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The prevalence of fimbrial pathology in patients with early stages of endometriosis

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KEYWORDS:
Early stages of endometriosis;
Fimbrial pathology

Abstract

STUDY OBJECTIVE: The presence of fimbrial pathology in advanced endometriosis is clearly understood. However, little is known about the prevalence of fimbrial pathology in early stages of endometriosis. The purpose of this study is to determine the prevalence of fimbrial pathology in patients with infertility with early stages of endometriosis.

DESIGN: Historical cohort study (Canadian Task Force classification II/III).

SETTING: Tertiary referral center.

PATIENTS: The study group (Group 1) consisted of 315 infertile women who were found to have stage I or stage II endometriosis, and the control group (Group 2) consisted of 152 infertile women without endometriosis (Group 2).

INTERVENTION: Laparoscopic evaluation for the presence and type of fimbrial pathology.

MEASUREMENTS AND MAIN RESULTS: The prevalence of fimbrial pathology was significantly higher in infertile patients with early stages of endometriosis (50.2%) compared with infertile patients with no endometriosis (17.8%, $p < .0001$).

CONCLUSION: These preliminary data suggest the presence of fimbrial pathology in many patients with early stages of endometriosis. Such pathology may act as a mechanical factor interfering with the ovum pick-up mechanism.

The presence of adhesive disease that may entrap the fimbria in infertile patients with moderate and severe endometriosis is clearly understood. It represents part of fallopian tube involvement in adhesion formation as a result of healing of active pelvic endometriosis. However, little is known about the prevalence of fimbrial pathology in early stages of endometriosis. Peritubal and periovarian adhesions are considered the main mechanisms by which advanced endometriosis causes infertility.[1,2] On the other hand, the mechanisms by which early stages of endometriosis interfere with fertility are not fully understood.[3] The purpose of this study was to determine the prevalence of

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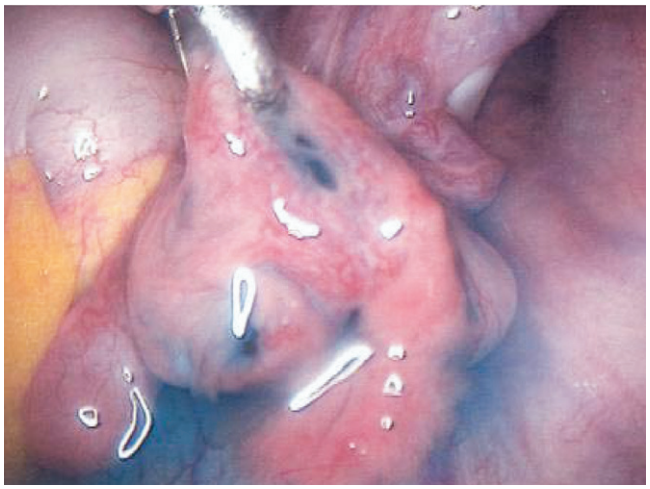

Figure 1 Fimbrial agglutination. One or more adhesive bridges of fimbria across the ostium.

fimbrial pathology in early stages of endometriosis in comparison with a control group of infertile women in whom endometriosis was not found.

Materials and methods

This is an historical cohort study conducted after obtaining approval by the local institutional research board of Wayne State University. The study was conducted at an infertility center (IVF Michigan) from December 1993 through December 2003. The study group (Group 1) consisted of 315 infertile patients who were found to have stage I or stage II endometriosis, and the control group (Group 2) consisted of 152 infertile patients who had no endometriosis and who fulfilled all criteria identified below.

In Group 1, endometriosis was diagnosed at the time of diagnostic laparoscopy. Group 2 consisted of women who had undergone gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer, or tubal embryo transfer (TET) for unexplained or male factor infertility (54); laparoscopic reversal of tubal ligation (20); or diagnostic laparoscopy for infertility evaluation (78). All patients in both groups had no history of pelvic or abdominal surgery except for tubal ligation, no history of chlamydia or gonorrhea infection, no history of pelvic inflammatory disease (PID), and had negative serology for *Chlamydia trachomatis* antibodies.

The majority of surgeries were performed by the same reproductive surgeon (the first author) under similar operative settings in all patients. Three- to four-portal entry laparoscopy was always performed. During laparoscopy, detailed pelvic findings were examined and reported. The data for each patient for this report were collected from a dictated operative report and from a detailed diagram that was drawn by the first author describing the presence and type of any fimbrial pathology.

Endometriosis, if present, was staged according to the Revised American Fertility Society Classification of Endometriosis.[4] Tubal perfusion with diluted indigo carmine dye for the assessment of tubal patency, and to confirm subtle fimbrial pathology, was performed in all patients in Group 1 and 78 patients who underwent diagnostic laparoscopy in Group 2. In the remaining 74 patients in Group 2, the absence of fimbrial pathology was determined based on careful evaluation before GIFT, TET, or laparoscopic reversal of tubal ligation. If fimbrial pathology was found, it was classified as unilateral or bilateral and its type was determined. Of note is that 1 or more fimbrial pathologies can be present on the same fallopian tube.

Three types of fimbrial pathology were identified: fimbrial agglutination, fimbrial blunting, and fimbrial phimosis. Fimbrial agglutination was defined as 1 or more adhesive bridges of fimbria across the ostium (Figure 1). Such pathology was confirmed by lifting the ridges with a laparoscopic Teflon probe (Elmed, Chicago, IL). Fimbrial blunting describes fimbrial adherence side by side, giving rise to a mitten rather than a glove appearance of the fimbriated end (Figure 2). Fimbrial phimosis describes an actual narrowing of the fimbriated end. Some patients with fimbrial phimosis have a concentric stricture of the fallopian tube at its distal end noted at the ampullary fimbrial junction (Figure 3). During tubal perfusion in these patients, there was dilation of the distal ampullary portion of the fallopian tube, and the dye was spilled out as a narrow stream. The techniques used to assess the fimbria depended not only on inspection by grasping the fimbria with a fimbrial-grasping forceps (Ubef, Vernon Hills, IL) and use of Teflon probe while injecting diluted indigo carmine, but also on inspecting the fimbria by underwater examination.

Statistical analysis was performed using χ^2 square analysis where appropriate, considering $p < .05$ statistically significant. Confidence intervals of the difference of the proportion between the 2 groups were calculated.

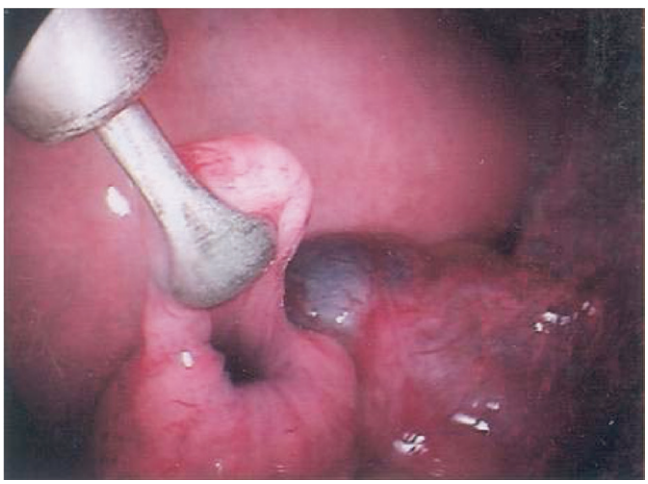

Figure 2 Fimbrial blunting. Fimbrial adherence side by side, giving rise to a mitten rather than a glove appearance of the fimbriated end.

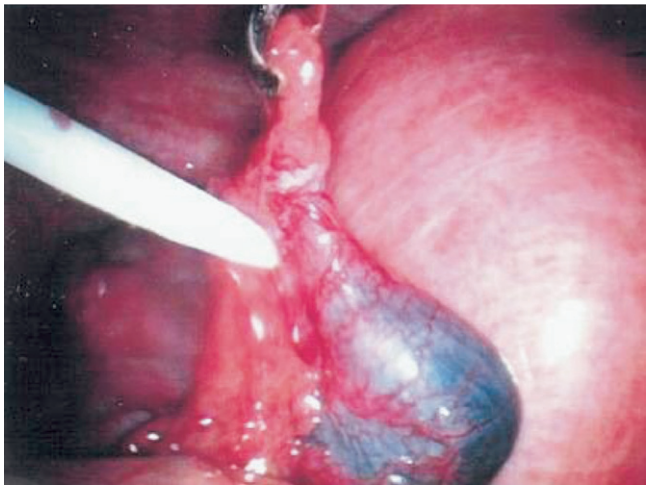

Figure 3 Fimbrial phimosis. Describes an actual narrowing of the fimbriated end. Some patients with fimbrial phimosis have a concentric stricture of the fallopian tube at its distal end noted at the ampullary fimbrial junction.

Results

At least 1 fimbrial pathology was found in 158 patients (50.2%) in Group 1, compared with 27 patients (17.8%) in Group 2 ($p < .0001$, CI 0.24–0.41) (Figure 4). Fimbrial pathology was unilateral in 61 patients (19.4%) in Group 1 and in 10 patients (6.6%) in Group 2 ($p < .001$, CI 0.07–0.19), and bilateral in 97 patients (30.8%) in Group 1 and 17 patients (11.2%) in Group 2 ($p < .0001$, CI 0.12–0.27) (Figure 4).

There was no significant difference in the incidence of unilateral fimbrial agglutination between the 2 groups: 38 patients (12.1%) and 10 patients (6.6%) in Group 1 and Group 2, respectively (Table 1, Figure 5). The incidence of unilateral fimbrial phimosis and blunting was significantly higher in Group 1: 59 patients (18.7%) and 31 patients (9.8%), respectively, compared with Group 2: 5 patients (3.3%) and 1 patient (0.7%), respectively ($p < .05$, CI 0.10–0.21; $p < .05$, CI 0.06–0.13, respectively) (Table 1, Figure 5).

In addition, there was no significant difference in the incidence of bilateral fimbrial agglutination between the 2 groups: 16 patients (5.1%) and 4 patients (2.6%) in Group 1 and Group 2, respectively. (Table 1, Figure 5). In contrast, the incidence of bilateral fimbrial phimosis and blunting was significantly higher in Group 1: 71 patients (22.5%) and 39 patients (12.4%), respectively, compared with Group 2: 11 patients (7.2%) and 3 patients (2%), respectively ($p < .05$, CI 0.09–0.21; $p < .05$, CI 0.06–0.15, respectively) (Table 1, Figure 5). Figure 5 illustrates that fimbrial phimosis (unilateral or bilateral) was the most common type of fimbrial pathology in the study group ($p < .05$).

Discussion

The role of mechanical factors in infertility secondary to stage III and IV endometriosis is well understood. As a result of widespread adhesion formation in advanced stages of endometriosis, tubal and ovarian involvement is common and to be expected. The mechanisms by which adhesion formation in advanced endometriosis reduces fecundity rate include reduced ovum pick-up mechanism, luteinized unruptured follicle syndrome, poor follicular growth, and tubal occlusion.[1] In addition, endometriosis per se even without adhesions may play a role in reducing fertility potential.[5]

However, little is known about the presence of fimbrial pathology in early stages of endometriosis. In addition, a detailed search in the English-language literature failed to illustrate a possible involvement of the fimbrial portion of the fallopian tube in the mechanisms by which early stages of endometriosis cause infertility. The following mechanisms were postulated as the underlying cause of infertility in early stages of endometriosis: prostaglandin theory, macrophage theory, immune theory, disturbance of ovulation, decreased implantation rate, recurrent miscarriage, and reduced ovum pick-up mechanisms.[4] No clear mechanism was described in the literature to explain how ovum pick-up could be reduced in stage I and II endometriosis. However, some filmy adhesions around tubes and ovaries may be present in advanced cases of stage II (almost stage III), and obviously these adhesions may interfere with ovum pick-up mechanism.

The first report of subtle fimbrial abnormalities in early stages of endometriosis was published by Fakih and Marshall.[6] These authors used a very similar fimbrial grading system of fimbrial pathology. In their report, the incidence of fimbrial pathology was 30%, 42%, and 55% in mild, moderate, and severe endometriosis, respectively. Their findings were determined at the time of GIFT procedure; therefore, tubal perfusion was not performed. In addition, PID as a possible underlying etiology in their study was ruled out based on a negative history of such a disease. However, many patients who have PID do not experience any symptoms. In our paper, every patient underwent a *C. trachomatis* antibody titer (immunoglobulin [Ig] G and IgM), and any patient who had a positive titre was excluded. In addition, any patient who had a history of gonorrhea and/or PID was excluded. Therefore, we believe

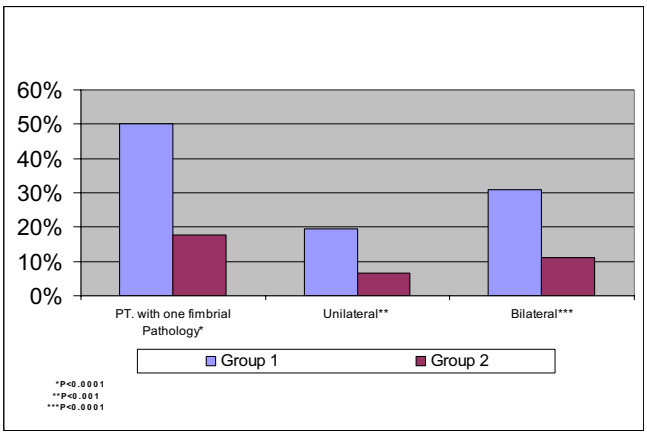

Figure 4 Summary of fimbrial pathology in patients with endometriosis (Group 1) and controls (Group 2).

Table 1 Summary of the type of fimbrial pathology in patients with endometriosis (Group 1) and controls (Group 2)

Group	Unilateral			Bilateral		
	Agglutination No. of patients (%)	Blunting* No. of patients (%)	Phimosis* No. of patients (%)	Agglutination No. of patients (%)	Blunting* No. of patients (%)	Phimosis* No. of patients (%)
Group 1	38 (12.1)	31 (9.8)	59 (18.7)	16 (5.1)	39 (12.4)	71 (22.5)
Group 2	10 (6.6)	1 (0.7)	5 (3.3)	4 (2.6)	3 (2.0)	11 (7.2)

*p <.05

that our data reflect more accurately the likelihood that the findings of fimbrial pathology in our patients did not appear to be due to PID.

Our study is the first case controlled study that compares the incidence of fimbrial pathology in patients with early stages of endometriosis and those with no endometriosis in the absence of any other etiology that may predispose to adhesion formation. The incidence of fimbrial pathology in patients with early stages of endometriosis (50.2%) was significantly higher than its incidence in other infertile patients (17.8%). Such significance was maintained when we analyzed data of unilateral or bilateral fimbrial pathology. However when the type of fimbrial pathology was analyzed, there was no significant difference in the incidence of fimbrial agglutination between patients with or without endometriosis. Therefore, one may assume that the sole presence of such fimbrial pathology may not be related to endometriosis. However, it is worth noting that the sample size for fimbrial agglutination was not large enough to achieve strong power. It is possible that if a large group of patients is added while maintaining the same rates of the tested outcomes, a statistical significance may be achieved. There are no data available on the incidence of fimbrial agglutination in fertile women. In contrast, the incidence of fimbrial phimosis and fimbrial blunting in patients with endometriosis was significantly higher than in patients without endometriosis, respectively. These data may suggest cause and effect between endometriosis and some cases of fimbrial phimosis and blunting, or they may reflect a correlation only. Our data are similar to the data published by Fakih and Marshall in selected groups of patients with endometriosis who underwent GIFT procedure.[6]

Lack of careful evaluation of the fimbria once blue dye is seen, suggesting tubal patency, may account for the failure of detecting such subtle pathology. The performance of a 2-puncture laparoscopy limits the ability of the gynecologist to thoroughly evaluate the fimbria, especially on the left side. In the authors' opinion, careful evaluation of the fimbria requires 3-portal entry and the use of fimbrial-grasping forceps. Our group first observed this subtle fimbrial pathology in patients with early stages of endometriosis while performing GIFT procedures. Such findings were similar to the findings by Fakih and Marshall.[6] During the GIFT procedure, the fimbriated end of the fallopian tube is grasped with fimbrial-grasping forceps before the GIFT catheter is cannulated into the ampullary portion of the tube. After repeated observations, we adopted this technique for evaluation of the fimbria during diagnostic laparoscopy.

Subtle variations in tubal anatomy, including accessory tubes, single diverticulum of the fallopian tube, and convoluted oviducts, have been cited as making significant contribution to infertility.[7–10] Cohen and Katz reported that convoluted oviducts may be associated with infertility, endometriosis, and fimbrial phimosis.[10] Some investigators reported that infertile women had significantly more tubal variations, including fimbrial pathology, than did their fertile counterparts.[11]

One question would be, what is the origin of such fimbrial pathology in early stages of endometriosis? One possibility is the presence of certain factors in the peritoneal fluid of patients with endometriosis that may lead to agglutination, blunting, or even phimosis. One such factor was proposed by Suginami and Yano.[12] Initially, Suginami et al[13] proposed the presence of a factor inhibiting ovum capture by the oviductal fimbria to be present in endometriosis peritoneal fluid. This was an in vitro study on the oviductal fimbria of the golden hamster, which was incubated with endometriosis and non-endometriosis peritoneal factor, and its ability of ovum capture of the mouse oocyte-cumulus complex was studied. Subsequently, Suginami and Yano,[12] in a similar experiment, confirmed their initial results and demonstrated by scanning electron microscopy (SEM) the presence of ovum capture inhibitor (OCI)-related membrane on the fimbria, by which fimbrial cilia were

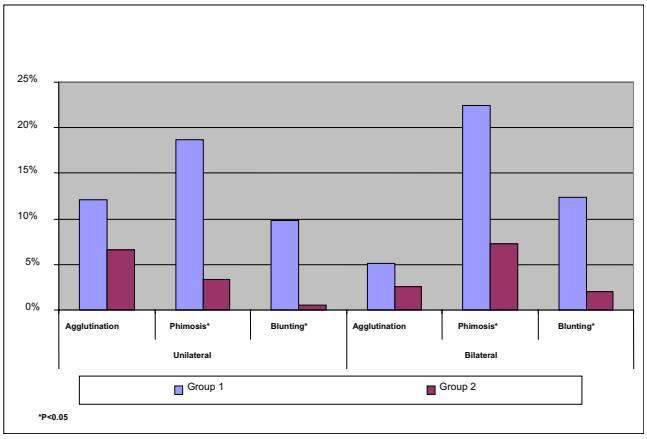

Figure 5 Summary of the type of fimbrial pathology in patients with endometriosis (Group 1) and controls (Group 2).

completely concealed. In addition, in their experiment using a high-magnification SEM and immunohistochemical staining, they demonstrated that the OCI-related membrane appeared to consist primarily of amorphous aggregates and, to a much lesser extent, filamentous aggregates of what look like fibrin polymers. The latter was found to be positively stained with antifibrin antibody. These authors hypothesized that in endometriosis-associated infertility, the increase in fecundity after hysterosalpingography or after hydrotubation is due to removal of OCI-related membrane through these maneuvers. The finding of fimbrial pathology in 50.2% of patients with early stages of endometriosis may be due to further change in such OCI-related membrane, resulting ultimately in the type of pathology observed in our study.

Alternatively, the presence of fimbrial pathology may be related to a subtle developmental anomaly during differentiation of the Müllerian ducts. In turn, the association between endometriosis and fimbrial pathology may be a subtle clinical picture of what has already been described in the literature of higher incidence of endometriosis in patients with obstructive Müllerian anomalies[14,15] and, more recently, in nonobstructive anomalies.[16–18] There are limitations in our study. First, this is a retrospective observational study and therefore is prone to clinical bias. However, most of the surgeries were performed by one surgeon (first author). Therefore, for such an observational study, this represents an area of strength by reducing interpersonal variation, but has the weakness of the risk of personal bias by just one observer. Second, although every effort was made to exclude patients who may have had their fimbrial pathology as a result of PID due to *C. trachomatis*, gonococci, and other organisms, the possibility still exists that in some patients in Group 1 fimbrial pathology may have been due to PID and not endometriosis. Therefore, further studies are needed to support our findings.

It is possible that careful evaluation of the fimbriated ends of the fallopian tubes in infertile patients with early stages of endometriosis may detect such subtle anomalies. Our preliminary data suggest improvement in fertility potential after surgical correction of such fimbrial pathology.[19]

Conclusion

In summary, these preliminary data suggest the presence of fimbrial pathology in many patients with early stages of endometriosis. Such pathology may act as a mechanical factor interfering with the ovum pickup mechanism. Additional studies will be necessary to confirm our findings and to determine if the surgical correction of these forms of fimbrial pathology associated with early stages of endometriosis will enhance fertility.

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