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Research Article

Latent Genital Tuberculosis – A Causative Factor for Ectopic Pregnancy- A Retrospective Analysis

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Abstract

Background: Ectopic tubal pregnancy (ETP) is a dreadful situation for both the patient and the doctor. Prevalence of ETP is increasing because of availability of convenient and modern modalities for the diagnosis of ectopic pregnancy. Patients are aware of the condition and many lives can be saved when diagnosed and managed at an early stage; still almost 10% of maternal deaths are due to ETP. The etiology of ETP remains unknown in almost half of the cases and hence the risk of recurrence remains high. The present study has been conducted to screen patients with history of tubal ectopic pregnancyand to determine the role of tubercular infestation of the eutopicendometrium as an important etiological factor in 'unexplained' ectopic.

Results: This retrospective analysis was conducted at Calcutta Fertility Mission in Kolkata, India, from January 2010 to December 2018. Of 282 patients with history of ETP,who were selected, 109 were in Group A, 72 of them in Group B and 101 in Group C. Tubercular infestation of the endometrium (DNA-PCR positive) was found in all (109) patients in Group A, and others in Group B and C had previous history of pelvic surgery or endometriosis, pelvic infection or unexplained infertility associated with tubercular infestation of the endometrium. In our study latent genital tuberculosis has been proved to be a statistically significant factor for ETP. (p value - <0.001) Moreover other factors like tubal surgeries (p value - <0.001) or correction of minor tubal defects (p value – 0.024); endometriosis (p value- <0.001) and pelvic inflammatory disease (p value -<0.001), have shown statistical significance in causing ectopic pregnancy. Clinical pregnancy rate (p value -0.002) and live birth rate (p value-<0.001) has been proved to be statistically significant after treatment of ETP.

Conclusion: Along with the documented causes of ETP tubercular infestation of the endometrium should be considered as an important etiology for ectopic pregnancy and should be screened on a routine basis for early intervention and treatment.

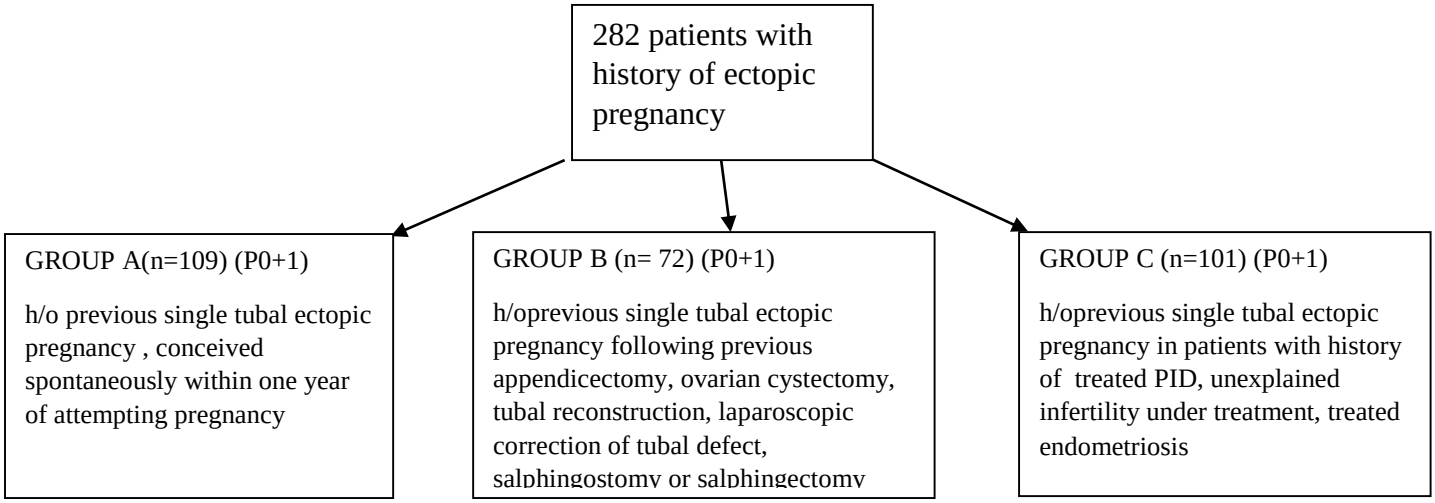
Keywords: tubercular infestation; endometrium; ectopic tubal pregnancy; latent genital tuberculosis; infertility

Background

Ectopic tubal pregnancy (ETP) is an alarming condition both for the expectant mother and for the treating physician. ETP occurs when the developing blastocyst gets implanted at either of the fallopian tubes instead of the eutopicendometrium. It eventually ends up in pregnancy loss which is a frustrating situation for the patient. The prevalence of ETP is on the rise because of increased awareness, availability of transvaginal ultrasonography (TVUS), estimation of beta-human chorionic gonadotropin (βhCG) in serum and urine. Many cases of "silent" or asymptomatic ETP which resolve automatically may be picked up on a larger scale by modern diagnostic methods; thereby adding to the prevalence as well. Today, early intervention saves lives and reduces morbidity, but ectopic pregnancy still accounts for 4% to 10% of maternal deaths and leads to a high incidence of ectopic site gestations in subsequent pregnancies.[1]Several risk factors for ETP have been documented including age,sociodemographic characteristics, reproductive history (multiple sexual partners, pelvic inflammatory disease (PID), Chlamydia trachomatis infection, certain forms of contraception, smoking, DES exposure, endometriosis, utero-tubal anomalies and treatment for infertility. [2]In about 50% cases the etiology of ETP remains uncertain and hence the risk of recurrence remains high. [3]In the present study patients with history of tubal ectopic pregnancywere evaluated to determine role of tubercular bacilli infestation of endometrium as an important etiological factor.

Methods

This retrospective study was conducted at Calcutta Fertility Mission in Kolkata, India, from January 2010 to December 2018. The data were collected from a total of 282 patients as cases between 20-35years of age, who had previous history of ectopic pregnancy diagnosed by serialβhCG estimation, TVUS. 150 of them (72 patients in Group B and 78 patients in Group C) were treated by salphingostomy or salphingectomy and the rest of 132 patients were either treated with methotrexate or had spontaneous remission.They did not have any history of cigarette smoking or alcoholism. These patients were either scared to attempt another pregnancy or could not conceive after they started the attempt between last 6-9months. Patients were grouped into Group A, B and C depending on the predisposing factors for ETP.



They had undergone physical examination, routine blood tests, TVUSalong with the PCR test with an endometrialaspirate. Patients were grouped as Group A, B, C depending on DNA-PCR test positive report, previous history and possible etiology of ETP.

Statistical Analysis:

Categorical variables are expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate.Within group Frequency distributions are compared using Binomial Test.The statistical software SPSS version 20 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

Results

282 women were divided into three groups: Groups A, B, and C in which 109 (38.6%) patients were in Group A who had history of single ETP had only latent female genital tuberculosis (FGTB) as the etiological factor (only TB-PCR Positive) .Group B consisted of 72 (25.5%) women in which 26 (36.11%) patients with history of single ETP were found to have tubercular bacilli infestation in the endometrium, along with previous history of surgical intervention as pre-disposing factors for ETP. Group C included 101 (35.8%) patients of whom 66 (65.35%) had endometrialtubercular infestation associated with other pelvic pathology as etiology. These patients were treated with anti-tubercular drugs (ATD) and the clinical pregnancy rate (CPR), rate of miscarriage, recurrent ectopic pregnancy and live birth rate (LBR) were recorded, within one year of treatment.

		GROUP			Total		
		GROUP A	GROUP B	GROUP C		p Value	Significance
AGE	21-25	22(20.18)	29(40.28)	29(28.71)	80(28.37)	0.068	Not Significant
	26-30	40(36.7)	20(27.78)	35(34.65)	95(33.69)		
	31-35	47(43.12)	23(31.94)	37(36.63)	107(37.94)		
Total		109(100)	72(100)	101(100)	282(100)		

Table 1 - Age of patients: Data analysis done by Fisher's Exact Test

Etiology		Group A	Group B	Group C	p Value	Statistical Significance
TUBERCULAR INFESTATION (PCR POSITIVE)		109(100)	26(36.11)	66(65.35)	<0.001	Significant
PCR NEGATIVE		0(0)	46(63.89)	35(34.65)		
LAPAROSCOPIC CORRECTION OF TUBAL DEFECTS	YES	0(0)	26	0(0)	0.024	Significant
	NO	0(0)	46	0(0)		
OVARIAN CYSTECTOMY	YES	0(0)	29	0(0)	0.125	Not Significant
	NO	0(0)	43	0(0)		

APPENDICECTOMY	YES	0(0)	7	0(0)	<0.001	Significant
	NO	0(0)	65	0(0)		
TUBAL SURGERY	YES	0(0)	10	0(0)	<0.001	Significant
	NO	0(0)	62	0(0)		
ENDOMETRIOSIS	YES	0(0)	0(0)	32	<0.001	Significant
	NO	0(0)	0(0)	69		
PID	YES	0(0)	0(0)	28	<0.001	Significant
	NO	0(0)	0(0)	73		
UNEXPLAINED INFERTILITY	YES	0(0)	0(0)	43	0.163	Not Significant
	NO	0(0)	0(0	58		

Table 2- Participants' etiology:Data analysis done by Binomial test

PCR POSITIVE		GROUP A	GROUP B	GROUP C	p Value	Statistical significance
CLINICAL PREGNANCY RATE	NO	53(48.62)	16(61.54)	50(75.76)	0.002	Significant
	YES	56(51.38)	10(38.46)	16(24.24)		
MISCARRIAGE	NO	94(86.24)	24(92.31)	60(90.91)	0.522	Not Significant
	YES	15(13.76)	2(7.69)	6(9.09)		
RECURRENT ECTOPIC	NO	103(94.5)	22(84.62)	61(92.42)	0.227	Not Significant
	YES	6(5.5)	4(15.38)	5(7.58)		
LIVE BIRTH RATE	NO	74(67.89)	22(84.62)	61(92.42)	<0.001	Significant
	YES	35(32.11)	4(15.38)	5(7.58)		

Table 3 Data analysis done by Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test

PCR NEGATIVE		GROUP A	GROUP B	GROUP C	p Value	Statistical significance
CLINICAL PREGNANCY RATE	NO	0(0)	40(86.96)	24(68.57)	0.044	Significant
	YES	0(0)	6(13.04)	11(31.43)		
MISCARRIAGE	NO	0(0)	45(97.83)	32(91.43)	0.188	Not Significant
	YES	0(0)	1(2.17)	3(8.57)		
RECURRENT ECTOPIC	NO	0(0)	43(93.48)	30(85.71)	0.246	Not Significant
	YES	0(0)	3(6.52)	5(14.29)		
LIVE BIRTH RATE	NO	0(0)	44(95.65)	32(91.43)	0.434	Not Significant
	YES	0(0)	2(4.35)	3(8.57)		

Table 4 Data analysis done by Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test

Discussion

Almost one half of women with ectopic pregnancy have no identifiable causal factors (ACOG 2018). ETP has been seen to be on an increasing trend in women with more than 35 years of age. [3]The relevance of age along with the effect on the fallopian tube or delay of oocyte transport has been questioned time and again by many authors.[4,5]In our study we have included nulliparous women < 35years of age as the prevalence was seen to be more in the elderly age group though it was not statistically

significant (p value – 0.068).Lifestyle has also been seen to play a role in the rising incidence of ETP. Smokinghas a dose-dependent relationship in ETP as the likelihood of ETP was three times higher among smokers.[6]Other factors responsible for tubal inflammation and dysfunction leads to upregulation of pro-inflammatory cytokines and increased chances of ETP.[7]Pelvic infections like *Chlamydia trachomatis* , *Neisseria gonorrhoeae*, *Mycoplasma* and schistosomiasis causingpelvic inflammatory disease(PID), is associated with increased risk for subsequent ETP.[8,9]Interleukin 1 (IL-1), produced by tubal epithelial cells following *Chlamydia trachomatis* infection, macrophages and intraepithelial lymphocytes promote embryo receptivity, invasion and angiogenesis in the tube predisposing to ETP. [10-13]The incidence rate for developing ectopic pregnancy in patients with PID was 0.05% and they had a 2.121 times (P = 0.003) higher risk of developing ectopic pregnancy compared to those without PID.[14]In our study PID has been seen to be a statistically significant factor for ETP.(p value- <0.001)

Pelvic infection,abnormal implantation, placentation or blood vessel transformation can result in miscarriage.[15,16] In our study the miscarriage rate in Group A was as high as 13.76% even after treatment, which can be correlated with our previous study.[17] Miscarriage rates in our overall patients with (p value - 0.522) or without (p value – 0.188) genital tuberculosis was not statistically significant.

Pelvic adhesions due to endometriosis, appendicitis, or other pelvic infections, may distort the anatomy of the fallopian tube resulting in an abnormal tubo-ovarian relation, impair oocyte release, alter sperm motility, cause abberant myometrial contractions, as well as affect embryo transport. [18][19]
In women with endometriosis, there can be impaired endometrial growth, structural and molecular alterations in eutopic endometrium resulting in implantation failure or progesterone resistance in the endometrium.[20-23]
Women with endometriosishad a significantly higher risk of early pregnancy complications or ETP.**[**24**]** Other authors also indicated higher risk of miscarriage (about 76%) and nearly three times higher for ectopic pregnancy in women with endometriosis.[19]The findings of our study also support the fact where endometriosis has been seen to be a statistically significant factor for ectopic pregnancy. (p value- <0.001)

Previous surgical interventions like tubal reanastamosis, salpingostomy, tuboplasty, ovarian cystectomy, laparoscopic correction of tubal defects are obvious risk factors of ETP. 2–13 % women suffered from ETP after tubal reanastomosis performed manually or by robotic approaches[25, 26]
Correction of minor tubal defects arising from mild or minimal endometriosis (Stage I and II) or subclinical pelvic infection result in about 25% pregnancy rate within one year of the procedure. Similar result is obtained with laparoscopic ovarian cystectomy as well. In both the conditions ETP is a possible sequelae.[27,28] In the present study laparoscopic tubal surgery has been seen to be statistically significant factor for ETP (p value <0.001) in contrary to laparoscopic ovarian cystectomy which has shown no statistical significance in causing ETP.(p value – 0.125)

The association of infertility and ectopic pregnancy is complex, as ectopic pregnancy has been observed to be a cause as well as a consequence of infertility and it can be presumed that they have common causal factors.Previous history of tubal damage or rupture ; use of ovulation induction drugs increase risk of ETP.[29,30]Unexplained infertility or treatment for the same like use of Ovulation Induction drugs like Clomiphene citrate (CC) or Gonadotrophins (GnRH) as well as ART increases risk of ectopic pregnancy**.[**31]Long term treatment with CC leads to alteration of ESR2 (especially ESR2A) expression and activation in cilia were seen before the onset of CC-induced tubal apoptosis, suggesting a mechanism for CC-induced ETP.[32]

Although many of these factors have always been screened and sometime the possible cause of ectopic pregnancy has been detected, in about 50% of cases the cause still remains unknown.Endometrial inflammation has been proved to be hostile for implantation and the movement of the embryo comes to a halt in the fallopian tube or it might as well move to the other tube by trans-uterine migration. In order to find out the cause in these patients with unexplained ETP we had screened them for LGTB using DNA-PCR test.Presence of tubercular bacilli is responsible for inflammation of the fallopian tubes resulting in presence of pro-inflammatory interleukins which might facilitate tubal implantation leading to ETP as seen in cases of *Chlamydia trachomatis* infection. Tubercular insult of the female genital tract is responsible solely or in association with other predisposing factors for ETP as documented by other authors.**[**33,34]

31 to 59 % patients treated with Anti-tubercular drugs (ATD) for FGTB conceived spontaneously and even those who had undergone IVF had live birth, spontaneous abortion or ectopic pregnancy.[35-38] In the present study clinical pregnancy rate (CPR) has been seen to be statistically significant in both the section of patients who had tubercular infestation i.e. PCR positive (p value -0.002) as well as who did not have genital tuberculosis i.e. PCR negative (p value – 0.044).

In our study live birth rate (LBR) has statistical significance in women with post-ATD treatment (p value - <0.001) whereas patients who were PCR negative but had other risk factors for ETP had a low LBR. (p value –0.434)This can be correlated with the study by Bapna et al and Shende P etal.where the pregnancy rate was 19.1% per transfer, live birth was about 24.4% and 16% respectively. [39,40, 41]

Risk of ETP increases by 7- to 13-fold after one episode of tubal ectopic pregnancy. A patient with prior pregnancy has a 50%-80% chance of having a subsequent intrauterine pregnancy (IUP) and a 10%-25% risk of a future tubal pregnancy.[31] Recurrent ETPs were significantly more likely to have a positive history of tubal or pelvic surgery (61.5 % vs. 3.5 %, $p < 0.05$ and 53.8 vs. 14 %, $p < 0.05$) and positive history of previous tubal surgery and previous ectopic pregnancy differ in women at risk of a recurrent ETP when compared to women not at risk (AUC, 0.844), according to Hurrell A et al.[42]In the present study recurrent ectopic pregnancy rate has no statistical significance in the overall cohort of participants. (p value – 0.227, p value – 0.246)

Conclusion

Ectopic pregnancy needs immediate attention and intervention due to its fatal consequence. In about 50% cases it is stated to be idiopathic.According to the present study, LGTB which is detected by tests at the molecular level (DNA-PCR) are found to be a major contributory factor in development of this condition. Treating LGTB properly prevents recurrence in many instances. Pregnancy rate following complete treatment of LGTB has also been documented to be quite encouraging.

Declarations

Ethical considerations: Our study was a retrospective study which included patient records, and we did not directly get in contact with them, but our study was confirmed by Ethical Committee of Calcutta Fertility Mission.

Availability of data and material – Retrospective data of a prospective database of our institution

Competing interests–There is no conflict of interest among the authors.

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Authors' contributions –

Dr. Siddhartha Chatterjee – concept of study, preparation and editing of manuscript
Dr. Bishista Bagchi – data collection, preparation of manuscript, follow-up of patients, sample collection
Dr.RajibGon Chowdhury– data collection, preparation of manuscript
Ms. Abira Dutta – laboratory procedures and reporting, sample collection

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