IntroducTion

Endometriosis is a common gynecologic disorder, affecting 3–10% of reproductive-aged women. Prevalence of endometriosis, in fact, changes by diagnosis. In women undergoing tubal ligation, the prevalence of mainly asymptomatic endometriosis was found to vary from 1 to 7%. On the other hand, in women with primary infertility the prevalence varied from 9 to 50%. There is also racial difference. Two studies have showed that Africans may have a lower risk and East Asians may have higher risk for the disease than Caucasians.

Endometriosis is characterized by the growth of endometrial tissue outside the uterine cavity. Nearly more than a century has passed since the first description of endometriosis by von Rokitansky in 1860, but our current understanding of the pathogenesis and pathophysiology of the disease still remains unclear. Various theories have been put forth to explain the mechanisms for the development of this disease. The three main theories accepted presently are implantation of endometrial tissue following retrograde menstruation, coelomic metaplasia and induction theories. Among these theories, Sampson’s theory of retrograde menstruation has gained the most supportive evidence. This evidence includes the presence of viable endometrial tissue in the peritoneal fluid that is capable of growth, and the anatomical distribution of endometriotic implants.

In fact, no single theory explains all cases adequately. Although retrograde menstruation occurs in at least 76–90% of women undergoing peritoneal dialysis and laparoscopy, the much lower prevalence of endometriosis (6.2–8.2%), suggests that other factors must determine the susceptibility to developing endometriosis.

The ability of endometrial implants to survive in ectopic locations may be related to an aberrant immune response. The role of the immune system in endometriosis has been studied extensively, and numerous immune anomalies have been identified. Yet, whether immune anomalies are a cause or a result of endometriosis has not been resolved. This article will address the pathogenesis of endometriosis from an immunologic perspective, and characterize immune defects related to this disorder.

Immunology and Endometriosis

Many investigators have suggested that there is an association between the presence of endometriosis and
an altered immune system. The theory of an altered immune system and endometriosis suggests that changes in cell-mediated immunity and humoral immunity may contribute to the development of the disease.\(^{22}\)

**Cell-Mediated Immunity and Endometriosis**

In rhesus monkeys with spontaneous endometriosis cellular immunity to autologous endometrium is suppressed.\(^{23}\) This observation led to a speculation that endometriosis can develop only in women with altered cellular immunity.\(^{24}\) A diminished cellular-mediated immune response would make the ectopic implantation of the translocated endometrial cells possible.

**Natural killer cells.** The mechanisms by which the clearance of regurgitated endometrial cells occurs in the peritoneal cavity of the majority of women are poorly understood. However, it has been suggested that natural killer (NK) cells may play a role. There is a decreased cytotoxicity of peripheral and peritoneal fluid NK cells from patients with endometriosis to autologous and heterologous endometrium.\(^{25,26}\) Furthermore, the decrease in local NK-mediated cytotoxicity in the peritoneal fluid is more pronounced in the moderate and severe stages of endometriosis. It was also shown that the peritoneal fluid from women with endometriosis contained significantly greater NK cell suppressive activity than that of the peritoneal fluid from fertile controls.\(^{27}\) These findings were confirmed by other researchers in the serum\(^{28}\) and peritoneal fluid\(^{29}\) of women with endometriosis.

Thus, it is postulated that the decrease in NK cytotoxicity to retrogradely shed endometrial tissue may allow for the establishment of endometriosis within the peritoneal cavity. The mechanisms that suppress NK cell activity are not clear. Wu et al. reported increased killer inhibitory receptor (KIR) expression on peritoneal NK cells from women with endometriosis, which represents a likely cause of decreased peripheral NK activity in these patients.\(^{30}\) In a recent study, it was shown that the proportion of a subclass of killer inhibitory receptors (KIR2DL1) was increased on NK cells in the peritoneal fluid and peripheral blood\(^{31}\) suggesting a local and systemic decrease in NK activity.

Although it is generally accepted that there is a decrease in NK cytotoxicity, there are discrepancies in the percentage, and the number of these cells in women with endometriosis. Different studies have shown that the number or the percentage of NK cells in women with the disease may be decreased,\(^{32}\) increased,\(^{33}\) or unchanged.\(^{25}\)

It is interesting to note that in women with endometriosis there are progressive increases in both NK cell number\(^{34}\) and activity\(^{35}\) following GnRH agonist treatment, which may be because of a direct effect of GnRH agonist or a consequence of decreased estradiol levels.

**Macrophages.** Factors responsible for the suppression of cellular immunity are thought to be products of monocytes or macrophages. It is known that monocyte and macrophage products are modulators of both immune and non-immune cells, and therefore these cells and their products have been investigated intensively in the pathogenesis of endometriosis. Zeller et al. showed that the activational status of peripheral monocytes is increased in women with endometriosis, but they found no difference between the percentage of the peripheral monocytes in women with the disease and that in women without the disease.\(^{36}\) Furthermore, some other studies showed that peritoneal macrophages are increased in total number, concentration and activational status.\(^{37-41}\) In association with the activational status of the macrophages there is an increase in the release of their products, such as growth factors and cytokines, which can affect the survival and growth of ectopic endometrial cells.\(^{42}\)

Scavenger function is one of the vital functions of macrophages in the face of an invading foreign material or when encountering cellular debris and apoptotic cells.\(^{43,44}\) A variety of surface receptors are involved in this activity.\(^{43-46}\) A number of factors, including cytokines, glucocorticoids, lipopolysaccharides, interferons, macrophage colony-stimulating factor, and retinoids can regulate these receptors.\(^{47-49}\) As these cytokines and hormones are present in abnormal levels in the peritoneal fluid of women with endometriosis, they may cause defective scavenger receptor function, which might be another mechanism for abnormally functioning macrophages that could contribute to the growth of ectopic endometrial cells.\(^{50}\) In addition, it was shown that when macrophages are not adherent and are not attached to the extracellular matrix in tissues, they do not express scavenger receptors of the A-type.\(^{51}\) Thus, in contrast to tissue macrophages, when the peritoneal macrophages are not attached to extracellular matrix components, they may not be competent scavengers despite their differentiated status. Indeed, the number of non-adherent macrophages is increased in the peritoneal fluid of women with endometriosis.\(^{52}\) This property may play a causal role in the etiology of this disease through decreased macrophage scavenger activity.

**Lymphocyte.** In endometriosis, it was shown that there is a decrease in the proliferation of peripheral blood lymphocytes in response to recognition of endometrial antigen and cells.\(^{23,24}\) Similarly, Steele et al. observed that there is a reduced cytotoxic effect of peripheral
blood lymphocytes against autologous endometrial cells, and they suggested that the destruction of endometrial cells is decreased in women with endometriosis.24 Although the changes in peripheral blood leukocyte profiles were reported in women with endometriosis, data are inconsistent. In one study, the ratio of T helper to T suppressor lymphocytes was found to be increased in peripheral blood of women with endometriosis.53 But two other studies revealed that peripheral lymphocyte profiles are not markedly affected in endometriosis.33,54 In addition, data obtained from studies on peripheral lymphocytes must be carefully interpreted because the biologic activities of peripheral lymphocytes may not reflect the biologic activities of lymphocytes from specific tissue sites.55 Peritoneal T cell and macrophage numbers were increased in baboons with spontaneous endometriosis, but not in those with surgically induced disease.56 Increase in the T helper to T suppressor ratio and concentration of both T cell types were reported in the peritoneal fluid33,57 and ectopic endometriotic tissue58 compared to eutopic endometrium in women with endometriosis. On the other hand, by immunohistochemistry no significant difference in the ratio of T helper to T suppressor lymphocytes could be shown between eutopic endometria of patients with and without endometriosis.59 A recent study has reported that GnRH agonist treatment in women with endometriosis causes an up-regulation of T cell proliferative activity.35 In all, there appear to be inconsistencies in the alterations in T cells and their role in endometriosis.

Immune surveillance. Defective immune surveillance is another interesting concept in the etiology of endometriosis. It has been postulated that the defective immune surveillance predisposes susceptible women to develop the syndrome. Several mechanisms have been put forth on how endometriotic cells evade leukocyte recognition. One mechanism could be the secretion of proteins that interfere with immunocyte-endometrial implant recognition. One such factor is the soluble form of the intercellular adhesion molecule (ICAM)-1. ICAM-1, a cell surface molecule, acts as a ligand for leukocyte function antigen-1 (LFA-1), and the ICAM-1/LFA-1 system mediates various cell–cell interactions involved in immunity. Soluble ICAM-1 (sICAM-1) is a circulating substance generated by cleavage of the extracellular domain of ICAM-1. It binds with LFA-1 of leukocytes, thus, making leukocytes less available for binding with cell surface ICAM-1 on target cells. As a result, this prevents the activation of these leukocytes. It has been shown that isolated endometriotic stromal cells express more ICAM-1 mRNA and secrete more sICAM-1 than the matched stromal cells from eutopic endometrium.60

Another hypothesis involves the Fas–Fas ligand (FasL) system. When a FasL-expressing cell binds a Fas-bearing immune cell, it triggers the Fas-bearing cell’s death by apoptosis. Garcia-Velasco et al. have shown that macrophage-conditioned media induces FasL expression by endometrial stromal cells in a concentration-dependent manner, and they have suggested that the proinflammatory nature of the peritoneal fluid of women with endometriosis induces the FasL expression by regurgitated endometrial cells, and signals Fas-mediated cell death of activated immune cells; this could be a mechanism for endometrial cells to escape immune surveillance.61 Selam et al. have shown that eutopic endometrial stromal cells from women with endometriosis demonstrate higher FasL expression compared with those from women without endometriosis when they attach to extracellular matrix proteins (fibronectin, laminin and collagen IV).62 These results suggest that the attachment of endometrial stromal cells during retrograde menstruation to a new environment such as peritoneum with increased expression of laminin, fibronectin and collagen IV could lead to an increase in FasL expression. This induction of FasL may take part in the development of a relative immunotolerance by inducing apoptosis of cytotoxic T lymphocytes, which will allow further development of ectopic implants (Fig. 1).

Humoral Immunity
Autoantibodies. In addition to alterations in cell-mediated immunity, considerable evidence has been gathered indicating that there are alterations in B-cell activity and an increased incidence of autoantibodies in women with endometriosis (Table I). Nearly two decades ago, it was shown that there is an increased B-cell function in women with endometriosis as well as with adenomyosis.63 Later, Weed et al. demonstrated IgG and complement deposits in the eutopic endometrium and a corresponding reduction in the serum total complement level in women with endometriosis.64 They hypothesized that ectopic endometrium might act as a foreign trigger to induce an autoimmune response, resulting in infertility. Mathur et al. detected IgG and IgA autoantibodies in sera, cervical and vaginal secretions of women with endometriosis.65 Later, they found that these autoantibodies recognize endometrial antigens (ranging in molecular weight from 34 to 140 kD) that are candidates for the autoantigens responsible for the immune response.66 In addition, complement C3 and C4 levels were found to be higher in the serum and the peritoneal fluid of women with endometriosis than those in controls.67 The theory that endometriosis could be regarded as an autoimmune disease, since there is an increase in the frequency of autoantibodies, was first introduced by
**Apoptosis**

Gleicher et al. These include autoantibodies to a variety of phospholipids, histones, polynucleotides as well as lupus. Some of these autoantibodies are organ-specific such as antiendometrial and antiovian antibodies. Like classical autoimmune diseases, endometriosis has polyclonal B-cell activation, immunological abnormalities in T- and B-cell functions, increased apoptosis, tissue damage, and multiorgan involvement. Moreover, there are familial occurrence, a possible genetic basis, female preponderance, and

---

*Fig. 1.* Peritoneal macrophages and extracellular matrix proteins (ECM) can induce Fas ligand expression by endometrial stromal cells, which in turn may result in apoptosis of cytotoxic lymphocytes.
increased likelihood of other autoimmune diseases. However, there are still some problems in postulating and accepting endometriosis as an autoimmune disease. Autoimmune diseases are associated with certain HLA alleles. Although a strong genetic component exists in endometriosis, no association with specific HLA haplotypes has been demonstrated yet. To define a disease truly autoimmune in nature, it needs to be manifested in normal animals following adaptive transfer of immunoglobulin from the blood or affected tissues of subjects with autoimmune disease, but there is still no such study performed to investigate this phenomenon. There is also no proof that complement activation occurs specifically in the endometrium of women with endometriosis. The increased endometrial autoimmunity in endometriosis patients is also thought to be because of enhanced immune reactivity to normal self-antigens because of a genetic predisposition to autoimmunity or an excess of endometrial autoantigens in the peritoneal cavity because of retrograde menstruation. However, there are some investigators who have been able to document these autoantibodies, and this subject remains controversial.

Recognized tissue antigens include the human chorionic gonadotropin receptor, isoforms I and II of the enzyme carbonic anhydrase, CA 125, serum transferrin, α₂-Heremans Schmidt glycoprotein, and receptors for polynucleotides. These antigens have also been described and proposed as diagnostic markers. However, none of these tests has provided sufficient evidence concerning the disease and stage specificity to be used for screening. It has recently been shown that a common carbohydrate epitope, the Thomsen–Friedenreich-like (T) antigen, found on many of these antigens is secreted to the extracellular environment. These molecules exert their effects on the same (autocrine activity) or nearby cells (paracrine activity). They are also key mediators of intercellular communication within the immune system. Cytokines may have proliferative, cytostatic, chemoattractant or differentiative effects. In the peritoneal fluid of women with endometriosis, several proinflammatory chemoattractant cytokines for monocytes, macrophages and granulocytes have been identified.

**Table I. Summary of Immunologic Abnormalities Related to Autoantibodies**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased B cell function</td>
<td>Startseva et al.</td>
</tr>
<tr>
<td>Polyclonal B cell activation</td>
<td>Hang et al.</td>
</tr>
<tr>
<td>IgG and complement deposits in eutopic endometrium</td>
<td>Weed et al.</td>
</tr>
<tr>
<td>IgG and IgA autoantibodies against endometrial antigens</td>
<td>Mathur et al.</td>
</tr>
<tr>
<td>Increased C3 and C4 levels in the serum and peritoneal fluid</td>
<td>Badawy et al.</td>
</tr>
<tr>
<td>Increased autoantibodies of IgG, IgM and IgA against phospholipids, histones, polynucleotides</td>
<td>Moncayo et al., D'Cruz et al., Barbieri et al., Mathur et al., Pilai et al.</td>
</tr>
<tr>
<td>Antibodies to human chorionic gonadotropin receptor, isoforms I and II of the enzyme carbonic anhydrase, CA 125, serum transferrin, α₂ -Heremans Schmidt glycoprotein</td>
<td>Lang et al.</td>
</tr>
</tbody>
</table>

The association between autoantibody abnormalities and endometriosis could explain endometriosis-related infertility. An increased risk of pregnancy loss has been clearly associated with the presence of abnormal non-organ specific as well as organ-specific autoantibodies. There are some studies showing that treatment with Danazol or GnRH analogues suppresses the levels of autoantibodies associated with endometriosis. Dmowski et al. also showed the effect of autoantibodies on in vitro fertilization (IVF) success rates among women with endometriosis. They did a retrospective analysis of IVF cycles of 193 patients and measured autoantibodies in 50 of them who had a history of endometriosis. They found those women with evidence of more than three autoantibodies (‘positive’) had a significantly lower pregnancy rate per transfer (22.9 versus 45.7%) than women with less than two autoantibodies (‘negative’). Among 10 autoantibody-positive patients treated with corticosteroids, eight of them became pregnant, whereas none of the antibody-positive endometriosis patients who were not treated with glucocorticoids conceived. These data can be interpreted to suggest that abnormal autoantibodies may play a role in the infertility associated with endometriosis.

**Cytokines and Growth Factors**

Cytokines and growth factors are proteins or glycoproteins produced by leukocytes or other cells, and secreted to the extracellular environment. These molecules exert their effects on the same (autocrine activity) or nearby cells (paracrine activity). They are also key mediators of intercellular communication within the immune system. Cytokines may have proliferative, cytostatic, chemoattractant or differentiative effects. In the peritoneal fluid of women with endometriosis, several proinflammatory chemoattractant cytokines for monocytes, macrophages and granulocytes have been identified.
Interleukin-1. Interleukin (IL)-1 is a cytokine playing an important role in inflammation and immune response. It is secreted mainly by activated monocytes and macrophages and also by T and B cells, and NK cells. It affects the activation of T cells and the differentiation of B cells. There are two distinct molecular forms of IL-1 (IL-1α and IL-1β) derived from two different genes. An IL-1 receptor antagonist (IL-1ra) has also been defined and acts as an endogenous receptor inhibitor. IL-1 has been isolated from the peritoneal fluid of women with endometriosis. Most researchers found increased levels in such women, although others found no difference. It has been suggested that IL-1β plays a role in promoting angiogenesis in endometriotic lesions by inducing the angiogenic factors (vascular endothelial growth factor and IL-6) in endometriotic stromal cells but not in normal endometrial stromal cells. It has also been found that IL-1β increased sICAM-1 shedding from endometrial cells, which may interfere with peritoneal immune surveillance.

Interleukin-6. IL-6 is a cytokine mainly produced by T cells, and also secreted by macrophages, fibroblasts and endothelial cells. It has B cell stimulatory activity. It enhances the differentiation of T cells, induces the secretion of other cytokines, and also acts as a growth regulator for various human cell lines. It has been shown that IL-6 can inhibit the proliferation of the human endometrial stromal cells. Yoshioka et al. observed that IL-6 has no effect on the growth of endometrial stromal cells from the proliferative phase, but it inhibits proliferation of endometrial stromal cells from the secretory phase. On the other hand, they also found that stromal cells of endometriotic tissues are resistant to IL-6, showing no inhibitory response. Endometriotic cells may behave differently from their eutopic endometrial counterpart in terms of the inhibitory regulation exerted by IL-6. Tabibzadeh et al. reported that IL-6 levels are low in the proliferative phase of the cycle while estrogen concentrations are high, and IL-6 levels are high during the secretory phase of the cycle while estrogenic activity is low. Therefore, they suggested that IL-6 fluctuations during the menstrual cycle reflect an inverse relationship to estrogen action. Peritoneal fluid levels of IL-6 correlate well with the severity of endometriosis, and a high peritoneal fluid level of this cytokine in severe endometriosis is also accompanied by a decrease in IL-6 soluble receptor concentration. For this reason, the endometriotic implants may be resistant to growth inhibition by IL-6. However, other investigators reported an increased concentration of this soluble receptor.

Interleukin-8. IL-8 is a chemokine that induces chemotaxis of neutrophils and is a potent angiogenic factor.Besides mesothelial cells that form the majority of the peritoneal cells, macrophages and endometrial cells are potential sources of this chemokine. We have found that there are menstrual cycle-dependent changes in IL-8 mRNA in the endometrium. IL-8 mRNA levels in the late secretory and early mid-proliferative phase samples are higher than the level observed in the middle of the cycle. It can be speculated that IL-8 may modulate the timely recruitment of neutrophils and lymphocytes into the endometrium. Moreover, it has been shown that IL-8 significantly stimulates cell proliferation in endometrial and endometriotic stromal cells. Iwabe et al. also observed that TNF-α stimulates proliferation of endometriotic stromal cells through induction of IL-8 gene and protein expression. We and other investigators have previously shown that IL-8 is elevated in the peritoneal fluid of women with endometriosis. We also observed that IL-8 level is correlated with the severity of the disease. We have recently shown that IL-8 stimulates the adhesion of endometrial cells to fibronectin. Thus, IL-8 may be relevant for stimulating the attachment of endometrial implants in the pathogenesis of endometriosis. In addition, the adherence of endometrial cells induces further IL-8 expression by an integrin-dependent mechanism. In summary, IL-8 may act as an autocrine growth factor in the endometrium and may play a role in the pathogenesis of endometriosis by promoting a vicious circle of endometrial cell attachment, cell growth, and further secretion of this cytokine.

Interleukin-12. IL-12 is secreted by macrophages and monocytes. It plays an important role in the regulation of NK cell activity. It stimulates secretion of various cytokines, cytotoxicity of NK cells, and also proliferation of T cells and NK cells. Zeyneloglu et al. demonstrated that IL-12 is present in peritoneal fluid of women with endometriosis as well as in women without endometriosis. It was shown that the most likely source of IL-12 in peritoneal fluid is macrophages, and IL-12 does not have value in predicting the inflammatory status of peritoneal fluid. It was found that higher levels of free p40 subunit of IL-12 are present in the peritoneal fluid of women with endometriosis compared to those in women without the
T cell activation in peritoneal fluid. The pattern of peritoneal macrophages and T lymphocytes after secretion of RANTES may result in the recruitment of the severity of the disease. It has been postulated that women with endometriosis and its level correlates with RANTES is increased in the peritoneal fluid of chymal cells. It has been shown that the concentration is secreted by T cells, some epithelial cells and mesenchymal cells. It has been shown that the concentration of RANTES is increased in the peritoneal fluid of women with endometriosis and its level correlates with the severity of the disease. It has been postulated that secretion of RANTES may result in the recruitment of peritoneal macrophages and more T lymphocytes after T cell activation in peritoneal fluid. The pattern of RANTES protein distribution, which shows localization primarily in stromal compartment in endometriotic lesions, is similar to that found in normal endometrium. Moreover, there is an important difference between normal endometrial stromal cell cultures and those derived from endometriomas that are under similar conditions. The latter cells show significantly greater secretion of RANTES.

Transforming growth factor-β (TGF-β). TGF-β is mainly produced by platelets, activated lymphocytes and macrophages. It is a potent chemoattractant for monocytes, which induces angiogenesis, and inhibits T and B lymphocyte and NK cell activity. It was shown that there are increased concentrations of TGF-β in peritoneal fluid in women with endometriosis as compared to both fertile and infertile patients without endometriosis.

Tumor necrosis factor-α (TNF-α). Neutrophils, activated lymphocytes, macrophages, NK cells, and several nonhematopoietic cells produce TNF-α, whereas TNF-β is produced by lymphocytes. These TNFs were initially identified for their ability to kill certain cell lines. But it is now known that they have the ability to initiate the cascade of cytokines and other factors associated with inflammatory responses. In vitro, epithelial cell TNF secretion is increased by IL-1, and also modulated by progesterone and plasma protein-14. TNF-α has been shown to increase the adherence of cultured stromal cells to mesothelial cells. This finding suggests that the presence of TNF-α in peritoneal fluid may play a facilitory role in adherence of ectopic endometrial tissue to the peritoneum, allowing implants to develop. Several researchers have found that TNF-α concentrations are increased in the peritoneal fluid of women with endometriosis, and that its level correlates with the stage of the disease. It has also been demonstrated that TNF-α affects sperm motility in vitro, but only at very high concentrations. In addition, Hill et al. have tested various cytokines and found significant embryotoxicity only by TNF-α and IFN-γ.

Vascular endothelial growth factor (VEGF). VEGF is a heparin-binding glycoprotein. It is a very potent mitogen for endothelial cells, and induces vascular permeability and acts as a chemoattractant for monocytes. It is also one of the most potent angiogenic factors. It is produced by monocytes, macrophages and smooth muscle cells. VEGF binds to a family of tyrosine kinase receptors including Flt-1 and KDR, leading to dimer formation, autophosphorylation of the receptor, and activation of mitogen-activated protein kinases. It has been shown that VEGF protein is localized predominantly in endometrial glands, Estradiol increases the expression of VEGF gene in normal human endometrium. Hypoxia, IL-1, platelet-derived growth factor and TGF-β, epidermal growth factor, and prostaglandin E2 are other factors known to up-regulate VEGF expression. The expression of VEGF by endometriotic implants provides a mechanism for the neovascularization, which is commonly observed around these lesions. VEGF immunostaining is observed in the epithelium of endometriotic implants, particularly in hemorrhagic red implants. In endometriosis, peritoneal fluid VEGF concentrations are significantly higher in women with moderate to severe endometriosis than in women with minimal to mild endometriosis.

Impact of Endometriosis on Fertility

There is also substantial evidence that these immunologic alterations may play a role in endometriosis-associated infertility. There are some studies showing that there is an impairment of implantation in patients with endometriosis, which might be because of the peritoneal fluid inflammation or some abnormalities related to the endometrium or embryos themselves. It has been demonstrated that peritoneal macrophages phagocytize spermatozoa in vitro. Sperm velocity and the proportion of motile spermatozoa decrease when peritoneal fluid from women with endometriosis is added to the medium in vitro.
Fertilization of murine oocytes *in vitro* is inhibited by the peritoneal fluid from women with endometriosis more than the peritoneal fluid from women without endometriosis. In addition, peritoneal fluid from women with endometriosis is embryotoxic and decreases mouse embryo cleavage rate. On the other hand, there are also some other reports suggesting that there is no adverse effect of peritoneal fluid from women with endometriosis on fertilization and embryo development in mice.

**CONCLUSION**

Although there are many gaps in our understanding of the pathogenesis of endometriosis, there is substantial evidence to support that the immunologic factors play a role in the pathogenesis of this disease and endometriosis-associated infertility. Immunologic factors may affect a woman’s susceptibility to the implantation of exfoliated endometrial cells. Immune alterations include increased number and activation of peritoneal macrophages, decreased T cell reactivity and NK cytotoxicity, and increased autoantibodies, and changes in the cytokine network (Fig. 2). Owing to the presence of these immune alterations and its resemblance to some autoimmune diseases such as rheumatoid arthritis and Crohn’s disease, both of which having elevated levels of autoantibodies and several cytokines, some immune modulatory drugs are also being tried in the treatment of endometriosis. Among these drugs, pentoxifylline andloxoribine have been shown to induce some regression of endometriotic implants in rodent models for endometriosis. Furthermore, these drugs do not induce an estrogen deficiency, and therefore it appears that drugs that can modulate immune interactions would become a promising alternative to conventional treatments for endometriosis in the near future. In addition, some of these immune alterations have been used as diagnostic markers, but none of these tests has provided sufficient evidence concerning the disease and stage specificity to be used for screening. This is probably because of the fact that the environment of the peritoneal cavity may also play a decisive role in the development of endometriosis.

Nevertheless, further studies are still needed to determine whether these changes lead to the disease, are coincidental to it, or result from it.

**REFERENCES**

43. Ramprasad MP, Fischer W, Witztum JL et al.: The 94- to 97-kDa mouse macrophage membrane protein that recognizes oxidized low-density lipoprotein and phosphatidylserine-rich liposomes is identical to macroscialin, the mouse homologue of human CD68. Proc Natl Acad Sci USA 1995; 92:9580–9584.


