[Frontiers in Bioscience 11, 595-619, January 1, 2006]

Endometriosis: harmful survival of an ectopic tissue

Janos Garai [1], Valeria Molnar [1], Tamas Varga [2], Miklos Koppan [2], Attila Torok [2], and Jozsef Bodis [2]

[1]Department of Pathophysiology, Faculty of Medicine, University of Pecs, Hungary, [2]Obstetrics and Gynecology Department, Baranya County Teaching Hospital, Pecs, Hungary

TABLE OF CONTENTS

1. ABSTRACT

Endometriosis results from implantation of endometrial tissue outside the uterine cavity. Endometriosis might remain asymptomatic and discovered accidentally. However, it may cause symptoms, which include chronic pelvic pain, bleeding, infertility, and increases susceptibility to development of adenocarcinoma. The most prevailing hypothesis is that endometriosis results from implantation of endometrial tissue that gains access to peritoneal cavity by retrograde flow during menstruation. The factors contributing to the establishment and persistence of the endometriotic lesions (plaques) most probably include abnormalities of the genital tract, genetic predisposition, hormonal imbalance, altered immune surveillance, inflammatory response and abnormal regulation of the endometrial cells. The mediators that contribute to survival and progression of endometriosis are likely involved in the development of the symptoms of this process. Genomic studies have started to delineate the wide array of mediators involved and the complex genetic background required in the development of endometriosis. This review summarizes our current knowledge regarding the pathogenesis of endometriosis, including progress made with transgenic animals, and a clinical perspective on the diagnosis and management of this common process.

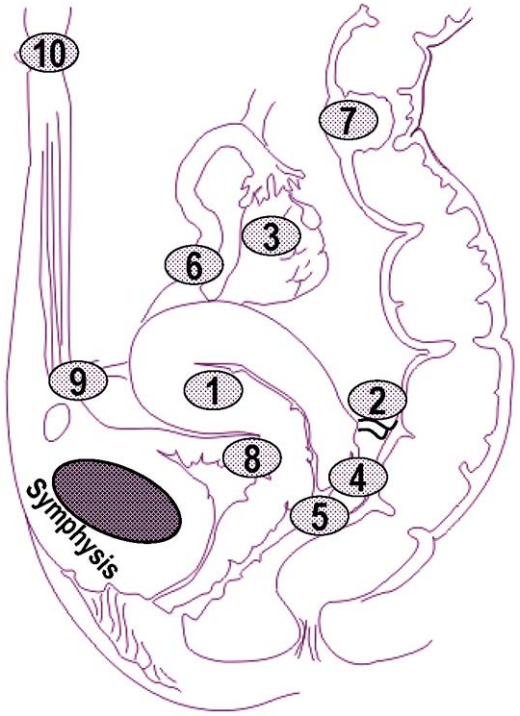

Figure 1. Pelvic and abdominal predilection sites of endometriosis and adenomyosis. 1: Adenomyosis of the uterine myometrial wall;Endometriotic implants on/in the - 2: Sacrouterine ligament, 3: Ovary (superficial, deep endometriomas and chocolate cysts), 4: Cul de Sac, 5: Rectovaginal septum,6: Tubal wall, 7: Bowel wall, 8: Urinary bladder, 9: Inguinal canal, 10: Abdominal wall

2. INTRODUCTION

2.1. Disease or "*condition*"?

Endometrium constitutes the lining of the uterine cavity. Endometriosis is the condition when endometrial tissue persists outside the uterine cavity (Figure 1). It is recognized as the third leading cause of gynecologic hospitalization in developed countries, and a leading cause of hysterectomy (1). This entity has been described long ago (2) and termed first "*adenomyoma*".

It may occur in up to 45% of reproductive age women if the existence of ectopic endometriotic lesions verified by laparoscopy is the sole parameter considered (3). Not all these women, however, present with the typical clinical symptoms and consequences: chronic pelvic pain, pelvipathy, infertility, and increased pelvic cancer susceptibility (4).

It is peculiar, that symptom severity does not correlate well with the extent or progression of the lesions (5). Minor laparoscopic findings might come with severe complaints, while extensive lesions might remain undetected and revealed only accidentally. The exact roles of the different factors contributing to the establishment and persistence of the endometriotic lesion (plaque) are still not fully understood. These most probably include developmental or acquired abnormalities of the uterus and/or the tuba, genetic constitution, hormonal anomalies, altered immune surveillance as well as deranged cellular regulation of the ectopic endometrial cells.

The factors involved in development of the symptoms and consequences of endometriosis also await further clarification. Among them inflammatory mediators are suspected to be responsible for a major part of the untoward effects: pain of dysmenorrhea, altered tubal motility and eventually for the infertility as well. It seems, nevertheless, that certain inflammatory mediators also contribute to enhance the ability of the endometriotic cells to survive in a hostile environment like the peritoneal cavity and to evade immuno-surveillance.

The occasional and transient occurrence of dislocated endometrial tissue at ectopic sites may be a norm for almost every fertile woman (6). Hence its milder forms have been proposed to represent a *condition* rather than a disease (7). Nonetheless, the factors that permit or favor the survival and progression rather than disappearance of this tissue, as well as the consequences inevitably turn this condition into a – sometimes debilitating – *disease*.

3. ETIOLOGY AND PATHOGENESIS

3.1. Dislocation or metaplasia?

The first attempt to address the pathogenesis of endometriotic lesions is often cited and referred as *Sampson's theory* (8). According to his theory the disorder results from retrograde menstruation sloughed through patent fallopian tubes into the peritoneal cavity (Figure 2). Currently it represents the most recognized pathogenic model for pelvic endometriosis. The presence of endometrial tissue in certain distant extrapelvic sites has been explained by possible lymphatic or vascular metastasis (9). The major shortcoming of this theory is the fact that nearly all women of reproductive age exhibit some degree of retrograde menstruation (10), but only 10-16% develops symptomatic endometriosis.

The *metaplastic theory* (11) is based on the ability of coelomic epithelium to convert into different types of tissue. The induction theory extends the metaplastic theory by emphasizing the role of menstrual effluent in the initiation of coelomic metaplastic process (12). Endometrial metaplasia might be induced by soluble factors released from the effluent (13). Although these two chief theories might be considered complimentary the most evidence has been accumulated in support of Sampson's theory.

Nonetheless, not a single theory can explain the versatile occurrence of endometriosis. Coelomic metaplasia theory might account to some extent for the development of endometriosis in the ovaries, peritoneum, and urinary bladder due to their common origin in the coelomic epithelium. Lesions in the rectovaginal space and uterine ligaments are predominantly characterized by smooth muscle hyperplasia more resemblant to adenomyotic tissue, while menstrual shedding occurs predominantly in

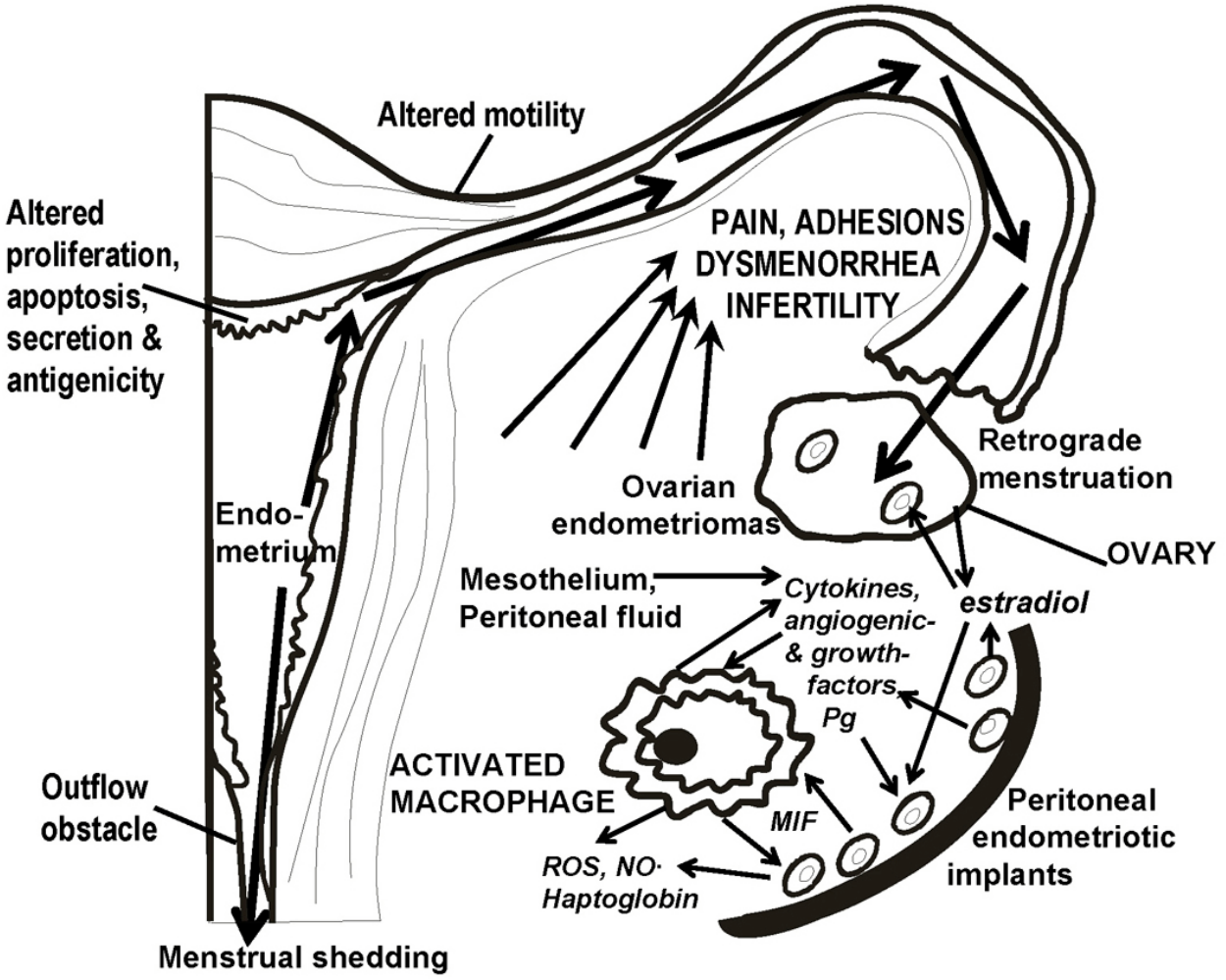

Figure 2. An excerpt on major factors in the pathogenesis of endometriosis.

peritoneal and ovarian but not in rectovaginal endometriosis (14, 15). Others propose that metaplasia of primitive pericytes serve as the source of aberrant endometrial proliferation in both, adenomyosis that infiltrates the uterine wall and endometriosis outside of the uterus (16, 17).

A third theory has been put forward to explain isolated endometriotic lesions in distant organs without signs of pelvic endometriosis, or where reflux menstruation can be excluded as a source: e.g. prostate of estrogen-treated men (18), or in teenage girls prior to the menarche (19). The "*embryonic rest müllerianosis*" (20) considers embryonic residuals of the Müllerian duct that have preserved their ability to proliferate as the source of isolated endometriosis.

3.2. Endogenous etiologic factors

3.2.1. Genital tract abnormalities

Women suffering from endometriosis tend to have higher volumes of refluxed menstrual blood and endometrial-tissue fragments than women without the disorder (21). Obstructions affecting the route of the menstrual outflow plausibly promote retrograde dissemination of the shed endometrial fragments. Müllerian duct abnormalities (22) especially outflow obstructions (23) and narrowing of the cervical os (24) are considered the main contributing factors. Abnormal motility of the uterus (hyperistalsis) may also play a role (25, 26).

3.2.2. Alterations of the eutopic endometrium

It has been shown recently, that the eutopic endometrium of women with endometriosis shares certain alterations with the ectopic lesions that are not found in the endometrium of disease-free women. It implies that the primary defect is actually rooted in the eutopic endometrium of affected women. This is reflected in enhanced proliferation (27), aromatase activity (28) and cytokine expression (29) or decreased apoptosis (30), as well as altered local hormone metabolism detailed below. Endometrial cells from women with endometriosis seem to over-express the anti-apoptotic gene Bcl-2 (31, 32). As a ramification a new concept holds that the basal endometrial layer with stem cell characteristics exhibits enhanced potential for dislocation and proliferation in women suffering from endometriosis (33).

Support for this theory might come from studies investigating stem cell factor and its receptor in endometriosis (see the section on endometriosis related carcinogenesis)

3.2.3. Hormonal factors

Clinical wisdom and laboratory evidence support the role of estrogen in the establishment and maintenance of endometriosis (34, 35). Active disease used to affect almost exclusively menstruating women and regress after the menopause (1, 36). The recent practice of menopausal hormone replacement, however, brought some postmenopausal cases to attention (37), sometimes even in women who have not had symptoms during their fertile period (38, 39).

Numerous studies investigated the content and fluctuations of the ovarian steroid hormone receptors in the endometriotic lesions in comparison with the eutopic endometrium, as well as in the endometrium of affected subjects compared with disease free women (for a review see:(40, 41)). The results remain inconsistent. There are data on receptor polymorphisms of both estrogen receptor subtypes, ERalpha and ERbeta, in endometriosis (42, 43, 44). Alterations in progesterone receptors' (PR-A and PR-B) expression and receptor polymorphism has also been found in association with endometriosis (45, 46, 47).

Tamoxifen, a selective estrogen receptor modulator (SERM) long used in the adjuvant endocrine therapy of breast cancer has been repeatedly reported to induce growth of endometriotic tissue (48, 49, 50). The partial estrogen agonistic behavior of tamoxifen in the uterus is the probable explanation for these cases. Local production of estradiol by aromatase or deficient inactivation of the hormone by 17beta hydroxysteroid dehydrogenase (17beta-HSD) enzyme might also contribute to the development of endometriosis (28, 51).

3.2.4. Genetic factors

The risk for first-degree relatives of women with endometriosis has been reported to be higher compared with the general population (52, 53, 54). Familial aggregation of endometriosis has also been observed in non-human primates (55). Studies of monozygotic twins found high concordance for endometriosis (56, 57, 58). It has been suggested that the genetically transmitted trait alters immune surveillance to allow for the attachment and growth of ectopic endometrium (59).

By use of linkage analysis and affected siblings, various groups have reported candidate genes, among them alterations of detoxification enzymes, which could lead to susceptibility to environmental stimuli. These include Glutathione-S-transferase, N-acetyltransferase, AHR, PPAR-gamma and Cytochrome-P450 (60, 61, 62, 63). Involvement of Galactose-1-phosphate uridyl transferase (GALT) is debated (64, 65). Genes possibly associated with malignant transformation (PTEN, p53, estrogen-progesterone- and androgen receptors) have also been studied in conjunction with endometriosis (66, 67, 68). A comprehensive list of these candidate genes and their polymorphisms described is accessible at: http://www.well.ox.ac.uk/~krinaz/genepi_endo.htm.

3.2.5. Altered immune surveillance and immune-evasion of the endometriotic tissue

Subtle peritoneal implants (flame-like or red lesions) may represent '*physiological endometriosis*' (7). These tend to evolve toward cicatrisation, resolve or stay steady (white or black lesions). Some implants in certain women could, however, develop into 'endometriotic disease' presenting with either considerable adherences, endometriotic ovarian cysts or profound endometriotic nodules. The peritoneal environment of most women is capable of resorbing misplaced endometrial tissue. In some women - who become endometriotic - this system of cleansing is inefficient or overwhelmed. Underlying factors might be anomalies of the endometrial tissue or of the peritoneal microenvironment (69).

Endometriotic cells seem to resist cell mediated immune attack (70). Endometrial cells from women with endometriosis are resistant to *in vitro* cytolysis by autologous peritoneal macrophages (71). Their antigenicity seems to be altered in a way that could be protective against cytotoxicity of Natural Killer cells (NK cell) due to overexpression of HLA class I (72, 73).

Decrease of cell-mediated immunity against ectopic endometriotic tissue in women with endometriosis has been amply documented (74, 75, 76). Studies concerning T-helper to T-suppressor ratio produced inconsistent results (77). Natural killer cell activity is suppressed by sera (78) or by peritoneal fluid (PF) (79) of women with endometriosis. Mediators derived from peripheral blood monocytes (PBMs) or peritoneal macrophages (PMs) might be responsible for this suppressive effect, since these are known modulators of immune cells. Alterations of both, PBM and PM have been reported in endometriosis (80, 81).

Eutopic and ectopic endometrial tissue of women with early stage (I-II) endometriosis is infiltrated by higher number of macrophages when compared either to non-affected women or to women with advanced stage (III-IV) endometriosis (82). These data correlate with macrophage numbers found in PFs of affected and non-affected women (83). On the other hand, in the early proliferative phase decreased number of macrophages has also been reported in eutopic endometrium of women with endometriosis when compared with healthy women (84). This study found a correlation between the decreased number of apoptotic endometrial cells and the lower macrophage infiltration. Whether these discrepancies are attributable to the (minor) differences of the process used to prepare the tissue samples for immunohistochemistry, or to the different anti-CD68 antibody clone used to detect the infiltrating macrophages remains to be resolved.

The proliferative activity of endometrial cells from women with endometriosis is enhanced when cocultured with autologous monocytes, whereas the proliferation of endometrial cells from controls is

suppressed by autologous monocytes (85). Macrophages of the PF from patients with endometriosis might be resistant to apoptosis due to increased Bcl-2 expression and decreased expression of Bax, the opponent of Bcl-2 (86). Increased FAS ligand expression has also been suggested as a mechanism making ectopic endometrium able to gain an '*immuno-privileged*' status (87).

Another aspect of the deranged immune surveillance is the high prevalence of certain autoimmune diseases among women with endometriosis (88, 89). Autoantibodies against cardiolipin, carbonic anhydrase, smooth muscle cells and antinuclear antibodies have been reported in conjunction with endometriosis (90, 91, 92).

3.2.6. Cytokines, chemotactic factors, inflammatory mediators

The PF of women with endometriosis has high concentrations of immune- and inflammatory mediators. Chemotactic factors recruit macrophages and lymphocytes to the lesion sites (93, 94, 95). Among these, RANTES (Regulated upon Activation Normal T-cell Expressed and Secreted) has been claimed to be responsible for about two third of monocyte migration in PF from women with endometriosis (96). Granulocyte–macrophage colony-stimulating factor (GM-CSF) expression is increased in endometriotic lesions compared with matched eutopic endometrium during the luteal phase (97).

Cytokines are thought to play a role in the development of the endometriosis-related chronic inflammatory processes (98, 99). Hsu *et al*. investigated the expression of Th1 (IL-2 and interferon-gamma) and Th2 (IL-4 and IL-10) cytokines in peripheral blood monocytes and PF from patients with endometriosis (100). The shift in the balance toward the Th2 cytokine products is proposed to contribute to the derangement of the immune defense in endometriosis.

Haptoglobin is synthesized in large amounts by endometriotic lesions that acts on PMs to block their phagocytic function while also upregulates production of inflammatory cytokines, including interleukin-6 (IL-6) (101). IL-6 in turn exaggerates haptoglobin production of the endometriotic tissue (102) hence establishing a feed-forward circuitry. Haptoglobin seems to have a role in embryo implantation and fertility as well (103).

Interleukin-6 is one of the key mediators in the cytokine cascade of endometriosis, its elevated levels correlate with disease activity (104) and it is also derived from the endometriotic cells themselves (105, 106, 107). IL-6 inhibits proliferation of endometrial stromal cells derived from the secretory phase endometrium, but the stromal cells of ovarian chocolate cysts are resistant to this inhibitory effect (108). IL-6 promoter polymorphism 174 G/C predispose the carrier to development of endometriotic ovarian chocolate cysts, but does not increase the overall risk of endometriosis (109). Though increased levels of IL-1beta were also reported in PFs of endometriotic women (110), no association was found between IL-1beta polymorphism and endometriosis (111, 112).

Women suffering from endometriosis have higher levels of tumor necrosis factor alpha (TNF-alpha) in their PF when compared to non-affected women (113). TNF-alpha stimulates the expression of matrix metalloproteinases and inhibits their inhibitors' expression, hence contributing to the invasion and extracellular matrix remodeling of endometrioid lesions (114, 115). Association between endometriosis and polymorphism of TNF-alpha gene promoter has been reported (116). Prostaglandin F_{2alpha} and Prostaglandin E_2 production of endometrial cells is promoted by TNF-alpha (117).

PMs from women with endometriosis release significantly more prostaglandins (PGE_2 and PGF_{2alpha}) (118) and express the cyclooxigenase COX-2 at higher rate than macrophages from healthy women (119). COX-1 enzyme was found elevated only in advanced stages. These prostaglandins have become acknowledged pathogenic factors involved in the development and complications of endometriosis (120); moreover, they have a role in inducing pelvic pain and contribute to excessive local estrogen production (121). Estrogen promotes PGE_2 synthesis, establishing a positive feedback loop to induce transcription of COX-2, synthesis of PGE_2 and expression of aromatase (122, 123). Dietary supplementation with fish oil containing omega-3 polyunsaturated fatty acids (PUFA) was reported to retard the growth of surgically induced endometriotic implants in rabbits attributable to suppression of peritoneal prostaglandins (124). Human endometrial explant cultures also show reduced survival when grown in medium supplemented with high omega-3: omega-6 PUFA ratios (125). It remains to be determined whether women suffering from endometriosis respond favorably to dietary intervention with food containing high amounts of omega-3 PUFA. It has been postulated that elevated peritoneal level of lipoxigenase products – leukotrienes – might also have a role in the development of the untoward consequences of endometriosis including dysmenorrhea and infertility (126).

Both TNF-alpha and IL-8 concentrations in PF have been reported to correlate with the size and number of active endometriotic lesions (127). TNF-alpha induces Il-8 expression in endometriotic stromal cells that might contribute to its proliferative action (128). Activation of NF-kappaB is critical for TNF-alpha-induced IL-8 expression in endometriotic stromal cells and treatment with GnRH agonist attenuates the expression of IL-8 by reducing TNF-alpha-induced NF-kappaB activation (129). IL-8 production of ectopic endometrium is promoted by estradiol (130) Adhesion to the extracellular matrix via integrins is also an important stimulus for IL-8 secretion from endometrial stromal cells (131).

Upregulation of fas ligand by IL-8 may produce a local immunotolerant environment for the development of ectopic endometriotic implants (132). The lipopolysaccharide-driven inflammatory response of endometriotic stromal cells promotes their proliferation through concerted induction of TNF-alpha and IL-8 (133). It has been suggested therefore, that pelvic infections might also contribute to development of endometriotic lesions.

Ligands of the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) stimulate IL-6, IL-8 and CSF-1 secretion of cultured human endometrial cells (EM42) (134). It is worth mentioning that the ligands for this receptor include prostaglandin derivatives, non-steroid anti-inflammatory drugs (135), lipid components of oxidized LDL (ox-LDL) (136), and thiazolidinedione antidiabetic drugs (137) since these might have either pathogenetic or therapeutic relevance concerning endometriosis.

Endothelial NO synthase (eNOS) protein expression was found higher in the endometrial epithelium of patients with endometriosis compared with fertile controls (138). Excessive amounts of NO are expected to modulate endometrial inflammation, and vasodilation. Genotyping by PCR amplification revealed that a common polymorphism of exon 7 at nucleotide 894 (Glu298>Asp mutation) in the eNOS gene is associated with high incidence of endometriosis (odds ratio: ~10) in a genetically homogeneous Greek population (139). Exaggerated NO production in women with endometriosis has been implicated as a causative factor of their infertility (140).

Chronic inflammation in the pelvis with endometriosis constitutes oxidative stress (141, 142). This is reflected by the accumulation of malondialdehyde-modified and oxidized proteins – like ox-LDL - in the PF (143). Peritoneal macrophages of women with endometriosis avidly take up ox-LDL by their abundant scavenger receptors (144) that leads to macrophage activation. Peritoneal mesothelial and endometriotic stromal cells respond to ox-LDL exposure by releasing monocyte chemotactic protein-1 (MCP-1) (145). MCP-1 levels are elevated in the PF of women with endometriosis (146, 147), and correlate with the stage of the disease (29, 148). The mere presence of syngenic epithelial and stromal endometrial cells in the peritoneal cavity of mice is able to elicit an inflammatory response of the mesothelium with release of MCP-1 and other mediators (149).

The complexity and interrelatedness of the vast array of mediators described in conjunction with the development and maintenance of endometriotic lesions might give the perception of an orchestra without a conductor. At the present stage of our knowledge, however, it would be rather premature to pinpoint one or even only a couple of these mediators as more relevant than the other ones. In fact, the disarrayed regulation of the several mediators might be the major pathogenetic factor for endometriosis. Chemotactic factors, cytokines, prostaglandin derivatives and free radicals (including NO) surely contribute either to the pathogenesis or to the consequences of endometriosis. Due to its multifaceted effects one particular cytokine, the migration inhibitory factor (MIF) might still deserve special attention, since it seems to behave not only as a cytokine, but also as an angiogenic- and growth promoting agent in endometriosis.

3.2.7. Macrophage migration inhibitory factor: an emerging key mediator in endometriosis

The first cytokine described, macrophage migration inhibitory factor (MIF) (150), has recently gained particular interest concerning endometriosis. Yang *et al*. have identified MIF as an endometriotic cell-derived product that promotes growth of endothelial cells (151), hence they postulated that it could contribute to the enhanced angiogenesis of endometriomas. Elevated level of MIF immunoreactivity was found in PF of women with endometriosis especially with active disease at the early stages (I-II) (152). There was no correlation of PF MIF levels with the depth of invasion or with the stage of the disease in another study, though levels were significantly higher in affected women (153).

Macrophages isolated from PF of affected women have a tendency to secrete more MCP-1 and MIF, and respond to LPS stimulus with higher secretions of these mediators when compared to PF macrophages of controls (154). Elevated levels of MIF were detected by immunohistochemistry in the endometrium of women with endometriosis and its cycle dependence has been noted (155). The endometriotic cells seem to express higher levels of MIF mRNA at the early stage active lesions (156). Human chorial gonadotrophin (hCG) induces MIF expression and secretion of endometrial stromal cells (157) similarly to the ovarian granulosa cell MIF secretion (158).

Enzymatic tautomerase (159, 160) and thiol-protein oxidoreductase (161) activities of this cytokine have been revealed recently. There is a notion that some aspects of MIF signaling might involve its enzymatic action on target proteins and/or on small molecule substrates. We have evaluated tautomerase activities of peritoneal fluids obtained from women who underwent diagnostic laparoscopy due to infertility (162). No correlation could have been obtained between enol-keto conversion rates of phenylpyruvate and MIF immunoreactivities assessed by Duo-Set MIF ELISA kit from R&D Sciences. On the other hand, compelling correlation was found between phenylpyruvate keto-enol conversion rates and MIF immunoreactivities (Figure 3). Both of these parameters show significantly higher values in PFs of women with stage I and II endometriosis compared to patients without endometriosis.

The exact role of the enigmatic enzymatic activity of this cytokine remains to be delineated. Nevertheless, MIF tautomerase has already attained a reputation as a promising pharmacologic target in inflammatory conditions (163). Overexpressed in many types of tumors, MIF has been shown to facilitate malignant cell transformation, inhibit tumor cell-specific immune cytolytic responses and promote neovascularization (164). It counteracts growth inhibitory and pro-apoptotic functions of the p53 tumor suppressor (165), activates mitogen activated protein kinases (166) and modulates AP-1 transcription factor activity that participates in the transcription of IL-1, IL-2, IFN-gamma and other pro-inflammatory proteins (167). Therefore Thierry Calandra´s term on MIF - “most interesting factor” (168) - also appears to apply in endometriosis research owing to its proinflammatory, angiogenic and growth promoting activities. Its action mechanism needs to be further investigated to establish whether targeting MIF in

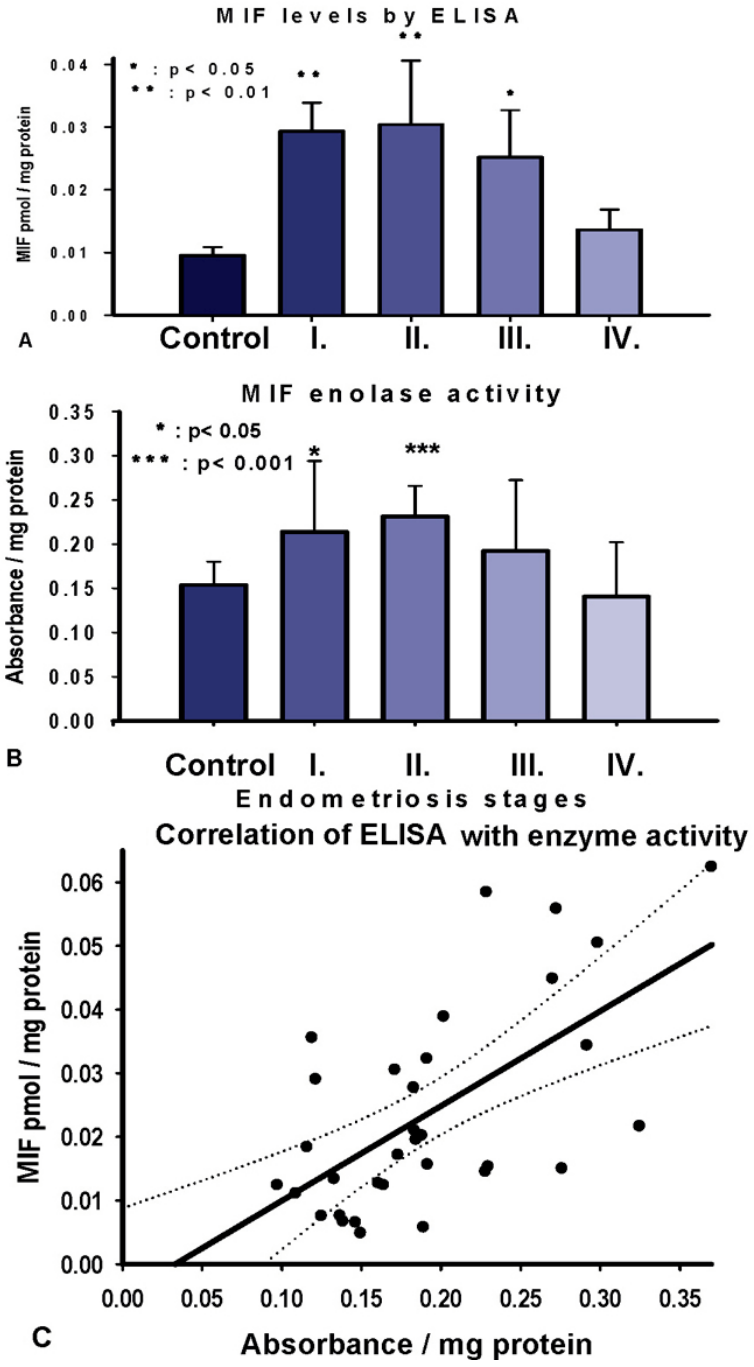

Figure 3. MIF immunoreactivity and tautomerase activity in peritoneal fluid samples.A: MIF levels by ELISA, Serum MIF levels were measured in each stage by an enzyme-linked immunosorbent assay (ELISA) with a Duo set ELISA Development System from R&D Systems, Minneapolis, MN, US according to the manufacturer's instructions. Amount of MIF was calculated to pmol/mg protein. Control n=11; stage I n=20; stage II n=6; stage III n=6; stage IV n=3. Mean ± SE values, Statistical significance compared to control group has been obtained by two tailed Student (t) test. B: MIF enolase activity, The keto-enol tautomeric conversion of sodium-phenylpyruvate was assessed at room temperature by monitoring the increase in absorbance at 300 nm on a dual path Shimadzu 2100 UV spectrophotometer. The reaction mixture contained in 200 mM sodium-phosphate reaction buffer (pH 6.2) 0.9 M boric acid, 200 microM sodium-phenylpyruvate, and 100microL abdominal lavage (containing MIF). The reaction was followed for 15 minutes according to Stamps (346). Statistical significance compared to control group has been obtained by two tailed Student (t) test.C: Correlation of MIF immunoreactivity with the tautomerase (enolase) activity of MIF, Correlation coefficient (r) = 0,624 ± 0.013 (SE); Dotted lines represent 95% confidence intervals.Analysis of variance for regression: P= 0.0001 (F: 19.74) at DF 1.

endometriosis therapy (or prevention?) could qualify as a viable concept.

3.2.8. Angiogenic- and growth factors

Increased serum levels of soluble intercellular adhesion molecule-1 (ICAM-1) have been noted in women with endometriosis (169, 170). Shedding of the protein is significantly increased in women with endometriosis (171). ICAM-1 is believed to interfere with immune surveillance, promoting cellular spreading potential (172). Interferon-gamma stimulates peritoneal ICAM-1 secretion hence it might also be a factor in the establishment of endometrial lesions (173, 174).

Endometrioid plaques depend on angiogenesis for survival. Vascular endothelial growth factor (VEGF) has been detected in high concentration in PFs from women with moderate to severe endometriosis (175, 176) and ovarian steroids directly regulate its expression (177). It is proposed as the main angiogenic factor secreted by endometriotic cells. Endometrial grafts implanted into Institute of Cancer Research (ICR) strain mice expressed more VEGF and matrix metalloproteinase -2 (MMP-2) when obtained from patients with endometriosis in comparison with healthy donors (178). These findings suggest that the increased production of VEGF and MMP-2 might play a role in adhesion and development of ectopic endometrioid plaques.

Endometrioid cysts have high levels of both, VEGF and IL-8 (179). VEGF secretion of endometrioid cysts' stromal cells was found inhibited by IFN-beta, but not by IFN-alpha (180). Elevated VEGF serum levels decline with successful treatment of endometriosis (181). The levels of angiogenin (ANG) - another factor involved in vessel formation - was also found elevated in PFs of endometriosis patients especially at the advanced stages (III-IV) (182). Platelet-derived endothelial cell growth factor has been implicated in angiogenesis of ovarian endometriomas (183).

Macrophage-produced transforming growth factor beta 1 (TGF-beta1) and platelet-derived growth factor (PDGF) are elevated in PFs when endometriosis is present and have been shown to upregulate fas ligand in endometriotic cells (184). In endometriosis there are alterations in the insulin-like growth factor (IGF) system. IGF-1 levels in eutopic endometrium are lower in severe endometriosis (185), whereas ectopic endometrium and peritoneal fluids show higher levels (186, 187). There was no association found, however, between serum levels of IGFBP-3, alpha-fetoprotein (AFP) and EGF and the existence of endometriosis (188).

Hepatocyte growth factor and its transmembrane tyrosine kinase receptor, c-Met - the product of c-met proto-oncogene – are reportedly elevated in the eutopic endometrium of women with endometriosis and in their ectopic peritoneal red lesions (189). A correlation with microvessel density, proliferating cell nuclear antigen and VEGF was also detected in this study.

3.3. Exogenous etiologic factors

3.3.1. Endocrine disruptors

Endocrine disruptors are exogenous substances that alter functioning of the endocrine system - either alone or in mixtures -, and consequently cause adverse health effects in an intact organism, or its progeny, or (sub)populations. Compounds that affect the function(s) of the nuclear receptors, such as the estrogen receptor(s) and/or the aryl-hydrocarbon receptor (AhR) (190), are of particular interest concerning the pathomechanism of endometriosis. Female offspring exposed in utero to the synthetic estrogen diethylstilbestrol (DES) presents with increased frequency of endometriosis (191, 192).

Polyhalogenated aromatic hydrocarbons like (among others) polychlorinated biphenils (PCBs) or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) are known to act through the AhR (193). The target genes include cytochrome P450 and genes involved in cellular growth, differentiation and inflammation (194). Rier *et al*. reported a dose-response increased incidence and severity of endometriosis in adult Rhesus monkeys exposed to TCDD in food (195). Their results have recently been confirmed in Cynomolgus monkeys (196). In subchronic exposure, higher doses resembling to occupational or accidental exposure in humans promoted survival of plaques, while a lower dose was found to exert inhibitory effect in this species (197). TCDD could promote the growth of surgically induced endometriosis in rats and mice as well (198). Nevertheless, plasma estrogen levels, sub-acute dosing or TCDD treatment prior to surgical induction of the lesions might all have an influence on the effect. Regression of the endometrial implants has been observed when mice were exposed to TCDD and high levels of exogenous estrogen after the induction of the disease (199). It has been proposed, that dioxin might promote ectopic endometrial cell proliferation by inducing CYP450-1A1 enzyme that in turn activates procarcinogens or produces catecholestrogens (200). Alternatively activation of AhR and PPAR might induce estrogen responsive genes independent of the estrogen receptor (201). A cell-specific interaction between ER and AhR system in the action of TCDD has also been described (202).

In 1976, an explosion in Seveso, Italy exposed the surrounding population to among the highest levels of TCDD recorded in humans. The "*Seveso Women's Health Study"* that has addressed the relation between TCDD exposure and endometriosis in the largest population of women so far with a wide range of exposure found a doubled but statistically nonsignificant risk (OR: 2.1; CI: 0.5-8.0) for endometriosis in women with serum TCDD levels of 100 ppt or higher (203). There was also no statistically convincing evidence of a dose–response relationship. The existence of endometriosis, however, has not been verified by surgery in this study. Consonant results were obtained in a small-scale study (204) conducted in Belgium where endometriosis incidence and severity, as well the dioxin pollution are among the highest in the world (205). Paradoxical decrease in endometriosis incidence was detected in women who have possibly had

been exposed to dioxin in mother's milk while breast-fed in their infancy (206). Nevertheless, the possibility that breast-feeding per se decreases the occurrence of endometriosis cannot be ruled out.

The possible adverse effects of phytoestrogens are of concern in relation with estrogen dependent diseases. In a rat model of endometriosis induced by surgical implantation dietary genistein was unable to support survival of endometriotic implants, but high pharmacologic doses administered parenterally exerted growth promoting effect comparable to the estrogen treatment (207).

3.3.2. Miscellaneous factors

Although cadmium is a cumulative environmental toxicant that might mimic estrogen's action under certain experimental conditions no association was found between endometriosis and cadmium exposure in a pilot study (208). A large scale study in the US found increased risk of endometriosis in women born with low birth weight or from twin deliveries (192). The mechanism underlying this association remains to be revealed.

Analysis of data collected from a huge prospective cohort study of premenopausal U.S. nurses identified 1,721 women with laparoscopically confirmed endometriosis but with no past infertility (209). Greater incidence of endometriosis was observed among women who have gone through menarche at earlier age or who have had shorter cycle length during late adolescence. Among parous women, a linear decrease in risk was observed with number of live born children and lifetime duration of lactation.

The behavior of endometriosis during pregnancy has not been thoroughly documented. In the spontaneous endometriosis model of baboons no significant change was observed in the stage of endometriosis, or in the number, size and type of endometriotic lesions during gestation (210).

3.4. Is endometriosis a natural model for inflammation-driven carcinogenesis?

Endometriosis shares features of cancer: it invades, metastasizes to, and compromises the function of various organs, and it is associated with a heightened risk for malignant transformation. Virchow's theory on inflammation-driven cancer (211) may well apply to cancers developing in endometriosis. Epidemiologic observations have amply documented the malignant potential of endometriosis, in particular, the association between endometriosis and ovarian carcinomas (212, 213). Endometriosis may be the precursor for most of endometrioid and clear-cell ovarian cancers (214).

Malignant transformation-associated genes (i. e., PTEN, p53, estrogen- progesterone- and androgen receptors) are implicated in the development of endometriosis (66, 67). Defects in the p53 gene may be involved in the malignant transformation of endometriosis. Overexpression of this tumor suppressor, on the other hand, potentially might become an immunohistochemical marker for patients with endometriosis having higher risk of developing atypia and cancer (68). A Taiwanese study found that Arg homozygosity at the codon 72 of the p53 gene is related to lower risk for endometriosis, while Pro homozygosity and heterozygosity are related to higher risk for endometriosis in Chinese women (215). However, no association was found between p53 codon 72 polymorphism and endometriosis in Japanese women (216).

Changes in the expression of the proto-oncogene c-*kit* are associated with aggressive behavior of malignant tumors. C-kit and its ligand, stem cell factor (SCF) might also be involved in the pathogenesis of endometriosis. Women with stage I and II disease have higher SCF levels in PF, compared with those without endometriosis or with stage III and IV disease, while the expression of mRNA for c-kit was detected in both the endometriotic tissue and the eutopic endometrium (217). Strong c-kit protein expression by immunohistochemitry was found associated with invasive endometriotic lesions (218).

Genes of detoxifying enzymes might also be altered in both endometriosis and cancer (60, 219). In patients being treated with unopposed estrogen, adenocarcinoma has been reported arising in pelvic endometriosis (220, 221, 222). Adenosarcoma of the vaginal cuff has developed after several years in a patient who had been administered conjugated estrogens transiently following hysterectomy and bilateral salpingo-oophorectomy due to treatment of resistant pelvic endometriosis (223). Extraovarian cancer arising concomitant with endometriosis is more likely to be associated with hormone replacement therapy (HRT) use than ovarian cancer (224). Higher prevalence of adenomyosis uteri and myoma uteri in the patients with endometrial carcinomas was detected (225) that could possibly be attributed to hyperestrogenism, a common risk factor for these conditions. Endometrial adenocarcinomas accompanied by adenomyosis or endometriosis externa and myoma uteri are likely to be well-differentiated and have a relatively good prognosis (226).

Danazol, a 17-ethinyltestosterone derivative that has been widely used as a therapeutic agent for endometriosis, efficiently decreased endometrial expression of c-fos and c-jun mRNA and their oncoproteins induced by estradiol in mice (227). Atypical and complex endometrial hyperplasias were also prevented by the danazol treatment. Its androgenic action, however, might also contribute to the decrease in endometrial growth.

4. EXPERIMENTAL MODELS OF ENDOMETRIOSIS

Endometriosis occurs naturally only in humans and nonhuman primates that have menstrual cycles. The rhesus monkey (228) the cynomolgus monkey and the baboon (229) are known to be afflicted with spontaneous endometriosis. The baboon model of spontaneous endometriosis has been documented in the most detail (230, 231).

Induction of endometriosis has been successful in baboons by injecting menstrual endometrium into the pelvic cavity (232). Injection of dispersed endometrial cells has also been used in rabbits (233), as well as surgical implant techniques (234, 235). Implantation is useful for induction of endometriosis in mice (236, 237) and rats (238, 239). Injecting human endometrium into the peritoneal cavities of severely combined immunodeficient (SCID) nude mice is an established xenograft model of endometriosis (240, 241). Biopsied human endometrium is able to invade and form endometriosis-like lesions even on chicken chorioallantoic membrane (242).

5. PROGRESS WITH GENOMICS AND TRANSGENESIS IN THE INVESTIGATION OF ENDOMETRIOSIS

Several groups have applied genetic techniques to identify the aberrant molecular and cellular mechanisms in endometriosis with the intention of providing much-needed insights that might, in turn, lead to new therapies (243). Because of its complexity, endometriosis is ideally suited as a target for genome-wide scanning. *Affymetrix* chips with microarrayed oligonucelotides were used to confirm that glycodelin-A mRNA expression was reduced in mid-secretory, eutopic endometrium of women with endometriosis compared to levels in mid-secretory, eutopic endometrium from normal subjects (244,245). This finding bears relevance concerning effects on fertility since endometrial glycodelin-A has strong local immune modulatory functions related to e.g. embryo implantation (246).

In human endometriotic stromal cells, markedly high levels of aromatase P450 (P450arom) mRNA and its promoter II (gonadal type promoter) activity are present whereas aromatase expression is either only barely detectable or most commonly absent in the eutopic endometrium (28). Experiments conducted in transgenic mice with disrupted P450arom gene (ArKO) (247) showed that intact P450arom gene and the presence of aromatase enzyme activity were essential for the growth of ectopic uterine tissue.

Aromatase is overexpressed in the ovaries of C/EBPbeta knockout mice, indicative of an inhibitory role of C/EBPbeta for the P450arom gene (248). By disrupting several potential sequences in *cis*-acting elements in promoter II of the P450arom gene it was found that mutations of a -211/-197-bp cAMP-response element (CRE) and a -317/-304-bp C/EBP binding site abolished both baseline and cAMP (prostaglandin) -induced promoter II activity. It was concluded that *in vivo* down-regulation of C/EBPbeta in endometriotic stromal cells and its up-regulation in endometrial stromal cells may in part account for the induction of P450arom expression in endometriosis (249). Site-directed disruption of the steroidogenic factor-1 (SF-1) binding site (-136/-124 bp) in the P450arom promoter-II also abolished basal or cAMP/SF-1-induced promoter activity (250).

Progesterone is known to inhibit estrogen-induced proliferation of the uterine epithelium. In a mouse model of surgical endometriosis progesterone treatment was able to antagonize estrogen's proliferative effect on the ectopic endometrium of ovariectomized wild type mice, but was ineffective in progesterone receptor knockout (PRKO) mice (251). Endometriosis is one of the diseases associated with infertility due to implantation failure that is attributable in part to decreased expression of the HOXA10 gene (252). Eutopic uterine endometrium in mice has been successfully transfected by lipofection with HOXA10 phosphothiorated antisense DNA (blocks HOXA10 expression) or pcDNA3.1/HOXA10 (a plasmidic construct that constitutively expresses HOXA10) to delineate the role of this gene in the implantation (253). A phase I clinical trial has used lipofection-mediated E1A gene transfer via the peritoneal route in ovarian cancer patients to enhance apoptosis and decrease DNA replication (254). Perhaps in the future a similar approach might also prove itself useful in severe cases of endometriosis.

Transient transfection of endometriotic stromal cells with RANTES promoter vectors with and without a mutagenized PPAR-gamma response element (PPRE), and treatment with PPAR-gamma ligands showed the inhibitor effect of PPAR-gamma on RANTES expression of endometriotic lesions (255). Since RANTES is considered a major chemokine in endometriosis (96) this finding might have relevance in alleviating concomitant peritoneal inflammation. Successful treatment of induced endometriosis has been demonstrated in estrogen-supplemented ovariectomized mice by transient over expression of the natural angiogenesis inhibitor angiostatin, delivered to the peritoneum with a replication-deficient adenovirus vector (AdAngiostatin) (256).

Specific immunologic aspects of endometriosis have been studied in beta2-microglobulin-deficient (beta2-m-/-) and in IL-12p40–deficient (p40 -/-) mice (257). While the former are known to have a greatly reduced number of CD81 T cells (258), IL-12 is known to have a role in the implantation of ectopic endometriotic lesions (259). Markedly reduced total weight and surface area of endometriotic lesions was found in beta2-microglobulin–deficient BALB/c mice than in wild-type BALB/c controls. A slight but nonsignificant increase in these parameters was observed in interleukin-12– deficient C57BL/6 mice compared to wild-type C57BL/6 controls A xenograft endometriosis model has been developed by injecting human endometriotic cells into the lymphoid-specific immunoglobulin heavy chain recombinase activating gene 2 (RAG-2 -/-)- and IL-2 receptor gamma (common gamma-chain -/-) double knockout (RAG/gamma-c KO) immunodeficient mice.(260)

6. CLINICAL ASPECTS

6.1. Symptomatology and quality of life issues

Endometriosis is a disease that is wide-ranging in location and highly varied in clinical presentation (261). This condition is a significant public health issue because of the large number of women it affects and because of its associated morbidities. It is one of the most commonly encountered gynecologic diseases requiring medical and/or surgical therapy.

The most frequent symptoms of genital tract endometriosis are dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility. It affects quality of life that can be quantified (262). Endometriosis occurs in the pelvis, most commonly the ovaries and the dependent areas covered with peritoneum. Diagnosis requires surgical intervention performed usually by laparoscopy. In women being evaluated for pelvic pain, the diagnosis of endometriosis is made frequently (40-60%) and varies with the population being studied. Pelvic pain and dysmenorrhea might be related to hypermotility and adenomyosis often observed in endometriosis (263). Endometriotic infiltration in deep adenomyotic nodules might be a determinant of dysmenorrhoic pain. Although women with infertility may have pelvic pain, often subfertility (20-30%) can be the only presenting symptom. In asymptomatic reproductive-age women the diagnosis of endometriosis might reach 22%. Its true incidence and natural history, however, remain to be clarified (264) since not all women with infertility undergo laparoscopy.

Association of infertility and endometriosis has long been purported, but the issue remains controversial, especially for milder presentations of the disease. In baboons stage II, III and IV but not stage I endometriosis decreases fertility (265). Discussion continues as to whether endometriosis produces infertility, and if so, whether it should be treated and in what way (266, 267). Abnormal uterine motility might contribute to defective sperm transport to the presumed tubal site of fertilization (268). The aberrant tissue appears to incite an inflammatory reaction and its extent seems to affect symptom severity: chronic pelvic pain and subfertility. Although the immune response is ineffective in eliminating the disease, it can be quite effective in causing fibrosis and adhesions. Macrophage secretory products contribute to endometriosis-associated infertility through the interference of sperm binding to the zona pellucida (269). TNF-alpha is a key cytokine responsible for this effect.

6.2. Diagnostic tools & Classification

The clinical presentation of endometriosis is by either pelvic pain, infertility, the finding of a pelvic mass at gynecological examination or sonography or, rarely, its complications, such as rupture or infection. In the absence of typical symptoms, the detection and characterization of ovarian masses by imaging techniques is a continuing challenge. The laparoscopy, however, remains the gold standard for diagnosis (270).

Ultrasound investigation fails to demonstrate superficial implants and small endometriomas. Endometriomas present different sonographic patterns, such as purely cystic, cystic with few septations or minimal debris, complex combinations of cystic and solid elements and largely solid (271, 272). The sensitivity and specificity of this method is reported as 75% and 75% respectively (273). Aspiration of the cyst under ultrasonographic guidance can reveal the chocolate content but a similar chocolate-colored hemorrhagic content may be found in some follicle hematomas or even cystadenomas. Transvaginal ultrasound was found reliable in detecting ovarian but not extraovarian endometriosis (274). A technically improved ultrasound method (sonovaginography) has been proposed to perform better than traditional transvaginal ultrasound in detection of rectovaginal endometriosis (275). "*Kissing ovaries*" has been recognized as a special ultrasonographic sign particularly associated with infiltrating ovarian endometriomas (276).

Magnetic resonance imaging (MRI) has a higher accuracy than ultrasonography and appears to be the most accurate method of differentiating an endometrioma from other gynecologic masses. In addition, MRI can reflect some specific macroscopic features of endometriomas, such as the anatomical localization of the adhesions, by the indistinct interface and irregular lining of the wall in this area. The overall diagnostic sensitivity, specificity and accuracy for MRI diagnosis of endometrial cyst are reported as 90%, 98% and 96%, respectively (277). For this reason MRI is an acceptable and useful technique for the diagnosis of endometrioma.

Laparoscopy is the gold standard for the diagnosis of endometriosis. As there is no correlation between the anatomical lesions and the clinical findings in patients with endometriosis, the term pelvic endometriosis has to be illustrated using a score to provide some information about the extent of the disease (278). Because it included a complete and simple description of surgical findings and easily comprehensible, the American Fertility Society (AFS) endometriosis classification system became internationally accepted (279). Going through the scoring scheme and summing up scores results in the following categories of endometriosis: minimal (scores 1-5: stage I); mild (scores 6-15: stage II); moderate (scores 16-40: stage III) and severe (scores over 40: stage IV). Nevertheless, even the revised American Fertility Society (RAFS) classification (280) needed to be perpetually improved and adapted to new treatments.

A classification should be a broadly accepted expert system, in order to provide guidelines for the treatment and prognosis for post-treatment fertility, relief of pelvic pain and recurrences. Although surgical staging is now considered the gold standard, no statement has been made concerning the best surgical approach, laparoscopy or laparotomy, and what surgical procedures are required to accurately stage a patient. Operative laparoscopy is the best surgical staging technique. As ovarian punctures and adhesiolysis are often required, prerequisites for laparoscopic staging are very similar to those for laparoscopic treatment of endometriosis (281). The laparoscopic staging includes the following steps:

1. The bowel and the omentum are pushed over the superior pelvic brim (Trendelenburg position, atraumatic forceps).
2. The magnification provided by the laparoscope is used to inspect the anterior and posterior cul-de-sac, looking for small and atypical peritoneal implants.
3. Peritoneal cytology is sampled.
4. The tubes and the ovaries are mobilized, looking for tubal and ovarian adhesions.

5. To diagnose ovarian endometriomas a complete ovariolysis is required.
6. The broad ligaments and the anterior ovarian surface are inspected.
7. Enlarged ovarian scars are routinely punctured, looking for small endometriomas.(282)
8. The posterior cul-de-sac and the rectum are assessed, using vaginal examination and/or vaginal and rectal probes (283).
9. If an ovarian endometrioma has been opened, the pelvis is copiously irrigated; the internal cyst wall is inspected and biopsied in order to rule out malignancy and to differentiate endometriomas from functional chocolate cysts (284, 285)
10. The upper part of the abdomen is carefully inspected, looking for bowel or appendicular endometriosis.

Concerning the implants and their peritoneal environment it has been proposed to evaluate endometriosis activity, because clinical consequences of endometriosis are more related to the "activity" than the extent of the disease. In the last decade, increasing attention has been drawn to atypical forms of endometriosis (286, 287, 288). Atypical lesions are thought to be more biologically active than the typical forms (289, 290) and red petechial lesions of endometriosis produce higher amounts of prostaglandin F than typical powder-burn implants.

The American Society for Reproductive Medicine (ASRM) has recently produced a new classification of endometriosis (291). The only difference between the former and new classification is that the latter includes information on the morphologic appearance of the disease. In the new ASRM classification, peritoneal and ovarian implants are categorized into three subgroups: red, white, and black. The percentage of surface involvement of each implant type must be recorded on the apposite form. The new ASRM classification is more accurate, although a study (292) could not demonstrate any correlation between the ASRM classification of endometriosis, and disease-associated dysmenorrhea. In addition, the biochemical activities of the different implants seemed similar, although the sample size in this study was relatively small to draw firm conclusions. The new ASRM classification of endometriosis remains, however, the gold standard to clearly document the extent and location of the disease.

Non-invasive laboratory tests has long been sought to detect early forms of endometriosis, since therapeutic success is expected there to be the highest – especially concerning pregnancy rates. A recent review found, however, that the most extensively studied and used marker, serum CA-125, has limited diagnostic utility (293). Serum interleukin-6 and peritoneal fluid TNF-α were found to show some promise as possible diagnostic markers for endometriosis (294). Others found preoperative CA-125 levels useful in predicting the extent of bowel adhesions (295). Urinary VEGF levels were unable to predict presence of endometriosis (296).

6.3. Extragenital, extrapelvic and extraabdominal locations of endometriosis

Endometriosis affects the intestinal tract in 15% to 37% of patients with pelvic endometriosis (297) and it may mimic a number of GI (gastrointestinal) tract diseases both clinically and pathologically. Endometriosis often seems to coexist with certain bowel motility dysfunction (298). Alteration of the intestinal microflora and higher prevalence of bowel inflammation has been reported in rhesus monkeys affected by endometriosis (299).

Extrapelvic endometriotic lesions might be detected in up to 12% of all cases (300). These could be most commonly encountered in the abdominal wall, especially with cesarean section scars or other incisions (301, 302). They might present as vulvar mass (303), or even as a mass in the buttock in a case of sciatic nerve associated endometriosis (304). Endometriotic lesions could be found in the upper abdomen as far as the diaphragm (305). Hepatic endometriosis is rare and it might be attributed to rest müllerianosis (306). Ascites due to the rupture of endometriotic cysts also represents a rarity (307).

Thoracic endometriosis is the most common extra abdominal location (308) signified by periodic hemoptysis occurring at the time of menstruation (309). Exotic locations of endometriosis have been reported in the meninges, in vertebrae (310) and the pleural membranes (311).

Endometriosis between thelarche and menarche although not common might occur with unexpected frequency (312). A diligent diagnostic workup therefore has to take this possibility into account in case of typical signs even at this age group.

6.4. The oncologic awareness

Endometriosis is a common disease that does not create a cachectic or catabolic state, and is rarely fatal. Still, like cancer, endometriosis can be both locally and distantly metastatic; it attaches to other tissues, invades, and damages them. There are numerous reported cases of malignancy arising from endometriotic deposits and substantial histologic evidence that endometriosis is associated with endometrioid carcinoma and clear cell carcinoma of the ovary. A review article by Mostoufizadeh and Scully investigated the association between endometriosis and endometrioid carcinoma, noting that women who had both diseases tended to be younger (313). They found no association between endometriosis and serous or mucinous carcinoma of the ovary, and reported that malignant transformation of endometriosis was rare and associated with the use of exogenous estrogens.

Significantly increased risk was observed for ovarian cancer, breast cancer and hematopoietic cancer (chiefly due to an excess of non–Hodgkin lymphoma) in a large Swedish study that followed over 20,000 women with proven diagnosis of endometriosis for a mean of 11.4 years (314). The risk for ovarian cancer was particularly elevated among patients with ovarian endometriosis, but no association was observed for endometrial cancer in this study. Endometriotic implants share not only a common histology with the endometrium, but also similar function and responsiveness to the hormonal milieu. Hence the use of unopposed estrogen may present a risk factor for malignant transformation of endometriosis (315).

6.5. Management

6.5.1. Primary treatment options

Symptomatic endometriosis can be managed surgically and/or medically. The aim is pain relief and/or amelioration of infertility. It is achieved by removal of the ectopic endometrial tissue. In case of surgery it is performed nowadays almost exclusively by laparoscopy in a way very similar to the diagnostic staging procedure (281). In the infertility treatment assisted reproduction techniques are used, including controlled ovarian hyperstimulation and intrauterine insemination or in vitro fertilization and embryo transfer (IVF-ET).

Some authors report no improvement in IVF outcome after operative endometriosis therapy (316, 317). Others find that IVF outcome for women with endometriosis is not posterior to women with tubal disease (318). A recent meta-analysis, on the other hand, has described considerable reduction in clinical pregnancy rate in endometriosis versus tubal factor infertility (319). A particular aspect is that recurrence is lower and fertility is higher when endometriosis is located only in the right side of the pelvis (320). Sufficient underlying basic knowledge would be desperately needed to design proper trials for testing key questions and devise new treatment strategies concerning infertility in endometriosis (321).

All medical treatments seem to be equally effective in managing endometriosis; about 80-85% of patients have improvement in their symptoms (322) Medical treatment tends not to remove the implants but merely to suppress them. Consequently amenorrhea develops, since all endometrial tissue becomes inactive. It is now universally accepted that there is no place for medical treatment with drugs that are also potent contraceptives in the treatment of infertility related to endometriosis.

The difference between various medical treatments is in their side effects, with some treatments being more acceptable than others (4). Agents used to suppress ovarian function hence limit growth and activity of endometriosis and the associated pain include steroidal contraceptives, androgens (Danazol; Gestrinone), progestagens (Norethisterone acetate, Medroxyprogesterone acetate; Dydrogesterone), GnRH analogues (Leuprorelin; Buserelin; Goserelin; Triptorelin; Nafarelin) (323). To alleviate the consequences of hypoestrinism elicited by the GnRH analogues "*addback*" hormone replacement could be used (324). It does not reduce the efficacy of GnRHa treatment. Non-steroid antiinflammatory drugs might be supplemented to control pain (325). It has been argued recently that hormonal suppressive therapy confers oncologic risks to the patient that have been overlooked (326). Medical treatment is usually long term, and recurrence is frequent after its cessation.

The recurrence of pelvic endometriosis some time after the initial treatment is a common finding in clinical practice. When symptoms of endometriosis reappear several months after treatment, it is difficult to distinguish between recurrence and persistence of the disease. Recurrence rates vary considerably following different treatment modalities because investigators fail to agree on specific definitions of recurrence and persistence. Tools available for the diagnosis of recurrent endometriosis and some therapeutic options to treat recurrent endometriosis have been discussed by Revelli *et al.* (327). It has been argued that the only definitive cure for the woman with endometriosis is total hysterectomy and bilateral salpingo-oophorectomy, and yet the rates of recurrence after "curative" surgery are as great as 5–10% (328).

6.5.2. Second line and experimental treatments

Innovative new treatment modalities are about to enter the clinical praxis these years. These are mostly targeted against steps of the pathomechanism that have been delineated in the last decades.

6.5.2.1. Treatments targeting hormone mechanisms

Aromatase inhibitors are promising options to suppress estrogen levels (329, 330). Furthermore, aromatase activity is blocked not only within the ovary but also in the endometriotic tissue, lowering local estrogen levels and PGE2 production as well (331). These agents, nevertheless, are still considered being in the experimental phase for treatment of endometriosis.

Antiestrogens or SERMs (selective estrogen receptor modulators) might also counteract the hormone action on endometriotic tissue proliferation. Raloxifene is used against menopausal bone loss. There has been a single human trial that reported success so far with this drug in endometriosis (332). Likewise, the progesterone antagonist Mifepristone (RU486) has also been evaluated for the treatment of endometriosis (333).

6.5.2.2. Treatments targeting immune-and inflammatory mechanisms

Laparoscopic intraperitoneal (i.p.) injection of human interferon-alpha-2b to women with pelvic endometriosis has shown clear benefits in a small scale clinical study (334). Recombinant human tumor necrosis factor-binding protein-1 (r-hTBP-1), - a soluble form of tumor necrosis factor-alpha receptor type-1 – was able to reduce the size of endometriotic peritoneal lesions in an experimental endometriosis model of rats (335). TNF neutralization by Etanercept -a fusion protein consisting of human recombinant soluble TNF receptor-2 conjugated to a human Fc antibody subunit – has been shown to suppress the development of spontaneous endometriotic lesions in baboons (336). Antiangiogenic therapy targeting VEGF has also been successful in preventing proliferation of human endometrial cells transplanted into nude mice (337).

Based on its immunmodulatory activity pentoxyfilline has been tried with limited success in a pilot study against infertility associated with endometriosis (338). Apart from their analgesic effect, cyclooxigenase-2 inhibitors might also have suppressive effect on the establishment of the endometriotic tissue (339, 340). PPARgamma ligands seem to counteract chemokine production and inflammation, therefore also show promise in future endometriosis therapy (341). The inflammatory

oxidant damage might possibly be alleviated by antioxidants (342). Since most herbal remedies contain antioxidant agents, it is peculiar that a literature survey could not identify randomized controlled trials that would have addressed efficacy of herbal treatments in endometriosis (343).

7. CONCLUSIONS AND PERSPECTIVES

Endometriosis remains an enigmatic condition that deserves further efforts to delineate its pathogenetic mechanisms. That approach will surely lead to more sophisticated treatment options in the near future concerning either infertility or pelvipathic complaints. Despite the huge number of mediators studied in conjunction with the endometriotic process there are still some aspects that have not been addressed in depth so far. The improvement in the spontaneous endometriosis of monkeys kept on a calorically restricted diet for a longevity study (344) brings metabolism to the agenda of endometriosis research. Moreover, it is perplexing, that only three genes have been found to show parallel changes in three longevity models (two genetic and one calorically restricted): 17-beta hydroxysteroid dehydrogenase 2 (17-beta HSD); IGF binding protein-2 (IGFBP-2) and MIF (345). All of them are directly or indirectly involved with endometriosis as well.

8. ACKNOWLEDGEMENT

The authors are grateful to Jozsef Szakacs for his technical assistance with the illustrations. J. Garai and V. Molnar participate in EU FP6 NoE No.506319: CASCADE

9. REFERENCES

1. Eskenazi B. & M. L. Warner: Epidemiology of endometriosis. *Obstet Gyn Clin N Am* 24, 235-258 (1997)
2. Von Rokitansky C.: Über uterusdrusen-neubildung in uterus and ovarilsarcomen. *Z Gesellsch Ärzte Wien*; 37, 577-593 (1860)
3. Sangi-Haghpeykar H. & A. N. Poindexter: Epidemiology of endometriosis among parous women. *Obstet Gynecol* 85, 983-992 (1995)
4. Giudice L. C. & L. C. Kao: Endometriosis. *Lancet* 364(9447), 1789-1799 (2004)
5. Balasch J., M. Creus, F. Fabregues, F. Carmona, J. Ordi, S. Martinez-Roman & J. A. Vanrell: Visible and non-visible endometriosis at laparoscopy in fertile and infertile women and in patients with chronic pelvic pain: A prospective study. *Hum Reprod* 11, 387-391 (1996)
6. Kruitwagen R. F. P. M., I. J. de Ronde, L. G. Poels, P. H. Jap, W. N. Willemsen & R. Rolland: Endometrial epithelial cells in peritoneal fluid during the early follicular phase. *Fertil Steril* 55, 297-303 (1991)
7. Koninckx P. R., D. Oosterlynck, T. D'Hooghe & C. Meuleman: Deeply infiltrating endometriosis is a disease whereas mild endometriosis could be considered a nondisease. *Human Endometrium* 734, 333-341 (1994)
8. Sampson J. A.: Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol* 14, 442-469 (1927)
9. Javert C. T.: Observations on the pathology and spread of endometriosis based on the theory of benign metastasis. *Am J Obstet Gynecol* 62, 477-487 (1951)
10. Liu D. T. Y. & A. Hitchcock: Endometriosis: its association with retrograde menstruation, dysmenorrhea, and tubal pathology. *Brit J Obstet Gynaec* 93, 859-886 (1986)
11. Iwanoff N. S.: Drusiges cystenhaltiges Uterusfibromyom compliciert durch Sarcom und Carcinom. (Adenofibromyoma cysticum sarcomatodes carcinomatosum). *Monatsch Geburtshilfe Gynäkol* 7, 295-300 (1898)
12. Levander G. & P. Normann: The pathogenesis of endometriosis. An experimental study. *Acta Obstet Gyn Scan* 34, 366-398 (1955)
13. Merrill J. A.: Endometrial induction of endometriosis across Millipore filters. *Am J Obstet Gynecol* 94, 780-790 (1966)
14. Donnez J., M. Nisolle, P. Smoes, N. Gillet, S. Beguin & F. CasanasRoux: Peritoneal endometriosis and 'endometriotic' nodules of the rectovaginal septum are two different entities. *Fertil Steril* 66, 362-368 (1996)
15. Nisolle M. & J. Donnez: Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. *Fertil Steril* 68, 585-596 (1997)
16. Anaf V., P. Simon, I. Fayt & J. Noel: Smooth muscles are frequent components of endometriotic lesions. *Hum Reprod* 15, 767-771 (2000)
17. Mai K. T., H. M. Yazdi, D. G. Perkins & W. Parks: Pathogenetic role of the stromal cells in endometriosis and adenomyosis. *Histopathology* 30, 430-442 (1997)
18. Beckman E. N., S. O. Pintado, G. L. Leonard & W.H. Sternberg: Endometriosis of the prostate. *Am J Surg Pathol* 9, 374-379 (1985)
19. Reese K. A. & S. Reddy J. A. Rock: Endometriosis in an adolescent population: The Emory experience. *J Pediatr Adol Gynecol* 9, 125 (1996)
20. R E Batt, R A Smith, G M Buck, M F Severino & J D Naples: Müllerianosis. In: Current concepts in endometriosis, Progress in clinical and biological research. 323 Eds: Chadha D, Buttram V, *Alan R. Liss Press*, NewYork, NY 413-426 (1990)
21. Halme J., M. G. Hammond, J. F. Hulka, S. G. Raj & L. Talbert: Retrograde menstruation in healthy women and in patients with endometriosis. *Obstet Gynecol* 64, 151-154 (1984)
22. Olive D. L. & D. Y. Henderson: Endometriosis and Mullerian anomalies. *Obstet Gynecol* 69, 412-415 (1987)
23. Ugur M., C. Turan, T. Mungan, E. Kuscu, S. Senoz, H. T. Agis & O. Gokmen: Endometriosis in association with mullerian anomalies. *Gynecol Obstet Inves* 40, 261-264 (1995)
24. Barbieri R. L., M. Callery & S. E. Perez: Directionality of menstrual flow; cervical os diameter as a Barbieri determinant of retrograde menstrualtion. *Fertil Steril* 57, 727-730 (1992)
25. Salamanca A. & E. Beltran: Subendometrial contractility in menstrual phase visualized by transvaginal sonography in patients with endometriosis. *Fertil Steril* 64, 193-195 (1995)

26. Kunz G., D. Bell, P. Huppert & G. Leyendecker: Structural abnormalities of the uterine wall in women with endometriosis and infertility visualised by vaginal sonograpy and magnetic resonance imaging. *Hum Reprod* 15, 76-82 (2000)
27. Wingfield M., A. Macpherson, D. L. Healy & P. A. W. Rogers: Cell proliferation is increased in the endometrium of women with endometriosis. *Fertil Steril* 64, 340-346 (1995)
28. Noble L. S., K. Takayama, K. M. Zeitoun, J. M. Putman, D. A. Johns, M. M. Hinshelwood, V. R. Agarwal, Y. Zhao, B. R. Carr & S. E. Bulun: Prostaglandin E2 stimulates aromatase expression in endometriosis derived stromal cells. *J Clin Endocr Metab* 82, 600-606 (1997)
29. Jolicoeur C., M. Boutouil, R. Drouin, I. Paradis, A. Lemay & A. Akoum: Increased expression of monocyte chemotactic protein-1 in the endometrium of women with endometriosis. *Am J Pathol* 152, 125-133 (1998)
30. Dmowski W. P., J. Ding, J. Shen, N. Rana, B. B. Fernandez & D. P. Braun: Apoptosis in endometrial glandular and stromal cells in women with and without endometriosis. *Hum Reprod* 16, 1802-1808 (2001)
31. Jones R. K., R. F. Searle & J. N. Bulmer: Apoptosis and bcl-2 expression in normal human endometrium, endometriosis and adenomyosis. *Hum Reprod* 13, 3496-3502 (1998)
32. Meresman G. F., S. Vighi, R. A. Buquet, O. Contreras-Ortiz, M. Tesone & L. S. Rumi: Apoptosis and expression of Bcl-2 and Bax in eutopic endometrium from women with endometriosis. *Fertil Steril* 74, 760-766 (2000)
33. Leyendecker G., M. Herbertz, G. Kunz & G. Mall: Endometriosis results from the dislocation of basal endometrium. *Hum Reprod* 17 2725-2736 (2002)
34. Dizerga G. S., D. L. Barber & G. D. Hodgen: Endometriosis - Role of Ovarian-Steroids in Initiation, Maintenance, and Suppression. *Fertil Steril* 33, 649-653 (1980)
35. Olive D. L., L. B. Schwartz: Endometriosis. *New Eng J Med* 328, 1759-1769 (1993)
36. Barbieri R. L.: Etiology and epidemiology of endometriosis. *Am J Obstet Gynecol* 162, 565-567 (1990)
37. Cust M. P., K. F. Gangar, T. C. Hillardand & M. I. Whitehead: A risk-benefit assessment of estrogen therapy in postmenopausal women. *Drug Safety* 5, 345-358 (1990)
38. Bellina J. H. & D. Schenck: Large postmenopausal ovarian endometrioma. *Obstet Gynecol* 96, 846-846 (2000)
39. Goumenou A. G., C. Chow, A. Taylor & A. Magos: Endometriosis arising during estrogen and testosterone treatment 17 years after abdominal hysterectomy: a case report. *Maturitas* 46, 239-241 (2003)
40. Fujishita A., P. K. Nakane, T. Koji, H. Masuzaki, R. O. Chavez, T. Yamabe & T. Ishimaru: Expression of estrogen and progesterone receptors in endometrium and peritoneal endometriosis: an immunohistochemical and in situ hybridization study. *Fertil Steril* 67, 856-864 (1997)
41. Kitawaki J., N. Kado, H. Ishihara, H. Koshiba, Y. Kitaoka & H. Honjo: Endometriosis: the pathophysiology as an estrogen-dependent disease. *J Steroid Biochem* 83, 149-155 (2003)
42. Fujimoto J., S. Ichigo, R. Hirose, H. Sakaguchi & T. Tamaya: Expression of estrogen receptor wild type and exon 5 splicing variant mRNAs in normal and endometriotic endometria during the menstrual cycle. *Gynecol Endocrinol*11, 11-16 (1997)
43. Kitawaki J., H. Obayashi, H. Ishihara, H. Koshiba, I. Kusuki, N. Kado, K. Tsukamoto, G. Hasegawa, N. Nakamura & H. Honjo: Oestrogen receptor-alpha gene polymorphism is associated with endometriosis, adenomyosis and leiomyomata. *Hum Reprod* 16, 51-55 (2001)
44. Wang Z., S. Yoshida, K. Negoro, S. Kennedy, D. Barlow & T. Maruo: Polymorphisms in the estrogen receptor gene beta but not estrogen receptor alpha gene affect the risk of developing endometriosis in a Japanese population. *Fertil Steril* 81, 1650-1656 (2004)
45. Misao R., S. Iwagaki, J. Fujimoto, W. Sun & T. Tamaya: Dominant expression of progesterone receptor form B mRNA in ovarian endometriosis, *Horm Res* 52, 30-34 (1999)
46. Attia G. R., K. Zeitoun, D. Edwards, A. Johns, B. R. Carr & S. E. Bulun: Progesterone receptor isoform A but not B is expressed in endometriosis. *J Clin Endocr Metab* 85, 2897-2902 (2000)
47. Wieser F., C. Schneeberger, D. Tong, C. Tempfer, J. C. Huber & R. Wenzl: PROGINS receptor gene polymorphism is associated with endometriosis. *Fertil Steril* 77, 309-312 (2002)
48. Cohen I., M. M. Altaras, S. Lew, Y. Beyth & G. Ben-Baruch: Ovarian endometrioid carcinoma and endometriosis developing in a postmenopausal breast cancer patient during tamoxifen therapy: a case report and review of the literature. *Gynecol Oncol* 55, 443-447 (1994)
49. Chang C. K., P. Chen, F. J. Leu & M. A. Lou: Florid Polypoid Endometriosis Exacerbated by Tamoxifen Therapy in Breast Cancer *Obstet Gynecol* 102, 1127-1130 (2003)
50. de Velasco L. A. & A. Cano: Acute abdomen due to endometriosis in a premenopausal woman taking tamoxifen. *Eur J Obstet Gynecol R B* 109, 234-235 (2003)
51. Zeitoun K., K. Takayama, H. Sasano, T. Suzuki, N. Moghrabi, S. Andersson, A. Johns, L. Meng, M. Putman, B. Carr & S. E. Bulun: Deficient 17beta-hydroxysteroid dehydrogenase type 2 expression in endometriosis: failure to metabolize 17beta-estradiol. *J Clin Endocr Metab* 83, 4474-4480 (1998)
52. Kennedy S., H. Mardon & D. Barlow: Familial Endometriosis. *J Assist Reprod Gen* 12, 32-34 (1995)
53. Moen M. H. & P. Magnus: The Familial Risk of Endometriosis. *Acta Obstet Gyn Scan* 72, 560-564 (1993)
54. Stefanson H., R. T. Geirsson, V. Steinthorsdottir, H. Jonsson, A. Manolescu, A. Kong, G. Ingadottir, J. Gulcher & K. Stefansson: Genetic factors contribute to the risk of developing endometriosis. *Hum Reprod* 17, 555-559 (2002)
55. Zondervan K. T., D. E. Weeks, R. Colman, L. R. Cardon, R. Hadfield, J. Schleffler, A. G. Trainor, C. L. Coe, J. W. Kemnitz & S. H. Kennedy: Familial aggregation of endometriosis in a large pedigree of rhesus macaques. *Hum Reprod* 19, 448-455 (2004)
56. Moen M. H.: Endometriosis in Monozygotic Twins. *Acta Obstet Gyn Scan*, 73, 59-62 (1994)
57. Hadfield R. M., H. J. Mardon, D. H. Barlow & S. H. Kennedy: Endometriosis in monozygotic twins. *Fertil Steril*, 68, 941-942 (1997)
58. Treloar S. A., D. T. O'Connor, V. M. O'Connor & N. G. Martin: Genetic influences on endometriosis in an Australian twin sample. *Fertil Steril*, 71, 701-710 (1999)
59. Oral E. & A. Arici: Pathogenesis of endometriosis. *Obstet Gyn Clin N Am* 24, 219-& (1997)

60. Baxter S. W., E. J. Thomas & I. G. Campbell: GSTM1 null polymorphism and susceptibility to endometriosis and ovarian cancer. *Carcinogenesis* 22, 63-65 (2001)
61. Nakago S., R. M. Hadfield, K. T. Zondervan, H. Mardon, S. Manek, D. E. Weeks, D. Barlow & S. Kennedy: Association between endometriosis and N-acetyl transferase 2 polymorphisms in a UK population. *Mol Hum Reprod* 7, 1079-1083 (2001)
62. Cramer D. W., M. D. Hornstein & R. L. Barbieri: Endometriosis associated with the N314D mutation of galactose-1-phosphate uridyl transferase. *Mol Hum Reprod* 2, 149-152 (1996)
63. Bischoff F. Z. & J. L. Simpson: Heritability and molecular genetic studies of endometriosis. *Hum Reprod Update* 6, 37-44 (2000)
64. Zondervan K. T., L. R. Cardon & S. H. Kennedy: The genetic basis of endometriosis. *Curr Opin Obstet Gyn* 13, 309-314 (2001)
65. Stefansson H., A. Einarsdottir, R.T. Geirsson, K. Jonsdottir, G. Sverrisdottir, V. G. Gudnadottir, S. Gunnarsdottir, A. Manolescu, J. Gulcher & K. Stefansson: Endometriosis is not associated with or linked to the GALT gene. *Fertil Steril* 76, 1019-1022 (2001)
66. Campbell I. G. & E. J. Thomas: Endometriosis: candidate genes. *Hum Reprod Update* 7, 15-20 (2001)
67. Bischoff F. Z., M. Heard & J. L. Simpson: Somatic DNA alterations in endometriosis: high frequency of chromosome 17 and p53 loss in late-stage endometriosis. *J Reprod Immunol*55, 49-64 (2002)
68. Cuesta de la R. S., M. Izquierdo, M. Canamero, J. J. Granizo & F. Manzarbeitia: Increased prevalence of p53 overexpression from typical endometriosis to atypical endometriosis and ovarian cancer associated with endometriosis. *Eur J Obstet Gynecol R B* 113, 87-93 (2004)
69. Vinatier D., M. Cosson & P. Dufour: Is endometriosis an endometrial disease? *Eur J Obstet Gynecol R B* 91, 113-125 (2000)
70. Dmowski W. P., H. Gebel & D. P. Braun: Decreased apoptosis and sensitivity to macrophage mediated cytolysis of endometrial cells in endometriosis. *Hum Reprod Update* 4, 696-701 (1998)
71. Braun D. P., H. Gebel, N. Rana & W. P. Dmowski: Cytolysis of eutopic and ectopic endometrial cells by peripheral blood monocytes and peritoneal macrophages in women with endometriosis. *Fertil Steril* 69, 1103-1108 (1998)
72. Ota H. & S. Igarashi: Expression of major histocompatibility complex class II antigen in endometriotic tissue in patients with endometriosis and adenomyosis. *Fertil Steril* 60, 834-838 (1993)
73. Semino C., S. Barocci, A. Semino, P. L. Venturini, G. Pietra, N. Ragni, M. C. Mingari & G. Melioli: Role of Major Histocompatibility Complex Class-I Expression and Natural Killer-Like T-Cells in the Genetic-Control of Endometriosis. *Fertil Steril* 64, 909-916 (1995)
74. Dmowski W. P., R. W. Steele & G. F. Baker: Deficient Cellular-Immunity in Endometriosis. *Am J Obstet Gynecol* 141, 377-383 (1981)
75. Steele R. W., W. P. Dmoswki & D. J. Marmer: Immunologic aspects of human endometriosis. *Am J Reprod Immunol* 6, 33-36 (1984)
76. Oosterlynck D. J., F. J. Cornillie, M. Waer, M. Vandeputte & P. R. Koninckx: Women with Endometriosis Show a Defect in Natural-Killer Activity Resulting in a Decreased Cytotoxicity to Autologous Endometrium. *Fertil Steril* 56, 45-51 (1991)
77. Mettler L., N. I. Volkov, V. I. Kulakov, A. Jurgensen & M. R. Parwaresch: Lymphocyte subsets in the endometrium of patients with endometriosis throughout the menstrual cycle. *Am J Reprod Immunol* 36, 342-348 (1996)
78. Kanzaki H., H. S. Wang, M. Kariya & T. Mori: Suppression of Natural-Killer-Cell Activity by Sera from Patients with Endometriosis. *Am J Obstet Gynecol* 167, 257-261 (1992)
79. Oosterlynck D. J., C. Meuleman, M. Waer, P. R. Koninckx & M. Vandeputte: Immunosuppressive Activity of Peritoneal-Fluid in Women with Endometriosis. *Obstet Gynecol* 82, 206-212 (1993).
80. Zeller J. M., I. Henig, E. Radwanska & W. P. Dmowski: Enhancement of Human Monocyte and Peritoneal Macrophage Chemiluminescence Activities in Women with Endometriosis. *Am J Reprod Immunol* 13, 78-82 (1987)
81. Halme J., S. Becker & S. Haskill: Altered Maturation and Function of Peritoneal-Macrophages - Possible Role in Pathogenesis of Endometriosis. *Am J Obstet Gynecol* 156, 783-789 (1987)
82. Khan K. N., H. Masuzaki, A. Fujishita, M. Kitajima, I. Sekine & T. Ishimaru: Differential macrophage infiltration in early and advanced endometriosis and adjacent peritoneum. *Fertil Steril* 81, 652-661 (2004).
83. Hill J. A., H. M. P. Faris, I. Schiff & D. J. Anderson: Characterization of Leukocyte Subpopulations in the Peritoneal-Fluid of Women with Endometriosis. *Fertil Steril*, 50, 216-222 (1988)
84. Braun D. P., J. Ding, J. Shen, N. Rana, B. B. Fernandez & W. P. Dmowski: Relationship between apoptosis and the number of macrophages in eutopic endometrium from women with and without endometriosis. *Fertil Steril* 78, 830-835 (2002)
85. Braun D. P., A. Muriana, H. Gebel, C. Rotman, N. Rana & W. P. Dmowski: Monocyte-Mediated Enhancement of Endometrial Cell-Proliferation in Women with Endometriosis. *Fertil Steril* 61, 78-84 (1994)
86. McLaren J., A. Prentice, D. S. CharnockJones, A. M. Sharkey & S. K. Smith: Immunolocalization of the apoptosis regulating proteins Bcl-2 and Bax in human endometrium and isolated peritoneal fluid macrophages in endometriosis. *Hum Reprod* 12, 146-152 (1997)
87. Sbracia M., R. Poverini, B. Szabolcs & E. Zupi: Is the ectopic endometrium an immuno-privileged tissue? Expression of FAS-receptor/FAS-ligand and bcl2 in endometriotic lesions. *Fertil Steril* 77, S16-S16 (2002)
88. Sinaii N., S. D. Cleary, M. L. Ballweg, L. K. Nieman & P. Stratton: High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. *Hum Reprod* 17, 2715-2724 (2002)
89. Pasoto S., M. S. Abrao, C. Bueno, V. S. T. Viana & E. Bonfa: Rheumatic clinical manifestations and fibromyalgia in association with endometriosis. *Fertil Steril*, 77, S7-S7 (2002)
90. Taylor P. V., M. D. Maloney, J. M. Campbell, S. M. Skerrow, M. M. C. Nip, R. Parmar & G. Tate: Autoreactivity in Women with Endometriosis. *Brit J Obstet Gynaec* 98, 680-684 (1991)

91. D'Cruz O. J., R. A. Wild, G. G. Haas & M. Reichlin: Antibodies to carbonic anhydrase in endometriosis: Prevalence, specificity, and relationship to clinical and laboratory parameters. *Fertil Steril* 66, 547-556 (1996)
92. Reimand K., I. Talja, K. Metskula, U. Kadastik, K. Matt & R. Uibo: Autoantibody studies of female patients with reproductive failure. *J Reprod Immunol*51, 167-176 (2001)
93. Weil S. J., S. Y. Wang, M. C. Perez & C. R. Lyttle: Chemotaxis of macrophages by a peritoneal fluid protein in women with endometriosis. *Fertil Steril* 67, 865-869 (1997)
94. Murphy A. A., N. Santanam, A. J. Morales & S. Parthasarathy: Lysophosphatidyl choline, a chemotactic factor for monocytes/T-lymphocytes is elevated in endometriosis. *J Clin Endocr Metab* 83, 2110-2113 (1998)
95. Perez M. C., P. V. N. Bodine, M. C. Leiva, K. B. Isaacson & B. S. Komm: Signal transduction pathways involved in macrophage migration induced by peritoneal fluid chemotactic factors in stages I and II endometriosis. *Fertil Steril* 77, 1261-1268 (2002)
96. Hornung D., F. Bentzien, D. Wallwiener, L. Kiesel & R. N. Taylor: Chemokine bioactivity of RANTES in endometriotic and normal endometrial stromal cells and peritoneal fluid. *Mol Hum Reprod* 7, 163-168 (2001)
97. Sharpe-Timms K. L., P. L. Bruno, L. L. Penney & J. T. Bickel: Immunohistochemical Localization of Granulocyte-Macrophage Colony-Stimulating Factor in Matched Endometriosis and Endometrial Tissues. *Am J Obstet Gynecol* 171, 740-745 (1994)
98. D. I. Lebovic, M. D. Mueller & R. N. Taylor: Immunobiology of endometriosis. *Fertil Steril* 75, 1-10 (2001)
99. Harada T., T. Iwabe & N. Terakawa: Role of cytokines in endometriosis. *Fertil Steril* 76, 1-10 (2001)
100. Hsu C. C., B. C. Yang, M. H. Wu & K. E. Huang: Enhanced interleukin-4 expression in patients with endometriosis. *Fertil Steril* 67, 1059-1064 (1997)
101. Sharpe-Timms K. L., R. L. Zimmer, E. A. Ricke, M. Piva & G. M. Horowitz: Endometriotic haptoglobin binds to peritoneal macrophages and alters their function in women with endometriosis. *Fertil Steril* 78, 810-819 (2002)
102. Piva M., G. M. Horowitz & K. L. Sharpe-Timms: Interleukin-6 differentially stimulates haptoglobin production by peritoneal and endometriotic cells in vitro: A model for endometrial-peritoneal interaction in endometriosis. *J Clin Endocr Metab* 86, 2553-2561 (2001)
103. Bottini N., A. Gimelfarb, F. Gloria-Bottini, M. La Torre, P. Lucarelli & N. Lucarini: Haptoglobin genotype and natural fertility in humans. *Fertil Steril* 72, 293-296 (1999)
104. Harada T., H. Yoshioka, S. Yoshida, T. Iwabe, Y. Onohara, M. Tanikawa & N. Terakawa: Increased interleukin-6 levels in peritoneal fluid of infertile patients with active endometriosis. *Am J Obstet Gynecol* 176, 593-597 (1997)
105. Tseng J. F., I. P. Ryan, T. D. Milam, J. T. Murai, E. D. Schriock, D. V. Landers & R. N. Taylor: Interleukin-6 secretion in vitro is up-regulated ectopic and eutopic endometrial stromal cells from women with endometriosis. *J Clin Endocr Metab* 81, 1118-1122 (1996)
106. Akoum A., A. Lemay, I. Paradis, N. Rheault & R. Maheux: Secretion of interleukin-6 by human endometriotic cells and regulation by proinflammatory cytokines and sex steroids. *Hum Reprod* 11, 2269-2275 (1996)
107. Tsudo T., T. Harada, T. Iwabe, M. Tanikawa, Y. Nagano, M. Ito, F. Taniguchi & N. Terakawa: Altered gene expression and secretion of interleukin-6 in stromal cells derived from endometriotic tissues. *Fertil Steril* 73, 205-211 (2000)
108. Yoshioka H., T. Harada, T. Iwabe, Y. Nagano, F. Taniguchi, M. Tanikawa & N. Terakawa: Menstrual cycle-specific inhibition of the proliferation of endometrial stromal cells by interleukin 6 and its soluble receptor. *Am J Obstet Gynecol* 180, 1088-1094 (1999)
109. Wieser F., G. Fabjani, C. Tempfer, C. Schneeberger, M. Sator, J. Huber & R. Wenzl: Analysis of an interleukin-6 gene promoter polymorphism in women with endometriosis by pyrosequencing. *J Soc Gynecol Invest* 10, 32-36 (2003)
110. Keenan J. A., T. T. Chen, N. L. Chadwell, D. S. Torry & M. R. Caudle: Il-1-Beta, Tnf-Alpha, and Il-2 in Peritoneal-Fluid and Macrophage-Conditioned Media of Women with Endometriosis. *Am J Reprod Immunol* 34, 381-385 (1995)
111. Wieser F., L. Hefler, C. Tempfer, U. Vlach, C. Schneeberger, J. Huber & R. Wenzl: Polymorphism of the interieukin-1 beta gene and endometriosis. *J Soc Gynecol Invest* 10, 172-175 (2003)
112. Hsieh Y. Y., C. C. Chang, F. J. Tsai, J. Y. Wu, Y. R. Shi, H. D. Tsai & C. H. Tsai: Polymorphisms for interleukin-1 beta (IL-1 beta)-511 promoter, IL-1 beta exon 5, and IL-1 receptor antagonist: Nonassociation with endometriosis. *J Assist Reprod Gen* 18, 506-511 (2001)
103. Eisermann J., M. J. Gast, J. Pineda, R. R. Odem & J. L. Collins: Tumor Necrosis Factor in Peritoneal-Fluid of Women Undergoing Laparoscopic Surgery. *Fertil Steril* 50, 573-579 (1988)
114. Sillem M., S. Prifti, A. Koch, M. Neher, J. Jauckus & B. Runnebaum: Regulation of matrix metalloproteinases and their inhibitors in uterine endometrial cells of patients with and without endometriosis. *Eur J Obstet Gyn R B* 95, 167-174 (2001)
115. Osteen K. G., K. L. Bruner-Tran, D. Ong & E. Eisenberg: Paracrine mediators of endometrial matrix metalloproteinase expression - Potential targets for progestin-based treatment of endometriosis. *Ann NY Acad Sci* 955, 139-146 (2002)
116. Wieser F., G. Fabjani, C. Tempfer, C. Schneeberger, R. Zeillinger, J. C. Huber & R. Wenzl: Tumor necrosis factor-alpha promotor polymorphisms and endometriosis. *J Soc Gynecol Invest* 9, 313-318 (2002)
117. Chen D. B., Z. M. Yang, R. Hilsenrath, S. Ple & M. J. K. Harper: Stimulation of Prostaglandin (Pg) F2-Alpha and Pge(2) Release by Tumor-Necrosis-Factor-Alpha and Interleukin-1-Alpha in Cultured Human Luteal-Phase Endometrial Cells. *Hum Reprod* 10, 2773-2780 (1995)
118. Karck U., F. Reister, W. Schafer, H. P. Zahradnik & M. Breckwoldt: PGE(2) and PGF(2 alpha) release by human peritoneal macrophages in endometriosis. *Prostaglandins* 51, 49-60 (1996)
119. Wu M. H., H. S. Sun, C. C. Lin, K. Y. Hsiao, P. C. Chuang, H. A. Pan & S. J. Tsai: Distinct mechanisms

regulate cyclooxygenase-1 and-2 in peritoneal macrophages of women with and without endometriosis. *Mol Hum Reprod* 8, 1103-1110 (2002)
120. Sales K. J. & H. N. Jabbour: Cyclooxygenase enzymes and prostaglandins in pathology of the endometrium. *Reproduction* 126, 559-567 (2003)
121. Bulun S. E., B. Gurates, Z. J. Fang, M. Tamura, S. Sebastian, H. F. Zhou, S. Amin & S. J. Yang: Mechanisms of excessive estrogen formation in endometriosis. *J Reprod Immunol* 55, 21-33 (2002)
122. Bulun S. E., S. J. Yang, Z. J. Fang, B. Gurates, M. Tamura, J. F. Zhou & S. Sebastian: Role of aromatase in endometrial disease. *J Steroid Biochem* 79, 19-25 (2001)
123. Bulun S. E., S. J. Yang, Z. J. Fang, B. Gurates, M. Tamura & S. Sebastian: Estrogen production and metabolism in endometriosis. *Ann NY Acad Sci* 955, 75-85 (2002)
124. Covens A. L., P. Christopher & R. F. Casper: The Effect of Dietary Supplementation with Fish Oil Fatty-Acids on Surgically Induced Endometriosis in the Rabbit. *Fertil Steril* 49, 698-703 (1988)
125. Gazvani M. R., P. Smith, P. Haggarty, P. A. Fowler & A. Templeton: High omega-3:omega-6 fatty acid ratios in culture medium reduce endometrial-cell survival in combined endometrial gland and stromal cell cultures from women with and without endometriosis. *Fertil Steril* 76, 717-722 (2001)
126. Abu J. I. & J. C. Konje: Leukotrienes in gynaecology: the hypothetical value of anti-leukotriene therapy in dysmenorrhoea and endometriosis. *Hum Reprod Update* 6, 200-205(2000)
127. Harada T., A. Enatsu, M. Mitsunari, Y. Nagano, M. Ito, T. Tsudo, F. Taniguchi, T. Iwabe, M. Tanikawa & N. Terakawa: Role of cytokines in progression of endometriosis. *Gynecol Obstet Invest* 47, 34-39 (1999)
128. Iwabe T., T. Harada, T. Tsudo, Y. Nagano, S. Yoshida, M. Tanikawa & N. Terakawa: Tumor necrosis factor-alpha promotes proliferation of endometriotic stromal cells by inducing interleukin-8 gene and protein expression. *J Clin Endocr Metab* 85, 824-829 (2000)
129. Sakamoto Y., T. Harada, S. Horie, Y. Iba, F. Taniguchi, S. Yoshida, T. Iwabe & N. Terakawa: Tumor necrosis factor-alpha-induced interleukin-8 (IL-8) expression in endometriotic stromal cells, probably through nuclear factor-kappa P activation: Gonadotropin-releasing hormone agonist treatment reduced IL-8 expression. *J Clin Endocr Metab* 88, 730-735 (2003)
130. Akoum A., C. Lawson, S. McColl & M. Villeneuve: 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. *Mol Hum Reprod* 7, 859-866 (2001)
131. Garcia-Velasco J. A. & A. Arici: Interleukin-8 expression in endometrial stromal cells is regulated by integrin-dependent cell adhesion. *Mol Hum Reprod* 5, 1135-1140 (1999)
132. Selam B., U. A. Kayisli, J. A. Garcia-Velasco, G. E. Akbas & A. Arici: Regulation of Fas ligand expression by IL-8 in human endometrium. *J Clin Endocr Metab* 87, 3921-3927 (2002)
133. Iba Y., T. Harada, S. Horie, I. Deura, T. Iwabe & N. Terakawa: Lipopolysaccharide-promoted proliferation of endometriotic stromal cells via induction of tumor necrosis factor alpha and interleukin-8 expression. *Fertil Steril* 82, 1036-1042 (2004)
134. Wanichkul T., S. W. Han, R. P. Huang & N. Sidell: Cytokine regulation by peroxisome proliferator-activated receptor gamma in human endometrial cells. *Fertil Steril* 79, 763-769 (2003)
135. Jiang, C. Y. A. T. Ting & B. Seed: PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. *Nature* 391(6662), 82-86 (1998)
136. Couturier C., A. Brouillet, C. Couriaud, K. Koumanov, G. Bereziat & M. Andreani: Interleukin 1 beta induces type II-secreted phospholipase A(2) gene in vascular smooth muscle cells by a nuclear factor kappa B and peroxisome proliferator-activated receptor-mediated process. *J Biol Chem* 274, 23085-23093 (1999)
137. Lehmann J. M., L. B. Moore, T. A. Smitholiver, W. O. Wilkison, T. M. Willson & S. A. Kliewer: An Antidiabetic Thiazolidinedione Is a High-Affinity Ligand for Peroxisome Proliferator-Activated Receptor Gamma (PPAR-Gamma). *J Biol Chem* 270, 12953-12956 (1995)
138. Khorram O. & B. A. Lessey: Alterations in expression of endometrial endothelial nitric oxide synthase and alpha(v)beta(3) integrin in women with endometriosis. *Fertil Steril* 78, 860-864 (2002)
139. Zervou S., E. Karteris, A. G. Goumenou, M. Vatish, E. E. Koumantakis & E. W. Hillhouse: The Glu(298)-> Asp polymorphism of the endothelial nitric oxide synthase gene is associated with endometriosis. *Fertil Steril* 80, 1524-1525 (2003)
140. Osborn B. H., A. F. Haney, M. A. Misukonis & J. B. Weinberg: Inducible nitric oxide synthase expression by peritoneal macrophages in endometriosis-associated infertility *Fertil Steril* 77, 46-51 (2002)
141. Ota H., S. Igarashi, J. Hatazawa & T. Tanaka: Endometriosis and free radicals. *Gynecol Obstet Invest* 48, 29-34 (1999)
142. Van Langendonckt A., F. Casanas-Roux & J. Donnez: Oxidative stress and peritoneal endometriosis. *Fertil Steril* 77, 861-870 (2002)
143. Santanam N., A. A. Murphy & S. Parthasarathy: Macrophages, oxidation, and endometriosis. *Ann NY Acad Sci* 955, 183-198 (2002)
144. Murphy A. A., W. Palinski, S. Rankin, A. J. Morales & S. Parthasarathy: Macrophage scavenger receptor(s) and oxidatively modified proteins in endometriosis. *Fertil Steril* 69, 1085-1091 (1998)
145. Rong R., S. Ramachandran, N. Santanam, A. A. Murphy & S. Parthasarathy: Induction of monocyte chemotactic protein-1 in peritoneal mesothelial and endometrial cells by oxidized low-density lipoprotein and peritoneal fluid from women with endometriosis. *Fertil Steril* 78, 843-848 (2002)
146. Akoum A., A. Lemay, S. McColl, L. TurcotLemay & R. Maheux: Elevated concentration and biologic activity of monocyte chemotactic protein-1 in the peritoneal fluid of patients with endometriosis. *Fertil Steril* 66, 17-23 (1996)
147. Arici A., E. Oral, E. Attar, S. I. Tazuke & D. L. Olive: Monocyte chemotactic protein-1 concentration in peritoneal fluid of women with endometriosis and its modulation of expression in mesothelial cells. *Fertil Steril* 67, 1065-1072 (1997)

148. Garcia-Velasco J. A. & A. Arici: Chemokines and Hum Reprod. *Fertil Steril* 71, 983-993 (1999)
149. Cao X., D-Z. Yang, M-Q. Song, A. Murphy & S. Parthasarathy: The presence of endometrial cells in the peritoneal cavity enhances monocyte recruitment and induces inflammatory cytokines in mice: implications for endometriosis. *Fertil Steril* 82, 999-1007 (2004)
150. Bloom B. R. & B. Benett: Mechanism of a reaction in vitro associated with delayed -type hypersensitivity *Science* 153(731), 80-82 (1966)
151. Yang Y. B., P. Degranpre, A. Kharfi & A. Akoum: Identification of macrophage migration inhibitory factor as a potent endothelial cell growth-promoting agent released by ectopic human endometrial cells. *J Clin Endocr Metab* 85, 4721-4727 (2000)
152. Kats R., T. Collette, C. N. Metz & A. Akoum: Marked elevation of macrophage migration inhibitory factor in the peritoneal fluid of women with endometriosis. *Fertil Steril* 78, 69-76 (2002)
153. Mahutte N. G., I. M. Matalliotakis, A. G. Goumenou, G. E. Koumantakis, S. Vassiliadis & A. Arici: Elevations in peritoneal fluid macrophage migration inhibitory factor are independent of the depth of invasion or stage of endometriosis. *Fertil Steril* 82, 97-101(2004)
154. Akoum A., J. Kong, C. Metz & M. C. Beaumont: Spontaneous and stimulated secretion of monocyte chemotactic protein-1 and macrophage migration inhibitory factor by peritoneal macrophages in women with and without endometriosis. *Fertil Steril* 77, 989-994 (2002)
155. Akoum A., R. Kats, C. Lawson & C. Metz: Macrophage migration inhibitory factor expression in the human endometrium is cycle phase-dependent and markedly increased in women having endometriosis. *Fertil Steril* 78, S200-S200 (2002)
156. Kats R., C. N. Metz & A. Akoum: Macrophage migration inhibitory factor is markedly expressed in active and early-stage endometriotic lesions. *J Clin Endocr Metab* 87, 883-889 (2002)
157. Akoum A., C. Metz & M. Morin: Marked increase in macrophage migration inhibitory factor synthesis and secretion in human endometrial cells in response to human chorionic gonadotropin hormone. *J Clin Endocr Metab* 90, 2904-2910 (2005)
158. Wada S., T. Kudo, M. Kudo, N. Sakuragi, H. Hareyama, J. Nishihira & S. Fujimoto: Induction of macrophage migration inhibitory factor in human ovary by human chorionic gonadotrophin. *Hum Reprod* 14, 395-399 (1999)
159. Rosengren E., R. Bucala, P. Aman, L. Jacobsson, G. Odh, C. N. Metz & H. Rorsman: The immunoregulatory mediator macrophage migration inhibitory factor (MIF) catalyzes a tautomerization reaction. *Mol Med* 2, 143-149 (1996)
160. Rosengren E., P. Aman, S. Thelin, C. Hansson, S. Ahlfors, P. Bjork, L. Jacobsson & H. Rorsman: The macrophage migration inhibitory factor MIF is a phenylpyruvate tautomerase. *FEBS Letters* 417, 85-88 (1997)
161. Kleemann R., A. Kapurniotu, R. W. Frank, A. Gessner, R. Mischke, O. Flieger, S. Juttner, H. Brunner & J. Bernhagen: Disulfide analysis reveals a role for macrophage migration inhibitory factor (MIF) as thiol-protein oxidoreductase. *J Mol Biol* 280, 85-102 (1998)
162. Garai J., V. Molnar, T. Varga, A. Torok & J. Bodis: Macrophage migration inhibitory factor enzymatic activity of peritoneal fluid in endometriosis. *J Reprod Immunol* 58, 186 (2003) abstract No. 11.1 (O)
163. Lolis E.: Glucocorticoid counter regulation: macrophage migration inhibitory factor as a target for drug discovery. *Curr Opin Pharmacol* 1, 662-668 (2001)
164. Mitchell R. A.: Mechanisms and effectors of MIF-dependent promotion of tumourigenesis *Cell Signal* 16, 13-19 (2004)
165. Hudson J. D., M. A. Shoaibi, R. Maestro, A. Carnero, G. J. Hannon & D. H. Beach: A proinflammatory cytokine inhibits p53 tumor suppressor activity. *J Exp Med* 190, 1375-1382 (1999)
166. Mitchell R. A., C. N. Metz, T. Peng & R. Bucala: Sustained mitogen-activated protein kinase (MAPK) and cytoplasmic phospholipase A2 activation by macrophage migration inhibitory factor (MIF) - Regulatory role in cell proliferation and glucocorticoid action. *J Biol Chem* 274, 18100-18106 (1999)
167. Kleemann R., A. Hausser, G. Geiger, R. Mischke, A. Burger-Kentischer, O. Flieger, F. J. Johannes, T. Roger, T. Calandra, A. Kapurniotu, M. Grell, D. Finkelmeier, H. Brunner & J. Bernhagen: Intracellular action of the cytokine MIF to modulate AP-1 activity and the cell cycle through Jab1. *Nature* 408(6809), 211-216 (2000)
168. Bucala R.: A most interesting factor. *Nature* 408(6809), 146-147 (2000)
169. Somigliana E., P. Vigano, B. Gaffuri, D. Guarneri, M. Busacca & M. Vignali: Human endometrial stromal cells as a source of soluble intercellular adhesion molecule (ICAM)-1 molecules. *Hum Reprod* 11, 1190-1194 (1996)
170. Wu M. H., B. C. Yang, C. C. Hsu, Y. C. Lee & K. E. Huang: The expression of soluble intercellular adhesion molecule-1 in endometriosis. *Fertil Steril* 70, 1139-1142 (1998)
171. Vigano P., B. Gaffuri, E. Somigliana, M. Busacca, A. M. Di Blasio & M. Vignali: Expression of intercellular adhesion molecule (ICAM)-1 mRNA and protein is enhanced in endometriosis versus endometrial stromal cells in culture. *Mol Hum Reprod* 4, 1150-1156 (1998)
172. P Vigano., E. Somigliana, B. Gaffuri, R. Santorsola, M. Busacca & M. Vignali: Endometrial release of soluble intercellular adhesion molecule 1 and endometriosis: Relationship to the extent of the disease. *Obstet Gynecol* 95, 115-118 (2000)
173. Fukaya T., J. Sugawara, H. Yoshida, T. Murakami & A. Yajima: Intercellular adhesion molecule-1 and hepatocyte growth factor in human endometriosis: Original investigation and a review of literature. *Gynecol Obstet Invest* 47, 11-16 (1999)
174. Wu M. H., B. C. Yang, Y. C. Lee, P. L. Wu & C. C. Hsu: The differential expression of intercellular adhesion molecule-1 (ICAM-1) and regulation by interferon-gamma during the pathogenesis of endometriosis. *Am J Reprod Immunol*51, 373-380 (2004)
175. McLaren J., A. Prentice, D. S. CharnockJones & S. K. Smith: Vascular endothelial growth factor (VEGF) concentrations are elevated in peritoneal fluid of women with endometriosis. *Hum Reprod* 11, 220-223 (1996)

176. McLaren J.: Vascular endothelial growth factor and endometriotic angiogenesis. *Hum Reprod Update* 6, 45-55 (2000)
177. McLaren J., A. Prentice, D. S. CharnockJones, S. A. Millican, K. H. Muller, A. M. Sharkey & S. K. Smith: Vascular endothelial growth factor is produced by peritoneal fluid macrophages in endometriosis and is regulated by ovarian steroids. *J Clin Invest* 98, 482-489 (1996)
178. Ning W. X., H. F. Huang & F. Jin: The role of VEGF and MMP-2 in the early stage of evolution of endometriosis. *International Congress Series* 1271, 240-243 (2004)
179. Fasciani A., G. D'Ambrogio, G. Bocci, M. Monti, A. R. Genazzani & P. G. Artini: High concentrations of the vascular endothelial growth factor and interleukin-8 in ovarian endometriomata. *Mol Hum Reprod* 6, 50-54 (2000)
180. Fukuda J., Y. Kawano, K. Nasu, M. Nishida, H. Narahara & I. Miyakawa: Differential effects of interferon-alpha and -beta on the secretion of vascular endothelial growth factor by eutopic and ectopic endometrial stromal cells. *Fertil Steril* 82, 749-751 (2004)
181. Matalliotakis. I. M., A. G. Goumenou, G. E. Koumantakis, M. A. Neonaki, E. E. Koumantakis, E. Dionyssopoulou, I. Athanassaki & S. Vassiliadis: Serum concentrations of growth factors in women with and without endometriosis: the action of anti-endometriosis medicines. *Int Immunopharmacol* 3, 81-89 (2003)
182. Suzumori N., X. X. Zhao & K. Suzumori: Elevated angiogenin levels in the peritoneal fluid of women with endometriosis correlate with the extent of the disorder. *Fertil Steril* 82, 93-96 (2004)
183. Fujimoto J., H. Sakaguchi, R. Hirose & T. Tamaya: Expression of platelet-derived endothelial cell growth factor (PD-ECGF) related to angiogenesis in ovarian endometriosis. *J Clin Endocr Metab* 84, 359-362 (1999)
184. Garcia-Velasco J. A., A. Arici, T. Zreik, F. Naftolin & G. Mor: Macrophage derived growth factors modulate Fas ligand expression in cultured endometrial stromal cells: a role in endometriosis. *Mol Hum Reprod* 5, 642-650 (1999)
185. Sbracia M., E. Zupi, P. Alo, C. Manna, D. Marconi, F. Scarpellini, J. A. Grasso, U. DiTondo & C. Romanini: Differential expression of IGF-I and IGF-II in eutopic and ectopic endometria of women with endometriosis and in women without endometriosis. *Am J Reprod Immunol* 37, 326-329 (1997)
186. Maiorano E., G. Loverro, G. Viale, T. Giannini, A. Napoli & E. Perlino: Insulin-like growth factor-I expression in normal and diseased endometrium. *Int J Cancer* 80, 188-193 (1999)
187. Gurgan T., O. Bukulmez, H. Yarali, M. Tanir & S. Akyildiz: Serum and peritoneal fluid levels of IGF I and II and insulinlike growth binding protein-3 in endometriosis. *J Reprod Med* 44, 450-454 (1999)
188. F Philippoussis., D. Gagne, P. Hugo & D. Gosselin: Concentrations of alpha-fetoprotein, insulin-like growth factor binding protein-3, c-erbB-2, and epidermal growth factor in serum of patients with endometriosis. *J Soc Gynecol Invest* 11, 175-181 (2004)
189. Khan K. N., H. Masuzaki, A. Fujishita, M. Kitajima, I. Sekine & T. Ishimaru: Immunoexpression of hepatocyte growth factor and c-Met receptor in the eutopic endometrium predicts the activity of ectopic endometrium. *Fertil Steril* 79, 173-181 (2003)
190. Pitt J. A., L. Feng, B. D. Abbott, J. Schmid, R. E. Batt, T. G. Costich, S. T. Koury & D. P. Bofinger: Expression of AhR and ARNT mRNA in cultured human endometrial explants exposed to TCDD. *Toxicol Sci* 62, 289-298 (2001)
191. Berger M. J. & M. M. Alper: Intractable Primary Infertility in Women Exposed to Diethylstilbestrol Inutero. *J Reprod Med* 31, 231-235 (1986)
192. Missmer S. A., S. E. Hankinson, D. Spiegelman, R. L. Barbieri, K. B. Michels & D. J. Hunter: In utero exposures and the incidence of endometriosis. *Fertil Steril* 82, 1501-1508 (2004)
193. Rier S. & W. G. Foster: Environmental dioxins and endometriosis. *Toxicol Sci* 70, 161-170 (2002)
194. Whitlock J. P.: Genetic and Molecular Aspects of 2,3,7,8-Tetrachlorodibenzo-P-Dioxin Action. *Ann Rev Pharmacol* 30, 251-277 (1990)
195. Rier S. E., D. C. Martin, R. E. Bowman, W. P. Dmowski & J. L. Becker: Endometriosis in Rhesus-Monkeys (Macaca-Mulatta) Following Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-P-Dioxin. *Fund Appl Toxicol* 21, 433-441 (1993)
196. Yang J., W. G. Foster: Chronic Exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin modulates the growth of endometriosis in the Cynomolgus Monkey. *Organohalogen Compounds* 37, 75 (1998)
197. Yang J. Z., S. K. Agarwal & W. G. Foster: Subchronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin modulates the pathophysiology of endometriosis in the cynomolgus monkey. *Toxicol Sci* 56, 374-381 (2000)
198. Cummings A. M., J. L. Metcalf & L. Birnbaum: Promotion of endometriosis by 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats and mice: Time-dose dependence and species comparison. *Toxicol Appl Pharm* 138, 131-139 (1996)
199. Yang J. Z. & W. G. Foster: Continuous exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin inhibits the growth of surgically induced endometriosis in the ovariectomized mouse treated with high dose estradiol. *Toxicol Ind Health* 13, 15-25 (1997)
200. Bulun S. E., K. M. Zeitoun & G. Kilic: Expression of dioxin-related transactivating factors and target genes in human eutopic endometrial and endometriotic tissues. *Am J Obstet Gynecol* 182, 767-775 (2000)
201. Nunez S. B., J. A. Medin, O. Braissant, L. Kemp, W. Wahli, K. Ozato & J. H. Segars: Retinoid X receptor and peroxisome proliferator-activated receptor activate an estrogen responsive gene independent of the estrogen receptor. *Mol Cell Endocrinol* 127, 27-40 (1997)
202. Kitajima M., K. N. Khan, A. Fujishita, H. Masuzaki & T. Ishimaru: Histomorphometric alteration and cell-type specific modulation of arylhydrocarbon receptor and estrogen receptor expression by 2,3,7,8-tetrachlorodibenzo-p-dioxin and 17 beta-estradiol in mouse experimental model of endometriosis. *Reprod Toxicol* 18, 793-801 (2004)
203. Eskenazi B., P. Mocarelli, M. Warner, S. Samuels, P. Vercellini, D. Olive, L. L. Needham, D. G. Patterson, P. Brambilla, N. Gavoni, S. Casalini, S. Panazza, W. Turner & P. M. Gerthoux: Serum dioxin concentrations and

endometriosis: A cohort study in Seveso, Italy. *Environ Health Persp* 110, 629-634 (2002)
204. Pauwels A., P. J. C. Schepens, T. D'Hooghe, L. Delbeke, M. Dhont, A. Brouwer & J. Weyler: The risk of endometriosis and exposure to dioxins and polychlorinated biphenyls: a case-control study of infertile women. *Hum Reprod* 16, 2050-2055 (2001)
205. Koninckx P. R., P. Braet, S. H. Kennedy & D. H. Barlow: Dioxin Pollution and Endometriosis in Belgium. *Hum Reprod* 9, 1001-1002 (1994)
206. Tsutsumi O., M. Momoeda, Y. Takai, M. Ono & Y. Taketani: Breast-fed infants, possibly exposed to dioxins in milk, have unexpectedly lower incidence of endometriosis in adult life. *Int J Gynecol Obstet* 68, 151-153 (2000)
207. Cotroneo M. S. & C. A. Lamartiniere: Pharmacologic, but not dietary, genistein supports endometriosis in a rat model. *Toxicol Sci* 61, 68-75 (2001)
208. Heilier J. F., V. Verougstraete, F. Nackers, R. Tonglet, J. Donnez & D. Lison: Assessment of cadmium impregnation in women suffering from endometriosis: a preliminary study. *Toxicol Lett* 154, 89-93 (2004)
209. Missmer S. A., S. E. Hankinson, D. Spiegelman, R. L. Barbieri, S. M. Walter C. Willett & D. J. Hunter: Reproductive history and endometriosis among premenopausal women. *Obstet Gynecol* 104, 965-974 (2004)
210. D'Hooghe T. M., C. S. Bambra, I. De Jonge, J. M. Lauweryns, B. M. Raeymaekers, P. R. Koninckx: The effect of pregnancy on endometriosis in baboons (*Papio anubis, Papio cynocephalus*). *Arch Gynecol Obstet* 261 15-19 (1997)
211. Balkwill F. & A. Mantovani: Inflammation and cancer: back to Virchow? *Lancet* 357(9255), 539-545 (2001)
212. Heaps J. M., R. K. Nieberg & J. S. Berek: Malignant Neoplasms Arising in Endometriosis. *Obstet Gynecol* 75, 1023-1028 (1990)
213. Vercellini P., F. Parazzini, G. Bolis, S. Carinelli, M. Dindelli, N. Vendola, L. Luchini & P. G. Crosignani: Endometriosis and Ovarian-Cancer. *Am J Obstet Gynecol* 169, 181-182 (1993)
214. Thomas E. J. & I. G. Campbell: Evidence that endometriosis behaves in a malignant manner. *Gynecol Obstet Invest* 50, 2-7 (2000)
215. Chang C. C., Y. Y. Hsieh, F. J. Tsai, C. H. Tsai, H. D. Tsai & C. C. Lin: The proline form of p53 codon 72 polymorphism is associated with endometriosis. *Fertil Steril* 77, 43-45 (2002)
216. Omor, I. S. Yoshida, S. H. Kennedy, K. Negoro, S. Hamana, D. H. Barlow & T. Maruo: Polymorphism at codon 72 of the p53 gene is not associated with endometriosis in a Japanese population. *J Soc Gynecol Invest* 11 232-236 (2004)
217. Osuga Y., K. Koga, O. Tsutsumi, T. Igarashi, R. Okagaki, Y Takai, H. Matsumi, H. Hiroi, T. Fujiwara, M. Momoeda, T. Yano & Y. Taketani: Stem cell factor (SCF) concentrations in peritoneal fluid of women with or without endometriosis. *Am J Reprod Immunol* 44, 231-235 (2000)
218. Uzan C., A. Cortez, C. Dufournet, R. Fauvet, J-P. Siffroid & E. Daraï: Endometrium from women with and without endometriosis, and peritoneal, ovarian and bowel endometriosis, show different c-kit protein expression. *J Reprod Immunol* 65, 55-63 (2005)
219. Hadfield R. M., S. Manek, D. E. Weeks, H. J. Mardon, D. H. Barlow, S. H. Kennedy, O. C. Grp &: Linkage and association studies of the relationship between endometriosis and genes encoding the detoxification enzymes GSTM1, GSTT1 and CYP1A1. *Mol Hum Reprod* 7, 1073-1078 (2001)
220. Gucer F., D. Pieber & M. G. Arikan: Malignancy arising in extraovarian endometriosis during estrogen stimulation. *Eur J Gynaecol Onc* 19, 39-41 (1998)
221. Zanetta G. M., M. J. Webb, H. Z. Li & G. L. Keeney: Hyperestrogenism: A relevant risk factor for the development of cancer from endometriosis. *Gynecol Oncol* 79, 18-22 (2000)
222. Lavery S. & M. Gillmer: Malignant transformation of residual endometriosis in women on unopposed oestrogen hormone replacement therapy. *Brit J Obstet Gynaec* 108, 1106-1107 (2001)
223. Anderson J., K. Behbakht, K. De Geest & P. Bitterman: Adenosarcoma in a patient with vaginal endometriosis. *Obstet Gynecol* 98, 964-966 (2001)
224. Modesitt S. C., G. Tortoler-Luna, J. B. Robinson, D. M. Gershenson & J. K. Wolf: Ovarian and extraovarian endometriosis-associated cancer. *Obstet Gynecol* 100, 788-795 (2002)
225. M Koshiyama., Y. Morita, H. Fujii, Y. Kobashi & M. Yoshida: Gynecologic malignancies accompanied by benign hormone-dependent diseases. *Menopause* 8, 149-150 (2001).
226. Koshiyama M., T. Okamoto & M. Ueta: The relationship between endometrial carcinoma and coexistent adenomyosis uteri, endometriosis externa and myoma uteri. *Cancer Detect Prev* 28, 94-98 (2004)
227. Niwa K., M. Hashimoto, S. Morishita, Y. Yokoyama, Z. L. Lian, K. Tagami, H. Mori & T. Tamaya: Preventive effects of danazol on endometrial carcinogenesis in mice. *Cancer Lett* 158, 133-139 (2000)
228. McCann T. O. & R. E. Myers Endometriosis in rhesus monkeys. *Am J Obstet Gynecol* 106, 516-523 (1970)
229. Merrill J. A.: Spontaneous endometriosis in the Kenya baboon. *Am J Obstet Gynecol* 101, 569-570 (1968)
230. D'Hooghe T. M., C. S. Bambra, B. M. Raeymaekers & P. R. Koninckx: Development of spontaneous endometriosis in baboons. *Obstet Gynecol* 88, 462-466 (1996)
231. D'Hooghe T. M.: Clinical relevance of the baboon as a model for the study of endometriosis. *Fertil Steril* 68, 613-625 (1997)
232 D'Hooghe. T. M., C. S. Bambra, B. M. Raeymaekers, I. Dejonge, J. M. Lauweryns & P. R. Koninckx: Intrapelvic Injection of Menstrual Endometrium Causes Endometriosis in Baboons (Papio-Cynocephalus and Papio-Anubis). *Am J Obstet Gynecol* 173, 125-134 (1995)
233. Manyak M. J., L. M. Nelson, D. Solomon, W. Degraff, R. J. Stillman & A. Russo: Fluorescent Detection of Rabbit Endometrial Implants Resulting from Monodispersed Viable Cell-Suspensions. *Fertil Steril* 54, 356-359 (1990)
234. Schenken R. S. & R. H. Asch: Surgical Induction of Endometriosis in the Rabbit - Effects on Fertility and

Concentrations of Peritoneal-Fluid Prostaglandins. *Fertil Steril* 34, 581-587 (1980)
235. Silva J. C. R., A. C. J. S. R. Silva, F. J. C. Reis, S. B. Garcia, M. F. S. Sa & A. A. Nogueira: Development of an experimental model of endometriosis in rabbits. *International Congress Series* 1271, 248- 251 (2004)
236. Cummings A. M. & J. L. Metcalf: Induction of Endometriosis in Mice - a New Model Sensitive to Estrogen. *Reprod Toxicol* 9, 233-238 (1995)
237. Rossi G., E. Somigliana, M. Moschetta, R. Santorsola, S. Cozzolino, P. Filardo, A. Salmaso & B. Zingrillo: Dynamic aspects of endometriosis in a mouse model through analysis of implantation and progression. *Arch Gynecol Obstet* 263, 102-107 (2000)
238. Barragan J. C., J. Brotons, J. A. Ruiz & P. Acien: Experimentally Induced Endometriosis in Rats - Effect on Fertility and the Effects of Pregnancy and Lactation on the Ectopic Endometrial Tissue. *Fertil Steril* 58, 1215-1219 (1992)
239. Ortegamoreno J.: Receptor Concentrations for Estradiol and Progesterone in Surgically Induced Endometriosis in the Rat. *Eur J Obstet Gyn R B* 54, 123-126 (1994)
240. Awwad J. T., R. A. Sayegh, X. J. Tao, T. Hassan, S. T. Awwad & K. Isaacson: The SCID mouse: an experimental model for endometriosis. *Hum Reprod* 14, 3107-3111 (1999)
241. Nisolle M., F. Casanas-Roux & J. Donnez: Early-stage endometriosis: adhesion and growth of human menstrual endometrium in nude mice. *Fertil Steril* 74, 306-312 (2000)
242. Nap A., P. G. Groothuis, A. D. Weusten, A. F. P. de Goeij, G. A. J. Dunselman & J. Evers: Development and characterization of endometriotic lesions in the chick chorioallantoic membrane model. *Fertil Steril* 77, S4-S4 (2002)
243. Barlow D. H. & S. Kennedy: Endometriosis: New Genetic Approaches and Therapy. *Annu Rev Med* 56 345-356 (2005)
244. Taylor R. N., S. G. Lundeen & L. C. Giudice: Emerging role of genomics in endometriosis research. *Fertil Steril* 78, 694-698 (2002)
245. Kao L. C., S. Tulac, S. Lobo, B. Imani, J. P. Yang, A. Germeyer, K. Osteen, R. N. Taylor, B. A. Lessey & L. C. Giudice: Global gene profiling in human endometrium during the window of implantation. *Endocrinology* 143, 2119-2138 (2002)
246. Clark G. F., A. Dell, H. R. Morris, M. Patankar, S. Oehninger & M. Seppala: Viewing AIDS from a glycobiological perspective: potential linkages to the human fetoembryonic defence system hypothesis. *Mol Hum Reprod* 3, 5-13 (1997)
247. Fang Z. J., S. J. Yang, B. Gurates, M. Tamura, E. Simpson, D. Evans & S. E. Bulun: Genetic or enzymatic disruption of aromatase inhibits the growth of ectopic uterine tissue. *J Clin Endocr Metab* 87, 3460-3466 (2002)
248. Sterneck E., L. Tessarollo & P. F. Johnson: An essential role for C/EBP beta in female reproduction. *GeneDev* 11, 2153-2162 (1997)
249. Yang S. J., Z. J. Fang, T. Suzuki, H. Sasano, J. F. Zhou, B. Gurates, M. Tamura, K. Ferrer & S. E. Bulun: Regulation of aromatase P450 expression in endometriotic and endometrial stromal cells by CCAAT/enhancer binding proteins (C/EBPs): Decreased C/EBP beta in endometriosis in associated with overexpression of aromatase. *J Clin Endocr Metab* 87, 2336-2345 (2002)
250. Gurates B., S. Sebastian, S. J. Yang, J. F. Zhou, M. Tamura, Z. J. Fang, T. Suzuki, H. Sasano & S. E. Bulun: WT1 and DAX-1 inhibit aromatase p450 expression in human endometrial and endometriotic stromal cells. *J Clin Endocr Metab* 87, 4369-4377 (2002)
251. Fang Z. J., S. J. Yang, J. P. Lydon, F. DeMayo, M. Tamura, B. Gurates & S. E. Bulun: Intact progesterone receptors are essential to counteract the proliferative effect of estradiol in a genetically engineered mouse model of endometriosis. *Fertil Steril* 82, 673-678 (2004)
252. Taylor H. S., C. Bagot, A. Kardana, D. Olive & A. Arici: HOX gene expression is altered in the endometrium of women with endometriosis. *Hum Reprod* 14, 1328-1331 (1999)
253. Bagot C. N., P. J. Troy & H. S. Taylor: Alteration of maternal Hoxa10 expression by in vivo gene transfection affects implantation. *Gene Ther* 7, 1378-1384 (2000)
254. Hortobagyi G. N., N. T. Ueno, W. Y. Xia, S. Zhang, J. K. Wolf, J. B. Putnam, P. L. Weiden, J. S. Willey, M. Carey, D. L. Branham, J. Y. Payne, S. D. Tucker, C. Bartholomeusz, R. G. Kilbourn, R. L. De Jager, N. Sneige, R. L. Katz, P. Anklesaria, N. K. Ibrahim, J. L. Murray, R. L. Theriault, V. Valero, D. M. Gershenson, M. W. Bevers, L. Huang, G. Lopez-Berestein & M. C. Hung: Cationic liposome-mediated E1A gene transfer to human breast and ovarian cancer cells and its biologic effects: A phase I clinical trial. *J Clin Oncol* 19, 3422-3433 (2001)
255. Pritts E. A., D. Zhao, S. H. Sohn, V. A. Chao, L. L. Waite & R. N. Taylor: Peroxisome proliferator-activated receptor-gamma ligand inhibition of RANTES production by human endometriotic stromal cells is mediated through an upstream promoter element. *Fertil Steril* 80, 415-420 (2003)
256. Dabrosin C., S. Gyorffy, P. Margetts, C. Ross & J. Gauldie: Therapeutic effect of angiostatin gene transfer in a murine model of endometriosis. *Am J Pathol* 161, 909-918 (2002)
257. Somigliana E., P. Vigano, P. Filardo, M. Candiani, M. Vignali & P. Panina-Bordignon: Use of knockout transgenic mice in the study of endometriosis: insights from mice lacking beta(2)-microglobulin and interleukin12p40. *Fertil Steril* 75, 203-206 (2001)
258. Smyth M. J. & M. B. Snook: Perforin-dependent cytolytic responses in beta 2-microglobulin-deficient mice. *Cell Immunol* 196, 51-59 (1999)
259. Somigliana E., P. Vigano, G. Rossi, S. Carinelli, M. Vignali & P. Panina-Bordignon: Endometrial ability to implant in ectopic sites can be prevented by interleukin-12 in a murine model of endometriosis. *Hum Reprod* 14, 2944-2950 (1999)
260. Greenberg L. H. & O. D. Slayden: Human endometriotic xenografts in immunodeficient RAG-2/gamma(c)KO mice. *Am J Obstet Gynecol* 190, 1788-1795 (2004)
261. Adamson D.: Endometriosis: Traditional perspectives, current evidence and future possibilities. *Int J Fertil Women M* 46, 151-168 (2001)
262. Jones G., S. Kennedy, A. Barnard, J. Wong, & C. Jenkinson: Development of an endometriosis quality-of-life instrument: The endometriosis health profile-30. *Obstet Gynecol* 98 258-264 (2001)

263. Leyendecker G.: Redefining endometriosis: endometriosis is an entity with extreme pleiomorphism. *Hum Reprod* 15, 4-7 (2000)
264. Murphy A. A.: Clinical aspects of endometriosis In Endometriosis: Emerging Research and Intervention Strategies. *Ann NY Acad Sci* 955, 1-10 (2002)
265. Hooghe T. M. D', C. S. Bambra, B. M. Raeymaekers, A. M. Riday, M. A. Suleman & P. R. Koninckx: The cycle pregnancy rate is normal in baboons wit stage I endometriosis but decreased with primates with stage II and stage III-IV disease. *Fertil Steril* 66, 809-813 (1996)
266. Bergqvist A. & T. D'Hooge: Mini symposium on pathogenesis of endometriosis and treatment of endometriosis associated infertility. Introduction: The endometriosis enigma. *Hum Reprod Update* 8, 79-83 (2002)
267. Gibbons W. E.: Management of endometriosis in fertility patients *Fertil Steril* 81, 1204-1205 (2004)
268. Leyendecker G., G. Kunz, L. Wildt, D. Beil & H. Deininger: Uterine hyperperistalsis and dysperistalsis as dysfunctions of the mechanism of rapid sperm transport in patients with endometriosis and infertility. *Hum Reprod* 11, 1542-1551 (1996)
269. Faber B. M., N. Chegini, M. C. Mahony & C. C. Coddington III.: Macrophage Secretory Products and Sperm Zona Pellucida Binding. *Obstet Gynecol* 98, 668-673 (2001)
270. I A Brosens: Ovarian endometriosis. In: Endometriosis. Current understanding and management. Ed: Shaw R W, *Blackwell Science*, 97-111 (1995)
271. Athey P. A. & D. D. Diment: The Spectrum of Sonographic Findings in Endometriomas. *J Ultras Med* 8, 487-491 (1989)
272. Fried A. M., R. A. Rhodes & I. R. Morehouse: Endometrioma - Analysis and Sonographic Classification of 51 Documented Cases. *South Med J* 86, 297-301 (1993)
273. Mais V., S. Guerriero, S. Ajossa, M. Angiolucci, A. M. Paoletti & G. B. Melis: The Efficiency of Transvaginal Ultrasonography in the Diagnosis of Endometrioma. *Fertil Steril* 60, 776-780 (1993)
274. Eskenazi B., M. Warner, L. Bonsignore, D. Olive, S. Samuels & P. Vercellini: Validation study of nonsurgical diagnosis of endometriosis. *Fertil Steril* 76, 929-935 (2001)
275. Dessole S., M. Farina, G. Rubattu, E. Cosmi, G. Ambrosini & G. B. Nardelli: Sonovaginography is a new technique for assessing rectovaginal endometriosis. *Fertil Steril* 79, 1023-1027 (2003)
276. Ghezzi F., L. Raio, A. Cromi, D. G. Duwe, P. Beretta, M. Buttarelli & M. D. Mueller: "Kissing ovaries": a sonographic sign of moderate to severe endometriosis. *Fertil Steril* 83, 143-147 (2005)
277. Togashi K., K. Nishimura, I. Kimura, Y. Tsuda, K. Yamashita, T. Shibata, Y. Nakano, J. Konishi, I. Konishi & T. Mori: Endometrial Cysts - Diagnosis with MR Imaging. *Radiology* 180, 73-78 (1991)
278. Canis M J, F H Loh, A. Wattiez, J L Pouly, E Glowaczover & J Raiga: Classification of endometriosis. In: Endometriosis. Current understanding and management. Ed: Shaw R W, *Blackwell Science*, 168-183 (1995)
279. American Fertility Society: Classification of Endometriosis. *Fertil Steril* 32, 633-633 (1979)
280. American Fertility Society: Revised American Fertility Society classification of endometriosis. *Fertil Steril* 43, 351 (1985)
281. Canis M., J. B. Dejolinieres, A. Wattiez, J. L. Pouly, G. Mage, H. Manhes & M. A. Bruhat: Classification of Endometriosis. *Bailliere Clin Ob Gy* 7, 759-774 (1993)
282. Candiani G. B., P. Vercellini & L. Fedele: Laparoscopic Ovarian Puncture for Correct Staging of Endometriosis. *Fertil Steril* 53, 994-997 (1990)
283. Reich H., F. McGlynn & J. Salvat: Laparoscopic Treatment of Cul-De-Sac Obliteration Secondary to Retrocervical Deep Fibrotic Endometriosis. *J Reprod Med* 36, 516-522 (1991)
284. Mage G., M. Canis, H. Manhes, J. L. Pouly, A. Wattiez & M. A. Bruhat: Laparoscopic Management of Adnexal Cystic Masses. *J Gyn Sur* 6, 71-79 (1990).
285. Martin D. C. & J. D. Berry: Histology of Chocolate Cysts. *J Gyn Sur* 6, 43-46 (1990)
286. Jansen R. P. S. & P. Russell: Nonpigmented Endometriosis - Clinical, Laparoscopic, and Pathological Definition. *Am J Obstet Gynecol* 155, 1154-1159 (1986)
287. Brosens I. A., J. Donnez & G. Benagiano: Improving the Classification of Endometriosis. *Hum Reprod* 8, 1792-1795 (1993)
288. Muzii L., R. Marana, S. Pedulla, G. F. Catalano & S. Mancuso: Correlation between endometriosis-associated dysmenorrhea and the presence of typical or atypical lesions. *Fertil Steril* 68, 19-22 (1997)
289. Schenken R. S. & D. S. Guzick: Revised endometriosis classification: 1996. *Fertil Steril* 67, 815-816 (1997)
290. Vernon M. W., J. S. Beard, K. Graves & E. A. Wilson: Classification of Endometriotic Implants by Morphological Appearance and Capacity to Synthesize Prostaglandin-F. *Fertil Steril* 46, 801-806 (1986)
291. Canis M., J. G. Donnez, D. S. Guzick, J. K. Halme, J. A. Rock, R. S. Schenken & M. W. Vernon: Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 67, 817-821 (1997)
292. Muzii L., R. Marana, L. Brunetti, G. Orlando, B. Michelotto & P. B. Panici: Atypical endometriosis revisited: clinical and biochemical evaluation of the different forms of superficial implants. *Fertil Steril* 74, 739-742 (2000)
293. Bedaiwy M. A. & T. Falcone: Laboratory testing for endometriosis. *Clin Chim Acta* 340, 41-56 (2004)
294. Bedaiwy M. A., T. Falcone, R. K. Sharma, J. M. Goldberg, M. Attaran, D. R. Nelson & A. Agarwal: Prediction of endometriosis with serum and peritoneal fluid markers: a prospective controlled trial. *Hum Reprod* 17, 426-431 (2002)
295. Cheng Y. M., S. T. Wang & C. Y. Chou: Serum CA-125 in Preoperative patients at high risk for endometriosis. *Obstet Gynecol* 99(3), 375-380 (2002)
296. Potlog-Nahari C., P. Stratton, C. Winkel, E. Widra, N. Sinaii, S. Connors & L. K. Nieman: Urine vascular endothelial growth factor-A is not a useful marker for endometriosis. *Fertil Steril* 81, 1507-1512 (2004)
297. Yantiss R. K., P. B. Clement & R. H. Young: Endometriosis of the intestinal tract. *Am J Surg Pathol* 25, 445-454 (2001)

298. Mathias J. R., R. Franklin, D. C. Quast, N. Fraga, C. A. Loftin, L. Yates & V. Harrison: Relation of endometriosis and neuromuscular disease of the gastrointestinal tract: new insights. *Fertil Steril* 70, 81-88 (1998)
299. Bailey M. T. & C. L. Coe: Endometriosis is associated with an altered profile of intestinal microflora in female rhesus monkeys. *Hum Reprod* 17, 1704-1708 (2002)
300. Winkel C. A.: Evaluation and management of women with endometriosis. *Obstet Gynecol* 102, 397-408 (2003)
301. Blanco R. G., V. S. Parithivel, A. K. Shah, M. A. Gumbs, M. Schein & P. H. Gerst: Abdominal wall endometriomas. *Am J Surg* 185, 596-598 (2003)
302. Nirula R. & G. C. Greaney: Incisional endometriosis: an underappreciated diagnosis in general surgery. *J Am Coll Surgeons* 190, 404-407 (2000)
303. Su H. Y., W. H. Chen & C. H. Chen: Extra-pelvic endometriosis presenting as a vulvar mass in a teenage girl. *Int J Gynecol Obstet* 87, 252-253 (2004)
304. Lacroix M. -Triki, L. Beyris, P. Martel & B. Marques: Low-grade endometrial stromal sarcoma arising from sciatic nerve endometriosis. *Obstet Gynecol* 104, 1147-1149 (2004)
305. Nahir B., T. Eldar-Geva, J. Alberton & U. Beller: Symptomatic diaphragmatic endometriosis ten years after total abdominal hysterectomy. *Obstet Gynecol* 104, 1149-1151 (2004)
306. Tuech J. J., M. C. Rousselet, J. Boyer, P. Descamps, J. P. Arnaud & J. Ronceray. Endometrial cyst of the liver: case report and review. *Fertil Steril* 79, 1234-1236 (2003)
307. Donnez J. & P. Jadoul: Ascites and pelvic masses: an unusual case of endometriosis. *Fertil Steril* 83, 195-197 (2005)
308. Seeliger T., J-U Voigt, H. Singer, W. G. Daniel & H. Rupprecht: Pulsating thoracic tumor caused by extragenital endometriosis in a patient with Noonan syndrome. *Ann Thorac Surg* 77, 2204-2206 (2004)
309. . Matalliotakis M., A. Goumenou, G. E. Koumantakis, M. A. Neonaki, E. E. Koumantakis & A. Arici: Pulmonary endometriosis in a patient with unicornuate uterus and noncommunicating rudimentary horn. *Fertil Steril* 78, 183-185 (2002)
310. Bergqvist A.: Extragenital endometriosis: a review. *Eur J Surg* 158, 7-12 (1992)
311. Moffatt S. D. & J. D. Mitchell: Massive pleural endometriosis. *Eur J Cardio-thorac* 22, 321-323 (2002)
312. Batt R. E. & M. F. M. Mitwally: Endometriosis from thelarche to midteens: Pathogenesis and prognosis, prevention and pedagogy. *J Pediatr Adol Gynecol* 16, 337-347 (2003)
313. Mostoufizadeh M. & R. E. Scully: Malignant tumors arising in endometriosis. *Clinical Obstet Gynecol* 23, 951-963 (1980)
314. Brinton L. A., G. Gridley, I. Persson, J. Baron & A. Bergqvist: Cancer risk after a hospital discharge diagnosis of endometriosis. *Am J Obstet Gynecol* 176, 572-579 (1997)
315. DiSilvestro P. A., M. A. Gold, & N. S. Gould: Malignancies arising in ensometriosis. *Primary Care Update in Obstet Gynecol* 6, 122-124 (1999)
316. Garcia-Velasco J. A., N. G. Mahutte, J. Corona, V. Zúñiga, J. Gilés, A. Arici & A. Pellicer: Removal of endometriomas before in vitro fertilization does not improve fertility outcomes: a matched, case-control study. *Fertil Steril* 81, 1194-1197 (2004)
317. Ho H. Y., R. K. Lee, Y. M. Hwu, M. H. Lin, J. T. Su & Y. C. Tsai: Poor response of ovaries with endometrioma previously treated with cystectomy to controlled ovarian hyperstimulation. *J Assist Reprod Gen* 19, 507-511 (2002)
318. Olivennes F., D. Feldberg, H. C. Liu, J. Cohen, F. Moy, Z. Tosenwaks: Endometriosis: a stage by stage analysis - the role of in vitro fertilization. *Fertil Steril* 64, 392-398 (1995)
319. Barnhart K., R. Dunsmoor-Su & C. Coutifaris: Effect of endometriosis on in vitro fertilization. *Fertil Steril* 77, 1148-1155 (2002)
320. Ghezzi F., P. Beretta, M. Franchi, M. Parissis & P. Bolis: Recurrence of ovarian endometriosis and anatomical location of the primary lesion. *Fertil Steril* 75, 136-140 (2001)
321. Sharpe-Timms K. L. & S. L. Young: Understanding endometriosis is the key to successful therapeutic management. *Fertil Steril* 81, 1201-1203 (2004)
322. Prentice A.: Regular review: Endometriosis. *Brit Med J* 323, 93-95 (2001)
323. Teirney R. & A. Prentice: The medical management of endometriosis. *Rev Gynaecol Pract* 2, 91-98 (2002)
324. Surrey E. S. & M. D. Hornstein: Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. *Obstet Gynecol* 99, 709-719 (2002)
325. Cobelli L., S. Razzi, S. De Simone, A. Sartini, A. Fava, S. Danero, W. Gioffre, M. Mazzini & F. Petraglia: The treatment with a COX-2 specific inhibitor is effective in the management of pain related to endometriosis. *Eur J Obstet Gyn R B* 116, 100-102 (2004)
346. Blumenfeld Z.: Hormonal suppressive therapy for endometriosis may not improve patient health *Fertil Steril* 81, 487-492 (2004)
327. Revelli A., M. Modotti, C. Ansaldi & M. Massobrio: Recurrent endometriosis: a review of biological and clinical aspects. *Obstet Gynecol Surv* 50, 747-754 (1995)
328. Winkel C A: Medical and surgical treatment of endometriosis. In: Clinical obstetrics and gynecology. Ed: Schenken R S, Lippincott, *Williams and Wilkins,* Hagerstown, Maryland 645-663 (1999)
329. Bulun S. E., K. Zeitoun, K. Takayama, L. Noble, D. Michael, E. Simpson, A. Johns, M. Putman & H. Sasano: Estrogen production in endometriosis and use of aromatase inhibitors to treat endometriosis. *Endoc-Relat Cancer* 6, 293-301 (1999)
330. Shippen E. R. & W. J. West: Successful treatment of severe endometriosis in two premenopausal women with an aromatase inhibitor. *Fertil Steril* 81, 1395-1398 (2004)
331. Bulun S. E., K.M. Zeitoun, K. Takayama & H. Sasano: Molecular basis for treating endometriosis with aromatase inhibitors. *Hum Reprod Update* 6, 413-418 (2000)
332. Feigenbaum S.: Treatment of Severe Endometriosis with a Selective Estrogen Receptor Modulator. *Fertil Steril* 81, S24 (2004)

333. Kettel L. M., A. A. Murphy, A. J. Morales & S.S. C. Yen: Preliminary report on the treatment of endometriosis with low-dose mifepristone (RU 486). *Am J Obstet Gynecol* 178, 1151-1156 (1998)
334. Ali A. F. M., B. Fateen, A. Ezzet, H. Badawy, A. Ramadan, A. El-Tobge: Laparoscopic intraperitoneal injection of human interferon-alpha2b in the treatment of pelvic endometriosis: a new modality. *Obstet Gynecol* 95, 478-479 (2000)
335. D'Antonio M., F. Martelli, S. Peano, R. Papoian & F. Borrelli: Ability of recombinant human TNF binding protein-1 (r-hTBP-1) to inhibit the development of experimentally-induced endometriosis in rats. *J Reprod Immunol*48, 81-98 (2000)
336. Barrier B. F., G. W. Bates, M. M. Leland, D. A. Leach, R. D. Robinson & A. M. Propst: Efficacy of anti-tumor necrosis factor therapy in the treatment of spontaneous endometriosis in baboons. *Fertil Steril* 81, 775-779 (2004)
337. Hull M. L, D. S. Charnock-Jones, C. L. Chan, K. L. Bruner-Tran, K. G. Osteen, B. D. Tom, T. P. Fan & S. K. Smith: Antiangiogenic agents are effective inhibitors of endometriosis. *J Clin Endocr Metab* 88, 2889-2899 (2003)
338. Balasch J., M. Creus, F. Fábregues, F. Carmona, S. Martínez-Román, D. Manau & J. A. Vanrell: Pentoxifylline versus placebo in the treatment of infertility associated with minimal or mild endometriosis: a pilot study randomized clinical trial. *Hum Reprod* 12, 2046-2050 (1997)
339. Matsuzaki S., M. Canis, C. Darcha, R. Dallel, K. Okamura & G. Mage: Cyclooxygenase-2 selective inhibitor prevents implantation of eutopic endometrium to ectopic sites in rats. *Fertil Steril* 82, 1609-1615 (2004)
340. Efstathiou J. A., D. A. Sampson, Z. Levine, R. M. Rohan, D. Zurakowski, J. Folkman, R. J. D'Amato & M. A. Rupnick: Nonsteroidal antiinflammatory drugs differentially suppress endometriosis in a murine model *Fertil Steril* 83, 171-181 (2005)
341. Pritts E. A., D. Zhao, E. Ricke, L. Waite & R. N. Taylor: PPAR-gamma decreases endometrial stromal cell transcription and translation of RANTES in vitro. *J Clin Endocr Metab* 87, 1841-1844 (2002)
342. Foyouzi N., M. Berkkanoglu, A. Arici, J. Kwintkiewicz, D. Izquierdo & A. J. Duleba: Effects of oxidants and antioxidants on proliferation of endometrial stromal cells *Fertil Steril* 82, 1019-1022 (2004)
343. Fugh-Berman A. & F. Kronenberg: Complementary and alternative medicine (CAM) in reproductive-age women: a review of randomized controlled trials. *Reprod Toxicol* 17, 137-152 (2003)
344. Mattison J. A., M. A. Lane, G. S. Roth & D. K. Ingram: Calorie restriction in rhesus monkeys. *Exp Gerontol* 38, 35–46 (2003)
345. Miller R.A., Y. Chang, A. T. Galecki, K. Al-Regaiey, J. J. Kopchick & A. Bartke: Gene expression patterns in calorically restricted mice: partial overlap with long-lived mutant mice. *Mol Endocrinol* 16, 2657–2666 (2002)
346. Stamps S. L., M.C. Fitzgerald & C. P. Whitman: Characterization of the role of the amino-terminal proline in the enzymatic activity catalyzed by macrophage migration inhibitory factor. *Biochemistry* 37, 10195 (1998)

Keywords: Endometrium, Endometriosis, Inflammation, Immune Surveillance, Estrogen, Transgenic, MIF, Macrophage Migration Inhibitory Factor, Review

Send correspondence to: János Garai MD, CSc**,** Department of Pathophysiology, Faculty of Medicine, University of Pécs, 12 Szigeti Str., H-7624 Pécs, Hungary, Tel: 36-72-536-246, Fax: 36-72-536-247, E-mail: janos.garai@aok.pte.hu

http://www.bioscience.org/current/vol11.htm