

# Endometriosis: Pathogenesis, diagnosis, therapy and association with cancer (Review)

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**Abstract.** Endometriosis is a painful reproductive and immunological disease afflicting about 7-10% of women worldwide. It is one of the most frequent benign gynaecological diseases; however, little is known about the pathogenetic processes leading to the development and maintenance of this disease and the currently available therapeutic strategies are unsatisfactory. The goal of this article is to review the most recent advancements in the pathogenesis, diagnosis and therapy of this disease. The risk for cancer among women with endometriosis will be analyzed in light of the most recent epidemiological and functional studies focused on this disease.

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## 1. Introduction

Endometriosis is a gynaecological disease defined by the histological presence of endometrial glands and stroma outside the uterine cavity, most commonly implanted over visceral and peritoneal surfaces within the female pelvis, but rarely also in the pericardium, pleura, and even brain (1). Although the exact prevalence of endometriosis in the population is not clear, the prevalence in the general female population is 6-10%; in women with pain, infertility or both, the frequency increases to 35-60% (2). Endometriosis is usually associated with

infertility and pelvic pain such as chronic dysmenorrhea, intermenstrual abdominal and pelvic pain, back pain, dysuria, dyschezia and dyspareunia (1). This disease was first identified and described in 1860 by the Austrian pathologist von Rokitansky (3), but despite the fact that it is quite common among women, it is frequently misdiagnosed, the pathogenesis is not completely clear and the diagnostic and therapeutic strategies are still not adequate. In this report, the most recent findings on the pathogenesis, the diagnosis and therapy of this disease, as well as the associated risk of developing a malignancy, are reviewed.

## 2. Theories of pathogenesis

Although there are several theories the definitive cause of endometriosis is still unclear. In Table I the most common theories on the pathogenesis of this disease are summarized.

One widely accepted mechanism for the development of peritoneal endometriotic lesions is the adhesion and growth of endometrial fragments deposited into the peritoneal cavity via retrograde menstruation (4). The retrograde menstruation/transplantation theory is supported by the fact that the women with endometriosis have higher volumes of refluxed menstrual blood and endometrial-tissue fragments than healthy women (5). Moreover, endometriosis affects young women with primary amenorrhoea and outlet obstruction to menstrual flow (6), and it can be induced in baboons by ligation of the cervix (7). However, this theory fails to explain the presence of endometriosis in such remote areas as the lungs, skin, lymph nodes, breasts; nor does this theory account for the few described cases of male endometriosis (8).

The coelomic metaplasia theory claims that formation of endometriomas in the ovary or rectovaginal endometriosis is caused by metaplasia of the coelomic epithelium, perhaps induced by environmental factors (9-11). This theory would explain why most women have some degree of retrograde menstruation but only a small percentage have endometriosis, and the presence of the disease in absence of menses.

Anatomic abnormalities are also considered a possible precursor of endometriosis. Vercellini *et al* concluded that the depth and volume of the cul-de-sac (Pouch of Douglas), differs in patients with endometriosis with or without deep lesions as compared to women with a healthy pelvis (12).

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Table I. Theories on the pathogenesis of endometriosis.

Retrograde menstruation/transplantation
Coelomic metaplasia
Anatomic abnormalities
Genetic basis
Enviromental basis
Altered cellular immunity

Table II. Drugs used for the treatment of endometriosis.

Androgens	Danazol
GnRH agonists	Leuprolide, Leuprolide depot, Buserelin, Goserelin, Nafarelin
Progestagens	Gestrinone, Medroxyprogesterone
Oral contraceptives	Combination of oestrogen/progestagen

One very promising theory is that endometriosis is hereditary. The first demonstration of the heritable features of this disease was given in a study more than 25 years ago (13). By use of linkage analysis, various groups have reported candidate genes that have potential biological plausibility (14-19). In particular, by genetic polymorphism analysis it has been recently demonstrated that the combination of CYP1A1 m1 polymorphism and GSTM1 null deletion is closely associated with penetration of the endometriosis phenotype, whereas GSTT1 null deletion may add to the penetration of this trait (20). In a subsequent work of the same group the genetic contribution of CYP1A1, CYP19, GSTM1, and GSTT1 polymorphisms to endometriosis was better defined, showing that CYP19 VNTR (TTTA 10) allele as well as the combined genotype CYP1A1 m1 polymorphism and GSTM1 null deletion associate with the endometriosis phenotype, whereas the GSTT1 null deletion does not (21).

Enviromental factors may also play an important role in the disease. In particular, animal models of endometriosis have provided important information on the potential influence of proton irradiation and dioxin on development of endometriosis (22-24). It has to be underlined, however, that there is still no epidemiological study definitively linking one class of chemicals to the risk of endometriosis, although oestrogen-like compounds in the environment have been suggested (25). Our research group is presently investigating the molecular mechanisms possibly linking the exposure to oestrogen-like compounds to the insurgence of endometriosis.

Altered cellular immunity is another proposed pathogenetic mechanism and a lack of adequate immune surveillance in the peritoneum is thought to be a cause of the disease (26). Among the possible molecules responsible of this altered immunity, haptoglobin and monocyte chemoattractant protein 1 have been proposed (27,28). Several other findings support an autoimmune aetiology of endometriosis: abnormalities in function of B and T cells, high serum concentrations of IgG, IgA, and IgM autoantibodies, reduced natural-killer-cell activity and familial inheritance, among others (29-33).

### 3. Diagnosis and therapy

Endometriosis continues to remain a significantly underdiagnosed and under-treated disease (1). Despite recent progress in the understanding of this disease, the mainstay

of diagnosis is still the direct visualization of the lesions by invasive surgery through laparoscopy or laparotomy (34,35).

The therapeutic strategies have two principal aims: relief of pain, amelioration of infertility, or both. Drugs that have been classically used to treat endometriosis are summarized in Table II. Research in the field of endometriosis in the last few years has allowed a better understanding of the biology of pain at cellular level. In particular, it has been proposed that release of inflammatory agents, such as prostaglandins, bradykinin, interleukins, norepinephrine and adenosine, at the implant sites is an important mediator of hyperalgesia (36-38). Moreover, the specific type of innervation of the endometriotic lesions seems to play a role in the phenomenon of hyperalgesia (39-41). It is likely that new therapies will be established based on many of the molecular targets summarised above. To date, the principal agents that have been used to treat endometriosis are drugs able to suppress ovarian function and limit growth and activity of endometriosis and pain associated with the disease, including androgens, progestagens, GnRH agonists, and contraceptive steroids (42-46).

It is well known that medical therapies for pain are, in general, not useful for infertility. Surgery is commonly used to treat infertility related to endometriosis, even if the analysis of the non-randomised trials did not completely support this (47-49). Moreover, it must be considered that surgery could remove some healthy ovarian cortex with follicles, thus resulting in decreased ovarian response during reproduction treatment and in a potential increased risk of earlier menopause (50,51). Therefore, the risks and benefits associated with surgical treatment of patients with endometriosis must be carefully weighed. Nevertheless, it must be pointed out that assisted reproduction by controlled ovarian hyperstimulation and intrauterine insemination, or *in vitro* fertilisation are beneficial (52-54).

### 4. Endometriosis and the risk of cancer

Epidemiological studies have shown that women with endometriosis have an increased risk of different types of malignancies, especially ovarian cancer and non-Hodgkin's lymphoma (55-57). Nevertheless, recent reports show also an association between endometriosis, dysplastic nevi, and melanoma, and breast cancer (58-60).

Concerning ovarian cancer, several studies have indicated endometriosis as a risk factor and various histological and

molecular genetic studies have even indicated that endometriosis may transform into cancer or that it could be considered a precursor of cancer (61-65). In particular, by microsatellite analysis, it has been recently demonstrated that loss of heterozygosity on p16(Ink4), GALT, and p53, as well as on APOA2, a region frequently lost in ovarian cancer, occurs in endometriosis, even in stage II of the disease. The occurrence of such genomic alterations may represent, therefore, important events in the development of endometriosis. Moreover, the 9p21 locus where p16 is mapped, may contain a gene associated with the pathogenesis of the disease, and its loss may be a prognostic marker of the disease (66).

Although many of the risk factors associated with both diseases are similar, including earlier menarche, more regular periods, shorter cycle length and lower parity, endometriosis itself may be considered a risk factor for ovarian cancer. In a recent study it has been reported that, after adjusting for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy and breast feeding, women with ovarian cancer were 1.7-fold more likely to have a history of endometriosis than controls (67). However, despite the histological and epidemiological evidence linking endometriosis and ovarian cancer, it is still not clear if endometriosis is a real precursor of ovarian cancer, or whether there is an indirect link involving common environmental, immunological, hormonal or genetic factors (64). It has been clearly demonstrated that activation of a mutated K-ras gene is a fundamental step in the genesis and progression of ovarian cancer (68,69). Moreover, it has been proposed that aberrant transcriptional regulation of the H-ras proto-oncogene is caused by p53 protein alterations: in fact, the human c-H-ras1 gene contains within the first intron a p53 element, which functions as a transcriptional enhancer (70). Based on these observations, Dinulescu *et al* have engineered a new transgenic mouse both as model of endometriosis and as a model of endometrioid ovarian carcinoma (71). Briefly, by taking advantage of the Cre recombinase technology, Dinulescu *et al* first generated mice with a mutationally activated K-ras gene: these mice developed spontaneously benign endometrioid lesions on the ovarian epithelium in all mice and peritoneal endometriosis in about half of the cases. In the second phase, these mice were engineered to lack the expression of Pten. This second mutation caused the insurgence of invasive endometrioid carcinomas of the ovary. This model represents the first mouse model of spontaneous human endometriosis and strongly suggests that the endometriotic lesions are initiated by endometrium refluxed through the fallopian tubes into the peritoneal cavity.

In conclusion, further epidemiological and genetic studies are required for delineation of the risk of several malignancies and in particular of ovarian cancer in women with endometriosis. Nevertheless, appropriate physical screening, laboratory and imaging testing are recommended for early detection of malignant disorders in women with endometriosis.

## 5. Conclusions

Endometriosis still remains an underdiagnosed and debilitating disorder affecting a large cohort of women. It is hoped that biomedical research in the next few years will define effective

non-invasive methods to diagnose the disorder and new therapies combined with established medical and surgical therapies to offer relief from pain, prevent progression of the disease, and improve fertility.

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