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Pathogenic mechanisms in endometriosis-associated infertility

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Objective: To review the mechanisms by which endometriosis may affect reproductive function.

Design: Review of the English literature from 1986 to 2007 after searching Medline, EMBASE, Cochrane, and BIOSIS, as well as relevant meeting abstracts.

Setting: Fertility research center and obstetrics and gynecology department in a tertiary care hospital.

Result(s): There is compelling evidence in the literature that endometriosis has detrimental effects on ovarian and tubal function and uterine receptivity, resulting in female infertility. The mechanisms of infertility associated with endometriosis remain controversial and include abnormal folliculogenesis, elevated oxidative stress, altered immune function, and hormonal milieu in the follicular and peritoneal environments, and reduced endometrial receptivity. These factors lead to poor oocyte quality, impaired fertilization, and implantation.

Conclusion(s): Through unraveling the mechanisms by which endometriosis leads to infertility, researchers are sure to find a nonsurgical means to diagnose endometriosis, most likely through serum and peritoneal markers. Cytokines, interleukins, oxidative stress markers, and soluble cellular adhesion molecules all show potential to be used as a reliable marker for diagnosing endometriosis. After analyzing the pathogenic mechanisms of endometriosis, it seems that the future treatment of this entity may include cyclo-oxygenase-2 inhibitors, immunomodulators, or hormonal suppressive therapy to eliminate the need for surgical treatment of endometriosis. (*Fertil Steril*® 2008;90:247–57. ©2008 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, oocyte quality, fertilization, implantation, pregnancy, assisted reproduction

The controversy regarding whether endometriosis is a cause of subfertility or an incidental finding is ongoing. An association between endometriosis and infertility has repeatedly been reported in the literature, but an absolute cause-and-effect relationship has yet to be confirmed (1, 2). Numerous mechanisms have been proposed to account for fertility impairment. These include altered folliculogenesis (3), leading to ovulatory dysfunction and poor oocyte quality, as well as luteal phase defects (4), reduced fertilization (5), and abnormal embryogenesis (6).

Most studies report that pregnancy rates are lower in women with endometriosis than in normal controls, but the specific mechanisms that may account for this difference are

poorly understood. The monthly fecundity rate (MFR) for normal couples of reproductive ages typically range around 30% for the first three cycles and decline to 4% when the couples have been trying to conceive for >1 year. The couples conceiving within the earlier months are the most fertile, and 18% of the couples did not conceive at the end of 1-year in the study (7). However, the MFR in couples diagnosed with both endometriosis and infertility is between 2% and 10% per month (8). Even minimal endometriosis may be associated with marked subfertility (9).

In contrast, some studies reported no effect of the presence and severity of endometriosis on reproductive outcomes. In a large series of 2,080 women with infertility, 1,263 women (60.7%) were diagnosed with endometriosis by laparoscopy. The conception rates analyzed retrospectively by the χ^2 test were identical in women with and without endometriosis, casting uncertainty on a cause-and-effect relationship (10).

Amelioration of infertility associated with endometriosis has been investigated with medical and surgical therapeutic

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modalities, individually and in combination. Medical treatments have uniformly been unsuccessful and surgical trials have been inconsistent. Two randomized controlled trials investigating the effects of surgical treatment of minimal–mild endometriosis yielded conflicting results (11, 12). Studies on the surgical management of ovarian endometriomas before assisted reproduction also produced contradictory outcomes (13, 14).

In this article, we review the mechanisms by which endometriosis may affect reproductive function in the female as well as to examine the influence of endometriosis on the male gametes once deposited in the female genital tract.

FOLLICULAR ENVIRONMENT AND FOLLICULOGENESIS IN WOMEN WITH ENDOMETRIOSIS

Altered folliculogenesis in endometriosis patients may contribute to ovulatory dysfunction, poor oocyte quality, reduced fertilization rate, low grade embryos, and reduced implantation rates (15, 16). However, although abnormalities related to folliculogenesis have been documented in endometriosis patients, their negative impact on the MFR of endometriosis patients is thought to be subtle (17). In an observational IVF study using natural cycles, the follicular phase was significantly longer and the fertilization rate lower in patients with minimal to mild endometriosis compared with women with tubal factor and unexplained infertility (18). Women with endometriosis were noted to have a slower follicular growth rate (3) and reduced dominant follicle size compared with women with unexplained infertility (19). Trinder and Cahill (17) also concluded that endometriosis patients have abnormal follicle development, ovulation, and luteal function. Conversely, Mahmood et al. (20) found that women with endometriosis did not experience significant differences in the duration of their follicular phase, and that dominant follicle development was not effected by the disease. Establishing a definitive conclusion regarding the relationship of follicular modifications and endometriosis is difficult because of the aforementioned conflicting study outcomes.

GRANULOSA CELL FUNCTION

Changes in granulosa cell cycle kinetics may be responsible for impaired follicle growth and oocyte maturation in endometriosis patients (21). Flow cytometric analysis was used to determine the cell cycle of granulosa cells in endometriosis and nonendometriosis patients. A decreased number of granulosa cells in the G₂/M phase and an increase in both the S phase and apoptotic cells were documented in women with endometriosis (21, 22).

Oocyte quality may be influenced by granulosa cell apoptosis as well. Granulosa cell apoptosis increased proportionally with the severity of disease and resulted in poor oocyte quality and a reduction in fertilization and pregnancy rates (23). A higher percentage of granulosa cell apoptosis was associated with significantly reduced pregnancy rates in

patients with endometriosis or tubal factor infertility undergoing IVF (24).

Another factor studied in conjunction with endometriosis and granulosa cells is oxidative stress (OS). Oxidative stress markers such as 8-hydroxy-2-nonenal, used for the evaluation of oxidative DNA damage and 4-hydroxy-2-nonenal, a product of lipid peroxidation, were significantly elevated in granulosa cells of patients with endometriosis (21). It has been suggested that the elevated reactive oxygen species (ROS) causing OS are produced from erythrocytes and apoptotic endometrioma cells, as well as the activated macrophages that are recruited to phagocytize the apoptotic cells (25). Additionally, the ROS producing enzyme xanthine oxidase, which is considered another contributor of excess ROS, is expressed in greater quantities in women with endometriosis (26).

Oxidative stress plays a large role in infertility, and its effect is exerted through multiple mechanisms. In addition, OS has been shown to induce oocyte degeneration and apoptosis through disturbing the meiotic spindle. Another way in which cells are damaged through OS is via lipid peroxidation, which is the oxidative destruction of polyunsaturated fatty acids in the plasma membrane (27). It leads to “increased membrane permeability, degraded membrane integrity, inactivated enzymes and structural damage of the DNA; cell death rapidly follows” (28). Excessive ROS can also interfere with IVF by decreasing the likelihood of fertilization, inducing embryonic fragmentation when intracytoplasmic sperm injection is used and hampering the *in vitro* development of blastocysts (27). In addition, OS induces a local inflammation resulting in elevated levels of cytokines and other factors that promote endometriosis, as discussed later (25).

ALTERATIONS IN FOLLICULAR FLUID IMMUNE FUNCTION

Endometriosis is associated with inflammatory changes in the follicular fluid (FF) and peritoneal fluid (PF) environments. An increased percentage of B lymphocytes, natural killer cells, and monocyte-macrophages in the FF have been noted in a case-controlled study of patients with endometriosis compared with those with other causes of infertility. This suggests the possibility of altered immunologic function in the FF of patients with endometriosis (29).

Increased concentrations of interleukins IL-6, IL-1 β , IL-10, and tumor necrosis factor- α (TNF- α), as well as decreased vascular endothelial growth factor (VEGF) have been documented in the FF of endometriosis patients (30–32). Immunologic changes in the PF and serum of women with endometriosis may be responsible in part for the pathologic alterations associated with infertility in endometriosis patients (33). For example, VEGF has been shown to enhance follicular health and vascularization (33). The reduced VEGF levels in women with endometriosis (31) may be associated with reduced embryo quality and implantation rates (16). Significantly elevated concentrations of TNF- α in granulosa cell cultures of women with endometriosis have been reported (34) and may also be related to infertility. Tumor necrosis

factor- α was shown to increase the adhesiveness of endometrial stromal cells to peritoneal mesothelium. It was hypothesized that this was the result of TNF- α increasing the expression of cell adhesion molecules ICAM1 and Sele (35, 36).

Alterations of the granulosa cell cycle previously noted in endometriosis patients also may be influenced by cytokine changes (21). For example, elevated IL-10 was shown to prevent the natural down regulation of p27, thereby causing arrest in the G₀ phase (37). Many other cytokines, whose levels are elevated in the FF of endometriosis patients, such as IL-6, IL-1 β , IL-8, or IL-1 α , also induce various cell cycle abnormalities, most likely contributing to subfertility in such patients (Table 1) (21).

Changes in the ovarian steroid enzyme pathways may be modulated by cytokines secreted by ovarian and white blood cells (16, 38). Tedeschi et al. (39) reported that endothelin-1 was a potent inhibitor of rat granulosa cell steroidogenesis in vitro. According to Abae et al. (40), immunoreactive endothelin-1 was elevated in the FF of patients with endometriosis-associated infertility. It was also shown that increased levels of IL-6 in the preovulatory follicles of endometriosis patients result in decreased aromatase activity via the MAPK signal pathway. The decreased aromatase activity causes a decrease in intrafollicular conversion of androstenedione to estrone and then a diminished conversion of Androstenedione to testosterone, which is aromatized to E₂ (41, 42). The resulting decrease in follicular levels of E₂ can then give rise to fertility problems including decreased fertilizing capacity (41). Altered levels of progesterone have also been found in the FF of endometriosis patients, indicating that altered steroidogenesis most likely plays a significant role in endometriosis-associated infertility. However, a direct relationship between infertility and modified progesterone levels has yet to be established (16).

Others have implicated impaired luteinizing hormone (LH) production as the primary pathophysiology causing impaired ovulation (43). It was suggested that gonadotropin-surge attenuating factor (GnSAF), which is a small polypeptide in the FF primarily produced by small follicles, plays a role in the decreased levels of LH in endometriosis patients. Gonadotropin-surge attenuating factor decreases the ability of E₂ to sensitize the pituitary to gonadotropin-releasing hormone, thereby decreasing the pituitary's potential to produce LH. Because estrogen levels are lower in the FF of endometriosis patients, the antagonistic actions of GnSAF against LH production are likely to result in suboptimal LH levels and impaired ovulation (44).

ENDOMETRIOSIS, PERITONEAL ENVIRONMENT, AND IMMUNE FUNCTION

Alterations in the PF environment of endometriosis patients typically result in the growth, proliferation, and inflammation of ectopic endometrial tissue (Table 1) (45). Alterations in both humoral and cell-mediated immunity have been found in the peritoneal environment of endometriosis patients

(46). In addition, immunoglobulins and complement deposits were observed in the eutopic endometrium of patients with endometriosis (47). Mathur et al. (48) demonstrated the presence of autoantibodies to endometrial antigens in women with endometriosis. It is thought that these antiendometrial antibodies develop as a physiologic response to counter endometriosis. Polyclonal B-cell autoimmune activation has also been observed in association with endometriosis (49).

The various components of cell-mediated immunity such as activated pelvic macrophages are increased in the PF of infertile endometriosis patients, resulting in a local peritoneal inflammatory cascade (45). It was proposed that this inflammatory response can lead to increased ectopic implantation of endometrial tissue, as well as its growth and proliferation. PF T-lymphocytes and natural killer (NK) cells are also increased. The NK cells are responsible for the recognition and destruction of transplanted foreign cell lines, tumor cells, and infected host cells (45). Oosterlynck et al. (46) demonstrated that in women with endometriosis, there is significant suppressive activity of PF on the cytotoxicity of NK cells and leukocytes. The use of such suppression mechanisms may be a further attempt by the body to limit the progression of endometriosis, and supports the notion that the inflammatory cascade may be in part responsible for endometriosis-associated infertility.

Peritoneal immunologic abnormalities result in endometrial stromal cell proliferation, lymphocyte proliferation, increased cyclic activation of macrophages, and the presence of nonorgan specific autoantibodies. Leukocytes and other cells secrete cytokines and growth factors into the endometrial extracellular space where they function as intercellular communication mediators effecting paracrine activity of the immune system. PF cytokines and growth factors are increased as a direct response to the increase in leukocytes present in the peritoneal environment of endometriosis patients (45, 50). The secretion of RANTES (regulated on activation, normal T-cell expressed and secreted), a cytokine present in the PF, is increased in women with endometriosis (Table 1). It is a chemoattractant for monocyte and memory T-cells as well as a mediator of inflammation with numerous potential binding sites for transcription factors. RANTES is up-regulated in response to IL-1 β , whose secretion is induced by activated macrophages (45). As has been stated previously, these immunologic abnormalities can directly affect the development and inflammation of ectopic endometrial tissue, exhibit cytotoxic effects on healthy cells, and in addition, as will be discussed later, produce harmful free radicals that contribute to endometriosis-associated infertility (Table 1).

Increased E₂ levels in the PF of endometriosis patients was shown to stimulate cyclo-oxygenase-2 (COX-2) enzyme, which then up-regulates prostaglandin E₂ (PGE₂) production (Fig. 1). Prostaglandin E₂ is the most potent stimulator of aromatase expression in endometriotic tissue (51), and results in elevated E₂ production, further promoting its own proliferation and growth (52). E₂ and PGE₂ then up-regulate COX-2

TABLE 1**Role of altered immunologic factors in endometriosis-associated infertility.**

Affected immunologic factors	Levels of the immunologic factor in women with endometriosis	Mechanistic actions of affected immune factors	Effect of altered immune factor levels on fertility	Reference
Follicular fluid studies VEGF	Decreased	Decreases follicle health and vascularisation	Decreased embryo quality and implantation rates	(31)
IL-6	Increased	Decreases aromatase activity within follicles	Decreased intrafollicular E ₂ levels, leading to decreased fertility and fertilizing capacity	(30)
Peritoneal fluid studies RANTES	Increased	Attracts monocytes and memory T-cells to inflamed areas	Increased inflammation, cytotoxic effects on healthy cells, and OS produced, leading to decreased fertility	(101)
IL-10	Increased	Prevents p27 down regulation in developing granulosa cells	G ₀ arrest of granulosa cell cycle, resulting in low-quality oocytes	(55)
VEGF	Increased	Induces the formation of angiogenesis promoting fibrin matrix in the peritoneal cavity	Increased adhesion of free endometrial tissue within the peritoneal cavity	(57)
TNF- α	Increased	Causes increased prostaglandin production by endometrial epithelial cells	Increased adhesion of free endometrial tissue within the peritoneal cavity, and increased inflammation, leading to subfertility	(28)
TNF- α	Increased	Decreases the effect of TIMP	Increase effects of MMP, leading to increased endometriotic tissue invasiveness	(59)
PAPP-A	Increased	Increases follicular androstenedione syntheses	Increased conversion of androstenedione to E ₂ by endometriotic tissue, leading to increased tissue proliferation	(54)
Cathepsin D	Increased	Initiates harmful proteolytic events	Degradation of basement membrane and extracellular matrix components	(61)

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TABLE 1

Continued.

Affected immunologic factors	Levels of the immunologic factor in women with endometriosis	Mechanistic actions of affected immune factors	Effect of altered immune factor levels on fertility	Reference
Altered immune factors in peritoneal fluid and their adverse effects on spermatozoa	Increased	Induces the release of gp130 by sperm	Decreased sperm motility	(55)
IL-6	Increased	Initiates a Caspase cascade	Sperm apoptosis and a/ oligospermia	(28)
TNF- α	Increased	Induces ROS production from spermatozoa	Sperm plasma membrane lipid peroxidation and abnormal sperm function	(78)
TNF- α				

Note: ROS = reactive oxygen species; OS = oxidative stress; MMP = matrix metalloproteinases; TNF- α = tumor necrosis factor-alpha; PAPP-A = pregnancy-associated plasma protein; VEGF = vascular endothelial growth factor; TIMP = tissue inhibitors of MMP.

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to initiate a positive feedback loop, resulting in a persistent endometriotic state (51).

Pregnancy-associated plasma protein (PAPP-A) is produced by the endometrium, ovary and placenta, and exhibits protease activity toward insulin-like growth factor-binding protein-4 (IGFBP-4), which normally suppresses follicular E₂ production. The protease activity of PAPP-A leads to decreased IGFBP-4, resulting in increased levels of free insulin-like growth factors (IGF), which can then synergize with FSH (Fig. 2). IGF synergizes with LH to increase androstenedione and testosterone production, which are then aromatized under the influence of FSH to E₁ and E₂, respectively(42, 53). Normally, this conversion would be performed by follicular aromatase. However, because there is decreased aromatase activity in follicles of endometriosis patients, the conversion takes place in the endometriotic tissue where there is abnormally increased expression of aromatase, resulting in a more pronounced endometriotic state. This is supported by a study where increased PAPP-A in the peritoneal microenvironment of endometriosis patients was reported, and the degree of elevation was shown to be correlated with the severity of disease (54).

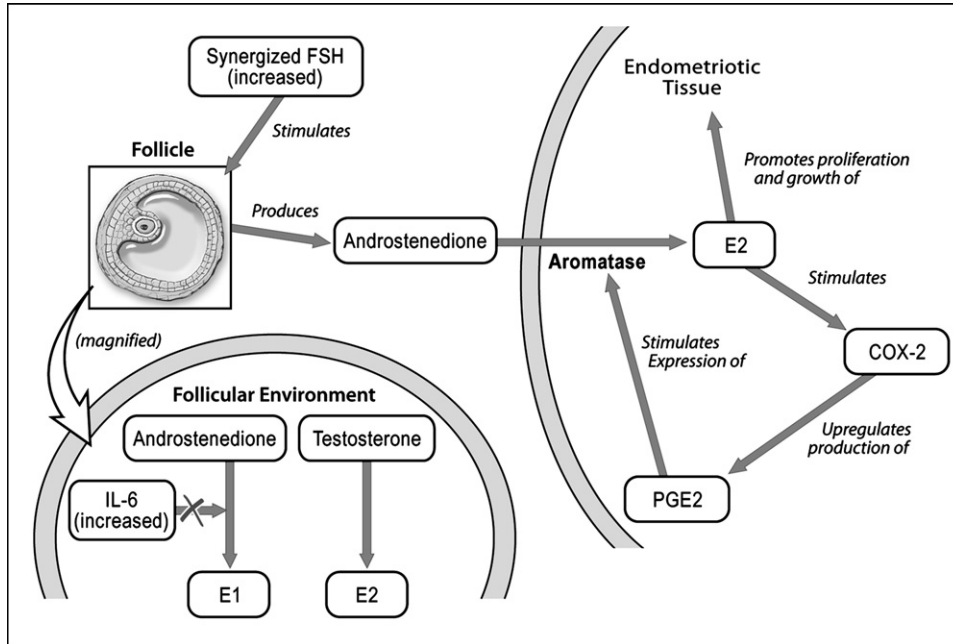
IL-6 is a cytokine that regulates inflammatory and immune responses in the peritoneal environment through the activation of T-lymphocytes, as well as the differentiation of B-lymphocytes. The PF concentrations of IL-6 have previously been reported variably as both elevated and normal in endometriosis patients (25, 55). IL-6 is produced by endometrial stromal and epithelial cells in response to estrogen's induction by IL-1 and TNF- α (56). An increase in the PF IL-6 levels may be associated with deleterious effects on sperm motility. The mechanism is discussed later (41).

Excess PF TNF- α is produced by activated lymphocytes, macrophages, and NK cells in endometriosis patients. It causes an increase of prostaglandin production by endometrial epithelial cells, initiates a surge of inflammatory cytokines, and also promotes the adherence of ectopic endometrial cells to the peritoneum (35). An increased concentration of VEGF in peritoneal fluid of women with endometriosis has also been reported (57). However, VEGF's origin of secretion in women with endometriosis has not yet been determined. Vascular endothelial growth factor induces the formation of an angiogenesis promoting fibrin matrix in the peritoneal cavity, which may contribute to pelvic adhesions and increase the capture rate of free endometrial tissue within the cavity. These factors would further promote the progression of endometriosis (45).

Tumor necrosis factor- α and IL-1 are up-regulators of matrix metalloproteinases (MMP) that regulate the turnover of the extracellular matrix and can increase the invasiveness of endometrial fragments. Because TNF- α and IL-1 levels are increased in the PF of endometriosis patients (28, 58), MMP is likely to be increased in such patients, although studies have not confirmed this notion. Tumor necrosis factor- α is thought to decrease the in vitro effect of tissue inhibitors of MMP (TIMP), thereby increasing the in vitro effect of MMP. T-like autoantibodies were also hypothesized to

FIGURE 1

Role of COX-2 and aromatase in a persistent endometriotic state.



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increase the pathologic effect of MMP by binding to an antigen bearing hemopexin domain present on most all MMP. This is thought to lead to dysregulation of MMP and TIMP expression, thereby promoting the invasiveness of endometriotic tissue (59).

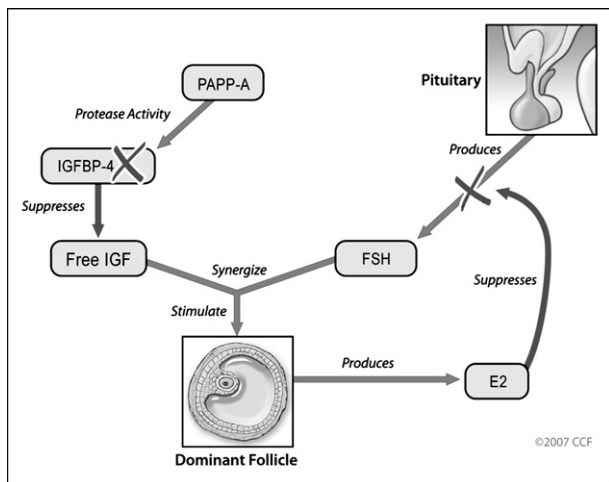
Therapeutic outcomes have provided some insight as to the causal relationship between TNF- α and endometriosis. In

a case report from our institution where a patient with severe endometriosis was treated with the immunomodulator Infliximab, the severity of the disease persisted. It could therefore be hypothesized that the altered immunologic environment is the result and not the cause associated with the disease (60).

Cathepsin D is an aspartyl acid protease widely distributed in animal and human cells whose gene expression is differentially regulated by sex-steroid hormones. It initiates proteolytic events resulting in the degradation of basement membrane and extracellular matrix components. Cathepsin D levels were elevated in the PF of stage III/IV patients compared with stage I/II patients and were lower in patients treated with GnRH agonists (61).

FIGURE 2

Endometriosis, peritoneal biologic window, and role of cytokines.

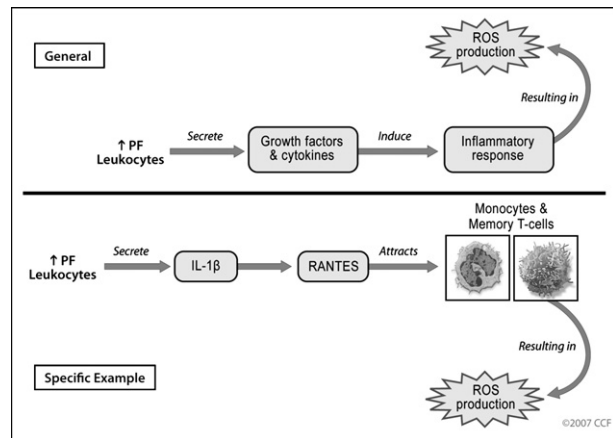


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ENDOMETRIOSIS, PERITONEAL ENVIRONMENT, AND OS

Production of large amounts of ROS by elevated numbers of macrophages and polymorphonuclear leucocytes in PF from endometriosis patients has been reported (62). Two studies from our group also found increased ROS in endometriosis PF, although the levels were not significantly different from the disease free controls (28, 63). With these studies, it is believed that the development of OS in the local peritoneal environment may be one of the links in the chain of events leading to endometriosis-associated infertility (Fig. 3) (25). It was also proposed that redox levels may modulate the severity, dynamics, and progression of the disease.

The increase in number and activity of macrophages in endometriosis is accompanied by a release of additional

FIGURE 3**Endometriosis, peritoneal environment, and OS.**

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cytokines and other immune mediators such as nitric oxide (NO) (64). Nitric oxide is a free radical and a bioregulator of apoptosis (65). Low levels of NO are important in ovarian function and implantation. However, higher amounts of NO and nitric oxide synthase (NOS) are seen in the endometrium of women with endometriosis (66). This is partly because of the fact that peritoneal macrophages express higher levels of NOS, have higher NOS enzyme activity, and have been shown to produce more NO in response to immune stimulation *in vitro* (67).

High levels of NO have been reported to decrease fertility by exhibiting deleterious effects on oviductal function and sperm motility, and NO has been shown to be toxic to embryos and inhibit implantation. It was therefore suggested that a reduction of NO production in the PF or blocking NO effects would improve fertility in women with endometriosis. IVF may improve the conception rate in women with endometriosis by avoiding contact of the gametes and embryos with potentially toxic peritoneal and oviductal factors (e.g., NOS, ROS) (67).

Activation of polymorphonuclear leukocytes and macrophages also results in increased ROS production (Fig. 3) (62). Some studies investigating the association of NO, lipid peroxide, and ROS in PF found no significant differences between patients with and without endometriosis. Conflicting results were obtained in other studies (68). However, indirect evidence was provided by reports of elevated PF levels of oxidized low density lipoproteins in women with established (69) and developing pelvic endometriosis. In the PF of women with endometriosis-associated infertility, the total antioxidant capacity was reduced, and individual antioxidant enzymes such as superoxide dismutase were significantly lower. In addition, lipid peroxide levels were the highest among patients with endometriosis, suggesting a possible ROS role in the development of endometriosis (68). The existence of antioxidant-oxidant imbalance has been reported in many of the studies investigating PF from women with endometriosis.

It has also been hypothesized that ROS may have a role in the formation of adhesions associated with endometriosis. Although adhesions because of endometriosis are known to decrease fertility, the mechanism by which this occurs is not yet fully understood (70). Additionally, folliculogenesis alterations, presumably caused by OS, may impair oocyte quality and have also been proposed as a cause of subfertility associated with endometriosis. Levels of the OS marker, 8-hydroxy 1-deoxyguanosine, were higher in patients with endometriosis than with tubal, male factor or idiopathic infertility (21). A sixfold increase in the levels of 8-hydroxy 1-deoxyguanosine and lipid peroxide was demonstrated in ovarian endometriomas compared with normal endometrial tissue.

Oxidative stress was also shown to induce genomic and mitochondrial DNA damage (71), which directly leads to a decrease in fertility (72). In recent studies from our center, spermatozoa were found to exhibit increased DNA fragmentation when they were incubated with PF from endometriosis patients, and the extent of fragmentation increased with the stage of endometriosis and duration of infertility (73). Likewise, oocytes exhibited increased DNA damage as they were incubated in PF of endometriosis patients, and the extent of the damage was dependent on the duration of PF exposure (74). As was expected, we found that embryos incubated in the PF of endometriosis patients also exhibited DNA fragmentation as indicated by increased apoptosis (75). The increased DNA damage in sperm, oocyte, and resulting embryo is proposed to be accountable for increased miscarriages and fertilization and implantation failures among endometriosis patients (73).

ENDOMETRIOSIS AND SPERM FUNCTION

As discussed above, an increased generation of ROS by activated macrophages has been reported in the PF of patients with endometriosis and can induce DNA fragmentation in sperm cells. Lipid peroxidation is one of the most destructive forms of oxidation, and is because of the direct effect of ROS on the polyunsaturated fatty acids found in cell membranes (76). Lipid peroxidation causes a number of detrimental effects such as an increase in membrane permeability, loss of membrane integrity, and enzyme inactivation in the spermatozoa (27). Additionally, severe OS can lead to infertility through its negative impact on the acrosome reaction and sperm-oocyte fusion (77).

Elevated levels of TNF- α in the PF of women with endometriosis have adverse effects on sperm function and integrity, as discussed in an *in vitro* study conducted by our group (Table 1). It was hypothesized that the toxic effects of TNF- α could be the result of its ability to stimulate apoptosis in sperm cells through initiation of a caspase cascade via TNF-receptor-interacting protein kinase 1. Another explanation could be that TNF- α stimulates spermatozoa to generate ROS, leading to lipid peroxidation and decreasing the sperm's potential to fertilize an egg and produce a healthy child (78).

Endometriosis may adversely affect the interaction between the sperm and the endosalpinx epithelium. Although little is known about the molecular pathways that mediate sperm and endosalpinx interaction, several related alterations have been observed in women with endometriosis, and it is thought that those alterations play an important role in the decreased fertility of such patients. For example, in endometriosis patients, the tubal ampulla epithelium tends to bind spermatozoa tighter than normal, resulting in a decreased quantity of free spermatozoa available to travel down the lumen to attempt fertilization (79).

Elevated PF levels of several cytokines, such as IL-1 and IL-6, are thought to contribute to the subfertility of endometriosis patients, in part because of their effect on sperm motility in the uterus (Fig. 4). One mechanism that was proposed is that IL-6 combines with a soluble IL-6 receptor, also present in PF, and together they associate with glycoprotein-130 (gp130) which is expressed in sperm. Although the mechanism by which gp130 promotes sperm motility is not yet clear, it was shown that sperm motility decreases when gp130 is bound to the IL-6 complex (41).

ENDOMETRIOSIS AND FERTILIZATION

There is conflicting data regarding a causal relationship between endometriosis and impaired fertilization. Several articles reported a reduced fertilization rate with IVF (5, 17, 18, 80–84). Pal et al. (82) reported a significant reduction in fertilization rates with stage III and IV endometriosis compared with stage I and II. In contrast to these studies, others were unable to identify a significant effect on the fertilization rate (85, 86). However, it has been demonstrated that PF from women with endometriosis inhibits the binding of spermatozoa to the zona-pellucida (87, 88).

One possible mechanism for reduced fertilization rates is compromised oocyte quality, because it has been shown that

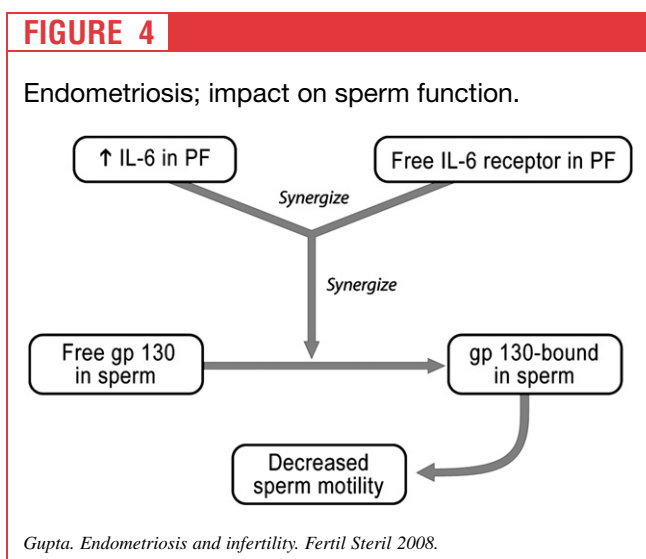
oocyte donors with endometriosis establish pregnancies at lower rates than normal donors (83, 89). One study by our center found microtubule and chromosomal changes in poor-quality oocytes, which could potentially explain the reduced fertilization rates, as well as reduced implantation rates (74). Additionally, a direct correlation between the disease and prevalence of nuclear and cytoplasmic aberrations was observed in preimplantation embryos obtained from women undergoing in vitro fertilization cycles for endometriosis-associated infertility (90).

Another possible mechanism involves the effect of FF on gamete interaction. Normal FF induces the acrosome reaction and enhances sperm binding to the zona-pellucida. Qiao et al. (91) reported that the FF from endometriosis patients undergoing IVF resulted in significantly decreased binding of spermatozoa to the zona compared with patients with tubal factor infertility.

ENDOMETRIOSIS AND IMPLANTATION

A lack of understanding about the normal physiologic mechanisms of embryo implantation makes it difficult to explain why women with endometriosis may have a decreased implantation capacity resulting in lower pregnancy rates (6). However, reduced endometrial receptivity may be secondary to delayed histologic maturation or biochemical disturbances (92, 93). Another proposed mechanism for impaired implantation involves the cellular adhesion molecule $\alpha v \beta 3$ integrin. Lessey et al. (92, 94, 95) demonstrated that $\alpha v \beta 3$ integrin expression is increased in the endometrium during the window of implantation, but it is reduced or absent in patients with endometriosis. In addition, such patients had increased $\alpha v \beta 3$ integrin expression in blood vessels, and cyclical variations in integrin expression were reported (96, 97). It was also found that dysregulation of other select genes in the endometrium of patients with endometriosis may lead to impaired embryonic attachment, embryotoxicity, immune dysfunction, and apoptosis during the window of implantation (98). A functional impairment of the zona was also proposed to cause impaired implantation in women with endometriosis. However, assisted hatching performed for overcoming this problem did not lead to improved implantation or pregnancy rates (99).

In an attempt to determine the primary cause of low MFR in endometriosis patients, oocyte donation studies were devised. These studies compared the success rates of normal women receiving oocytes from women with endometriosis, to women with endometriosis receiving normal oocytes. If it was found that normal women receiving oocytes from endometriosis patients had lower success rates, then it could be deduced that the main cause of subfertility in endometriosis patients stems from having dysfunctional oocytes, and not from the oocytes altered environment. Several oocyte donations studies have been conducted, and conflicting data was obtained. Some studies showed that normal women receiving donor oocytes from endometriosis patients had lower success rates, whereas the other studies found no significant difference (100).



In conclusion, the term enigmatic disease is frequently used in the endometriosis literature. There is no clear consensus whether milder stages of endometriosis are a cause of infertility or merely an incidental finding in some patients with unexplained infertility. Similarly, it is uncertain whether reduced fertility in severe stages of the disease is primarily because of anatomic disruption or from physiologic alteration. The discordant results are in part because of limitations of the study designs including heterogeneous patient groups, differences in severity of disease, lack of fertile endometriosis patients as controls, different medical and surgical therapeutic modalities used for treating endometriosis, varying IVF outcomes studied, lack of stringent inclusion criteria, and other compounding factors that influence IVF outcomes in endometriosis patients. Randomized controlled trials with comparable groups of patients are necessary to assess the impact of endometriosis on fertility.

We have reviewed the multiple hormonal, chemical, and immunologic changes reported with endometriosis as well as how they may affect ovulation and oocyte quality, tubal function, sperm function, fertilization, and implantation. A greater understanding of these mechanisms is necessary to achieve the goals of devising noninvasive methods for diagnosing endometriosis as well as to shift the current emphasis from surgical destruction and/or extirpation of disease to medical treatment.

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