Fallopian tube and endometriosis: an ambiguous relationship

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ABSTRACT

Background: The Fallopian tube, or oviduct, plays an essential role in mammalian reproduction. Endometriosis affects 2 to 10% of women of reproductive age. Infertility and nulliparity are regarded as risk factors for endometriosis, therefore an increased prevalence of this affliction in the population of infertile women may be expected. The literature shows that endometriosis affects 30% to 68% of infertile women. However, its prevalence varies considerably depending on the type of infertility (i.e. male or female), the presence of chronic pelvic pain, and whether or not a previous exploratory laparoscopy was performed. The effects of endometriosis on fertility are still debated. While the impact of moderate or severe endometriosis on fertility is well established, especially in the presence of adhesions, the role of minimal or mild lesions, which are the most common in infertile women, is still controversial. Therefore, different possible underlying mechanisms have been proposed, including tubal alterations associated with endometriosis.

Conclusion: Tubal pathologies have an influence on fertility in these patients. This short review analyzes the effect of tubal endometriosis on fertility.

KEYWORDS

Oviduct, tubal endometriosis, infertility, etiopathogenesis.

Introduction

The fallopian tube, or oviduct, plays an essential role in mammalian reproduction. Endometriosis affects 2 to 10% of women of reproductive age [1]. Infertility and nulliparity are regarded as risk factors for endometriosis, therefore an increased prevalence of this affliction in the population of infertile women may be expected. The literature shows that endometriosis affects 30% to 68% of infertile women [1]. However, its prevalence varies considerably depending on the type of infertility (i.e. male or female), the presence of chronic pelvic pain, and whether or not a previous exploratory laparoscopy was performed.

The effects of endometriosis on fertility are still debated. While the impact of moderate or severe endometriosis on fertility is well established, especially in the presence of adhesions, the role of minimal or mild lesions, which are the most common in infertile women, [2,3] is controversial [4]. Therefore, different possible underlying mechanisms have been proposed, including tubal alterations associated with endometriosis.

The aim of this study is to review tubal endometriosis (on which data are limited), in order to evaluate structural and functional alterations associated with endometriosis in the fallopian tube, and determine the contribution of the oviduct to endometriosis etiopathogenesis.

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Tubal location of endometriosis is rare

With only a few cases reported in the literature, tubal endometriosis seems to be a rare condition. In a well-known study, the anatomical distribution of endometriotic lesions was evaluated in a population of 182 infertile women [5]. The authors described endometriosis on the left tube in 4.3% of the pelvic locations and on the right tube in only 1.6%; tubal endometriosis thus accounted for about 6% of all the pelvic locations. In a similar study of 1101 patients, conducted by our group, tubal endometriosis was found in 50 patients (4.5%) (superficial implants or cornual occlusive nodules confirmed by pathological analysis) [6]. However, if all kind of lesions possible, superficial implants seem to be the most frequent (78% in our series) (Figures 1 and 2). In all the observed cases, lesions were located either on the ampulla or on the tubal isthmus, but never on the fimbriae. Tubal endometrioma appears to be very rare; only one adolescent case has been reported [7], while we also observed a case of endometrioma at the level of right tubal isthmus in our study (Figure 3). Rare complications associated with tubal endometriosis, such as hemoperitoneum or adnexal twisting, have been reported.

Although the oviduct is the first organ exposed to reflux of endometrial fragments, endoluminal lesions are unusual. This paradox is unexplained. The tubal epithelium is able to produce endometrial-like tissue, as demonstrated by the phenomenon of endometrialization observed in the tubal lumen after tubal sterilization [8]. Some cases of mid-segment occlusion of endometriotic nature origin have also been described. After tubal ligation (and especially after tubal coagulation), histological examination may reveal epithelial inclusions or localized endometriosis [9,10].

Several series, on the basis of the results of histological examinations, have reported a prevalence of endometriosis ranging from 12 to 14.3%. The data come mainly from patients undergoing microsurgical proximal tubal occlusion, and the vast majority of reported lesions were located in the intramural portion of either the fallopian tube or the isthmus. These are better known as proximal or cornual occlusive lesions. Without a histological examination, it is not always possible to distinguish tubal endometrial lesions from isthmic nodular salpingitis (Figure 4).

Impact of pelvic endometriosis on tubal function

The fallopian tube, by means of a still incompletely understood mechanism of communication between spermatozoa and the tubal mucosa [11,12], allows the transport, storage, capacitation and selection of the spermatozoa for fertilization. The tube also allows the uptake and reception of the oocyte. It provides the microenvironment in which fertilization and initial embryonic development take place. Finally, the fallopian tube also allows the embryo to reach the uterine cavity at the appropriate time, when endometrial receptivity is optimal. These physiological processes can be altered by different pathologies, mainly microbial infections and endometriosis.

1. Microenvironment and tubal function alterations

Abnormalities of the tubal environment associated with pelvic endometriosis are difficult to identify, requiring a lavage or an excision of the tube. Cytological analysis is also possible with

Figure 1 Implants located at the tubal level, close to the right infundibulum.

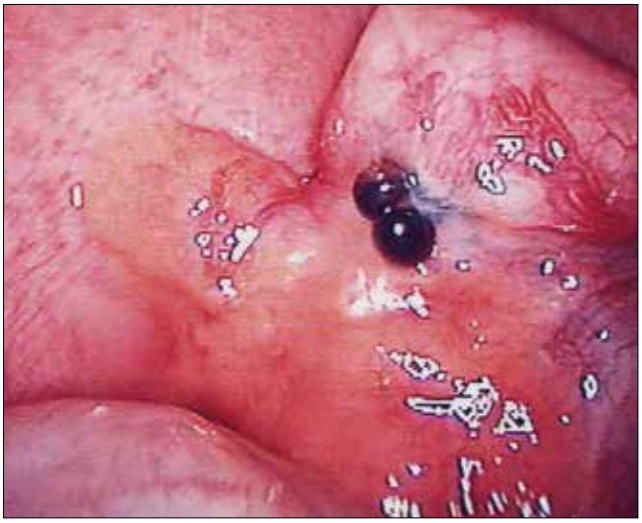


Figure 2 Tiny implants at the right tubal ampulla.

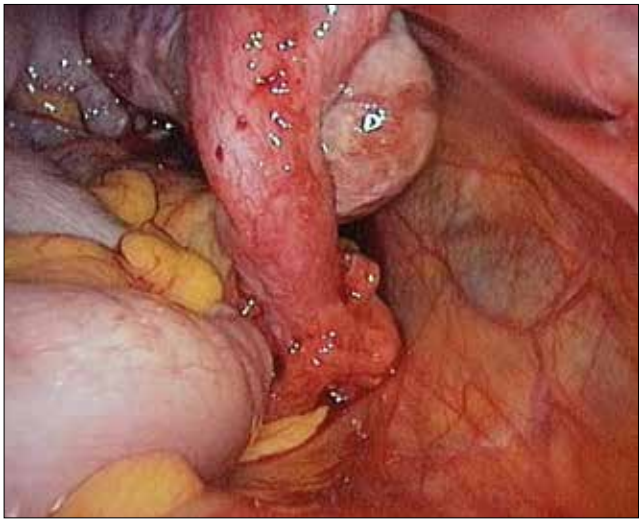


Figure 3 Endometrioma at the level of right tubal isthmus.

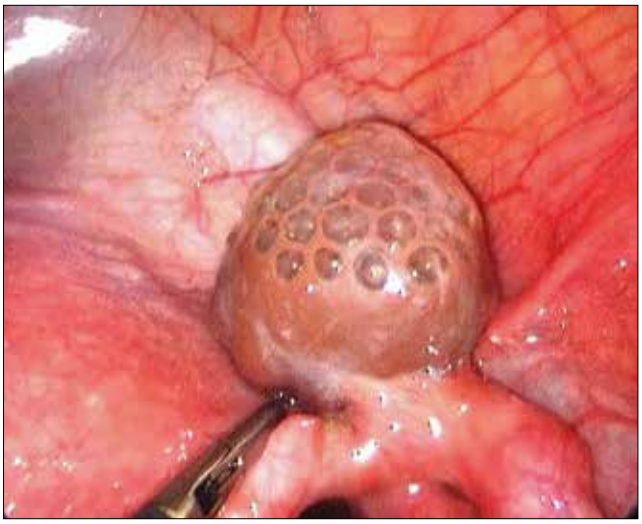
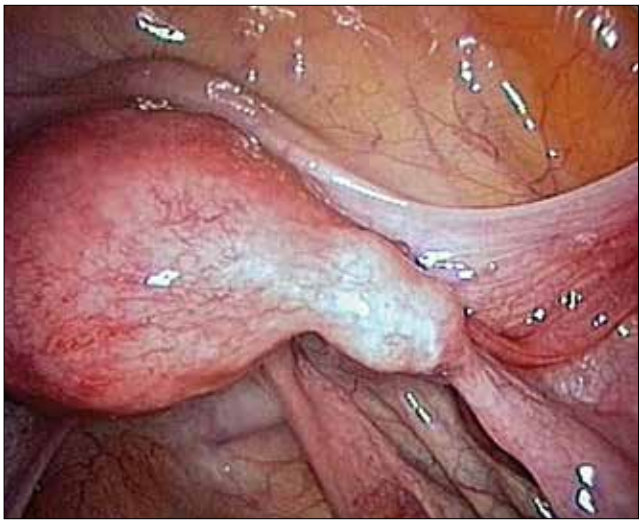


Figure 4 Proximal right nodule without methylene blue extravasation.



adequate instrumentation [13]. Several studies have shown modifications comparable to those observed in the peritoneum in a pro-inflammatory environment, namely:

- an increased concentration of inflammatory cells;
- an increased concentration of macrophages in the ampullary portion of the salpinx (compared with the concentration seen in sterilized women) [13,14];
- the presence of immunological cells such as leukocytes;
- the presence of cytokines in the distal portion of the fallopian tube, originating from the peritoneal fluid;
- dysregulation of prostaglandin production, i.e. increased production of prostaglandins E and F in the ampulla and the isthmus, resulting in a change in the PGF/PGE ratio.

Alterations of ciliary activity [15] and of tubal peristalsis have been observed in endometriosis, especially if it is associated with adenomyosis [16]. All these findings suggest that endometriosis may affect tubal functions.

2. Consequences on tubal function

Tubal dysfunction may occur in the presence of tubal or pelvic endometriosis. Observation of radionuclide migration through permeable fallopian tubes in infertile patients has shown that the pathway of these particles is impeded if endometriosis is present [17]. A reduction in GIFT (gamete intrafallopian transfer) in cases of endometriosis has been described. Thus, we can conclude that tubal dysfunctions observed in this condition may contribute to hypofertility, particularly in the presence of minimal or mild lesions.

a. Impact on spermatozoa migration, storage and function

Data on the tubal migration of spermatozoa in patients with endometriosis are contradictory. Spermatozoa seem to be found in smaller amounts in the peritoneal fluid of patients with endometriosis [18] and their presence has some favorable prognostic value. Other authors describe a reduction in their motility [19] or even completely immobile spermatozoa [20]. Prostaglandin F2 may be responsible for this decreased motility [21]. Sperm phagocytosis by macrophages has been reported to be increased in endometriosis [22]. Moreover, endometriosis may also affect the interactions between spermatozoa and the tubal mucosa [23]. The interactions that take place between spermatozoa and the tubal isthmus epithelium are an important step in spermatozoa migration and preparation for fertilization. Attachment of spermatozoa contributes to the storage role of this tubal portion and might reduce the risk of polyspermic fertilization. In the presence of endometriosis, more spermatozoa become attached to the epithelium of the tubal ampulla, suggesting that a consequent reduction in the number of free spermatozoa available to participate in fertilization may contribute to reduced fertility [23].

b. Oocyte uptake and transport

Oocyte uptake is an essential part of reproduction. Although the mechanism of this process is not completely known, contact between the infundibulum and the ovary (thanks to the contraction of muscles in myosalpinx and tubo-ovarian ligaments) is its first step. If this step is not capital (some oocytes are caught after transperitoneal migration), it improves the tubal migration of the oocyte. Direct contact between infundibulum cilia and the cumulus surrounding the oocyte permits oocyte uptake [24]. The journey of the oocyte in the fallopian tube lasts three days in mammals, with oocyte retention in the ampullary portion (the usual place of fertilization) lasting 72 hours. "Dialogue" between the oocyte and the tubal epithelium probably plays a role in this phenomenon, but the underlying molecular mechanisms are still poorly understood. The impact of the tubal microenvironment associated with endometriosis is also unknown.

Ciliary activity might be impaired even in endometriosis cases with apparently healthy fallopian tubes [25]. The presence of a macromolecular inhibitor has also been reported, but never confirmed by further studies [26].

Tubal abnormalities associated with endometriosis

In addition to endometriosis located in the fallopian tube, tubal abnormalities may also occur in association with pelvic endometriosis diagnosed elsewhere. The diagnosis of tubal abnormalities is based on imaging and laparoscopy. In women with endometriosis, imaging has shown contrasting performances, although the studies concerned small numbers of cases. In a study of 35 women, hysterography showed a sensitivity of 40% and a specificity of 83% in identifying tubal abnormalities associated with endometriosis [27]. A study of 42 women with laparoscopic confirmation of associated endometriosis reported better performances of contrast hysterosonography (hysterosalpingo-contrast-sonography), with a sensitivity of 85% and a specificity of 93% [28]. Finally, only laparoscopy and fertiloscopy allow correct assessment of the state of the fallopian tube, and particularly of the infundibulum.

Many fallopian tube abnormalities have been described: abnormalities of the infundibulum (phimosis, agglutination of the fimbriae, peritubal adhesions, for example), hydrosalpinx, diverticulum of the accessory infundibulum and cornual polyp, among others. They are located mainly in the infundibulum, although other parts of the tube may also be altered. Most of the abnormalities observed are considered subtle and their impact on fertility is thus uncertain. A study of 124 women submitted to laparoscopy for infertility associated with pelvic endometrial lesions evaluated their tubal state and arbitrarily classified the impact of lesions on fertility [29]. No impact of the lesions was reported in 75 of them, whereas there was a moderate impact in 32, and in the remaining 16 cases, no procreation seemed possible.

Finally, in a study of 87 women with ovarian endometriosis, surgically removed fallopian tubes were analyzed [30]. Chronic salpingitis scars were found in 33% of the cases. Unfortunately, these data have not been confirmed by other studies, but the presence of salpingitis associated with endometriosis might contribute to hypofertility.

1. Alterations of the tubal infundibulum

In a further study, 315 women with stage I/II endometriosis, no history of infection or pelvic surgery, and negative Chlamydia trachomatis serology were compared with a control group

of 152 infertile women without endometriosis [31]. Abnormalities of the fimbriae were assessed by laparoscopy. This study demonstrated a significantly increased prevalence of infundibulum alterations in the endometriosis group compared with the control group (50.2% vs 17.8%). The authors concluded that these abnormalities might contribute to the hypofertility observed in these women. However, a negative influence of tubal abnormalities on GIFT outcome was also reported [32].

Pregnancy is possible following fimbrioplasty treatment of these abnormalities. A retrospective study compared reproductive outcome after fimbrioplasty in a group of women with unexplained infertility or stage I endometriosis (n = 50) with reproductive outcome in a control group (n = 57) in whom no treatment had been administered [33]. The observed pregnancy rate was 40% in the treated group and 2.7% in the control group.

2. Other lesions found

Hydrosalpinx is usually caused by a microbial infection. There is no study in the literature reporting hydrosalpinx caused by endometriosis, although we have observed one case of hydrosalpinx associated with endometriotic nodules located on the tubal wall (Figure 5). However, an infectious cause could not be excluded in this patient, despite her negative Chlamydia trachomatis serology.

Tubal diverticulum and accessory infundibulum are rare findings, with only a few cases reported in the literature [34]. Accessory infundibulum is more often found in the ampullary portion of the fallopian tube. In a retrospective study involving 1113 women undergoing laparoscopy for infertility, only 21 cases of accessory infundibulum had been reported (1.9%) [35]. Among the 403 women with endometriosis, an accessory infundibulum was discovered in 19 (4.7%), while only 2 cases (0.3%) were identified in a control group of 701 patients without endometriosis (p = 0.001). In the 18 operated cases, 12 pregnancies followed (66.7%).

Cornual polyp (a polyp of the proximal portion of the oviduct) is composed of ectopic endometrial stromal and epithelial cells, which is the definition of endometriosis. According to hysterosalpingography data mainly obtained in infertile women, the prevalence of uterine horn polyps is 2 to 3%; on the other hand, when the diagnosis is based on the pathological analysis of hysterectomy pieces, the prevalence ranges from 1.2% to 33% [36].

In a prospective study conducted in 22 infertile women with uterine horn polyps, 4 cases were associated with anovulation and 6 cases with endometriosis 36. In line with previous observations, the authors concluded that infertile women with uterine horn polyps were more likely to have an associated endometriosis.

Role of the fallopian tube in the genesis of endometriosis

1. Regulation of menstrual reflux by the fallopian tube

Menstrual reflux through the fallopian tubes leading to peritoneal grafting of endometrial fragments is the most validated mechanism and also the one most often cited to explain the genesis of endometriosis. The importance of reflux is correlated with the abundance of menstruation and the presence of an obstacle to menstrual flow (iatrogenic cervical stenosis, obstructive malformation).

The fallopian tube plays an important role in the menstrual debris regurgitation theory (Figure 6), a notion first suggested in 1985 [37]. The reflux results from a functional asynchrony between cervical and utero-tubal junction pressure. Relative hypotonia of the utero-tubal junction has been found in women with endometriosis and the morphology of the intramural portion of the tube seems to be the reason for this hypotonia. Three morphologies have been described: linear, curved and tortuous. Two studies evaluated the risk of endometriosis based on these morphologies. The first one involved 154 dissected oviducts: the tube was tortuous in 74.02% of cases (n = 114), curved in 13.64% (n = 21) and had a linear path in 12.34% (n = 19).

Figure 5 Endometriosis implants located close to a hydrosalpinx adherent to the wall.

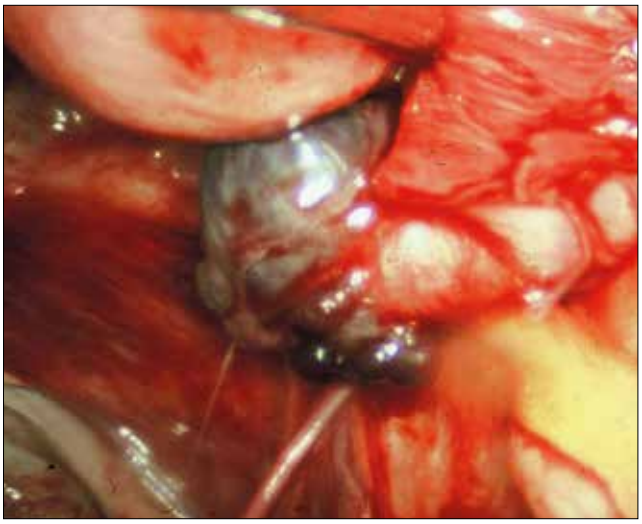
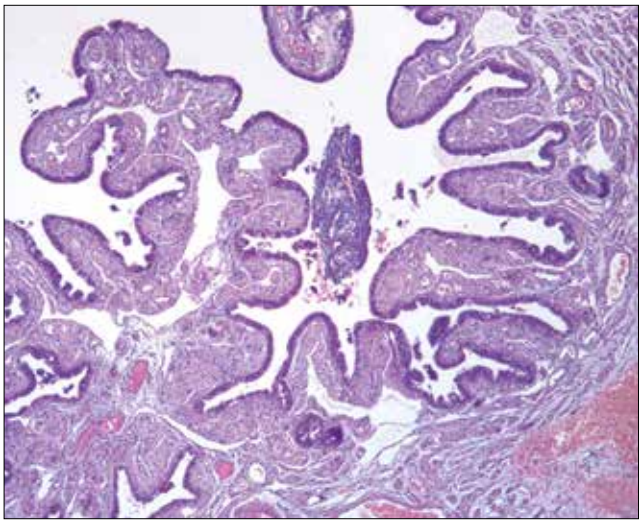


Figure 6 Presence of menstrual debris in the fallopian tube.



Endometriotic lesions were identified in 12 women with either a curved or a linear oviduct on at least one side. [38] Any woman with a bilaterally tortuous course of the interstitial part of the oviducts had no endometriosis. The second study involved 227 patients who underwent a hysterectomy, allowing a retrospective analysis of the tubal morphology and assessment of endometriosis risk [39]. Endometriosis was again less frequent in cases with a tortuous path of the intramural portion of the fallopian tube. These two studies, with concordant results, demonstrated that tortuous fallopian tube morphology diminishes the risk of endometriosis.

2. Role of the oviduct in the histogenesis of endometriosis

The ovary is the site most frequently affected by endometriosis. The hypothesis of a tubal origin of ovarian endometriosis was suggested in a study of epithelial ovarian carcinoma characterized by a tubal phenotype [40]. Other publications have confirmed the role of the fallopian tube in the origin of malignant ovarian lesions [41]. Genes (FMO3 and DMBT1) and their corresponding proteins, strongly expressed in the fallopian tube, were used as biomarkers for analyzing ovarian endometriosis in 32 patients [42]. The authors observed that 60% of ovarian endometriosis may have a fallopian tube origin and 40% an endometrial origin. This endometriotic cells migration is favored by close contact between the infundibulum and the ovary and by desquamation of tubal cells. However, the authors concluded that these data must be confirmed by further studies.

Conclusion

Tubal endometriosis seems to be rare. This location of endometriosis is found in only 4.5 to 6% of women affected by the condition. Tubal endometriosis essentially consists of superficial implants on the ampullary portion of the Fallopian tube or proximal occlusive lesions. In the presence of pelvic endometriosis, several tubal morphological abnormalities have been identified. These findings may help to explain the mechanism of hypofertility associated with endometriosis, especially stage I or II. Some abnormalities of tubal micro-environment and function have also been reported. Tubal abnormalities may disrupt gamete and embryo transport and function. The Fallopian tube also plays a major role in the genesis of endometriosis: the morphology of its proximal portion determines the importance of menstrual reflux and the risk of endometriosis. Finally, tubal cells seem to be at the origin of tubal endometriosis.

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