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Cytokines and Endometriosis - the Role of Immunological Alterations

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***Abstract* - Endometriosis is a debilitating condition, and a serious health threat to the individual patient. There has been a lot of advance in deepening its understanding since its original clinical description. There is no theory of pathogenesis that can explain all of the described manifestations of endometriosis and we still not fully understand the exact factor(s) that are responsible for the survival and subsequent implantation of the displaced endometrium.This establishment of endometriotic implants may be partly explained with the understanding of the innate or acquired properties of the endometrium and defective immune clearance. Among the several cytokines or chemokines identified in great number in the peritoneal fluid (PF) of patients with endometriosis are macrophage migration inhibitory factor, TNF-α, IL-1β, IL-6, IL-8, regulated on activation, normal T expressed and secreted (RANTES), and monocyte chemoattractant protein-1 (MCP-1). There is a tight connection between endometriosis-associated inflammatory response, tissue repair and neo-vascularization, on the one hand and the PF macrophages and their secretory products (cytokines), on the other. Further research is needed, however, to clarify whether observed cytokine profiles are a cause or a consequence of endometriosis.**

***Keywords* - endometriosis, immunological alterations, cytokines**

I. INTRODUCTION

Endometriosis is estimated to occur in 6–10% of the general female population and in 35–50% of women presenting pelvic pain, infertility or both. [1, 2] Endometriosis, a benign aseptic inflammatory disease, is mainly accompanied by adhesion formation and infertility. It is classically seen as the presence of responsive ectopic endometrial glands and stroma implants outside the uterus, primarily the pelvic peritoneum, ovaries, and rectovaginal septum.[3].

Though there are still unknowns as far as its pathogenesis is concerned, there is evidence showing that genetic, endocrine, immunological, and environmental factors play an important role in the genesis and development of endometriosis [4, 5] which is, therefore, considered both an estrogen-dependent and a chronic inflammatory disease.[3, 6, 7] Peritoneal environment may be involved in the pathogenesis of endometriosis and/or in the latter's symptoms. [8, 9] One of the theories is that peritoneal fluid (PF) in women with endometriosis is abundant in activated macrophages that secrete a variety of local products, such as growth factors and cytokines. [9, 10] Therefore, several growth factors, cytokines, immune cells and hormones in eutopic and ectopic endometrium, are seen as playing a role in the pathophysiology of endometriosis-related infertility. [3, 11] Abnormalities inherent to the eutopic endometrium that are not located in the endometrium of women without endometriosis are likely to be involved in the ectopic growth outside the uterine cavity. [12, 13] Different characteristics of eutopic endometrium of women with endometriosis, such as aberrant production of cytokine, growth, adhesion and angiogenic factors as well as specific cancer-related molecules, have been linked to the occurrence and maintenance of this disease. [14] Part of its etiology can be explained by the presence of endometrial cells or tissues in retrograde menstruation implant and their growth in the pelvic peritoneum. Not many women, however, are affected by endometriosis though many are affected by retrograde menstruation, suggesting that other pathogenic events are required for the development of this disease, such as inflammation and immune responses. [15-19] There are both local and systemic immunological alterations associated with endometriosis, though the mechanism through which they contribute to the development of endometriosis is still unclear.[20]

This paper intends to review the available literature data describing cytokines populations and cytokine receptors in uterine and ectopic endometrium and their proposed role in the regulation of immune processes and endometrial growth as well as current data on immune aspects of endometriosis.

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II. Peritoneal fluid cytokines

Endometriosis can be considered a chronic low-grade inflammatory disease. [4, 21] Chronic pelvic inflammation in endometriosis is associated with an abrogation of local and systemic immunity. The following are among the immunological abnormalities identified in infertile patients with minimal and mild endometriosis: abnormal natural killer (NK) cell function [22, 23], reduced cytotoxic effect of lymphocytes and macrophage [22], imbalanced Th1/Th2 response [24, 25] and high levels of cytokines in the peritoneal fluid. [26] It seems that these alterations contribute to the development and progression of endometriosis and infertility [9, 27, 28]. Within this context, recent researches have been targeting the role of the abnormal immunoinflammatory reaction in the pathogenesis of endometriosis. [29, 30]

The dynamic interplay among cytokines may play a role in the creation of a microenvironment which favors the implantation of endometrial cells and the progression of the disease. The presence and role of various cytokines in the serum and PF of women with endometriosis have been studied by various researches.[31-36], though the available data in the literature lacks consistency. [37] Instead of playing a role in eliminating sloughed endometrial cells, peritoneal immune cells may be responsible for their ectopic growth. As previously mentioned, the following have been identified as possible mechanisms of endometriosis development: altered immune recognition of endometrial cells, lack of adequate immune surveillance, depressed NK activity, and increased numbers of activated peritoneal macrophages, which display an altered phagocytotic function, but release numerous growth and proinflammatory factors. [38-41] There's a high chance that endometriotic implants stimulate leukocyte recruitment and activation and cyclical reflux of menstrual debris in the peritoneal cavity may increase the inflammatory reaction. [15, 42]

Intrinsic endometrial dysfunctions may be followed by the activation of immune cells in ectopic locations and play an important role in the pathogenesis of endometriosis.[43-45] Moreover, endometriosis may be considered an autoimmune disorder due to its immune deviations, including increased local production of some proinflammatory cytokines as well as elevated autoantibody production and abrogation of local and systemic cell-mediated immunity. [9,36,46-48] However, it is not known whether pelvic inflammatory reactions and immune deviations cause or trigger ectopic endometrial growth.[49]

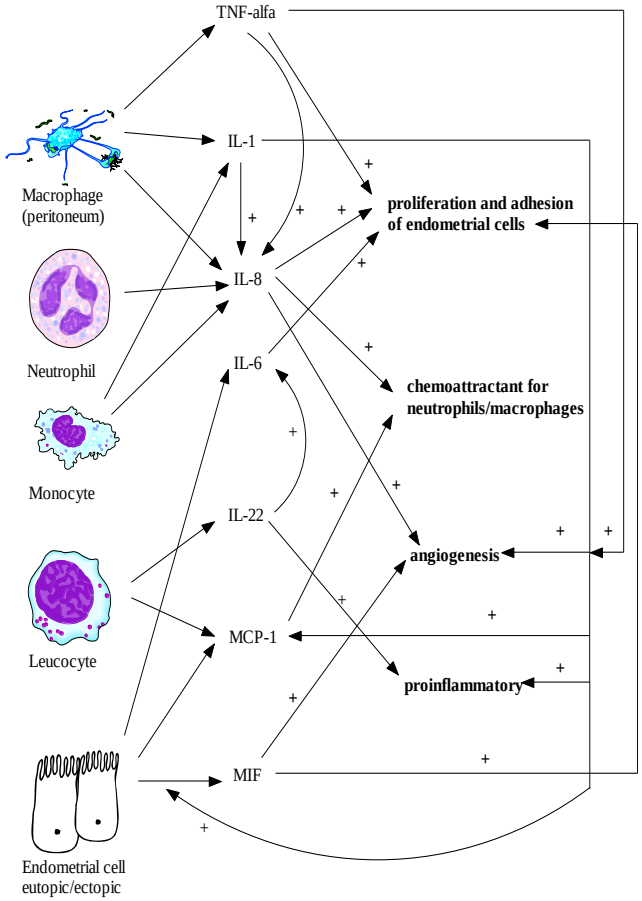

Figure 1. The cytokines interplay and their roles in endometriosis

TNF-alfa- tumoral necrosis factor-alfa; IL-1- interleukine-1; IL-6- interleukine-6; IL-8- interleukine-8; IL-22-Interleukine-22; MCP-1-Monocyte chemoattractant protein-1; MIF-Macrophage migration inhibitory factor

When infiltrated into endometriotic tissue proinflammatory cells such as macrophages are triggered by a release of proinflammatory cytokines and chemokines locally in the endometriotic tissue, which mediate the cellular communication during inflammatory responses. Due to the active lesions of endometriosis, chronic inflammation develops in the surrounding tissue and is accompanied by a fibrous reaction, with the formation of local scarring and adhesions.

An organism reacts to tissue injury with both immune cell recruitment and mediator release during inflammation[46] and significant lymphocytes proliferation and secretion of cytokines may play an important role in rebuilding host immunity. [47]

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There has been significant evidence that several cytokines, such as interleukin 1b (IL-1b) [48], tumor necrosis factor a (TNF-a) [49], IL-6, IL-10, IL-8, vascular endothelial growth factor (VEGF) [50], and monocyte chemoattractant protein 1 (MCP-1) [36] are elevated in the peritoneal fluid of women with endometriosis. [29, 51]

1. Tumor necrosis factor a (TNF-a)

The first cytokine secreted by endotoxin-activated macrophages that induced the necrosis of tumors [10, 52] and which also exert cytotoxic as well as differentiation and growth modulatory activities on many different target cells proved to be TNFα. [53, 54] TNFα is now known as a pluripotent mediator and angiogenic cytokine that enhances the production of other cytokines, including IL-8 in various cells as well as the production of cytokine in endometriotic tissue. TNFα may be viewed as a key cytokine that agitates many other cytokines in the peritoneal cavity of endometriosis patients. [10]

2. Interleukine-8 (IL-8)

On the other hand, IL-8, a chemoattractant for neutrophils and an angiogenic agent, is generated by many types of cells, including monocytes, lymphocytes, neutrophils, endothelial cells, and fibroblasts as well as macrophages and peritoneal mesothelial cells. [53, 55] IL-8 enhances the adhesion of endometrial stromal cells to extracellular matrix proteins, matrix metalloproteinase activity and endometrial stromal cell proliferation in a dose-dependent manner, all these promoting the implantation and growth of ectopic endometrium. [37, 56, 57]

Additionally, Arici *et al.* reported that IL-8 is produced in the human endometrium *in vivo*, especially in glandular cells.[58] IL-8 promotes the proliferation of endometrial stromal cells as a potential autocrine growth factor. [57] Though IL-8 has been suggested to play a role in the pathogenesis of endometriosis, there's no clear proof using endometriotic tissues that IL-8 enhances the growth. However, the results of Iwabe et al clearly demonstrated that IL-8 is a growth-promoting factor in normal endometrium as well as in endometriotic cells. [53]

The same researchers proved for the first time that TNFα stimulated proliferation of endometriotic stromal cells through induction of IL-8 gene and protein expression in endometriotic stromal cells in a dose-dependent fashion. The addition of TNFα boosted the proliferation of the endometriotic stromal cells, and the stimulatory effects of TNFα seemed to be neutralized by adding either anti-TNFα antibody or anti-IL-8 antibody. [53]

The level of TNFα in PF from women with endometriosis showed a positive correlation with the level of IL-8. These results are a proof of the fact that the TNFα action mediated by IL-8 may contribute to the pathogenesis of endometriosis [53] and that TNFα in the peritoneal fluid may also be an essential factor in the pathogenesis of this disease.

TNFα is also known to exert both growth inhibitory and growth stimulatory effects depending on its concentration and cell type. [59, 60] A low dose of TNFα reportedly triggered angiogenesis, whereas a high dose of TNFα, in contrast, inhibited angiogenesis.[61] Low doses of TNFα (10–1000 pg) induced angiogenesis, which reached its maximum at 100 pg, whereas high doses (1 and 5 mg) suppressed it. Thus, it seems that the mitogenic or antiproliferative effects of TNFα on neoplastic endometrial epithelial cells are dependent on the dose of this cytokine. [62] Moreover, the cell death produced by TNFα in epithelial cells was in tight correlation with the characteristic morphological changes in apoptosis and fragmentation of DNA into oligonucleosome size fragments. [53, 63] It has been shown that peritoneal fluid levels of TNFα vary from 5–300 pg/mL in women with endometriosis. [8, 64] Endometriotic tissues may be growth-stimulated in a low dose, picogram per mL concentration range, TNFα environment. The TNFα effects on the eutopic endometrial stromal cells were also investigated; the results of gene and protein expression of IL-8 were similar to those obtained using ectopic endometrial stromal cells. Due to the fact that tissue levels of this cytokine are currently unknown, TNFα might be involved in up- or down-regulatory endometrial cell proliferation. [53]

The activation of the transcription factor, nuclear factor-κB (NF-κB) is believed to mediate the inflammatory responses. NF-κB can be activated by different stimuli, including proinflammatory cytokines. Phosphorylation of IκB and its degradation are known as essential for the release of NF-κB from binding with IκB [65] and it has been demonstrated that TNFα induced the expression of phosphorylated IκB. Moreover, NF-κB activation stimulates the transcription of TNFα. TNFα, on the other hand, is known to activate NF-κB. [66] In their quest to grasp the pathophysiology of endometriosis, the same group of researchers demonstrated that NF-κB activation has played an important role in the induction of IL-8 in endometriotic tissues. They also showed for the first time that GnRHa treatment leads to a weakening of the IL-8 expression by reducing TNFα-induced NF-κB activation.[10]

3. Interleukine-1

IL-1, mainly produced by monocytes and macrophages, is another important mediator that is actively involved in the

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immune and inflammatory response in humans [51] and in particular in endometriosis-associated pelvic inflammation. On the other hand, several natural specific inhibitors, including soluble IL1 receptor accessory protein (sIL1RAcP) and soluble IL1 receptor type 2 (sIL1R2) are critical for counterbalancing the pleiotropic effects of IL1.[43]

IL-1 is known to enhance IL-6 and TNF-α – important cytokines which can be used to efficiently predict the progression of endometriosis. [48] Moreover, IL-1 stimulates the expression and production in vitro of chemokines in endometrial stromal cells and macrophages of women with endometriosis. IL-1 enhanced the expression of IL-8, growth-related oncogene-α (GRO-α) and epithelial neutrophil-activating peptide-78 (ENA-78). [67, 68]

Aberrant endometrial cells responsive to IL-1 in endometriosis are caused by the decreased ability of these cells to down-regulate IL-1 action, which may be triggered by an exaggerated inflammatory response at the onset of the disease. [69]

IL-1 RII works as a bait receptor that could be released in a soluble form after enzymatic cleavage of the cellular domain of the membrane-bound receptor. Rather than differential splicing, matrix metalloproteinase enzymes (MMPs) are involved in the production of soluble decoy enzymatic cleavage from the cell surface receptor.[51, 70]

Michaud et al. found and described for the first time that sIL1RAcP was greatly decreased in the peritoneal fluid of women with endometriosis. This was similar to previous results proving that sIL1RAcP expression levels in the eutopic endometrium were highly decreased in women with endometriosis as compared to controls. [71] IL1 was also significantly elevated in endometriotic women with infertility or pain, as demonstrated by the same study, but there was no relationship between sIL1RAcP and endometriosis-related infertility.[43]

However, there was significant decrease in sIL1RAcP particularly in women with endometriosis who experienced pelvic pain compared with normal controls. The role of proinflammatory mediators in endometriosis-related pain has been documented. [72, 73] Recent studies suggest that the generation of pain may be greatly influenced by the macrophages through interaction with nerve fibers. [40] IL1 is a major product of activated peritoneal macrophages and researchers have identified a relationship between the cytokine's levels and pelvic pain in endometriosis. [74] However, the direct effects of IL1 on nerve fibers and endometriosis-associated pelvic pains are yet to be clarified. [43]

This study may have an interesting pathophysiological relevance. IL1 have proved elevated not only in the peritoneal fluid of women with endometriosis, but also in endometriotic lesions and activated peritoneal macrophages. [74-77] This pleiotropic cytokine has proinflammatory, angiogenic, and growth-promoting abilities. [1, 78-83] It has been recently demonstrated that sIL1RAcP significantly inhibit IL1. This protein seems to augment the binding affinity of the decoy inhibitory sIL1R2 to IL1. [84] Consequently, smaller quantities of sIL1RAcP which become available in the peritoneal fluid, may influence sIL1R2 affinity to IL1 and further its inhibitory effect. Moreover, the decrease in the peritoneal levels of sIL1RAcP discovered by this team of researchers was accompanied by a decrease in the levels of sIL1R2 and an increase in those of IL1β, and was prominent in the secretory phase of the menstrual cycle. IL1 has significamt intrinsic proinflammatory, angiogenic, and mitogenic abilities, and a defect in sIL1RAcP may, in combination with peritoneal IL1/IL1R2 imbalance, increase IL1 effects on target cells as well as influence the pathogenesis of peritoneal endometriosis and the capability of endometrial cells to implant and grow into ectopic sites.[43]

4. Interleukine-18

Interleukin-18 (IL-18) is a cytokine in the IL-1 family [27], originally identified as interferon gamma (IFN-γ) in Kupffer cells and macrophages. [85] IL-18 activates natural killer (NK) cells and also protects against bacterial infections. It is vital in the inflammatory cascade and in the process of innate and acquired immunity due to the fact that it is able to induce the production of IFN-γ in T lymphocytes and NK cells. [85, 86] Moreover, IL-18 correlates with IL-12 to promote the development of the T helper response and a shift to the Th1 pattern.[24, 86] There are still contradictions regarding the role of IL-18 in endometriosis, and this might be explained by the lack of homogeneity among the patient groups studied and the fact that most of the studies did not focus on infertile patients with minimal/mild endometriosis.

Among the investigators who studied the association between IL-18 and endometriosis, Arici et al. and then Oku et al discovered that the measurable levels of IL-18 in the peritoneal fluid of patients with treated endometriosis were significantly higher than those of the control group with endometriosis without treatment.[86, 87] Moreover, Zhang et al. assessed the concentration of IL-18 in the peritoneal fluid and serum of women with endometriosis and identified to be significantly lower in patients with endometriosis than in women without endometriosis, submitted to tubal ligation. [88] Additionally, they could not find a correlation between peritoneal and serum concentrations of IL-18. Luo et al. also reported down-regulation of IL-18 mRNA expression in ectopic and eutopic endometrium of women with endometriosis. [89] Similarly to the results of Fairbanks et al. [90] who found no difference in IL-18 levels either in serum or in peritoneal samples from patients with endometriosis,

but identified a significant increase in IL-12 levels in patients with endometriosis and with more advanced stages of the disease, Glitz et al.reported that the concentration of IL-18 in serum or peritoneal fluid was not altered in women with minimal or mild forms of endometriosis. [27] They found no difference in IL-18 in patients or controls with or without infertility caused by minimal or mild endometriosis, which supports an alternative pathway in the induction of a Th1 inflammatory response in patients with endometriosis. However, the strong and positive correlation between serum and peritoneal IL-18 levels might indicate a systemic immunoregulatory role of IL-18 and not a solely local (peritoneal) production of IL-18.

The final different results of these studies might be greatly influenced by the use of different kits for the determination of IL-18 as well as the different selection criteria of subjects.[27]

5. Interleukine -6

Interleukin-6 is a pleiotropic cytokine that is generated by a variety of cell types, including monocytes, lymphocytes, fibroblasts, endothelial cells, and mesangial cells. IL-6 may also be involved in reproductive physiology, including the regulation of ovarian steroid production, folliculogenesis and early events related to implantation. IL-6 is produced by both eutopic and ectopic endometrium. [8, 37, 48, 91] Moreover, though not constantly, IL-6 seems to be involved in pelvic adhesion formation in both clinical situations and experimental systems. [92-94]

IL-6, which as previously said is secreted by endometriotic cells, plays a significant role in the pathogenesis of endometriosis and, in correlation with interferon-γ (IFN-γ) may upregulate soluble intercellular adhesion molecule −1 production by macrophages in patients with endometriosis. Several studies have associated the aberrant expression of transformation growth factor beta (TGF-β) and vascular endothelial growth factors (VEGF) with the pathogenesis of endometriosis. Moreover, TGF-β and platelet derived growth factor (PDGF) are known to encourage Fas ligand (FasL) expression by the endometrial stromal cells. Hence, immune cells that in normal conditions clear the peritoneal cavity of endometrial cells suffer death by apoptosis due to the interaction between the Fas on their surface and the FasL expressed by the endometrial cells. This increases the survival of ectopic endometrial cells culminating in endometriosis. [37]

Similarly to previous reports [9, 95-98] Barcz et al. reported that endometriosis correlates with increased concentrations of peritoneal fluid IL-6 and IL-8 and that the increased levels of both cytokines are associated with the more advanced stage of the disease.[92] However, they could not identify any statistically significant differences in the case of the other tested cytokines (IL-1β, TNF, IFN-γ, and IL-12), which is also consistent with previous results. [95, 96] The pathogenesis of endometriosis might be greatly influenced by these cytokines [9, 21, 36, 98, 99], but it should be underlined that their levels have not always been reported to be increased in the course of this disorder [37, 100, 101] Possible explanations for this might be the following: the unidentified differences between patient groups, depending on differences in the disease as well as genetic diversity, phase of the menstrual cycle, and possibly others, (for example, the not fully recognized factors such as energy balance regulatory agents). [92, 95, 96, 100].

It has been commonly recognized by various researchers that the inflammatory responses that may cause the induction of adhesion formation may primarily be associated with the production of proinflammatory cytokines interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF). [92, 102, 103]

Contrary to these, the study of Baracz et al.,confirmed the role of IL-6 and IL-8 in the pathogenesis and progression of endometriosis, but they excluded the primary role of these cytokines in the formation of endometriosis-associated peritoneal adhesions. Although they reported that the increased levels of this cytokine were statistically significantly associated with higher grades of pelvic adhesions, the multivariate regression analysis demonstrated that this effect was related to an increased revised AFS score of endometriosis. Thus, the present observations seem to sustain other results that demonstrate that this cytokine plays no role in the formation of adhesion. [104]

However, Bedaiwy *et al*. [48] demonstrated that serum IL-6 and PF TNF-α, could be surprisingly used to differentiate between patients with and without endometriosis with a high degree of sensitivity and specificity. This, however, was not confirmed by other results. They could not identify any significant differences in the concentration of IL-6 in the sera of women in the two groups. [37, 48]

On the other hand, development of pelvic adhesions during endometriosis is negatively correlated with increased levels of VEGF-A which can be accounted for by the stimulatory effect of this cytokine on fibrinolytic system. This might indicate the fact that the VEGF signaling pathway may serve as a therapeutic target in the prevention of peritoneal adhesion formation. [92]

6. Interleukine -22

Furthermore, IL-22, a member of the IL-10 cytokine family, stimulates the production of inflammatory mediator, such as IL-6. [105] IL-22 is also essential for the release of chemokine such as CXCL1, CXCL5, CXCL9, and CCL2. [106, 107] It has been previously confirmed that both

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chemokine CCL2 [108] and IL-8 [109] regulate endometrial stromal cells (ESCs) behavior, and are associated with endometriosis. Guo et al. reported that the higher level of IL-22 and its receptors in eutopic endometrium may promote the expression of CCL2, IL-8/CXCR1, and further, the growth of ESCs possibly through activating STAT5, MAPK/ERK1/2 and or AKT signal pathways, which may play a role in the occurrence and development of endometriosis. [14]

7. Corticotropin releasing hormone (CRH) and urocortin (UCN)

Moreover, corticotropin releasing hormone (CRH) and urocortin (UCN) are neuropeptides, being in a close relationship with stress and inflammation and their effects are mediated through CRHR1 and CRHR2 receptors. It may be interesting to note that Vergetaki et al. studied and demonstrated for the first time that not only CRH and UCN but also CRHR1 and CRHR2 are expressed in endometriotic lesions and that CRH, UCN, CRHR1 and CRHR2 are significantly in higher quantities in endometriotic lesions than the corresponding eutopic endometrium of endometriotic women as well as in eutopic endometrium of endometriotic women compared to healthy individuals. Taking also into account that there is a correlation between the high levels of stress and the progression of endometriosis[110] as well as the fact that CRH is activated by high levels of stress [111-113], these results may explain the neuroendocrine vicious circle of stress, mediated by CRH and UCN which is likely to keep a chronic inflammatory profile as well as infertility. [3]

8. Monocyte chemoattractant protein-1 (MCP-1) and other cytokines

Monocyte chemoattractant protein-1 (MCP-1) is a chemo-attractant that recruits macrophages into the peritoneal cavity. It is secreted by a variety of leukocytes and by mesothelial and endometrial cells. It is produced in higher quantities in ectopic endometrium. MCP-1 is upregulated by IL-1, in eutopic endometrial epithelial cells in women with endometriosis and in cultured ectopic endometrial cells. The estrogen further stimulates this action. [37, 114] It has been demonstrated in an early study that MCP-1 could substantially increase the production of Fas ligand in cultured endometrial and stromal cells. Surprisingly, this incremented production did not up-regulate the apoptosis of endometrial cells but increased the apoptosis of T lymphocytes. This might trigger the development of immunotolerance by stimulating the apoptosis of leukocytes and thereby helping the survival of ectopic endometrial cells. [29, 115]

Moreover, Kalu et al. investigated the possible implication of PDGF, VEGF, IL-6, RANTES, IL1-β, IL-8, TNF-α, MCP-1, sFas, and sFasL in the pathogenesis of endometriosis.[37] As in other studies, they have identified that the concentrations of IL-8 [31, 32, 116], IL-6 [8, 117] and MCP-1 [114, 118, 119] in the PF of women with active endometriosis are significantly higher. However, they could not find an equivalent increase in the concentration of these cytokines in the serum of these women, compared to the control group. This local enhancement of the cytokines in the PF, but not in serum, could be explained by the increased secretory PF macrophage activity, a major recruitment of peripheral blood monocytes and by the autocrine release by endometriotic cells.[37] However, they could not identify increased levels of sFas, sFasL, VEGF, IL-1 β, TNF-α, and PDGF either in PF or in serum of women with endometriosis. This could suggest that the alternative mechanisms play a major role in preventing macrophage mediated clearance of the endometriotic cells. [37]

Monocyte/macrophage recruitment and activation and exacerbation of local immuno-inflammatory reaction might be greatly influenced by the-overexpression of macrophage-activating factors in eutopic and ectopic endometrial tissues such as MCP1, macrophage migration inhibitory factor (MIF) and IL1. [43, 78, 114, 120-122]

Besides being a glucose-dependent islet cell product that regulates insulin secretion in an autocrine fashion MIF, a potent immuno-modulatory, angiogenic and tissue remodeling factor, which has anti-apoptotic, proliferative properties has a marked expression in ectopic endometrial implant [123, 124]. It can also be involved in the capability of this tissue to grow and develop into the host tissue. (IL)-1 may play a role in MIF synthesis and secretion by ectopic endometrial cells. [125-129]

MIF concentration also seems to further increase in endometriosis women who were infertile or suffer from pelvic pain. This uncovers a link between this factor and the endometriosis major symptoms.

Therefore, the increased expression of MIF in active and early stages endometriotic lesions may partially explain the involvement of this factor in the cell proliferation and angiogenesis that is required for the ectopic growth of endometrial tissue.

Additionally, the regulatory effect of MIF on the immune system and especially its effects on the activation and the accumulation of macrophages might explain the presence of feed-forward mechanisms by which macrophage-derived factors may play a role in MIF expression in ectopic endometrial tissue.[125]

III. Conclusions

There has been a lot of advance in deepening the understanding of this debilitating disease since the original clinical description of endometriosis as it has been a major cause of hysterectomy and hospitalization in the United States, with total annual healthcare costs estimated at $69.4 billion in 2009. [130] Due to the significant individual and public health concerns associated with endometriosis it is highly important to fully grasp its pathogenesis and pathophysiology. The PF of women with endometriosis establishes a microenvironment for the development of the disease and is subjected to a number of pathological changes, including inflammatory processes with locally and systemically altered function of the immune system. This review suggests that cytokine network contributes a lot to the etiology and pathogenesis of this disease, most of them displaying angiogenic properties. Deepening our understanding of endometriosis, the development of preventive strategies, novel non-surgical means of diagnosis and targeted therapeutics are all likely to become realities.

Disclosure:
The authors report no conflicts of interest.

References

[1] Bilotas M, Meresman G, Buquet R, Sueldo C, Baranao RI. Effect of vascular endothelial growth factor and interleukin-1beta on apoptosis in endometrial cell cultures from patients with endometriosis and controls. Journal of reproductive immunology. **2010**;84:193-8.
[2] Giudice LC, Kao LC. Endometriosis. Lancet. 2004;364:1789-99.
[3] Vergetaki A, Jeschke U, Vrekoussis T, Taliouri E, Sabatini L, Papakonstanti EA, et al. Differential expression of CRH, UCN, CRHR1 and CRHR2 in eutopic and ectopic endometrium of women with endometriosis. PloS one. 2013;8:e62313.
[4] Kobayashi H, Yamada Y, Morioka S, Niiro E, Shigemitsu A, Ito F. Mechanism of pain generation for endometriosis-associated pelvic pain. Archives of gynecology and obstetrics. 2013.
[5] Trovo de Marqui AB. Genetic polymorphisms and endometriosis: contribution of genes that regulate vascular function and tissue remodeling. Rev Assoc Med Bras. 2012;58:620-32.
[6] Minici F, Tiberi F, Tropea A, Miceli F, Orlando M, Gangale MF, et al. Paracrine regulation of endometriotic tissue. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology. 2007;23:574-80.
[7] Sampson J. Peritoneal endometriosis due to the menstrual dissemination of endothelial tissue into the peritoneal cavity. American journal of obstetrics and gynecology. 1927;14:422–69.
[8] Harada T, Yoshioka H, Yoshida S, Iwabe T, Onohara Y, Tanikawa M, et al. Increased interleukin-6 levels in peritoneal fluid of infertile patients with active endometriosis. American journal of obstetrics and gynecology. 1997;176:593-7.
[9] Harada T, Iwabe T, Terakawa N. Role of cytokines in endometriosis. Fertility and sterility. 2001;76:1-10.
[10] Sakamoto Y, Harada T, Horie S, Iba Y, Taniguchi F, Yoshida S, et al. Tumor necrosis factor-alpha-induced interleukin-8 (IL-8) expression in endometriotic stromal cells, probably through nuclear factor-kappa B activation: gonadotropin-releasing hormone agonist treatment reduced IL-8 expression. The Journal of clinical endocrinology and metabolism. 2003;88:730-5.
[11] Nothnick WB. Treating endometriosis as an autoimmune disease. Fertility and sterility. 2001;76:223-31.
[12] Ulukus M, Cakmak H, Arici A. The role of endometrium in endometriosis. Journal of the Society for Gynecologic Investigation. 2006;13:467-76.
[13] Li MQ, Hou XF, Lv SJ, Meng YH, Wang XQ, Tang CL, et al. CD82 gene suppression in endometrial stromal cells leads to increase of the cell invasiveness in the endometriotic milieu. Journal of molecular endocrinology. 2011;47:195-208.
[14] Guo Y, Chen Y, Liu LB, Chang KK, Li H, Li MQ, et al. IL-22 in the endometriotic milieu promotes the proliferation of endometrial stromal cells via stimulating the secretion of CCL2 and IL-8. International journal of clinical and experimental pathology. 2013;6:2011-20.
[15] Lebovic DI, Mueller MD, Taylor RN. Immunobiology of endometriosis. Fertility and sterility. 2001;75:1-10.
[16] Osuga Y, Koga K, Tsutsumi O, Yano T, Maruyama M, Kugu K, et al. Role of laparoscopy in the treatment of endometriosis-associated infertility. Gynecologic and obstetric investigation. 2002;53 Suppl 1:33-9.
[17] Osuga Y. Novel therapeutic strategies for endometriosis: a pathophysiological perspective. Gynecologic and obstetric investigation. 2008;66 Suppl 1:3-9.
[18] Osuga Y, Koga K, Hirota Y, Hirata T, Yoshino O, Taketani Y. Lymphocytes in endometriosis. Am J Reprod Immunol. 2011;65:1-10.
[19] Khan KN, Kitajima M, Hiraki K, Fujishita A, Sekine I, Ishimaru T, et al. Immunopathogenesis of pelvic endometriosis: role of hepatocyte growth factor, macrophages and ovarian steroids. Am J Reprod Immunol. 2008;60:383-404.

[20] Urata Y, Osuga Y, Izumi G, Takamura M, Koga K, Nagai M, et al. Interleukin-1beta stimulates the secretion of thymic stromal lymphopoietin (TSLP) from endometrioma stromal cells: possible involvement of TSLP in endometriosis. Hum Reprod. 2012;27:3028-35.
[21] Olive DL, Schwartz LB. Endometriosis. N Engl J Med. 1993;328:1759-69.
[22] Hernandez Guerrero CA, Vadillo Ortega F, Tlapanco Barba R, Arriaga Pizano L, Cerbulo Vazquez A, Gonzalez Jimenez MA, et al. [Changes in the systemic immunologic response in association with endometriosis using an animal model]. Ginecologia y obstetricia de Mexico. 2002;70:171-81.
[23] Somigliana E, Vigano P, Gaffuri B, Candiani M, Busacca M, Di Blasio AM, et al. Modulation of NK cell lytic function by endometrial secretory factors: potential role in endometriosis. Am J Reprod Immunol. 1996;36:295-300.
[24] Podgaec S, Abrao MS, Dias JA, Jr., Rizzo LV, de Oliveira RM, Baracat EC. Endometriosis: an inflammatory disease with a Th2 immune response component. Hum Reprod. 2007;22:1373-9.
[25] Antsiferova YS, Sotnikova NY, Posiseeva LV, Shor AL. Changes in the T-helper cytokine profile and in lymphocyte activation at the systemic and local levels in women with endometriosis. Fertility and sterility. 2005;84:1705-11.
[26] Candiani GB, Vercellini P, Fedele L, Colombo A, Candiani M. Mild endometriosis and infertility: a critical review of epidemiologic data, diagnostic pitfalls, and classification limits. Obstetrical & gynecological survey. 1991;46:374-82.
[27] Glitz C, Souza CA, Rodini GP, Genro V, Bilibio JP, Senger M, et al. Peritoneal and serum interleukin-18 levels are not increased in women with minimum or mild endometriosis. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica [et al]. 2009;42:1039-43.
[28] Kyama CM, Debrock S, Mwenda JM, D'Hooghe TM. Potential involvement of the immune system in the development of endometriosis. Reproductive biology and endocrinology : RB&E. 2003;1:123.
[29] Chen QH, Zhou WD, Su ZY, Huang QS, Jiang JN, Chen QX. Change of proinflammatory cytokines follows certain patterns after induction of endometriosis in a mouse model. Fertility and sterility. 2010;93:1448-54.
[30] Zhang X, Wen J, Deng L, Lin J. Decreased levels of peritoneal interleukin-1 receptor antagonist in patients with endometriosis and disease-related dysmenorrhea. Fertility and sterility. 2007;88:594-9.
[31] Calhaz-Jorge C, Costa AP, Barata M, Santos MC, Melo A, Palma-Carlos ML. Tumour necrosis factor alpha concentrations in the peritoneal fluid of infertile women with minimal or mild endometriosis are lower in patients with red lesions only than in patients without red lesions. Hum Reprod. 2000;15:1256-60.
[32] Iwabe T, Harada T, Tsudo T, Tanikawa M, Onohara Y, Terakawa N. Pathogenetic significance of increased levels of interleukin-8 in the peritoneal fluid of patients with endometriosis. Fertility and sterility. 1998;69:924-30.
[33] Maas JW, Calhaz-Jorge C, ter Riet G, Dunselman GA, de Goeij AF, Struijker-Boudier HA. Tumor necrosis factor-alpha but not interleukin-1 beta or interleukin-8 concentrations correlate with angiogenic activity of peritoneal fluid from patients with minimal to mild endometriosis. Fertility and sterility. 2001;75:180-5.
[34] Koninckx PR, Kennedy SH, Barlow DH. Endometriotic disease: the role of peritoneal fluid. Human reproduction update. 1998;4:741-51.
[35] D'Hooghe TM, Xiao L, Hill JA. Cytokine profiles in autologous peritoneal fluid and peripheral blood of women with deep and superficial endometriosis. Archives of gynecology and obstetrics. 2001;265:40-4.
[36] Gazvani R, Templeton A. Peritoneal environment, cytokines and angiogenesis in the pathophysiology of endometriosis. Reproduction. 2002;123:217-26.
[37] Kalu E, Sumar N, Giannopoulos T, Patel P, Croucher C, Sherriff E, et al. Cytokine profiles in serum and peritoneal fluid from infertile women with and without endometriosis. The journal of obstetrics and gynaecology research. 2007;33:490-5.
[38] Vigano P, Vercellini P, Di Blasio AM, Colombo A, Candiani GB, Vignali M. Deficient antiendometrium lymphocyte-mediated cytotoxicity in patients with endometriosis. Fertility and sterility. 1991;56:894-9.
[39] Dmowski WP, Gebel H, Braun DP. Decreased apoptosis and sensitivity to macrophage mediated cytolysis of endometrial cells in endometriosis. Human reproduction update. 1998;4:696-701.
[40] Tran LV, Tokushige N, Berbic M, Markham R, Fraser IS. Macrophages and nerve fibres in peritoneal endometriosis. Hum Reprod. 2009;24:835-41.
[41] Chuang PC, Lin YJ, Wu MH, Wing LY, Shoji Y, Tsai SJ. Inhibition of CD36-dependent phagocytosis by prostaglandin E2 contributes to the development of endometriosis. The American journal of pathology. 2010;176:850-60.
[42] Halme J, Becker S, Wing R. Accentuated cyclic activation of peritoneal macrophages in patients with endometriosis. American journal of obstetrics and gynecology. 1984;148:85-90.
[43] Michaud N, Al-Akoum M, Gagnon G, Girard K, Blanchet P, Rousseau JA, et al. Decreased concentrations of soluble interleukin-1 receptor accessory protein levels in the peritoneal fluid of women with endometriosis. Journal of reproductive immunology. 2011;92:68-73.

[44] Akoum A, Lemay A, Brunet C, Hebert J. Cytokine-induced secretion of monocyte chemotactic protein-1 by human endometriotic cells in culture. The Groupe d'Investigation en Gynecologie. American journal of obstetrics and gynecology. 1995;172:594-600.
[45] Tseng JF, Ryan IP, Milam TD, Murai JT, Schriock ED, Landers DV, et al. Interleukin-6 secretion in vitro is up-regulated in ectopic and eutopic endometrial stromal cells from women with endometriosis. The Journal of clinical endocrinology and metabolism. 1996;81:1118-22.
[46] Ellis A, Bennett DL. Neuroinflammation and the generation of neuropathic pain. British journal of anaesthesia. 2013;111:26-37.
[47] Mocan T, Iancu C. Effective colon cancer prophylaxis in mice using embryonic stem cells and carbon nanotubes. International journal of nanomedicine. 2011;6:1945-54.
[48] Bedaiwy MA, Falcone T, Sharma RK, Goldberg JM, Attaran M, Nelson DR, et al. Prediction of endometriosis with serum and peritoneal fluid markers: a prospective controlled trial. Hum Reprod. 2002;17:426-31.
[49] Machado DE, Abrao MS, Berardo PT, Takiya CM, Nasciutti LE. Vascular density and distribution of vascular endothelial growth factor (VEGF) and its receptor VEGFR-2 (Flk-1) are significantly higher in patients with deeply infiltrating endometriosis affecting the rectum. Fertility and sterility. 2008;90:148-55.
[50] Ulukus M, Ulukus EC, Tavmergen Goker EN, Tavmergen E, Zheng W, Arici A. Expression of interleukin-8 and monocyte chemotactic protein 1 in women with endometriosis. Fertility and sterility. 2009;91:687-93.
[51] Kondera-Anasz Z, Sikora J, Mielczarek-Palacz A, Jonca M. Concentrations of interleukin (IL)-1alpha, IL-1 soluble receptor type II (IL-1 sRII) and IL-1 receptor antagonist (IL-1 Ra) in the peritoneal fluid and serum of infertile women with endometriosis. European journal of obstetrics, gynecology, and reproductive biology. 2005;123:198-203.
[52] Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. Proceedings of the National Academy of Sciences of the United States of America. 1975;72:3666-70.
[53] Iwabe T, Harada T, Tsudo T, Nagano Y, Yoshida S, Tanikawa M, et al. Tumor necrosis factor-alpha promotes proliferation of endometriotic stromal cells by inducing interleukin-8 gene and protein expression. The Journal of clinical endocrinology and metabolism. 2000;85:824-9.
[54] Tabaran F CC, Clichici S, Mocanu T, Biris A, Simon S, et al. Immunohistochemical quantification of the tumor necrosis factor (TNF) receptor II expression in the hepatic tissue after systemic administration of the DNA-SWCNT. Bulletin of University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca. 2011;68:370-5.
[55] Arici A, Tazuke SI, Attar E, Kliman HJ, Olive DL. Interleukin-8 concentration in peritoneal fluid of patients with endometriosis and modulation of interleukin-8 expression in human mesothelial cells. Molecular human reproduction. 1996;2:40-5.
[56] Garcia-Velasco JA, Arici A. Interleukin-8 stimulates the adhesion of endometrial stromal cells to fibronectin. Fertility and sterility. 1999;72:336-40.
[57] Arici A, Seli E, Zeyneloglu HB, Senturk LM, Oral E, Olive DL. Interleukin-8 induces proliferation of endometrial stromal cells: a potential autocrine growth factor. The Journal of clinical endocrinology and metabolism. 1998;83:1201-5.
[58] Arici A, Seli E, Senturk LM, Gutierrez LS, Oral E, Taylor HS. Interleukin-8 in the human endometrium. The Journal of clinical endocrinology and metabolism. 1998;83:1783-7.
[59] Kalb A, Bluethmann H, Moore MW, Lesslauer W. Tumor necrosis factor receptors (Tnfr) in mouse fibroblasts deficient in Tnfr1 or Tnfr2 are signaling competent and activate the mitogen-activated protein kinase pathway with differential kinetics. The Journal of biological chemistry. 1996;271:28097-104.
[60] Tartaglia LA, Goeddel DV, Reynolds C, Figari IS, Weber RF, Fendly BM, et al. Stimulation of human T-cell proliferation by specific activation of the 75-kDa tumor necrosis factor receptor. J Immunol. 1993;151:4637-41.
[61] Fajardo LF, Kwan HH, Kowalski J, Prionas SD, Allison AC. Dual role of tumor necrosis factor-alpha in angiogenesis. The American journal of pathology. 1992;140:539-44.
[62] Ininns EK, Gatanaga M, Cappuccini F, Dett CA, Yamamoto RS, Granger GA, et al. Growth of the endometrial adenocarcinoma cell line AN3 CA is modulated by tumor necrosis factor and its receptor is up-regulated by estrogen in vitro. Endocrinology. 1992;130:1852-6.
[63] Tabibzadeh S. The signals and molecular pathways involved in human menstruation, a unique process of tissue destruction and remodelling. Molecular human reproduction. 1996;2:77-92.
[64] Taketani Y, Kuo TM, Mizuno M. Comparison of cytokine levels and embryo toxicity in peritoneal fluid in infertile women with untreated or treated endometriosis. American journal of obstetrics and gynecology. 1992;167:265-70.
[65] McKay LI, Cidlowski JA. Molecular control of immune/inflammatory responses: interactions between nuclear factor-kappa B and steroid receptor-signaling pathways. Endocrine reviews. 1999;20:435-59.
[66] Blackwell TS, Christman JW. The role of nuclear factor-kappa B in cytokine gene regulation. American journal of respiratory cell and molecular biology. 1997;17:3-9.

[67] Nishida M, Nasu K, Fukuda J, Kawano Y, Narahara H, Miyakawa I. Down-regulation of interleukin-1 receptor type 1 expression causes the dysregulated expression of CXC chemokines in endometriotic stromal cells: a possible mechanism for the altered immunological functions in endometriosis. The Journal of clinical endocrinology and metabolism. 2004;89:5094-100.
[68] Mueller MD, Mazzucchelli L, Buri C, Lebovic DI, Dreher E, Taylor RN. Epithelial neutrophil-activating peptide 78 concentrations are elevated in the peritoneal fluid of women with endometriosis. Fertility and sterility. 2003;79 Suppl 1:815-20.
[69] Akoum A, Jolicoeur C, Kharfi A, Aube M. Decreased expression of the decoy interleukin-1 receptor type II in human endometriosis. The American journal of pathology. 2001;158:481-9.
[70] Orlando S, Sironi M, Bianchi G, Drummond AH, Boraschi D, Yabes D, et al. Role of metalloproteases in the release of the IL-1 type II decoy receptor. The Journal of biological chemistry. 1997;272:31764-9.
[71] Guay S, Michaud N, Bourcier N, Leboeuf M, Lemyre M, Mailloux J, et al. Distinct expression of the soluble and the membrane-bound forms of interleukin-1 receptor accessory protein in the endometrium of women with endometriosis. Fertility and sterility. 2011;95:1284-90.
[72] Bondza PK, Maheux R, Akoum A. Insights into endometriosis-associated endometrial dysfunctions: a review. Front Biosci (Elite Ed). 2009;1:415-28.
[73] Asante A, Taylor RN. Endometriosis: the role of neuroangiogenesis. Annual review of physiology. 2011;73:163-82.
[74] Akoum A, Al-Akoum M, Lemay A, Maheux R, Leboeuf M. Imbalance in the peritoneal levels of interleukin 1 and its decoy inhibitory receptor type II in endometriosis women with infertility and pelvic pain. Fertility and sterility. 2008;89:1618-24.
[75] Fakih H, Baggett B, Holtz G, Tsang KY, Lee JC, Williamson HO. Interleukin-1: a possible role in the infertility associated with endometriosis. Fertility and sterility. 1987;47:213-7.
[76] Mori H, Sawairi M, Nakagawa M, Itoh N, Wada K, Tamaya T. Expression of interleukin-1 (IL-1) beta messenger ribonucleic acid (mRNA) and IL-1 receptor antagonist mRNA in peritoneal macrophages from patients with endometriosis. Fertility and sterility. 1992;57:535-42.
[77] Bergqvist A, Bruse C, Carlberg M, Carlstrom K. Interleukin 1beta, interleukin-6, and tumor necrosis factor-alpha in endometriotic tissue and in endometrium. Fertility and sterility. 2001;75:489-95.
[78] Akoum A, Lemay A, Brunet C, Hebert J. Secretion of monocyte chemotactic protein-1 by cytokine-stimulated endometrial cells of women with endometriosis. Le groupe d'investigation en gynecologie. Fertility and sterility. 1995;63:322-8.
[79] Lebovic DI, Bentzien F, Chao VA, Garrett EN, Meng YG, Taylor RN. Induction of an angiogenic phenotype in endometriotic stromal cell cultures by interleukin-1beta. Molecular human reproduction. 2000;6:269-75.
[80] Akoum A, Lawson C, McColl S, Villeneuve M. Ectopic endometrial cells express high concentrations of interleukin (IL)-8 in vivo regardless of the menstrual cycle phase and respond to oestradiol by up-regulating IL-1-induced IL-8 expression in vitro. Molecular human reproduction. 2001;7:859-66.
[81] Sillem M, Prifti S, Koch A, Neher M, Jauckus J, Runnebaum B. Regulation of matrix metalloproteinases and their inhibitors in uterine endometrial cells of patients with and without endometriosis. European journal of obstetrics, gynecology, and reproductive biology. 2001;95:167-74.
[82] Fan F, Stoeltzing O, Liu W, McCarty MF, Jung YD, Reinmuth N, et al. Interleukin-1beta regulates angiopoietin-1 expression in human endothelial cells. Cancer research. 2004;64:3186-90.
[83] Rossi M, Sharkey AM, Vigano P, Fiore G, Furlong R, Florio P, et al. Identification of genes regulated by interleukin-1beta in human endometrial stromal cells. Reproduction. 2005;130:721-9.
[84] Smith DE, Hanna R, Della F, Moore H, Chen H, Farese AM, et al. The soluble form of IL-1 receptor accessory protein enhances the ability of soluble type II IL-1 receptor to inhibit IL-1 action. Immunity. 2003;18:87-96.
[85] Dinarello CA. Interleukin-18. Methods. 1999;19:121-32.
[86] Arici A, Matalliotakis I, Goumenou A, Koumantakis G, Vassiliadis S, Mahutte NG. Altered expression of interleukin-18 in the peritoneal fluid of women with endometriosis. Fertility and sterility. 2003;80:889-94.
[87] Oku H, Tsuji Y, Kashiwamura SI, Adachi S, Kubota A, Okamura H, et al. Role of IL-18 in pathogenesis of endometriosis. Hum Reprod. 2004;19:709-14.
[88] Zhang Y, Peng LX, Meng L. [Measurements of interleukin-18 in peritoneal fluid and serum of patients with endometriosis]. Zhong nan da xue xue bao Yi xue ban = Journal of Central South University Medical sciences. 2005;30:731-2.
[89] Luo Q, Ning W, Wu Y, Zhu X, Jin F, Sheng J, et al. Altered expression of interleukin-18 in the ectopic and eutopic endometrium of women with endometriosis. Journal of reproductive immunology. 2006;72:108-17.
[90] Fairbanks F, Abrao MS, Podgaec S, Dias JA, Jr., de Oliveira RM, Rizzo LV. Interleukin-12 but not interleukin-18 is associated with severe endometriosis. Fertility and sterility. 2009;91:320-4.
[91] Jacobs AL, Sehgal PB, Julian J, Carson DD. Secretion and hormonal regulation of interleukin-6 production by

mouse uterine stromal and polarized epithelial cells cultured in vitro. Endocrinology. 1992;131:1037-46.
[92] Barcz E, Milewski L, Dziunycz P, Kaminski P, Ploski R, Malejczyk J. Peritoneal cytokines and adhesion formation in endometriosis: an inverse association with vascular endothelial growth factor concentration. Fertility and sterility. 2012;97:1380-6 e1.
[93] Buyalos RP, Funari VA, Azziz R, Watson JM, Martinez-Maza O. Elevated interleukin-6 levels in peritoneal fluid of patients with pelvic pathology. Fertility and sterility. 1992;58:302-6.
[94] Cheong YC, Laird SM, Shelton JB, Ledger WL, Li TC, Cooke ID. The correlation of adhesions and peritoneal fluid cytokine concentrations: a pilot study. Hum Reprod. 2002;17:1039-45.
[95] Milewski L, Barcz E, Dziunycz P, Radomski D, Kaminski P, Roszkowski PI, et al. Association of leptin with inflammatory cytokines and lymphocyte subpopulations in peritoneal fluid of patients with endometriosis. Journal of reproductive immunology. 2008;79:111-7.
[96] Dziunycz P, Milewski L, Radomski D, Barcz E, Kaminski P, Roszkowski PI, et al. Elevated ghrelin levels in the peritoneal fluid of patients with endometriosis: associations with vascular endothelial growth factor (VEGF) and inflammatory cytokines. Fertility and sterility. 2009;92:1844-9.
[97] Oral E, Olive DL, Arici A. The peritoneal environment in endometriosis. Human reproduction update. 1996;2:385-98.
[98] Matarese G, De Placido G, Nikas Y, Alviggi C. Pathogenesis of endometriosis: natural immunity dysfunction or autoimmune disease? Trends in molecular medicine. 2003;9:223-8.
[99] McLaren J. Vascular endothelial growth factor and endometriotic angiogenesis. Human reproduction update. 2000;6:45-55.
[100] Cheong YC, Shelton JB, Laird SM, Richmond M, Kudesia G, Li TC, et al. IL-1, IL-6 and TNF-alpha concentrations in the peritoneal fluid of women with pelvic adhesions. Hum Reprod. 2002;17:69-75.
[101] Pupo-Nogueira A, de Oliveira RM, Petta CA, Podgaec S, Dias JA, Jr., Abrao MS. Vascular endothelial growth factor concentrations in the serum and peritoneal fluid of women with endometriosis. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2007;99:33-7.
[102] Cheong YC, Laird SM, Li TC, Shelton JB, Ledger WL, Cooke ID. Peritoneal healing and adhesion formation/reformation. Human reproduction update. 2001;7:556-66.
[103] Chegini N, Rong H, Bennett B, Stone IK. Peritoneal fluid cytokine and eicosanoid levels and their relation to the incidence of peritoneal adhesion. Journal of the Society for Gynecologic Investigation. 1999;6:153-7.
[104] Rapkin A, Morgan M, Bonpane C, Martinez-Maza O. Peritoneal fluid interleukin-6 in women with chronic pelvic pain. Fertility and sterility. 2000;74:325-8.
[105] Rutz S, Eidenschenk C, Ouyang W. IL-22, not simply a Th17 cytokine. Immunological reviews. 2013;252:116-32.
[106] Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, et al. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nature medicine. 2008;14:275-81.
[107] Ikeuchi H, Kuroiwa T, Hiramatsu N, Kaneko Y, Hiromura K, Ueki K, et al. Expression of interleukin-22 in rheumatoid arthritis: potential role as a proinflammatory cytokine. Arthritis and rheumatism. 2005;52:1037-46.
[108] Li MQ, Li HP, Meng YH, Wang XQ, Zhu XY, Mei J, et al. Chemokine CCL2 enhances survival and invasiveness of endometrial stromal cells in an autocrine manner by activating Akt and MAPK/Erk1/2 signal pathway. Fertility and sterility. 2012;97:919-29.
[109] Li MQ, Luo XZ, Meng YH, Mei J, Zhu XY, Jin LP, et al. CXCL8 enhances proliferation and growth and reduces apoptosis in endometrial stromal cells in an autocrine manner via a CXCR1-triggered PTEN/AKT signal pathway. Hum Reprod. 2012;27:2107-16.
[110] Lima AP, Moura MD, Rosa e Silva AA. Prolactin and cortisol levels in women with endometriosis. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica [et al]. 2006;39:1121-7.
[111] Chrousos GP. Reproductive placental corticotropin-releasing hormone and its clinical implications. American journal of obstetrics and gynecology. 1999;180:S249-50.
[112] Chrousos GP, Torpy DJ, Gold PW. Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: clinical implications. Annals of internal medicine. 1998;129:229-40.
[113] Tariverdian N, Rucke M, Szekeres-Bartho J, Blois SM, Karpf EF, Sedlmayr P, et al. Neuroendocrine circuitry and endometriosis: progesterone derivative dampens corticotropin-releasing hormone-induced inflammation by peritoneal cells in vitro. J Mol Med (Berl). 2010;88:267-78.
[114] Jolicoeur C, Boutouil M, Drouin R, Paradis I, Lemay A, Akoum A. Increased expression of monocyte chemotactic protein-1 in the endometrium of women with endometriosis. The American journal of pathology. 1998;152:125-33.
[115] Selam B, Kayisli UA, Akbas GE, Basar M, Arici A. Regulation of FAS ligand expression by chemokine ligand 2 in human endometrial cells. Biology of reproduction. 2006;75:203-9.
[116] Ryan IP, Tseng JF, Schriock ED, Khorram O, Landers DV, Taylor RN. Interleukin-8 concentrations are elevated in

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peritoneal fluid of women with endometriosis. Fertility and sterility. 1995;63:929-32.
[117] Punnonen J, Teisala K, Ranta H, Bennett B, Punnonen R. Increased levels of interleukin-6 and interleukin-10 in the peritoneal fluid of patients with endometriosis. American journal of obstetrics and gynecology. 1996;174:1522-6.
[118] Akoum A, Jolicoeur C, Boucher A. Estradiol amplifies interleukin-1-induced monocyte chemotactic protein-1 expression by ectopic endometrial cells of women with endometriosis. The Journal of clinical endocrinology and metabolism. 2000;85:896-904.
[119] Pizzo A, Salmeri FM, Ardita FV, Sofo V, Tripepi M, Marsico S. Behaviour of cytokine levels in serum and peritoneal fluid of women with endometriosis. Gynecologic and obstetric investigation. 2002;54:82-7.
[120] Akoum A, Metz CN, Morin M. Marked increase in macrophage migration inhibitory factor synthesis and secretion in human endometrial cells in response to human chorionic gonadotropin hormone. The Journal of clinical endocrinology and metabolism. 2005;90:2904-10.
[121] Akoum A, Metz CN, Al-Akoum M, Kats R. Macrophage migration inhibitory factor expression in the intrauterine endometrium of women with endometriosis varies with disease stage, infertility status, and pelvic pain. Fertility and sterility. 2006;85:1379-85.
[122] Kats R, Collette T, Metz CN, Akoum A. Marked elevation of macrophage migration inhibitory factor in the peritoneal fluid of women with endometriosis. Fertility and sterility. 2002;78:69-76.
[123] Ilie I, Ilie R, Mocan T, Tabaran F, Iancu C, Mocan L. Nicotinamide-functionalized multiwalled carbon nanotubes increase insulin production in pancreatic beta cells via MIF pathway. International journal of nanomedicine. 2013;8:3345-53.
[124] Toso C, Emamaullee JA, Merani S, Shapiro AM. The role of macrophage migration inhibitory factor on glucose metabolism and diabetes. Diabetologia. 2008;51:1937-46.
[125] Herrmann Lavoie C, Fraser D, Therriault MJ, Akoum A. Interleukin-1 stimulates macrophage migration inhibitory factor secretion in ectopic endometrial cells of women with endometriosis. Am J Reprod Immunol. 2007;58:505-13.
[126] Ren Y, Law S, Huang X, Lee PY, Bacher M, Srivastava G, et al. Macrophage migration inhibitory factor stimulates angiogenic factor expression and correlates with differentiation and lymph node status in patients with esophageal squamous cell carcinoma. Annals of surgery. 2005;242:55-63.
[127] Yang Y, Degranpre P, Kharfi A, Akoum A. Identification of macrophage migration inhibitory factor as a potent endothelial cell growth-promoting agent released by ectopic human endometrial cells. The Journal of clinical endocrinology and metabolism. 2000;85:4721-7.
[128] Nishihira J. Macrophage migration inhibitory factor (MIF): its essential role in the immune system and cell growth. Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research. 2000;20:751-62.
[129] Zhang S, Lin R, Zhou Z, Wen S, Lin L, Chen S, et al. Macrophage migration inhibitory factor interacts with HBx and inhibits its apoptotic activity. Biochemical and biophysical research communications. 2006;342:671-9.
[130] Simoens S, Dunselman G, Dirksen C, Hummelshoj L, Bokor A, Brandes I, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. Hum Reprod. 2012;27:1292-9.