# Ovarian endometriosis and peritoneal endometriosis: are they different entities from a fertility perspective?

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This review summarizes the recent literature concerning new data on the pathogenesis of peritoneal endometriosis and its natural evolution. Indeed, the main concern in endometriosis is the choice of treatment in cases of infertility problems: medical or surgical. This concern could hypothetically be avoided if endometriosis were considered as a spontaneously regressive phenomenon. The present paper also discusses the risk of recurrence and the results of in-vitro fertilization and embryo transfer in cases of ovarian endometriosis. Whatever type of surgery is performed, the results of in-vitro fertilization and embryo transfer are not impaired, especially if damage to the ovarian cortex is avoided. Further studies are required to determine if oocytes from endometriosis patients are altered and could be responsible for the development of lower quality embryos. Curr Opin Obstet Gynecol 14:283–288. 

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**Abbreviations**

| | |
|---|---|
| **CA125** | cancer antigen 125 |
| **MPA** | medroxyprogesterone acetate |
| **IVF** | in-vitro fertilization |
| **GnRH** | gonadotropin-releasing hormone |


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## Introduction

Several theories relating to the pathogenesis of endometriosis have been proposed since its first detailed description in 1860 by von Rokitansky [1]. The most widely accepted theory, the transplantation theory, was proposed in 1927 by Sampson [2] who observed that endometrial cells were regurgitated through the fallopian tubes during menstruation. The extensive description of morphologic and morphometric similarities between eutopic endometrium and red lesions constitutes an argument in favor of the transplantation theory for peritoneal endometriosis [3]. This theory has recently been confirmed by the transplantation of cultured explants of human endometrium and the transplantation of human menstrual endometrium into nude mice [4,5]. The mechanism of adherence of endometrial cells to the peritoneum is still unclear and the question of the condition of the mesothelial layer (intact versus damaged) is still unanswered. Indeed, some studies support the hypothesis that the mesothelial layer acts as a barrier to the attachment of ectopic endometrium and that a damaged epithelial layer is a condition for the development of peritoneal endometriosis [6,7]. On the other hand, in-vitro and in-vivo models of endometriosis have demonstrated that intact mesothelium permits the implantation of endometrial cells and that endometrial stromal cells play a crucial role in this attachment step [5,8,9•]. The in-vivo model of peritoneal endometriosis has been validated by Grummer *et al.* [10] who described promising tools to test the effect of new therapeutic strategies, such as different hormone agonists/antagonists or antiangiogenic factors in endometriosis.

As endometriosis is an estrogen-related disease and some endocrine disrupters in humans mimic estrogen, the link between endometriosis and endocrine disrupters has been investigated [11]. In rhesus monkeys, chronic exposure to dioxin directly correlates with a significant increase in the incidence of endometriosis [12] but this has not been confirmed in humans [13].

The pathogenesis of ovarian endometriosis is a source of controversy. The findings of Hughesdon [14] suggested that adhesions are not the consequence, but rather the cause of endometrioma formation. Observations by Brosens *et al* [15], based on ovarioscopy and in-situ biopsies, were in agreement with the hypothesis of Hughesdon. In more than 90% of typical endometri-

omas, the pseudocyst is formed by an accumulation of menstrual debris from the shedding and bleeding of active implants located by ovarioscopy at the site of inversion, resulting in progressive invagination of the ovarian cortex [15]. Although there is a consensus concerning the invagination theory, there is controversy over the implantation theory and the metaplasia theory described by Nisolle and Donnez [3,16], in which the invaginated ovarian coelomic epithelium undergoes metaplasia in typical glandular epithelium and stroma. Even if peritoneal endometriosis and ovarian endometriosis are described as two different entities with different histogeny [3], similarities have also been noted. Indeed, immunohistochemical analysis of proliferative activity and steroid receptors [17] suggested relative hormonal independence, or at least the existence of a different mechanism of proliferation control, in both red peritoneal lesions and ovarian endometriosis compared with eutopic endometrium. The high proliferative activity of the stroma and the extensive vascular network in these two types of endometriotic lesions led us to suggest that the endometriotic stroma probably plays a primordial role in the development and growth of endometriosis [3,17].

The aim of this review is to analyze the impact of peritoneal and ovarian endometriosis on infertility and to answer the following question: from a fertility perspective, are these entities different? The impact of the third entity the rectovaginal adenomyosis, responsible mainly for pelvic pain, will not be discussed in the present paper.

## Diagnosis of endometriosis

Noninvasive approaches such as observation of symptoms (dysmenorrhea, pelvic pain, or dyspareunia), physical examination and ultrasound have been proposed to identify women with endometriosis [18]. Women with ovarian endometriosis were successfully identified preoperatively (100% of cases) but nonovarian endometriosis could not be predicted by such noninvasive methods (38% of cases). The authors concluded that with high-resolution ultrasound performed by experienced clinicians, in combination with signs noted on physical examination, ovarian endometriosis could be accurately diagnosed.

Toki *et al.* [19] described a strong correlation between serum cancer antigen 125 (CA125) levels and the proliferation marker (Ki-67) labeling index, suggesting that proliferating endometriotic epithelial cells are activated and may secrete CA125. Although it does not suggest a higher stage or wider spread of endometriosis, the clinical implications of a raised serum CA125 may be that the endometriotic lesions could be very active. The potential use of preoperative medical treatment, however, is not discussed.

When compared with standard laparoscopy, transvaginal hydrolaparoscopy [20•] seems to be superior for the detection of subtle endometriotic adhesions of the ovary. Filmy, microvascularized, nonconnecting adhesions were present in the majority of infertile patients with minimal to mild endometriosis, and were only observed on transvaginal hydrolaparoscopy. Such adhesions, whose primary role in the pathogenesis of ovarian endometriosis has been previously discussed, probably reflect subtle inflammation and early endometriotic disease of the ovary. If a 100% correlation [21] were noted in cases of tubal factors and adhesions, transvaginal hydrolaparoscopy could fail to identify endometriosis of the bladder, for example.

## Peritoneal endometriosis: transplantation theory

Previous animal models [5] revealed that endometrial cells play a crucial role in the attachment step. Very recently, Selam *et al.* [22] suggested that attachment of endometrial stromal cells to the peritoneum during retrograde menstruation could lead to an increase in the expression of Fas ligand, a mediator of the apoptotic pathway. Induction of Fas ligand expression by adhesion of endometrial stromal cells to the extracellular matrix may be involved in the development of a relative immunotolerance by inducing apoptosis of cytotoxic T lymphocytes, which will allow the development of endometriosis.

Dmowski *et al.* [23] found that spontaneous apoptosis is decreased in the endometrial glands of women with endometriosis, indicating that an increased viability of endometrial cells shed during menses facilitates the cells' survival and implantation.

Very recently, Chung *et al.* [24] described higher matrix metalloproteinase-9 and lower tissue inhibitor of metalloproteinases-3 messenger RNA expression in ectopic and eutopic endometrium from endometriosis patients than that observed in patients without endometriosis, suggesting that increased proteolytic activity of the endometrium could result in the development of endometriosis.

## Is endometriosis a spontaneously regressive phenomenon or a progressive phenomenon?

In 1997, Nisolle and Donnez described a hypothesis of evolution of peritoneal endometriosis [3]. Morphologic and morphometric data led them to consider, in agreement with Brosens, red lesions as early endometriosis and black lesions as advanced disease [3]. White lesions are believed to be healed endometriosis or quiescent or latent lesions. This hypothesis corroborates the clinical findings of Redwine [25] that red lesions precede the others and that with time, their presence

decreases as they are replaced by black and ultimately white lesions.

In a recent study [4], it was demonstrated that human endometrium obtained during the late secretory phase could be successfully transplanted into nude mice and that all the grafts revealed histological characteristics of the proliferative phase, even if the endometrial biopsy had been taken during the secretory phase. Moreover, transplantation of human menstrual endometrium [5] was also found to be successful and a high vascular endothelial growth factor score was observed in stromal cells, as early as 5 days after transplantation, suggesting that an active vascular network is a necessary condition for the survival of the graft.

Numerous recent data have confirmed the previously described hypothesis of evolution of peritoneal endometriosis [26••,27,28]. Indeed, differences in the expression of the cyclin-dependent kinase inhibitor $p27^{Kip1}$ [26] have been found between eutopic endometrium, red peritoneal and black peritoneal lesions. $p27^{Kip1}$ is involved in the progesterone induced growth suppression of eutopic endometrium and could be a unique negative regulator in eutopic endometrium glandular cells. p27 induces cell cycle arrest in response to extracellular antiproliferative signals such as transforming growth factor-$\beta$. As a significantly higher labeling index of glandular epithelial and stromal cells was detected for $p27^{Kip1}$ in black lesions than in red lesions, the results of this study support the idea that black and red peritoneal lesions may be different stages of the spontaneous evolution of endometriotic implants. Matsuzaki *et al.* also suggested that red lesions may evolve into black lesions, at least partly as a result of increased $p27^{Kip1}$ expression in both glandular epithelial and stromal cells. This study is in accordance with previous findings but the mechanism whereby $p27^{Kip1}$ protein expression is induced in peritoneal endometriosis is still unknown.

Matsuzaki *et al.* [27] demonstrated by immunohistochemical study that in black lesions, the majority of microvessels are mature and that red lesions have a much higher proportion of immature vessels. This study also supports the concept that black and red peritoneal lesions may be different stages of the spontaneous evolution of endometriotic implants. These authors [28] recently demonstrated that there was no significant difference in the relative ratio of estrogen receptor-$\alpha$ to estrogen receptor-$\beta$ between proliferative endometrium and red peritoneal lesions. The predominant expression of estrogen receptor-$\alpha$ in both glandular epithelial and stromal cells led them to suggest the essential role of estrogen receptor-$\alpha$ in the development and growth of peritoneal and ovarian endometriosis.

In conclusion, we may say that red peritoneal lesions represent the first stage of endometriosis and they evolve into black lesions but that no one totally understands the evolution into black lesions.

## Medical therapy for endometriosis

Few randomized controlled trials in which repeat laparoscopy was performed in women treated with placebos can be found in the literature. Cooke and Thomas [29] described spontaneous endometrial deposit resolution in 25% of patients, deterioration in nearly 50% and absence of change in the remainder. More recently, Harrison and Barry-Kinsella [30] compared the efficacy of medroxyprogesterone acetate (MPA) treatment with a placebo in infertile women with endometriosis. By comparative laparoscopy, they concluded that both MPA and placebos appear equally and significantly effective in treating endometriosis over a 3-month period. In both the MPA and placebo groups, there was a statistically significant decrease in the stages and scores of endometriosis at the end of the treatment. Surprisingly, they noted that endometriosis was totally eliminated in 28% of patients in the MPA group and 42% in the placebo group, suggesting that endometriosis is a spontaneously regressive rather than progressive phenomenon. Such rates of complete disappearance observed at second-look laparoscopy in the treated and untreated groups seem to be remarkably high. Wiegerinck *et al.* [31] also observed at second-look laparoscopy, after a 3-month cyclic treatment with dydrogesterone, regression and a changing pattern of the type and localization of 184 lesions, but no complete disappearance. Nisolle *et al.* [32] also found, by histologic study, the persistence of ovarian endometriosis after 6 months of hormonal therapy. In the study by Harrison and Barry-Kinsella [30], the visual identification of endometriosis was not confirmed by histology (peritoneal biopsy, endometrioma biopsy or drainage) in order to avoid a potential therapeutic effect during the diagnostic laparoscopy. The absence of correlation between the change in visual scoring and the morphologic response after short-term medical therapy led Brosens *et al.* [33,34] to suggest that it may be a visual illusion that medical treatment and placebos produce the same effect. In establishing a correlation between histologic and visual findings at laparoscopy, Walter *et al.* [35] reminded us that a diagnosis of endometriosis should be made only after histologic confirmation because of the low predictive positive value (45%).

The use of medical treatment for the management of endometriosis in the infertile couple remains controversial and at the present time, it seems difficult to draw firm conclusions [36••].

## Surgery according to the location of endometriosis

For the patient suffering from infertility, the goal of treatment [37] is the removal of implants, with a subsequent improvement in fecundity. There is evidence [38] that women with moderate or severe disease will have improved fecundity with the removal of implants. Indeed, Adamson and Pasta [38] concluded that medical therapy should not be used to treat minimal and mild endometriosis when infertility is the main symptom.

Only one randomized controlled trial comparing laparoscopic ablation or excision of endometriotic deposits and diagnostic laparoscopy can be found in the literature [39]. This involved 341 women with subfertility attributed to mild or moderate endometriosis. Fecundity significantly increased when mild disease was removed.

Superficial lesions of the ovary should be removed with minimal thermal damage to avoid the formation of postoperative adhesions. Endometriomas should be removed with minimal ovarian cortex damage to avoid the risk of premature ovarian failure.

## Risk of recurrence after ovarian endometriosis surgery

Several studies [40,41] have been conducted to investigate whether surgical treatment (laparotomy, laparoscopic excision of endometriomas and laser ablation of the lining) affect the recurrence rate of endometriosis. In 1998, Hemmings *et al.* [40] did not find any statistical difference in terms of recurrence rate after 36 months between laparoscopic ovarian fenestration with coagulation of endometriomas and ovarian cystectomy performed either by laparoscopy or laparotomy (12%, 8% and 9% respectively). However, in 1999, Saleh and Tulandi [41] did not confirm such good results. Indeed they observed a significantly higher recurrence rate after 18 months and 42 months in cases of laparoscopic fenestration and ablation (21.9% and 57.8%) than in cases of laparoscopic excision of endometriomas (6.1% and 23.6%). The reoperation rate was directly related to the size of the endometrioma only in the excision group. Recently, Ghezzi *et al.* [42] suggested that the risk of recurrence is lower when endometriosis is located only on the right side of the pelvis than when the left side is involved. In 1998, Vercellini *et al.* [43] found that ovarian endometriosis involves the left hemipelvis more frequently than the right hemipelvis. Chapron *et al.* [44] also observed that endometriotic lesions are located more frequently on the left and that the risk of postoperative adhesions at the resection site is significantly less commonly observed when the right uterosacral ligaments are resected. They suggested that the rectosigmoid loop tends to encourage formation of adhesions on the left due to contact between the left adnex and the left uterosacral ligament resection area.

Therefore, the patient with advanced-stage endometriosis localized mainly on the left adnex should be encouraged either to undergo a second-look laparoscopy for adhesiolysis, to try to conceive immediately after surgery or to take advantage of assisted reproduction.

## Ovarian endometriosis surgery and in-vitro fertilization

Appropriate surgical management of ovarian endometriomas remains controversial. Indeed, according to the invagination theory which demonstrates the presence of oocytes surrounding the endometrioma capsule, it has been suggested that cystectomy could provoke loss of normal ovarian tissue [16]. This could happen through the removal of ovarian stroma containing oocytes together with the capsule or by strong coagulation of the ovarian hilus in cases of severe bleeding.

Two retrospective studies [45,46•] analyzing the ovarian response during IVF-embryo transfer cycles after endometrioma surgery, have recently been published. In a series of 85 patients [45] with ovarian endometriomas treated by cyst wall vaporization, who failed to conceive within 1 year, the number of oocytes and embryos was similar to that obtained in a control group. Moreover, in patients with unilateral endometriomas, paired comparison confirmed a normal ovarian response in ovaries after surgery compared with the controlateral normal ovary. In the study by Canis *et al.* [46•] there was no difference between the group of patients who underwent laparoscopic ovarian cystectomy for endometriomas larger than 3 cm and the control group in terms of the number of oocytes and embryos. In the group of patients with endometriosis but without ovarian endometrioma, the results were similar. Canis *et al.* [46•] suggested that in experienced hands, the procedure of cystectomy may be a valuable tool for the treatment of large ovarian endometriomas. But care must be taken to avoid the loss of viable cortex and ovarian damage. Whatever type of surgery is performed in case of endometriomas, the results of IVF and embryo transfer are not impaired, provided the surgical technique has been carried out without damaging the ovarian cortex.

In order to decrease endometriosis recurrence after surgical therapy, Busacca *et al.* [47•] analyzed the effect of postoperative gonadotropin-releasing hormone (GnRH) analogue treatment in women with symptomatic endometriosis at stages III–IV. This treatment does not confer any significant additional benefits in improving pregnancy rates. Regidor *et al.* [48], compared the efficacy of GnRH-agonist therapy with progestagens, in terms of postoperative revised American Fertility

Society (r-AFS) scores at first-look laparoscopy. With the scores after 6 months of treatment, they concluded that GnRH agonists should be used as first-choice drugs in the treatment of endometriosis. Moreover, the effectiveness of GnRH agonist treatment [49] was not reduced by the addition of add-back continuous combined hormone replacement therapy.

## Endometriosis and in-vitro fertilization

Although many studies demonstrate impaired oocyte quality, decreased fertilization, and compromised implantation rates, Arici [50] reminded us that endometriosis does not adversely affect IVF pregnancy rates. Moreover, the extent of endometriosis does not affect implantation and clinical pregnancy rates in patients undergoing intracytoplamsic sperm injection [51]. In a recent paper, in contrast to previous reports, Khamsi *et al*. [52] did not find any difference in fertilization and early embryo development for oocytes exposed to endometrioma fluid. However, controversy exists as Pellicer *et al*. [53•] observed a significantly reduced number of blastomeres per embryo in patients with endometriosis. In their oocyte donation program, they noted that patients who received embryos derived from oocytes from women with endometriotic ovaries showed a significantly reduced implantation rate compared with controls. They suggest that alterations within the oocyte could result in embryos of lower quality with a reduced ability to implant. Further prospectives studies should be conducted to confirm this hypothesis.

## Conclusion

According to recent data published, determining the specific causes of peritoneal and ovarian endometriosis is difficult. Nevertheless, numerous studies were able to confirm the transplantation theory for the development of peritoneal endometriosis and, especially, the primordial role of stromal cells in the first step of development. Even ovarian endometriosis has a different histogenesis; uncontrolled proliferation similar to that in peritoneal endometriosis has been observed. This has led us to suggest that, even if some peritoneal endometriotic lesions disappear with time, treatment of endometriosis (medical, surgical or medicosurgical) should be proposed to infertile couples. More randomized trials, however, analyzing the role of medical therapy and surgery, and comparing surgical and medical treatments, are required to adopt an evidence-based approach to treatment.

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