PATHOGENESIS OF ENDOMETRIOSIS

Engin Oral, MD, and Aydin Arici, MD

Endometriosis is a condition characterized by the presence of endometrial tissue in ectopic foci outside the uterus. Despite being one of the most frequently encountered gynecologic diseases, the exact cause and pathogenesis of endometriosis is unclear. The pathogenesis of endometriosis has long been debated, but essentially theories can be divided into those that suggest (1) development in situ by metaplasia or (2) development as a consequence of the dissemination of endometrium (Table 1). Research to date strongly suggests that the origin of epithelium is endometrium rather than the peritoneal mesothelium. This article critically examines the factors that may play a role in the cause and pathogenesis of endometriosis, with special emphasis on the potential immune mechanisms that may be involved.

MÜLLERIAN AND SEROSAL THEORIES

The first widely considered theory of histogenesis was that of celomic metaplasia, initially introduced at the turn of the century.[45] Because both ovary and müllerian ducts are derived from celomic mesothelium, the proponents of the müllerian theory believe that the germinal epithelium of the ovary may attempt to recapitulate endometrium that is derived from müllerian ducts.[13] This theory explains only the development of endometriosis in the ovary. In a broader context, because it is believed that peritoneal mesothelium is totipotential, it is natural that

From the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut

Table 1. THEORIES OF HISTOGENESIS OF ENDOMETRIOSIS

Endometrial	*Retrograde menstruation*
	Lymphatic dissemination
	Vascular dissemination
	Direct invasion
	Uterotubal
In situ	Celomic metaplasia
	Wolffian duct remnants
	Müllerian duct remnants
Combination	Endometrial induced metaplasia

other authors have suggested that endometriosis in the pelvis and peritoneum may develop from in situ metaplasia of the serosal mesothelium.[60]

There are several questions that must be addressed if this pathophysiologic mechanism is to be entertained seriously. The first is that endometriosis could develop in the absence of endometrium, that is, women with congenital absence of the uterus. Second, if peritoneal epithelium has the potential to undergo metaplasia, this phenomenon would be expected to occur in men as well as women. Third, celomic metaplasia should occur in those sites where the celomic membranes are present. Finally, if celomic metaplasia is similar to metaplasia elsewhere, it should occur with increasing frequency with advancing age. Until the above-noted concerns are addressed, there is little justification for considering celomic metaplasia a serious candidate in the histogenesis of endometriosis.

The induction theory is an extension of the celomic metaplasia theory and proposes that an endogenous biochemical factor can induce undifferentiated cells to develop into endometrial tissue. This theory has been supported by experiments in rabbits[43] but awaits substantiation in women and nonhuman primates.

IMPLANTATION AND METASTATIC THEORIES

A scientific approach to understanding the pathogenesis of endometriosis began in the course of a series of publications by Sampson.[61, 63] Based on his clinical experience, Sampson proposed that the menstrual effluent contained viable endometrial cells that could be transplanted to ectopic sites. Retrograde menstruation is a common physiologic event during which viable endometrial cells are shed into the peritoneal cavity.[37] Some 60 years ago, Novak[51] questioned why a physiologic event should frequently give rise to pathology, a question that as yet awaits a satisfactory answer. Keettel and Stein[34] proved that at least antegrade menstrual discharge contains viable endometrial cells. They cultured tissue fragments of human endometrium obtained from antegrade menstrual discharge and showed the presence of adhering and proliferating cells that were either fibroblastic or epithelioid in appearance. Koninckx

et al[36] found endometrial tissue most frequently during the follicular phase, the incidence decreasing progressively during the luteal phase. This observation correlates with the concept that these endometrial cells are retrogradely seeded during menstruation. Transtubal dissemination appears to be the most common route of dissemination by far, although several other routes of dissemination of transplantable endometrial cells have been observed, including lymphatic and vascular channels and iatrogenic deposition. Retrograde menstruation, retrograde peristalsis of the fallopian tubes, and presence of blood in the tubes and in the peritoneal cavity during menses are presented as evidence for this hypothesis. A substantial clinical database exists to support this hypothesis: (1) viable endometrial cells have been demonstrated in the menstrual effluent and peritoneal fluid[36]; (2) endometrium can be implanted experimentally and grown within the peritoneal cavity[27a]; (3) all women have some degree of retrograde menstruation[52]; (4) there is an association between obstructed menstrual outflow and endometriosis.[52] A deficient uterotubal control mechanism that favors tubal reflux of menstrual products has been proposed,[7] as has a narrow cervical ostium, which hampers antegrade menstruation.[6]

Dissemination of endometrial cells through lymphatic or vascular channels has long been appreciated,[66] which would account for the rare finding of endometrial tissue at sites distant from the pelvis. Metaplasia of serosal surface has been the idea that endometriosis represents endometrial tissue that grows following its dissemination from the endometrial cavity in distant sites as implants or metastasis.[62] These theories could account for the presence of endometriosis within the peritoneal cavity and in distant sites such as lung, nose, pelvic lymph nodes, and extremities. Some experimental data exist supporting these theories. Injection of endometrial tissue into the ear veins of rabbits is associated with endometrial metastases in the lungs of the rabbit.[8]

Numerous cases of endometriosis in episiotomy and laparotomy scars following gynecologic procedures and cesarean sections have been reported.[33] These observations suggest that ectopic endometrium can be induced iatrogenically by mechanical transplantation. Animal experiments have also confirmed viable heterotopic transplants of surgically excised endometrium.[64]

GENETIC FACTORS

A familial probability of developing endometriosis has long been suspected on the basis of case reports and retrospective reviews. Endometriosis is found more commonly in patients with familial history of the disease. The disease occurs with a frequency of 6.9% in the first-degree relatives of the patient, whereas it occurs at a rate of 1% in the female relatives of the patient's husband.[67] This appears to occur through a maternal inheritance pattern. Also, the disease is often more severe in women with a first-degree relative with endometriosis.[21] A recent study

from Norway[48] reviewed the reproductive histories of monozygotic twin sisters and mothers of patients with endometriosis. Of 515 patients with endometriosis, 8 had monozygotic twin sisters. Of this group, 6 (75%) also had endometriosis, compared with 3.8% among nonmonozygotic sisters. It also was found that among the twins with endometriosis, there was a high degree of bilateral disease and early onset. Although not conclusively proven, it has been postulated that endometriosis may occur on the basis of polygenic/multifactorial factors; however, no apparent relationship to the human leukocyte antigen (HLA) system seems to exist.[49]

HORMONAL FACTORS

There is evidence suggesting that steroid hormones play a significant role in the pathogenesis of endometriosis. Experimental and clinical observations suggest that endometriosis is estrogen dependent, and that estrogens seem to be important for growth and maintenance of endometriosis.[15] Endometriosis does not occur before menarche and is rarely seen in women with anovulatory cycles.[32] Artificial interruption of the menstrual cycles by hormonal therapy and menopause also cause regression of endometriosis. Although endometriosis can occur in postmenopausal women, this is often related to high levels of estrogen associated with obesity or estrogen therapy.[35] Endometriosis, although rare, has been reported to occur in men on high-dose estrogen therapy, arising apparently from prostatic utricle.[65] The initiation of ectopic growth of endometriotic tissue in the early 4 weeks of development did not require exogenous hormone; however, either estradiol or progesterone or combination of both was required for the long-term maintenance of endometriotic tissue in castrated monkeys.[15] A connection between the use of estrogen-containing contraceptive pills and the risk of endometriosis is controversial, because some authors find a lowered risk among users,[40] whereas others fail to confirm such a connection.[75]

MENSTRUAL FACTORS

Monkeys are the only animals that have cyclic menstrual periods, and only in such animals is endometriosis known to develop spontaneously. Although no cases of endometriosis have been reported prior to puberty, the disease certainly has been noted in the teenage years. Women with certain menstrual patterns offering a greater opportunity for contamination of the peritoneal cavity by menstrual debris are at greater risk for the development of endometriosis. In a comprehensive study, women with short cycles and longer flow had more than twice the risk of endometriosis than did women with long cycles and short duration of flow.[10] The increased risk in association with early menarche or delayed childbearing is apparently based on the observation that the

risk of developing endometriosis correlates with the cumulative menstrual exposure.[12] Menstrual blood outflow obstruction caused by congenital anomalies also has been shown to be associated with increased incidence of endometriosis.[52] It is not possible, however, to determine whether such menstrual factors are the consequence of the disease or have a causal role in its development.

IMMUNE FACTORS

Immune mechanisms have been suggested to play a role in the development of endometriosis because various abnormalities in immune functions have been widely reported to be associated with this disease. Such abnormalities can be grouped as either peritoneal or systemic (Table 2).[24] A normal immune mechanism involved in normal disposal of tissue fragments may also be overwhelmed if excess tissues reach the peritoneal cavity, as occurs from excessive retrograde menstrual flow. It was suggested that endometriosis may be a disorder originating from a derangement in the immune surveillance that is transmitted genetically. In susceptible subjects it results in unchecked ectopic implantation of the endometrium outside the uterus subsequent to its transport to the ectopic foci through the fallopian tube, blood, or lymphatic system. This derangement may include the humoral and cell-mediated responses. During the last decade, evidence has accumulated indicating an association between endometriosis and changes in humoral and cell-mediated

Table 2. IMMUNOLOGIC ABNORMALITIES IN ENDOMETRIOSIS

Systemic
Increased immunoglobulin production
Increased presence of helper (CD_4) cells
Deficient lymphocyte-mediated cytotoxicity against endometrium
Embryotoxic serum
Serum that suppresses natural killer cell activity
Deficient cellular immunity
Defective natural killer activity
Abnormal autoimmune function
Decrease in suppressor cell activity
Peritoneal
Endometrial stromal cell proliferation
Increased cytotoxicity of peritoneal macrophages
Decreased sperm binding to zona pellucida
Proliferation of lymphocytes
Increased sperm phagocytosis by peritoneal macrophages
Increased cytokine levels
Accentuated cyclic activation of macrophages
Presence of antiendometrial antibodies
Decreased natural killer activity of lymphocytes
Interleukin-1 receptor antagonist secretion by peritoneal macrophages
Presence of non–organ-specific autoantibodies

Data from Dmowski WP, Steele RW, Baker GF: Deficient cellular immunity in endometriosis. Am J Obstet Gynecol 141:377, 1981.

immunity. The cells involved are the B lymphocytes, T lymphocytes, granulocytes, monocytes, macrophages, and natural killer (NK) cells. The soluble factors include cytokines, lysozyme, acute phase proteins, complement, and immunoglobulins. Whether immunologic abnormalities precede endometriosis or endometriosis induces immunologic abnormalities has been an issue of dispute since immunologic abnormalities were first reported,[16] however. Alterations in humoral and cell-mediated immunity have been observed by several investigators in rhesus monkeys and in women with endometriosis, as well as in experimentally induced endometriosis in laboratory animals.[53, 69] Women with endometriosis appear to exhibit increased humoral immune responsiveness and macrophage activation, and diminished cell-mediated immunity with decreased T cell and NK cell responsiveness.[53, 69]

Humoral Response

Several studies published during the past decade indicate alterations in B cell activity and a high incidence of abnormal autoantibodies in women with endometriosis. The main areas of concern were the demonstration of immunoglobulins and complement factors in endometrium and endometriotic implants and the levels of nonspecific antiendometrial antibodies in serum and peritoneal fluid as a marker of the disease. In 1980, increased B cell function in women with endometriosis was shown.[68] In the same year Weed and Arquembourg[76] hypothesized that ectopic endometrium might act as a foreign antigen trigger to induce an autoimmune response, resulting in infertility. They based this hypothesis on the findings of deposition of complement C_3 and IgG in the uterine endometrium, and a corresponding reduction in the serum total complement levels in women with endometriosis. Two years later, Mathur et al[44] identified IgG and IgA autoantibodies against endometrial and ovarian tissue in sera, cervical secretions, and vaginal secretions of women with endometriosis. Complement C_3 and C_4 levels were found to be higher in serum and peritoneal fluid of patients with endometriosis than in controls.[4] This could not be confirmed by others.[17] Other investigators, using different techniques, have confirmed high levels of antiendometrial antibodies in the sera, peritoneal fluid, and endometrial tissue of women with endometriosis, but no correlation was found between antibody titers and severity of disease.[19] Moreover, the autoantibodies in endometriosis tend to decrease with the severity of the disease. It is difficult to assess the value of the results of the different investigators. There are considerable differences in the choice of controls and number of patients with different stages, but most important, because the exact antigen is not known, there is no simple antigen–antibody assay yet. Some major problems must be solved before a serum endometrial antibody assay can be developed. One major problem is the antigenicity of the endometrium: why do antibodies against a self-antigen, that is, the endometrial glands, develop? Another problem is that the autoantibod-

ies cannot be produced in an animal model. Third, disease cannot be induced in an animal model by the antigen. The three major conditions necessary to establish endometriosis as an autoimmune disease are therefore not fulfilled. In addition to antibodies directed against endometrial cells, autoantibodies of IgG, IgM, and IgA isotopes, directed against cell-derived antigens, also have been reported.[23] These include autoantibodies to a variety of phospholipids, histones, polynucleotides, as well as lupus anticoagulant. High incidence of these autoantibodies also has been demonstrated in women with reproductive failure (i.e., infertility and recurrent abortions). Treatment of endometriosis with danazol, as in autoimmune diseases, is associated with autoantibody suppression.[18] The presence of antiendometrial antibodies in endometriosis also has been proposed as a diagnostic test, with another marker, CA-125. Both tests have thus far failed to provide sufficient disease and stage specificity necessary for screening tests, although the latter may in some cases be useful in monitoring disease progression. More generalized autoantibodies have also been demonstrated in patients with endometriosis, and it has been suggested that endometriosis could be an autoimmune disease. Whether these antibodies coincide with a more generalized autoimmune syndrome is unclear. They may facilitate the escape of ectopic endometrium from T cell–mediated destruction, perhaps by blocking antigenic sites required for recognition by cytotoxic T cells or helper T cells, or they may be a consequence of the deranged immune response, in which displaced endometrium is processed by macrophages in a general inflammatory response leading to antibody production.

Cell-Mediated Response

A diminished cellular-mediated immune response would permit tolerance of the translocated endometrial cells and allow for ectopic implantation. In addition to alterations in humoral immunity, changes in cell-mediated immunity have also been reported in monkeys as well as in women with endometriosis. Women with endometriosis appear to exhibit increased macrophage activation and diminished T-cell reactivity. Peripheral blood leukocyte profiles in women with endometriosis have been investigated, with conflicting results. The total number of peripheral blood lymphocytes and the percentage of immune cell subsets appear to be unchanged in women with endometriosis.[22] Some studies suggest, however, that the ratio of T helper cells to T suppressor cells may be increased in the peripheral circulation, as well as in the peritoneal cavity.[14] In healthy rhesus monkeys and in women without endometriosis, peripheral blood lymphocytes recognize endometrial antigens and cells and respond in vitro and in vivo with proliferation. This effect is reduced in endometriosis, suggesting a decreased recognition of the autologous endometrial antigens. Similarly, cytotoxic effect of peripheral blood lymphocytes against labeled autologous endometrial cells in vitro is decreased in women with endometriosis; this effect appears to be NK

cell mediated.[69] *NK cells* are large granular lymphocytes that kill cells bearing an undefined target molecule and cells coated with antibody. In endometriosis, despite decreased NK-cell activity, the percentage of peripheral NK cell is not altered.[53] The percentage of peripheral monocytes seems to be unchanged in women with endometriosis, but their activational status is increased. In a co-culture system, significant differences of the effects of peripheral blood monocytes between patients with and without endometriosis were observed.[9] Peripheral blood monocytes from normal fertile women suppress endometrial cell proliferation; in contrast, peripheral blood monocytes from women with endometriosis stimulate endometrial cell proliferation in vitro. If this effect is present in vivo, it may play a role in the development of the disease. The stimulatory effect of peripheral monocytes on endometrial proliferation is abrogated by medical treatment, both in vitro and in vivo.

Peritoneal Factors

The monocyte/macrophage system plays a central role in the maintenance of cell-mediated immunity. In the peritoneal cavity, macrophages, which are the most numerous (more than 85%) immune cells, are thought to play a major role in the local immune status. The number of these cells and other leukocytes varies throughout the menstrual cycle, being greater in the follicular phase, immediately after menses.[37] Resident macrophages (derived from blood monocytes) remove red blood cells, damaged tissue fragments, and possibly endometrial cells that gain access to the peritoneal cavity through the fallopian tubes. In addition to phagocytic activities, peritoneal macrophages may also regulate local events related to reproduction by release of cytokines, prostaglandins, growth factors, complement components, and hydrolytic enzymes. For these reasons, studies have concentrated on the evaluation of monocyte/macrophage function in the peritoneal fluid (PF) of patients with endometriosis. Investigators have attempted to identify factors present in the peritoneal environment of women with endometriosis that may explain its pathogenesis.[25, 26]

PF arises primarily from two different sources: plasma transudate and ovarian exudate; other sources are tubal fluid, retrograde menstruation, and macrophage secretions. Peritoneal macrophages are increased in total number, concentration, and activational status.[26, 27] Infertile women with endometriosis appear to possess a greater number of peritoneal macrophages compared with normal fertile women.[30] Elevated numbers of macrophages in the peritoneal cavity of women with endometriosis may be the result of chronic stimulation by ectopic endometrial implants or of excessive reflux of menstrual debris.[7] The more likely stimulus responsible for eliciting this exudate is retrograde menstruation (rather than endometrial implants). Haney et al[29] have demonstrated that an *inverse* relationship exists between peritoneal inflammation and endometriosis, arguing against the chronic stimulation hypothesis. As

the stage of endometriosis advances, the degree of peritoneal inflammation decreases.

PF is an important contributor to the environment in which fertilization and early embryonic development take place. Interest in the humoral components of PF and their role in the development of endometriosis has increased. The two apparently opposite effects of the monocytes/macrophages (i.e., cytotoxicity and stimulation of cell proliferation) may be mediated through their secretory products. Growth factors and cytokines found in PF have been postulated to participate in the pathogenesis of endometriosis. A variety of secretory products of inflammatory cells may have adverse effects on sperm[50] or embryos.[72] Several studies have documented that the increased macrophage activation in endometriosis is accompanied by their production of growth factors, including platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), macrophage-derived growth factor (MDGF), and epidermal growth factor (EGF).[28, 56] These growth factors have been shown to stimulate the proliferation of endometrial stromal cells in vitro.[70] Thus, the secretion of growth factors can be important to the maintenance of ectopic endometrium. In addition, EGF receptors have been demonstrated in both eutopic and ectopic endometrium.[58] Finally, PDGF enhances endometrial stromal cell proliferation, with maximal stimulation of growth when PDGF and estrogen are both present in culture medium.[71]

Soluble cellular mediators, called *cytokines*, direct a variety of biologic activities, including modulation of growth, chemotaxis, and induction of gene expression. The number of cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-2, IL-6, IL-8, monocyte chemoattractant protein (MCP)-1, and interferon (INF)-γ are also elevated in the PF of women with endometriosis, suggesting that these cytokines may be involved in the progression of disease.[3, 20, 25] Cytokine levels in PF from women with endometriosis have also been reported to be reduced after medical treatment. There are many potential sources of growth factors and cytokines found in PF; most likely are mesothelial cells that cover the wide surface of the peritoneal cavity and macrophages that form the cell type found in greatest quantity in PF. Endometrial cells themselves have been shown to produce many of these growth factors; thus the refluxed or implanted endometrial tissue may also be a source. One other potential source is the follicular fluid released regularly in reproductive-aged women.

Recently, these authors have observed the presence of three proinflammatory chemoattractant cytokines, MCP-1[1] for monocyte/macrophages, IL-8,[3] and growth-regulated α (GROα)[57] for granulocytes in the PF from women with endometriosis. Concentrations of both IL-8 and MCP-1 were not only elevated in the PF of women with endometriosis compared with women without endometriosis, but the levels did correspond to the severity of the disease. These authors do not know if these changes precede or are a consequence of the disease, however.

The local NK-mediated cytotoxicity in PF might be important in the

pathogenesis of endometriosis by preventing implantation of regurgitated endometrial cells. Oosterlynck et al[55] demonstrated significantly decreased NK activity of PF mononuclear cells in women with endometriosis. In PF of women with stage III and IV endometriosis, there was a significant decrease of NK cytotoxicity compared with those without endometriosis.[31]

Complements C_3 and C_4, mediators of host responses to inflammation, also have been reported to be increased in the PF of patients with endometriosis.[4] In addition to complement components, an increase in prostaglandin levels has been reported by some but not all investigators.[5, 11]

Angiogenic factors released from peritoneal macrophages may also play a role in the development of endometriosis. Oosterlynck and coworkers[54] investigated the presence of angiogenic factors in PF from endometriosis patients, and angiogenesis was assayed by placing glass filters impregnated with PF on the exposed chorioallantoic membrane of chicken embryos. The PF of endometriosis patients appeared to contain more angiogenic activity than did the PF of controls. The reaction remained after charcoal treatment of the PF. Vascular endothelial growth factor (VEGF) is a potent angiogenic factor present in increased levels in the PF of women with endometriosis.[42] The levels of VEGF are also significantly higher in the proliferative phase than in the secretory phase. TGF-β, TNF-α, and IL-8 all having angiogenic properties have been found in increased levels in the PF of patients with endometriosis.[3, 25, 56] These angiogenic factors in the PF of women with endometriosis could be produced by retrograde menstruation of endometrial cells or by the ectopic endometriotic lesions themselves. Because the growth of endometriosis requires an accessible blood supply, it could be hypothesized that the release of angiogenic factors into the peritoneal compartment produces increased microvascularization of the parietal peritoneum.

Integrins

Integrins are a family of cell adhesion molecule receptors involved in diverse processes such as embryogenesis, wound healing, the immune response, and the behavior of malignancies. The assumption that regurgitated endometrium might cause endometriosis in some women but not in others because it adheres to the peritoneal surface has been claimed but not proved. It seems that expression of extracellular matrix components and integrins in normal endometrium and in endometriosis is highly complex. Regurgitated endometrial cells possess the capacity to attach to the peritoneal lining, as shown by van der Linden.[74] The demonstration of the expression of cell adhesion molecules by cells in menstrual effluent, endometrium, PF, and endometriotic lesions is not absolute evidence that endometriosis originates from endometrium by retrograde shedding of viable tissue fragments. One specific integrin,

the $\alpha_v\beta_3$ vitronectin receptor, has been shown to be expressed in the endometrium at the time of implantation.[39] Recently, aberrant expression of this integrin in the eutopic endometrium of the women with endometriosis was reported.[38] The reason for this aberrant expression is still unknown, but this finding may explain the reported decrease in the implantation rate observed in women with endometriosis.[2]

Other Factors

Original reports stated a lower incidence of endometriosis in black women.[44] This low incidence in black women may be related to multiple factors, including early marriage, frequent pregnancies, and access to contraception. When these variables are taken into consideration, however, no difference between black and white patients may be noted. The only documented racial predilection of endometriosis is that of Japanese women, who have shown twice the incidence of the disease over white women.[46] Smoking and regular exercise were associated with a decreased incidence of endometriosis, presumably related to the lowered endogenous estrogen levels by these activities.[12] It was shown that the length of time elapsed since the last childbirth influenced the risk of endometriosis developing in parous women who requested sterilization. The risk of endometriosis was 7.5% in the first 5 years, and 26.8% when 10 years had passed since last childbirth.[47]

CONCLUSION

Several theories of pathogenesis were put forth before the era of objective scientific inquiry. Unfortunately, several of these theories have continued to enjoy popularity among clinicians despite the absence of reasonable scientific data. The nearly universal phenomenon of retrograde menstruation and the inherent ability of pelvic tissues to support endometrial transplantation allow virtually all women the opportunity to develop endometriosis. Factors that determine the degree of retrograde menstruation remain to be elucidated. Immunologic factors may affect a women's susceptibility to the implantation of exfoliated endometrial cells. The major immune alterations include (1) increased presence of circulating autoantibodies, (2) increased numbers and activation of peritoneal macrophages, and (3) decreased T-lymphocyte reactivity and natural killing activity. Whether these changes predate the disease, are coincidental to it, or result from it remains to be determined. Increased concentrations of growth factors and cytokines found in PF of patients with endometriosis display a dual effect: while inducing proliferation of the endometrial implants, they may be inhibiting early reproductive events. These authors' interpretation of the literature, in conjunction with the research performed in our center, leads us to conclude that endometriosis is a systemic disease with immunologically mediated

pathogenesis. Although none of these factors have been linked conclusively to the development of endometriosis, many investigators believe that some genetic alteration leads to an immunologic state that causes or allows the progression of endometriosis.

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Address reprint requests to

Aydin Arici, MD
Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology and Infertility
Yale University School of Medicine,
P.O. Box 208063
333 Cedar Street
New Haven, CT 06520–8063