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Relationship between chronic endometritis and fallopian tube obstruction and its influence on pregnancy outcome after fallopian tubal recanalization

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Abstract

Background: Chronic endometritis (CE), frequently asymptomatic, is associated with female infertility. Fallopian tube obstruction (FTO) is also one of the factors contributing to female infertility. More than 90% of cases of proximal FTO can be successfully treated after fallopian tubal recanalization (FTR) and the spontaneous pregnancy rate of treated women after FTR is only about 30%. Potential factors affecting the success rate of FTR remain unclear. We speculate that CE may be one of the reasons affecting the recanalization of the fallopian tubes.

Objectives: To identify the correlation between CE and FTO, as well as the influence of CE on pregnancy outcomes following FTR.

Design: Retrospective observational study.

Methods: We retrospectively analyzed 498 women of childbearing age who underwent laparoscopy and hysteroscopy surgery for infertility. Endometrial samples were collected during surgery for CD138 immunohistochemistry staining for the diagnosis of CE. Based on the results of the tubal patency test, they were divided into two groups: the fallopian tubal patency group and the proximal FTO group. The prevalence of CE was compared between these two groups. All women with FTO underwent FTR during the operation until successful treatment was achieved. Pregnancy outcomes were assessed after a 12-month follow-up period following the procedures. Logistic regression was used to analyze factors that might affect pregnancy after FTR.

Results: The prevalence of CE in women with tubal obstruction was 30.5%, which was significantly higher than that in the fallopian tubal patency group (10.75%), $p < 0.001$. After FTR, the prevalence of CE in non-pregnant women was 40.18%, which was higher than that in pregnant women (40.18% vs 13.11%), and the difference was significant ($p < 0.001$). Multiple regression analysis showed that CE was a significant risk factor for FTO (OR: 2.54, 95% CI: 1.368–4.717, $p < 0.05$). In addition, CE was identified as a risk factor for infertility after FTR (OR: 4.730, 95% CI: 2.012–11.122).

Conclusion: The presence of CE seems to decrease the likelihood of achieving spontaneous pregnancy following FTR. This observation underscores the clinical importance of early detection and treatment of CE, emphasizing the necessity for immediate intervention to prevent potential fertility complications.

Plain language summary

Understanding chronic endometritis and its impact on fertility

Summary: Our research investigated the potential impact of chronic endometritis on a woman's fertility. Chronic endometritis is a condition where the endometrium, the

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inner lining of the uterus, experiences persistent inflammation. This inflammation can affect a woman's ability to conceive. We were particularly interested in whether chronic endometritis is related to blocked fallopian tubes, which are known to make it harder for a woman to get pregnant.

What We found: We discovered that women with blocked fallopian tubes were more likely to have chronic endometritis. After the unblocking procedure, women who still had chronic endometritis were less likely to get pregnant.

Takeaways: Chronic endometritis is common in women with blocked fallopian tubes. Treating chronic endometritis might help more women get pregnant after their fallopian tubes are unblocked. Early detection and treatment of chronic endometritis could be key to improving fertility.

Definitions: *Chronic Endometritis*: A condition characterized by ongoing inflammation of the endometrium, which can lead to various symptoms and complications, including potential fertility issues. *Fallopian Tubes*: A pair of muscular tubes in the female reproductive system that transport eggs from the ovaries to the uterus. They are essential for the process of fertilization. *Conceive*: The process of becoming pregnant, which involves the fertilization of an egg by sperm.

Keywords: chronic endometritis, fallopian tube, FTR, infertility, pregnancy

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Introduction

Chronic endometritis (CE) is a condition characterized by chronic inflammation and the infiltration of plasma cells in the endometrial stroma. Its clinical symptoms are often mild or even asymptomatic, making it easily overlooked by clinicians.[1] Previous studies have shown that biopsies of endometrial tissue from women who have undergone hysterectomy for other benign gynecological diseases reveal a CR prevalence rate of approximately 10%–11%.[2,3] In fact, Romero et al.[4] reported that 15% of infertile women who received in vitro fertilization (IVF) cycle had CE, and the prevalence of CE in patients with recurrent implantation failure was as high as 42%. In light of these findings, CE is significantly associated with female infertility, highlighting its importance and necessitating the focused attention of both clinicians and pathologists.

Usually, the diagnosis of CE is primarily based on the presence of plasma cell infiltration in endometrial biopsies.[5] However, the accuracy of histological diagnosis may be influenced by conditions such as infiltration of mononuclear inflammatory cells, proliferation of interstitial cells, plasma-like appearance of interstitial cells, or pre-decidual reaction of late secretory endometrium.[5] Therefore, the misdiagnosis rate of H&E staining alone in the diagnosis of CE is high.[6–8] In recent years, CD138 has been identified as a specific antigen on the surface of plasma cells. Detecting CD138 expression by immunohistochemistry can enhance the sensitivity of CE diagnosis.[9] Among female patients with recurrent abortion, the sensitivity of CD138 detection was as high as 56%, significantly higher than that of H&E staining (13%). Consequently, pathologists have increasingly recognized the value of CD138 detection for diagnosing CE.[9,10]

Fallopian tubal infertility is one of the factors of female infertility, with an incidence rate of nearly 25%–35%, which is increasing year by year.[11] Fallopian tubal obstruction (FTO) is divided into proximal, middle, and distal obstructions. Infertility due to proximal FTO occurs in approximately 10%–25% of women with fallopian tubal

infertility.[12] The causes of FTO include abnormal anatomical structures, spasms of tubal wall muscles, or mucus blockages.[13,14] In addition, inflammation is also a cause of tubal obstruction. Pelvic inflammatory disease (PID) is the main factor causing FTO. Among patients with fallopian tubal infertility, 35%–40% have a history of PID and about one-third of them have a history of repeated infections.[15] When inflammation occurs, the narrowest part of the fallopian tube and the fimbria end are prone to adhesion or complete atresia, which can result in infertility.[16] Inflammation can also cause stiffness and peripheral adhesion of the fallopian tube wall, affecting its peristalsis. Endometritis of the fallopian tube can destroy and affect the activity of cilia, hindering the delivery of embryos, fertilized eggs, and early embryos in the fallopian tube, and leading to infertility.[16–18]

Fallopian tube recanalization (FTR) is an effective method to treat proximal FTO.[19] Since the late 1980s, selective fallopian tube catheterization with fluoroscopic guidance, along with the use of a coaxial system of guidewires and catheters, has been employed to improve visualization of tubal anatomy and to treat proximal FTO.[19] According to previous studies, more than 90% of cases of proximal tubal obstruction can be successfully treated after FTR, nevertheless, the spontaneous pregnancy rate of treated women after FTR is only about 30%.[20] Therefore, identifying the factors that affect spontaneous pregnancy after FTR surgery is very important. The objective of this study is to investigate the factors influencing FTO and to identify the factors that may affect spontaneous pregnancy outcomes following FTR.

Materials and methods

Design and patient selection

The medical data of a total of 498 women aged 18–40 who underwent hysteroscopy combined with laparoscopy for infertility from June 2015 to January 2020 were included in the analysis. There were 102 women with distal FTO removed. After considering that most distal tubal obstructions are associated with pelvic adhesions, pelvic endometriosis, or obstructions caused by tubal surgery, we excluded these cases of distal tubal obstruction to minimize the impact of these factors on the study results. The remaining cases were divided into the tubal patency group (186 cases) and the proximal tubal obstruction group (210 cases). All women with proximal tubal obstruction underwent FTR until they achieved unilateral or bilateral tubal patency. In accordance with the inclusion and exclusion criteria delineated hereinafter. Inclusion criteria: (1) Infertility $\geqslant$1 year; (2) Women of childbearing age aged 18–40; (3) Ovulation; (4) Female patients with tubal infertility assessed by reproductive and gynecological endocrinologists. Exclusion criteria: (1) Male infertility; (2) Infertility caused by ovarian dysfunction; (3) Infertility caused by uterine malformation; (4) Pelvic tuberculosis; (5) Patients with thyroid dysfunction, hypertension, diabetes, rheumatic diseases, etc., who need treatment and are not recommended for pregnancy a period of time; (6) Those who have no intention of pregnancy a period of time due to social factors. A cohort of 168 women was enrolled in the follow-up study, with a 12-month observational period to monitor their spontaneous pregnancy outcomes (Figure 1). Our pregnancy preparation team gave guidance to these women and followed up their spontaneous pregnancy within 12 months after the operation. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Supplemental Material).[21]

Research procedure

This study involved the collection of information from all women, which included age, height, weight, infertility duration, body mass index (BMI), pregnancy history, ectopic pregnancy history, PID history, and other previous diseases. The data collected were used to ensure a comprehensive analysis of the study's subjects. All women underwent hysteroscopy and laparoscopy surgery 3–7 days after menstruation. The morphology of the uterine cavity was observed by hysteroscopy and a small amount of endometrial tissue was scraped out. The intimal tissue was sliced to detect CD138.

The patency of the fallopian tube was determined based on the outflow of methylene blue liquid from the ampulla of the fallopian tube, as observed under laparoscopy.

For women with FTO, FTR was performed until unilateral or bilateral fallopian tubes were unobstructed. All women with proximal tubal

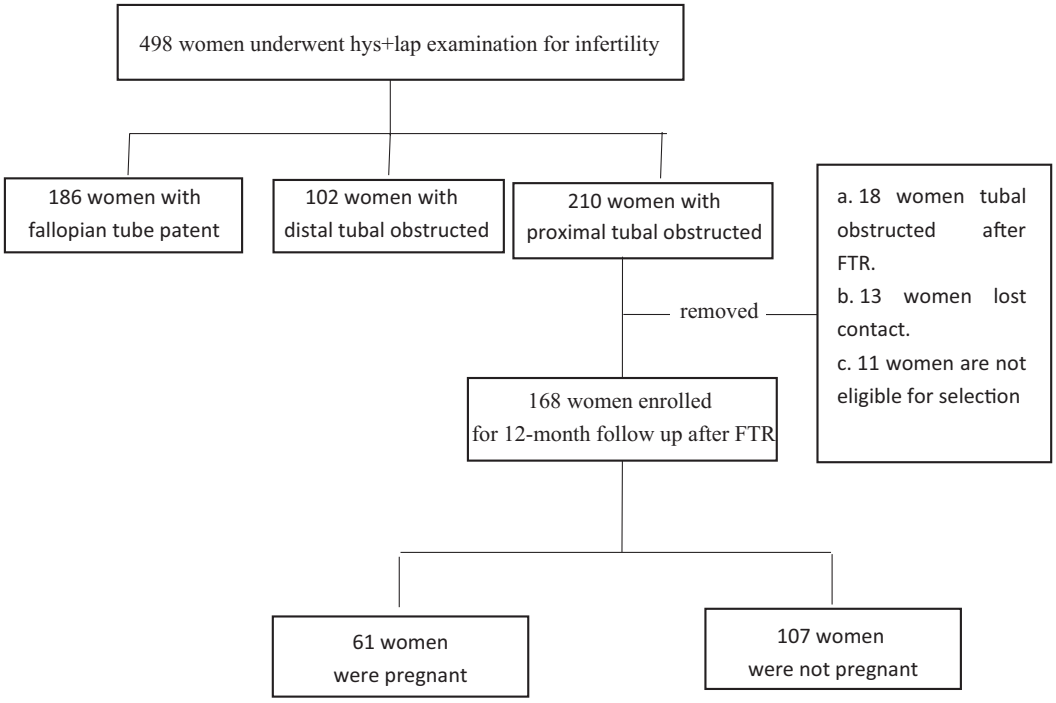

Figure 1. Flowchart of women enrolled.

obstruction underwent a hysterosalpingo contrast sonography (HyCoSy) 1 month after the operation to re-evaluate the patency of their fallopian tubes. HyCoSy shows that at least one fallopian tube is unobstructed, and it meets the inclusion and exclusion criteria mentioned above, which will be further included in the follow-up study. Within 12 months post-surgery, reproductive medicine specialists had offered fertility guidance to these women.

Surgical and histologic technique

All operations were performed under general anesthesia by reproductive surgeons. Hysteroscopy was conducted using a HEOS hysteroscope (France), which featured a 4.3 mm operating channel and a forward-oblique 30° viewing angle. A comprehensive observation of the uterine cavity, including the anterior, posterior, and lateral walls, as well as the cervix, was made. The endometrium was scraped with a curette, and the tissue collected was fixed with a 4% formalin solution and sent to the pathology department. Diagnostic criteria for CE: CE is defined by the presence of five or more plasma cells in at least one out of 30 high-power fields.[6]

FTR procedure

FTR procedure is shown in Figure 2. First, openings of bilateral fallopian tubes were identified under hysteroscopy. The Modified Novy Cornual Cannulation set was placed through a built-in surgical channel for observation under the hysteroscope (Figure 2(a)). At the other end of the catheter, a 20 ml syringe was used to inject methylene blue. If there was significant resistance during the injection and methylene blue did not flow out from the ampulla of the fallopian tube, this was defined as FTO. Secondly, the guide wire (COOK, USA) was inserted into the catheter. The diameter of the guide wire was approximately 0.38 mm, and the depth of the guide wire into the tubal interstitium was 2 cm (Figure 2(b)). After the guide wire was removed, methylene blue was injected through the catheter again. If methylene blue was observed at the end of the fallopian tubal ampulla, the operation was determined to be successful (Figure 2(c)).

Laparoscopic surgery

Laparoscopic surgery allowed for a comprehensive exploration of the uterus, bilateral fallopian tubes, ovaries, and pelvic abdominal organs, as

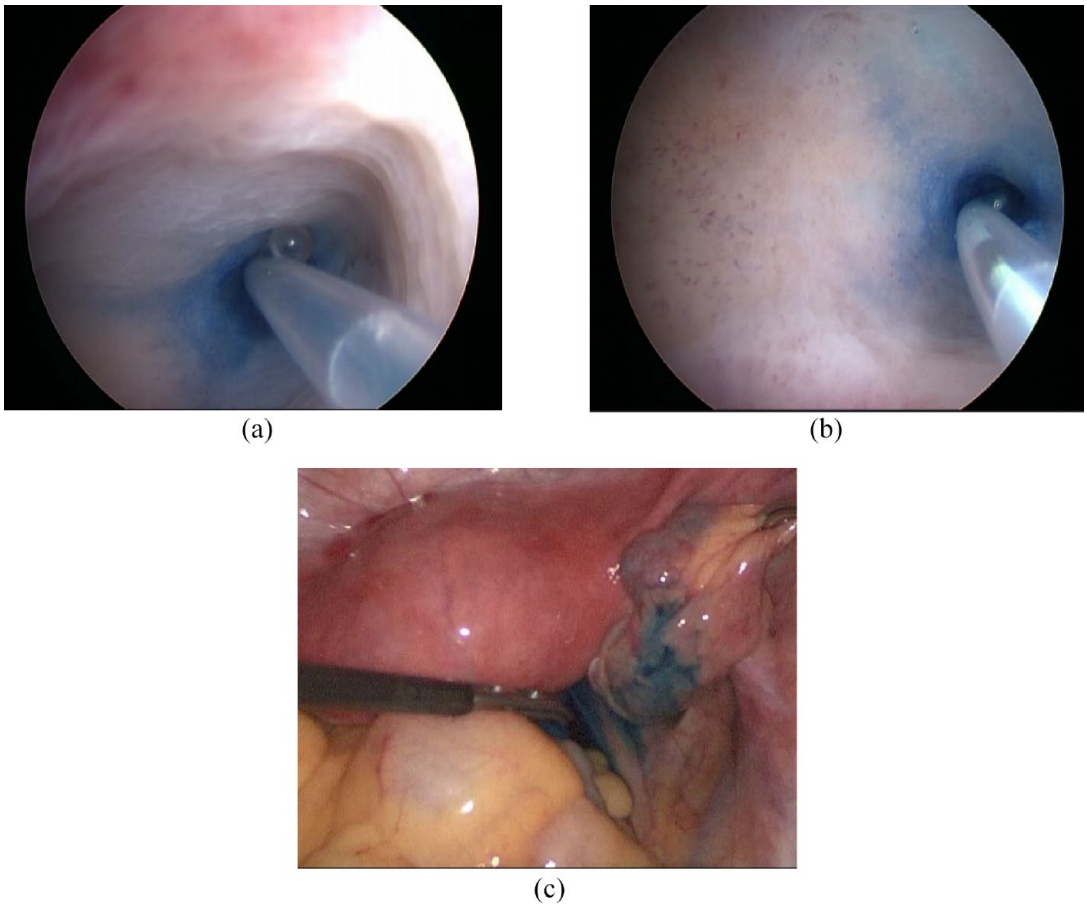

Figure 2. Fallopian tubal recanalization procedure. (a) Hysteroscopic insertion of uterine horn cannula. (b) The guide wire is inserted into the fallopian tube cannula to recanalized fallopian tube. (c) Laparoscopy shows that the fallopian tube is completely patency.

well as the performance of a methylene blue test. The diagnostic criteria for FTO were as follows: Proximal FTO (involving the tubal interstitial and isthmus segments): The resistance during the injection of methylene blue was high, and the liquid was not observed at the distal end of the fallopian tube. Distal tubal obstruction: The fimbriae end and ampulla of the fallopian tube expanded and turned blue, but no methylene blue flowed into the abdominal cavity from the fimbriae end.[22]

Statistical analysis

SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was utilized for statistical analysis. Numeric data with a normal distribution were reported as the mean and standard deviation, while numeric data without a normal distribution were reported as the median and interquartile range. Categorical data were reported as numbers and percentages. Categorical parameter differences between the groups were assessed using the chi-square test or Fisher's exact test, depending on the sample size and distribution. One-way ANOVA and logistic binary regression analysis were made on previous pregnancy and delivery history, PID, and CE. Logistic regression analysis was made to test the independent influence of any variable on the risk of tubal obstruction and spontaneous pregnancy after surgery. Differences were considered significant if $p < 0.05$.

Results

A total of 498 women underwent hysteroscopy combined with laparoscopy, including 210 women with bilateral proximal tubal obstruction (FTO) and 186 women with bilateral tubal patency. There were 102 women with distal FTO

Table 1. Characteristics of the two groups.

Index	Tubal obstruction	Tubal patency	*p* Value
Number of subjects	210	186	
Age (y)	32.57 ± 5.51	32.72 ± 4.47	0.798
Infertility type			
Primary infertility (*n*)	81	87	0.127
Secondary infertility (*n*)	129	99	
BMI	22.55 ± 3.13	23.23 ± 4.56	0.138
Infertility duration (m)	28.75 ± 8.55	27.26 ± 8.33	0.458
Prevalence of previous diseases			
Ectopic pregnancy (*n*, %)	17 (8.1%)	8 (4.3%)	0.189
Abortion (*n*, %)	118 (56.19%)	74 (39.78%)	0.048
Birth (*n*, %)	51 (24.28%)	27 (14.5%)	0.058
Acute PID (*n*, %)	65 (30.95%)	23 (12.36%)	0.007
Pelvic surgery (*n*, %)	5 (2.38%)	4 (2.15%)	0.915
Endometriosis (*n*, %)	25 (11.90%)	31 (16.67%)	0.213
Chronic endometritis (*n*, %)	54 (30.5)	20 (10.75%)	<0.001

BMI, body mass index; PID, pelvic inflammatory disease.

removed. Women with FTO underwent contrast-enhanced ultrasound of fallopian tubes within 1 month after FTR to test the patency of fallopian tubes. Out of the group, 18 women continued to exhibit bilateral FTO. It was suggested that these women underwent in vitro fertilization and embryo transfer (IVF-ET) treatment. According to the inclusion and exclusion criteria mentioned above, 11 women were removed. In addition, 13 women were lost to follow-up during the process. Finally, 168 women were successfully enrolled in the follow-up cohort and completed 12 months of follow-up (Figure 1).

The statistics for age, BMI, infertility types, previous history of gynecological diseases, and pelvic surgery of women in the tubal obstruction group and tubal patency group are shown in Table 1. The average age of women in the tubal patency group was 32.72 ± 4.47 years old, and that in the tubal obstruction group was 32.57 ± 5.51 years old. There was no statistical difference between the two groups in terms of age, BMI, infertility type, and average infertility duration ($p > 0.05$). Analysis of previous gynecological diseases revealed no statistically significant difference between the two groups regarding the history of endometriosis and the history of previous pelvic surgery. The proportion of women with previous abortions in the FTO group was 56.19%, which was higher than that in the fallopian tubal patency group (39.78%), and the difference between the two groups was statistically significant ($p = 0.048$).

The prevalence rate of history of PID in patients with tubal obstruction was 30.95%, which was significantly higher than that in patients with tubal patency (12.36%, $p = 0.007$). The history of ectopic pregnancy in FTO group was 8.1%, which was higher than that in the fallopian tubal patency group (4.3%), but there was no statistically significant difference between the two groups. Notably, the prevalence rate of CE in women with FTO was 30.5%, which was significantly higher than that in the fallopian tubal patency group (10.75%), and the difference between the two groups was

Table 2. Correlation analysis between predictive factors and tubal obstruction.

Preditor	Univariate		Binary logistic regression	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
History				
Ectopic pregnancy	1.966 (0.803–4.813)	0.189	1.460 (0.504–4.233)	0.486
Abortion	1.970 (1.286–3.017)	0.048	2.739 (1.443–5.198)	0.002*
Birth	1.663 (0.968–2.855)	0.058	1.365 (0.714–2.610)	0.346
Acute PID	3.240 (1.864–5.632)	0.007	2.441 (1.301–4.577)	0.005*
Endometriosis	0.680 (0.370–1.251)	0.213	0.879 (0.705–1.096)	0.126
Pelvic surgery	1.079 (0.266–4.486)	0.915	0.948 (0.886–1.015)	0.252
Chronic endometritis	3.717 (2.085–6.625)	<0.001*	2.540 (1.368–4.717)	0.003*

*Statistically significant, as indicated by $p < 0.05$.
CI, confidence interval; PID, pelvic inflammatory disease.

Table 3. Post-FTR pregnancy rates according to relevant characteristics.

Characteristics	Pregnancy		Non-pregnancy		Total	*p* Value
	n	%	*n*	%		
	61	36.31	107	63.69	168	
CE	8	13.11	43	40.19	51	<0.001*
Ectopic history	2	3.3	15	14.02	17	<0.001*
PID history	16	26.23	32	29.91	48	0.723
Abortion history	31	50.8	49	45.79	80	0.63
Abdominal operations	2	3.3	3	2.8	5	1
Primary infertility	27	44.26	40	37.38	67	0.42
Secondary infertility	34	55.74	67	62.62	101	0.42

*Statistically significant, as indicated by $p < 0.05$.
CE, chronic endometritis; FTR, fallopian tube recanalization; PID, pelvic inflammatory disease.

statistically significant ($p < 0.001$). The proportion of women with a previous abortion in the tubal obstruction group was 56.19%, which was higher than that in the tubal patency group (39.78%), and the difference between the two groups was statistically significant ($p = 0.048$).

The factors that may affect the patency of fallopian tubes were analyzed using binary regression (Table 2). CE was closely related to FTO, with an odds ratio (OR) of 2.54 (95% CI: 1.368–4.717, $p = 0.003$). A previous history of PID (OR: 2.44, 95% CI: 1.301–4.577, $p = 0.005$) and a previous history of induced abortion (OR: 2.739, 95% CI: 1.301–4.577, $p = 0.002$) were also related to tubal obstruction.

Follow-up of the 168 women who were included in the analysis after FTR was conducted over a period of 12 months (Table 3). A total of 61 (36.3%) women experienced spontaneous pregnancy, and among the women who had CE,

Table 4. Logistic regression analysis of risk factors of lower pregnancy rate after FTR.

Index	OR	95% CI	*p* Value
History of ectopic pregnancy	9.746	1.215–78.172	0.032*
Chronic endometritis	4.730	2.012–11.122	<0.001*

*Statistically significant, as indicated by $p < 0.05$.
CI, confidence interval; FTR, fallopian tube recanalization.

8 (13.1%) achieved spontaneous pregnancy. After 12 months of follow-up, a total of 107 women failed to conceive naturally after FTR, and among them, 43 (40.18%) had CE ($p < 0.0001$). In addition, 14.2% of non-pregnant women had a history of ectopic pregnancy, compared to 3.3% of pregnant women ($p < 0.05$). There was no significant difference between pregnant and non-pregnant women in the history of pelvic endometriosis, history of PID, abortion, and pelvic surgery ($p > 0.05$).

In the model of binary regression analysis, the factors associated with spontaneous pregnancy were evaluated (Table 4). We found that a previous history of ectopic pregnancy and CE were risk factors for the reduction of pregnancy rate after FTR, with ORs of 9.746 and 4.73, respectively.

Discussion

CE is associated with female infertility. However, CE is often overlooked by clinicians because it is often asymptomatic, especially in women with FTO.[5] This study explored the relationship between CE and FTO and found a potential relationship between them. Our study showed that the prevalence of CE in women with FTO was nearly three times higher than in the tubal patency group. In the binary logistic regression analysis model, we found that CE was a risk factor for FTO, which was consistent with the findings of Holzer et al.[23] We speculate that CE may be an intermediate link in PID infection, where inflammation spreads through the endometrium to the proximal fallopian tubes, potentially causing tubal obstruction, which is likely to cause more proximal tubal obstruction. Therefore, it is recommended that women with FTO be tested for CE.

FTR is a very effective method for treating proximal FTO, with a technical success rate of over 90%.[24–26] However, studies reported that only 33% of women with tubal obstruction were able to conceive naturally after tubal recanalization.[26] The pregnancy rate was much lower than the success rate of the operation. A previous study showed that the pregnancy rates following FTR significantly varied.[12] Potential factors affecting the success rate of FTR remain unclear.[27] In this study, FTR was performed for women with proximal tubal obstruction until the fallopian tubes were unobstructed, either unilaterally or bilaterally. We found that a total of 36.3% of women experienced spontaneous pregnancy following FTR, a rate consistent with previous studies.[24] A binary analysis of factors affecting pregnancy revealed no significant statistical differences in age and infertility type between the two groups. However, a significant statistical difference was observed in the history of previous ectopic pregnancy surgery and the presence of CE. This also indicated that a history of ectopic pregnancy surgery and CE were risk factors for reducing successful pregnancies after FTR surgery. A 2020 study by Shen et al.[28] also showed that ectopic pregnancy and types of infertility were the strongest risk factors for successful pregnancies following FTR surgery. Our study found that CE was associated with pregnancy failure after FTR. Possible reasons for this association are as follows: Firstly, women with CE may cause re-obstruction after FTR. The persistence of microorganisms is considered the main cause of CE.[29] Women with CE have a high rate of intrauterine bacteria detection, and these microorganisms are likely to affect the endometrium and the mucosa proximal to the fallopian tubes, causing re-obstruction of the fallopian tubes.[29] Secondly, CE may affect the implantation of the embryo.[31] Samantha L Margulies et al.[8] reported CE findings on hysteroscopy in 57.8% of women with a past history of three or more recurrent pregnancy losses. Most endometrial infections were due to common bacterial infections (58%), including gram-negative bacteria. *Mycoplasma hominis* was found in 10% of the cases. Chlamydia was found in 2.7% of the cases. Colonization by gram-negative bacteria reduced the embryo implantation rate. Endotoxins from gram-negative bacteria may induce a more dominant TH1 response at the decidua, stimulating the production of proinflammatory cytokines. This, in turn, created an endometrial paracrine environment that may lead

to embryonic injury, implantation failure, or spontaneous abortion.[28–31] After antibiotic therapy, the spontaneous pregnancy rate among women with CE who have been cured by antibiotics was higher than that among women with persistent CE.[32–36] Therefore, active treatment for women with CE may increase the spontaneous pregnancy rate in women with recanalized fallopian tubes.

This study has some limitations. The retrospective study design has inherent limitations. Considering that prospective cohort studies might be contrary to the subjects' interests, therefore, we opted for a retrospective study design. However, the sample size of this study was still relatively small. Future studies with larger sample sizes, preferably from multicenter cohorts, are needed to further validate our observations and to enhance the robustness of the conclusions.

Conclusion

CE is closely related to FTO. The presence of CE seems to decrease the likelihood of achieving spontaneous pregnancy following FTR. Pending further confirmation from larger, prospective studies, we suggest that women with FTO be tested for CE and receive appropriate treatment if diagnosed. This approach may help improve spontaneous pregnancy rates in this patient population.

Declarations

Ethics approval and consent to participate

This research was approved by the ethics committee of Beijing Shijitan Hospital, and its number is 2018-03. Considering that this study is a retrospective study, only the clinical data of patients are collected, which will not affect the treatment of patients and will not bring risks to their physiology. Researchers will do their best to protect patients' information from being leaked, so informed consent is exempted.

Consent for publication

All participants provided their consent for the publication of their data verbally. Verbal consent was obtained in a manner that ensured participant understanding and willingness to participate. This method was chosen to protect the participants' privacy and to maintain the confidentiality of the study. Verbal consent was recorded through secure audio recordings. This was done in compliance with the ethical standards and the conditions set by the ethics committee.

Author contributions

Yu Sun: Writing – original draft.

Dongyan Li: Data curation; Software.

Shuaihong Zhao: Supervision.

Mukun Yang: Data curation; Formal analysis.

Guangxia Cui: Methodology; Project administration.

Wenpei Bai: Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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