained” infertility. A strong association of LGTB has been noticed with these factors also. All these etiological factors have been found to be statistically significant in Group A and Group B (p value=0.003) (Table 4).

Our patients with early endometriosis were treated with estrogen-progestins or with dienogest for 6 months primarily and none of them required surgical intervention. 27.78% women in Group A and 25.4% in Group B had conceived after the treatment and ovulation induction.

Estrogen-progestins with the lowest possible estrogen dose should be chosen to combine optimal lesion suppression and thrombotic risk limitation. Progestins should be suggested in women who do not respond or manifest intolerance to estrogen-progestins [24]. According to Kitirat Techatraisak et al. dienogest has been seen to substantially improve endometriosis-associated symptoms such as debilitating chronic pelvic pain, and consequently, health-related quality of life [25]. Jacobson et al. in their study had shown laparoscopic resection or ablation of minimal and mild endometriosis enhances fecundity in infertile women [26].

After treatment of LGTB, early endometriosis and correction of minor tubal defects, 23.81% patients had spontaneous conception in Group A and 20.59% of women in Group B had conceived after treatment of endometriosis and laparoscopy.

Table 4: Other etiology of infertility in Group A and B.

		Group A	Group B	Total	p Value	Significance
Etiology	Mild/Moderate Endometriosis	36 (35.64)	126 (34.15)	162 (34.47)	0.003	Significant
	Tubal Defects	44 (43.56)	107 (29)	151 (32.13)		
	Both	21 (20.79)	136 (36.86)	157 (33.4)		
Total		101 (100)	369 (100)	470 (100)		

Pearson's Chi Square test for Independence of Attributes.

Conclusion

From the present study we can say that LGTB has a very important role in unexplained infertility and once detected and treated it can even yield spontaneous pregnancy. Persistence of infertility even after the treatment of LGTB, may be due to other associated problems like early endometriosis, minor tubal defects or both, which have also been in patients who did not have LGTB. These were undetected until they had undergone laparoscopy. There is strong possibility that presence of LGTB aggravates these conditions.

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Abbreviations: LGTB: Latent Genital Tuberculosis; ATD: Anti-Tubercular Drugs

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