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Pathogenesis of endometriosis

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Origin of endometriotic implants

Endometriosis is a common gynecologic disorder characterized by the presence of endometrial tissue outside the uterine cavity. Various theories have been put forth to explain the mechanisms for the development of this disease. The authors summarize the existing theories on the origins of endometriotic tissue. They also review the factors that affect the survival and growth of these implants.

Retrograde menstruation (implantation) theory

The retrograde menstruation theory, also known as implantation or Sampson's theory, proposes that viable endometrial tissue is refluxed through the fallopian tubes during menstruation and implants on peritoneal surface or pelvic organs [1]. This theory is based on three assumptions. First, there is retrograde menstruation through the fallopian tubes. Second, refluxed endometrial cells are viable in the peritoneal cavity. Third, the refluxed endometrial cells are able to adhere to peritoneum with subsequent invasion, implantation, and proliferation.

The implantation theory was neglected for a long time because of the presumption that retrograde menstruation was rare and endometrial tissue was not present in menstrual effluent [2–5]. Later, several studies confirmed the high incidence of retrograde menstruation. In 1938, Watkins observed blood dripping from fallopian tubes in women who underwent laparotomy during menstruation [6]. After this observation, Goodall reported that retrograde menstruation occurred in 50% of women who underwent laparotomy during menstruation [7]. The presence of blood in the peritoneal fluid was also observed in women who underwent peritoneal dialysis [8]. Recent studies using laparoscopy have shown

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that retrograde menstruation is a common phenomenon that occurs in 76% to 90% of women with patent fallopian tubes [9, 10].

Later came the demonstration of the viability of sloughed endometrial cells and their capacity to implant at ectopic sites. In 1951, Keettel and Stein cultured endometrial cells obtained from menstrual discharge of seven women who wore diaphragms [11]. Endometrial cells obtained from peritoneal fluid after uterine lavage also were cultured successfully [12, 13]. Endometrial cells collected from the peritoneal cavity after uterine lavage stayed viable in culture for up to 2 months [14]. Finally, endometrial cells obtained from peritoneal fluid also were cultured successfully [15]. These findings proved the viability of menstruated endometrial cells.

Once in the peritoneal cavity, retrogradely menstruated endometrial cells should be able to implant to cause endometriosis. In 1950, Scott and TeLinde reported that shed endometrial cells were able to implant [16]. In monkeys they inverted the uterus and diverted menstrual flow into the peritoneal cavity and showed that 50% of the monkeys developed endometriosis [17]. Similarly, it was demonstrated that endometriosis developed in four baboons after injection of menstrual endometrium into their retroperitoneal space [18]. Ridley and Edwards collected menstrual effluent from women during the second day of menstruation and injected it into the subcutaneous abdominal fat of patients who subsequently underwent laparotomy for other gynecologic indications 90 to 180 days after implantation. The site of injection was excised for histologic study, and viable endometrial glands and stroma were present at the site of implantation in these women [19]. These findings demonstrated that viable endometrial cells in menstrual effluent are able to implant and develop into endometriotic lesions.

Substantial clinical data also exist to support the implantation model of peritoneal endometriosis. There is an increased risk of endometriosis in patients with müllerian anomalies and obstructed flow [20, 21]. There is an increased frequency of endometriotic implants in the dependent areas of the pelvis [22]. This anatomic distribution of endometriosis also supports the concept of retrograde menstruation.

Coelomic metaplasia theory

The theory of coelomic metaplasia initially was introduced at the turn of the twentieth century by Meyer. This theory proposed that endometriosis develops from metaplasia of cells that line the pelvic endometrium [23–25]. Meyer suggested that infectious, hormonal, or other inductive stimuli may result in metaplasia, which in turn could result in endometriosis [26, 27].

Embryologic studies demonstrated that pelvic peritoneum, germinal epithelium of ovary, and müllerian ducts are derived from epithelium of the coelomic wall [28]. This type of transformation may cause ovarian surface endometriosis. Clinical evidence that supports the theory of coelomic metaplasia lies in case reports of endometriosis that occurs in men [29, 30], in prepubertal [31] and adolescent girls [32], in women who never menstruated [33], and in unusual sites, including pleural cavity [34–36].

The occurrence of endometriosis in men is generally thought of as proof of the theory of coelomic metaplasia. The men with endometriosis were undergoing estrogen therapy, however, and the possibility of estrogen stimulation of müllerian rests cannot be excluded. Similarly, although pleural endometriosis could result from local metaplasia of pleural mesothelium, it also might result from transdiaphragmatic passage of endometrial fragments. If coelomic metaplasia is similar to metaplasia elsewhere, an increase in its frequency would be expected with aging. Proofs for the theory of coelomic metaplasia are far from being conclusive.

Induction theory

The induction theory is an extension of the coelomic metaplasia theory and proposes that endogenous biochemical or immunologic factors can induce undifferentiated cells to differentiate into endometrial tissue. This theory is supported by observations in female rabbits. Initial evidence to support this theory came from Levander and Normann, who implanted sections of uterine wall obtained from pregnant rabbits into subcutaneous tissue of 2-month-old female rabbits stimulated with gonadotropins immediately before transfer. In 7 days, they observed cells characteristic of endometrium and cyst formation in the surrounding tissue [37].

Similar experiments were later performed in rabbits by Merill using Millipore filters that contained myometrium, fat, or endometrium [38, 39]. Implants were later excised with the surrounding tissue and examined histologically. Cysts lined with cells that resembled endometrial epithelium and occasional gland-like structures developed in tissues adjacent to filters that contained endometrium but not in tissues adjacent to filters that contained myometrium or fat. Endometrial stroma, an important component of endometriotic implants, was not present in the induced tissue.

More recently, Matsuura et al demonstrated in vitro coelomic metaplasia in vitro in ovarian surface epithelium co-cultured with endometrial stromal cells and treated with 17β-estradiol [40]. The used estradiol concentration was nearly ten times higher than that in the peritoneal fluid. The high concentration could be found in the vicinity of the ovary and may explain ovarian endometriosis. These findings suggest that induction of coelomic metaplasia may be responsible for some cases of endometriosis.

Embryonic rest theory

In the 1890s, Von Recklinghausen [41] and Russell [42] introduced the embryonic rest theory. This theory proposed that cell rests of müllerian origin could be activated to differentiate into endometrium in the presence of a specific stimulus. Transformation of embryonic rests is a plausible explanation for rare cases of endometriosis reported in men.

Lymphatic and vascular metastasis theories

In the 1920s, Halban [5] and Sampson [43] suggested that endometriosis also could result from lymphatic and hematogenous dissemination of endometrial cells. Considerable evidence suggests that endometrial cells can metastasize via lymphatic and hematogenous routes. Metastasis of endometrial cells through the lymphatic system to distant areas, such as pleura, umbilicus, retroperitoneal space, lower extremity, vagina, and cervix, is anatomically possible because of communication of lymphatics among these structures [24, 44–46].

Sampson demonstrated the presence of endometrial tissue in uterine veins in women with adenomyosis [47]. Hobbs and Borthnick induced pulmonary endometriosis by injecting endometrial tissue intravenously in rabbits [34]. Lymph node endometriosis was found to be present in 6.7% of 178 autopsy cases and in 6.5% of 153 women who underwent lymphadenectomy [48].

Lymphatic or vascular metastasis could explain rare cases of endometriosis that have been reported in bone, muscle, brain, nerve, lung parenchyma, vertebral space, and extremities [49, 50].

How do the endometriotic implants survive and grow?

Retrograde menstruation is a universal phenomenon, and of all the theories, implantation of exfoliated endometrial cells is the most widely accepted theory for the development of endometriosis. On the other hand, why endometriosis develops in some women but not others is unknown. Five critical steps have been postulated in the development of endometriotic lesions. The two initial steps are attachment of endometrial cells to the peritoneal surface and invasion of these cells into the mesothelium. After these steps, recruitment of inflammatory cells subservient to the implant, angiogenesis around the nascent implant, and endometrial cellular proliferation occur. Although the endometriotic tissue with its local hormonal environment influences each of these steps, immune cells and inflammatory cytokines and environmental factors also play a role.

Attachment of endometrial cells to mesothelial cells

According to retrograde menstruation theory, fragments of endometrium are refluxed through the fallopian tubes into the peritoneal cavity. Then they attach to and grow on peritoneal surfaces. The mechanisms involved in cell attachment to the peritoneum have been studied in vitro, using extracts of intact amniotic and peritoneal membranes.

First, van der Linden et al [51] evaluated the ability of endometrial fragments from early proliferative phase to adhere to amniotic membrane in vitro. They reported that amniotic membrane was similar to peritoneum with respect to expression of cytokeratins in epithelial lining and of extracellular matrix components. The endometrial fragments did not adhere to the epithelial side of the amniotic membrane, whereas adhesion did occur on the nonepithelial side.

These authors suggested that intact epithelial lining may prevent initial adhesion of retrogradely shed endometrium fragments to peritoneum [51]. After this report, Groothuis et al [52] evaluated the ability of endometrial fragments isolated in the proliferative and secretory phase of the menstrual cycle to adhere to amnion. Endometrial fragments obtained in either phase of the cycle were able to adhere to the epithelial side of the amnion, but only at locations where the amniotic epithelium was damaged or absent [52]. They produced similar results using proliferative endometrium and cultured peritoneal explants. Endometrial cells adhered to peritoneal explants only at locations where the mesothelium was absent or damaged and the basement membrane was exposed [53]. The same authors also evaluated the adherence of shed menstrual tissue to amnion and peritoneum in vitro. Results were similar [54]. They concluded that intact mesothelium constitutes a defense barrier that prevents adhesion of endometrial fragments. They hypothesized that trauma to the mesothelial lining is a prerequisite for endometrial cell adhesion [53].

Using similar techniques, another group of investigators reported contradicting findings. Witz et al [55] cultured whole fragments of mechanically dispersed endometrium obtained during the proliferative and secretory phase with whole explants of peritoneum for 24 to 48 hours. They found that endometrial fragments attached to the mesothelial side and the nonepithelial side of the mesothelium, and the menstrual cycle phase during which endometrial tissue was collected did not make a difference. Approximately 90% of attached endometrial fragments did not have an intact underlying mesothelium, although most had an intact mesothelium running up to the point of attachment. Contrary to the findings of Groothuis et al, however, they identified an intact mesothelium at the site of attachment in 10% of the endometrial implants [55]. When they repeated the experiment using a 1-hour incubation period, they demonstrated the rapid adhesion of endometrium to the peritoneum and confirmed their finding that endometrial cells can attach to intact mesothelium [56]. In most sites of attachment, endometrium adhered to mesothelium via endometrial stroma, although many sites of endometrial epithelium-mesothelium attachment also were detected [56].

These findings led to the investigation of molecular mediators of endometrial cell attachment to mesothelium. Several cell adhesion molecules, including integrins, intracellular adhesion molecule-1, vascular cell adhesion molecule-1, have been implicated. The $\alpha 2\beta 1$ and $\alpha 3\beta 1$ integrins are expressed at the mesothelial cell surface and could mediate endometrial-mesothelial adhesion [57]. Integrin-blocking antibodies do not interfere with endometrial stromal or epithelial cell adherence to mesothelium, however [58].

Recently, hyaluronic acid and CD44 have been implicated in the interaction of peritoneal mesothelium with endometrial cells. Peritoneal mesothelium produces hyaluronic acid. Hyaluronic acid is expressed along the cell membrane of peritoneal mesothelial cells, contributes to the pericellular matrix, and is a major component of the extracellular matrix ground substance. CD44 is the principal receptor for hyaluronic acid. It is involved in binding of gastric cancer and

ovarian cancer cells to mesothelium. Endometrial stromal end epithelial cells express CD44. Hyaluronidase pretreatment of mesothelial cells decreases the binding of endometrial stromal and epithelial cells to mesothelium by 40% [59]. These findings suggest that the hyaluronic acid/CD44 binding may be involved in the initial adherence of endometrium to peritoneal mesothelium.

Invasion of endometrial cells into the mesothelium: matrix metalloproteinases and endometriosis

Invasion of endometrial cells into the mesothelium follows their initial adhesion to the peritoneal wall. Matrix metalloproteinase (MMP) enzymes have been implicated in this invasion. MMPs and their inhibitors, the tissue inhibitors of matrix metalloproteinases (TIMPs), play a significant role in normal endometrial remodeling that accompanies menses [60–62]. The MMP family contains several structurally related Zn^{2+}-dependent endopeptidases, which collectively are responsible for the degradation of various extracellular matrix components, including several types of collagen, gelatins, proteoglycans, laminin, fibronectin, and elastin [60–64]. The TIMPs are the natural inhibitors of MMPs [60, 64]. In eutopic endometrium, the expression of MMPs and TIMPs is tightly regulated by steroid hormones and cytokines during each phase of the menstrual cycle [61, 63]. Coincident with the tissue breakdown and remodeling that occurs at menses and during the early proliferative phase of the cycle, a significant upregulation of MMP expression occurs [61, 63]. Then, MMPs are suppressed during progesterone-driven endometrial differentiation in the luteal phase.

A significant amount of data indicates that MMPs are involved in the pathogenesis of endometriosis. In endometriotic lesions, abnormal expression of specific members of the MMP and TIMP families has been identified [65–69]. For example, MMP-1, MMP-3, and MMP-7 are expressed constitutively in endometriotic lesions, whereas they are highly regulated in eutopic endometrium during the menstrual cycle [63, 65, 69]. Although endometriotic cells synthesize and secrete TIMP-1 protein in vitro [70], in vivo TIMP-1 concentrations are lower in the peritoneal fluid of women with endometriosis [71]. The role of MMPs in the establishment of ectopic lesions by human endometrium was evaluated in an animal model of endometriosis using athymic nude mice. In this model, suppression of MMP activity by pretreatment of human endometrial tissues with progesterone or intraperitoneal TIMP injections suppressed the development of endometriotic implants [72]. These findings suggest that increased MMP activity in and around the endometriotic implants may facilitate invasion and growth of lesions.

Progesterone downregulates endometrial MMP expression [68]. Paracrine factors that mediate progestin action on endometrial MMP expression have been investigated in an attempt to identify targets for treatments that would downregulate endometriotic MMP expression. One such factor is transforming growth factor-beta (TGF-β). TGF-β is produced by endometrial stroma in response to progesterone and can suppress expression of an epithelial MMP-7 independent of

progesterone. An antibody directed against the mammalian isoforms of TGF-β abolishes progesterone suppression of MMP-7 in stromal-epithelial co-cultures, which implicates TGF-β as the principal mediator of MMP-7 suppression in the human endometrium [73]. Similarly, in the nude mice model of endometriosis, blocking the action of TGF-β opposes progesterone-mediated suppression of MMP-3 and MMP-7 and blocks the ability of this steroid to prevent experimental endometriosis [74]. On the other hand, TGF-β alone does not lead to sustained suppression of MMPs, as observed after progesterone treatment, possibly because of resumption of MMP production in the absence of progesterone [74]. This finding is consistent with the fact that peritoneal fluid levels of TGF-β are elevated in endometriosis [75].

Another cytokine that regulates MMP expression is interleukin-1α (IL-1α). IL-1α is a potent stimulator of MMP-3 in proliferative phase endometrium in organ culture; however, progesterone exposure in vivo reduces the IL-1α stimulation of MMP-3 in secretory phase tissue [76]. The loss of sensitivity to IL-1α is duplicated in cultured endometrial stromal cells treated with progesterone in vitro. IL-1α stimulation of MMP-3 is restored in a dose-dependent manner with progesterone withdrawal [77]. Conversely, cultured endometriotic cells obtained from a rat endometriosis model express higher levels of MMP-3 mRNA than eutopic rat endometrial stromal cells when treated with progesterone. The elevated and persistent MMP-3 expression by endometriotic stromal cells cultured in the presence of progesterone correlates with elevated levels of IL-1α mRNA detected in the endometriotic stromal cells and IL-1α protein in their culture medium [69]. The production of IL-1α by the endometriotic lesions seems to be able to overcome the progesterone-induced suppression of MMP-3 in these cells, a phenomenon that is not observed in the cultured uterine stromal cells. It is plausible that an IL-1α– related mechanism promotes MMP-3 production by endometriotic cells even in the presence of progesterone.

Aberrant MMP and TIMP expression in the endometriotic environment caused by abnormal levels of paracrine regulators may induce a more aggressive behavior and facilitate invasion of endometriotic implants. The exact mechanisms that lead to the aberrant expression of MMPs and TIMPs have yet to be defined.

Survival and proliferation of ectopic endometrial cells

Immune factors

Impaired immune response that results in inadequate removal of refluxed menstrual debris has been proposed as a possible causative factor in the development of endometriosis. Endometriosis is associated with changes in cell-mediated and humoral component of innate and acquired immunity. Although the peritoneal fluid of women with endometriosis contains increased numbers of immune cells, they seem to facilitate rather than inhibit the development of endometriosis. Leukocytes that would be expected to clear endometrial cells from the peritoneal cavity seem to enhance their proliferation by secreting growth factors and cytokines. Although it is unclear whether these

immunologic alterations induce endometriosis or are a consequence of its presence, they seem to play an important role in allowing endometriosis implants to persist and progress.

Pelvic inflammation in women with endometriosis also seems to contribute to the development of their most common complaints: pain and infertility. Secretory products of immune cells in the peritoneal fluid, such as cytokines and prostaglandins, contribute to dysmenorrhea that may progress to dyspareunia and chronic pelvic pain. Pelvic inflammation also may lead to adhesion formation and scarring and disrupt fallopian tube patency. Similarly, the inflammatory environment may impair folliculogenesis, fertilization, and embryo implantation and result in infertility.

In this section the authors summarize the alterations in the immune parameters of women with endometriosis and discuss how they may play a role in the pathogenesis of endometriosis.

Macrophages. Macrophages are the most abundant nucleated cells found in peritoneal fluid [78]. Their number and activity is increased in the peritoneal fluid of women with endometriosis [79–83]. Although the increased number and activity of peritoneal fluid macrophages in women with endometriosis would be expected to facilitate the clearance of ectopic endometrial cells and slow down or inhibit the development of endometriosis, it seems to promote growth of ectopic endometrium. This effect may be caused by an increase in the release of growth-promoting cytokines and growth factors [84] combined with an impaired scavenger function. Abnormal levels of cytokines and hormones present in the peritoneal fluid [85] and the lack of interaction between macrophages and extracellular matrix components that results in a decreased expression of scavenger receptors [86] are believed to cause the decrease in scavenger function in women with endometriosis.

Secretory products of peritoneal macrophages and circulating monocytes of women with endometriosis seem to mediate growth and maintenance of ectopic endometrium [84]. Peritoneal fluid from women with endometriosis stimulates proliferation of cultured endometrial stromal cells [87]. Peripheral blood monocytes obtained from women with endometriosis enhance proliferation of co-cultured autologous endometrial cells, whereas monocytes from fertile women show the opposite effect and suppress endometrial cell proliferation [88]. In addition to their growth-stimulatory effect on endometriotic implants, macrophage products are also implicated in the pathophysiology of endometriosis-associated pain and infertility.

Natural killer cells. Natural killer (NK) cells are an important component of the innate immune system. Researchers have suggested that a decrease in NK cell activity may lead to impaired clearance of regurgitated endometrial cells from the peritoneal cavity and facilitate development of endometriosis. Initial studies that investigated NK cell numbers in peritoneal fluid of women with endometriosis reported conflicting results. Whereas some studies reported a decrease in peritoneal

NK cells [89], others reported no change [90] or an increase [83]. On the other hand, studies that investigated NK cell activity in women with endometriosis consistently showed a decrease in cytotoxic activity. NK cells from the peritoneal fluid and the peripheral blood of women with endometriosis were found to have decreased cytotoxic activity against autologous and heterologous endometrium [90, 91]. The decrease in NK cell cytotoxicity in the peritoneal fluid was more pronounced in the moderate and severe stages of endometriosis [92]. These findings suggest that the alteration in NK cell activity in women with endometriosis is caused by qualitative rather than quantitative changes.

Multiple mechanisms seem to be involved in the suppression of NK cell activity in women with endometriosis. Sera [93] and peritoneal fluid [94, 95] from women with endometriosis suppress NK cell cytotoxicity [93, 94], which suggests that soluble factors are also involved. Recently, Wu et al found that peritoneal NK cells of women with endometriosis have higher killer-inhibitory receptors expression [96]. When stimulated, killer-inhibitory receptors send inhibitory signals that override the kill signal and suppress cytotoxic activity.

Lymphocytes. More than 20 years ago, Dmowski et al showed that T-cell–mediated immunity to autologous endometrium is suppressed in Rhesus monkeys with spontaneous endometriosis [97]. Similarly, cytotoxic activity of peripheral blood lymphocytes against autologous endometrial cells is decreased in women with endometriosis [98]. These observations led to the speculation that endometriosis develops as a result of impaired cell-mediated immune response that is believed to be critical in clearing ectopic endometrial cells from the peritoneal cavity [99].

The functional alteration observed in T cells of women with endometriosis is not accompanied by a quantitative downregulation. Total lymphocyte numbers and the helper/suppressor ratio in the peripheral blood are not affected markedly in women with endometriosis [83, 100]. Similarly, there is no change in total lymphocyte content or helper/suppressor ratios in the eutopic endometrium of women with endometriosis compared to eutopic endometrium from normal controls [101]. On the other hand, T lymphocyte concentration is increased in the peritoneal fluid [83, 99] and endometriotic implants [102] of women with endometriosis. An increase in helper and suppressor subtypes contributes to this observed increase, although their relative ratio seems to be unchanged [83, 99, 102].

Autoimmunity. Endometriosis is associated with polyclonal B-cell activation and an increased incidence of autoantibodies [103, 104]. Although it seems that autoantibodies may be associated in certain cases of endometriosis-associated infertility, the relative importance of autoimmunity in the pathogenesis and pathophysiology of this disease is still controversial.

Cytokines and growth factors. Cytokines are a large family of low-molecular-weight soluble proteins involved in regulating cellular activity. They act as paracrine and autocrine messengers within the immune system and between the

immune system and other systems of the body. Their action is mediated by specific cytokine receptors. Cytokines and growth factors play an important role in regulating chemotaxis, mitosis, angiogenesis, and differentiation. Although impaired cellular immune response has been implicated as a permissive factor in survival of endometrial cells in the peritoneal cavity, cytokines and growth factors seem to promote implantation and growth of ectopic endometrium by inducing proliferation and angiogenesis.

Several cytokines and growth factors have elevated levels in the peritoneal fluid of women with endometriosis, including IL-1 [105–107], IL-8 [108, 109], monocyte chemotactic protein-1 [110, 111], Regulated upon activation, Normal T cell Expressed and Secreted (RANTES) [112], tumor necrosis factor-α [113], and vascular endothelial growth factor [114]. The growth factors and cytokines found in the peritoneal fluid of women with endometriosis have a multitude of effects that promote survival and growth of endometriotic implants. They induce chemotaxis of mononuclear cells into the peritoneal cavity, which causes a further increase in secretion of growth factors and cytokines. They stimulate adhesion of endometrial stromal cells to fibronectin, which facilitates the initial attachment of endometrial cells to the peritoneal surface [115]. They upregulate metalloproteinase activity that degrades extracellular matrix and facilitate invasion [116], they induce endometrial stromal cell proliferation [117], and they are involved in angiogenesis. They also seem to have adverse effects on fertilization [118] and early embryonal development [106]. In summary, many cytokines and growth factors are elevated in the peritoneal environment of women with endometriosis, and they seem to play an important role in the pathogenesis and pathophysiology of endometriosis.

Endocrine factors

Endometriosis is an estrogen-dependent disorder. Aberrant estrogen synthesis and metabolism have been implicated in the pathogenesis of endometriosis. Aromatase catalyzes the synthesis of estrone and estradiol from androstenedione and testosterone, respectively. It is expressed by many human cell types, including ovarian granulosa cells, placental syncytiotrophoblasts, adipose cells, and skin fibroblasts.

Estrogen action is classically believed to occur via an endocrine mechanism. In other words, circulating estradiol is believed to exert an estrogenic effect after delivery to target tissues via the bloodstream. Studies on aromatase expression in breast cancer demonstrated that paracrine mechanisms play an important role in estrogen action in this tissue [119]. Estrogen also displays an ''intracrine'' effect. Estrogen produced by aromatase activity in the cytoplasm of leiomyoma smooth muscle cells or endometriotic stromal cells can exert its effects by readily binding to its nuclear receptor within the same cell. Disease-free endometrium and myometrium, on the other hand, lack aromatase expression [120, 121].

In the ovary, the most important site of estrogen biosynthesis in a woman of reproductive age, binding of follicle stimulating hormone to its receptor in the granulosa cell membrane induces a rise in intracellular cAMP levels. This in turn

enhances the binding of transcription factors to the promoter region of the aromatase gene [122, 123]. As a result, there is an increase in aromatase expression and, consequently, in estrogen secretion from the preovulatory follicle [122, 124]. In postmenopausal women, estrogen production takes place in extraglandular tissues, such as the adipose tissue and the skin [125, 126]. This action is controlled primarily by cytokines and glucocorticoids [124].

Endometriomas and extraovarian endometriotic implants express high levels of aromatase. Cultured stromal cells derived from endometriotic implants and incubated with a cAMP analog display extraordinarily high levels of aromatase [121]. Growth factors, cytokines, and other factors have been investigated as possible inducers of aromatase activity via cAMP-dependent pathway in endometriosis. Prostaglandin E_2 was identified as the most potent inducer of aromatase activity in the endometriotic stromal cells [121]. Estrogen was found to upregulate prostaglandin E_2 formation by stimulating cyclo-oxygenase type 2 enzyme in endometrial stromal cells in culture [127]. There is a positive feedback loop for continuous local estrogen and prostaglandin E_2 production, possibly favoring the proliferative and inflammatory characteristic of endometriosis. Low levels of aromatase mRNA also are detected in the eutopic endometrial samples of women with moderate to severe endometriosis, whereas it is absent in eutopic endometrium of disease-free women [128]. This finding suggests that a genetic defect in aromatase expression may exist in women with endometriosis. When endometrial tissue with low levels of aberrant aromatase expression reaches the pelvic peritoneum by retrograde menstruation and induces an inflammatory reaction, this would exponentially increase local aromatase activity and local estrogen formation [121].

Although prostaglandin E_2 was identified as the most potent known inducer of aromatase activity by increasing cAMP levels in endometriotic stromal cells, neither cAMP analogs nor prostaglandin E_2 stimulates aromatase activity in cultured eutopic endometrial stromal cells. The mechanisms that mediate the differential regulation of aromatase activity in endometriotic cells and normal eutopic endometrium have been investigated. The cAMP-inducible promoter II seems to be responsible for in vivo aromatase expression in endometriotic tissue [129]. Two transcription factors, the stimulatory transcription factor (SF-1) and an inhibitory factor, chicken ovalbumin upstream promoter transcription factor (COUP-TF), compete for the same binding site in aromatase promoter II. COUP-TF is ubiquitously expressed in eutopic endometrium and endometriosis, whereas SF-1 is expressed specifically in endometriosis but not in eutopic endometrium and binds to aromatase promoter more avidly than COUP-TF [129]. SF-1 and other transcription factors (eg, Cyclic-AMP Response Element Binding Protein (CREB)) activate aromatase gene transcription in endometriosis, whereas COUP-TF, which occupies the same DNA site in eutopic endometrium, inhibits this process [129]. In summary, one of the molecular alterations that leads to local aromatase expression in endometrial cells but not in normal endometrium is the aberrant production of SF-1 in endometriotic cells, which overcomes the protective inhibition maintained normally by COUP-TF in the eutopic endometrium.

The primary substrate for aromatase activity in endometriosis is androstenedione of adrenal and ovarian origins in premenopausal women and adrenal androstenedione in postmenopausal women. The major product of aromatase activity in endometriosis, namely estrone, is only weakly estrogenic and must be converted to estradiol to exert a full estrogenic effect. The enzyme 17β-hydroxysteroid dehydrogenase (17β-HSD) type 1, which catalyzes the conversion of estrone to estradiol, is expressed in endometriosis [129, 130]. In contrast, 17β-HSD type 2 inactivates estradiol by catalyzing its conversion to estrone in eutopic endometrial glandular cells during the luteal phase [130]. Progesterone induces the activity of this enzyme in endometrial glandular cells in culture, which makes inactivation of estradiol to estrone one of the antiestrogenic properties of progesterone [129]. The expression of 17β-HSD type 2 is absent from endometriotic glandular cells [129]. Consequently, this protective mechanism that lowers estradiol levels is lost in endometriotic tissue [129].

In summary, aberrant expression of aromatase, the presence of 17β-HSD type 1, and the absence of 17β-HSD type 2 from endometriosis collectively give rise to elevated local levels of estradiol compared with eutopic endometrium and may promote survival and growth of endometriotic implants.

Genetic factors

The presence of familial tendencies in endometriosis has long been suspected. In 1980, Simpson et al [131] evaluated 123 women with histologically confirmed endometriosis. 8.1% of their mothers and 5.9% of their female siblings older than age 18 were affected. Their husbands' families were used as controls. Only 1% of the patients' husbands' first-degree relatives had endometriosis. Subsequent studies have been consistent with these initial observations. In a similarly designed study conducted in Norway, 3.9% of mothers and 4.8% of sisters of 522 women with endometriosis had endometriosis [132]. Only 0.6% of sisters of women who did not have endometriosis were affected. Lamb et al [133] used questionnaires received from 491 members of the Endometriosis Association, based in the United States. In sisters and mothers of women with endometriosis, they detected a 6.2% and 3.8% incidence of endometriosis, respectively. In Brazil, dos Reis et al reported that 8.6% of first-degree relatives of 81 women with endometriosis were affected, compared to no relatives of controls [134].

Consistent with these studies, higher concordance for monozygotic than dizygotic twins is observed [135, 136]. Monozygotic concordance does not reach 100% expected for a mendelian trait, however. Investigation of familial cases for linkage studies revealed familial aggregates [136].

Endometriosis seems to be heritable, but the precise mechanism is unclear. The increased risk of 5% to 8% for first-degree relatives suggests polygenic/multifactorial inheritance if one assumes that all endometriosis is a single disorder. The other possible explanation is that endometriosis is not a single disorder but several different disorders of distinct etiologies. That is, genetic heterogeneity may exist. One or more forms of endometriosis might be mendelian, despite the larger proportion being nongenetic or polygenic.

Environmental factors

Exposure to environmental toxins recently has been added to the list of factors that contribute to the pathogenesis of endometriosis. Among environmental toxins implicated in the development of endometriosis, 2,3,7,8-tetrachlorodibenzo-ρ-dioxin (TCDD) is the best studied [137, 138] and is reviewed in this section. TCDD belongs to the family of polychlorinated diaromatic hydrocarbons and is usually used as a reference compound for the effects of all other polychlorinated diaromatic hydrocarbons. Because of their lipophilic property, these chemicals degrade slowly and tend to accumulate in the food chain. It is believed that the exposure of TCDD and other polychlorinated diaromatic hydrocarbons is mostly through ingestion of contaminated foods, although various industrial accidents also may contribute [139–141]. TCDD and other dioxin-like compounds can exert their effects via aryl hydrocarbon receptor, an orphan nuclear receptor whose natural ligand is not known. Aryl hydrocarbon receptor can bind other compounds, including glucosinolates and constituents of cigarette smoke. This receptor is present in many tissues, including eutopic and ectopic endometrium [142, 143].

2,3,7,8-tetrachlorodibenzo-ρ-dioxin can inhibit ovarian progesterone synthesis [137]. It also inhibits progesterone-induced expression of TGF-β2 [144], a growth factor that suppresses endometrial MMPs. Although both of these effects may promote the development of endometriosis, TCDD also has an antiestrogenic action [145–147]. The exact mechanism by which TCDD, an antiestrogen, promotes the development of endometriosis remains to be elucidated.

The effect of TCDD on the development of endometriosis has been studied in animal models. Rier et al showed that endometriosis spontaneously developed in monkeys exposed to dietary TCDD for 5 years [148]. They performed laparoscopy and found that 71% and 86% of monkeys given 5- and 25-ppt doses of TCDD, respectively, developed moderate to severe endometriosis, although only 33% of control animals had minimal endometriosis. Yang et al studied the effects of TCDD on monkeys with surgically induced endometriosis [148]. They observed a bimodal effect of TCDD on implant sizes. The size of the implants was found to be significantly increased in 25-ppt dose group and decreased in the 1-ppt dose group compared to controls. The implants also were observed to regress in all groups over time.

Rodent studies for the effect of TCDD on endometriosis also have been conducted. In most of these studies TCDD was shown to enhance the growth of endometrial implants in mice [149–151]. In contrast to these findings, Yang and Foster demonstrated that TCDD resulted in regression of previously established implants in mice [152]. The dose of dioxin and the length of exposure may determine its effects on endometrial implants.

Few case-control studies investigated the association of environmental toxins with endometriosis in humans. Gerhand and Runnebaum showed a positive association between endometriosis and exposure to polychlorinated biphenyls ([153]. Similarly, Koninckx et al noted that in Belgium the level of dioxins in breast milk is among the highest in the world and that the incidence of endometriosis is also higher than other countries [154]. Mayani et al reported

that women with endometriosis compared to women with tubal infertility are more likely to have a history of TCDD exposure [155]. On the other hand, other studies found no association between endometriosis and dioxins or polychlorinated biphenyls [156]. Because of inadequacies in the design and sample size, it is not possible to establish a cause-and-effect relationship between these compounds and the development of endometriosis based on these trials.

Although their mechanism of action remains unclear, dioxin and related compounds seem to have potential adverse effects on the development of endometriosis. For a better understanding of the basic mechanisms underlying this disease, further studies are needed.

Summary

Endometriosis is a common gynecologic disorder characterized by the presence of endometrial tissue outside the uterine cavity. Various theories have been put forth to explain the mechanisms for the development of this disease. Although no single theory can explain all cases of endometriosis, the retrograde menstruation theory has gained the widest acceptance. This theory proposes that viable endometrial tissue is refluxed through the fallopian tubes during menstruation and implants on peritoneal surface or pelvic organs. Retrograde menstruation occurs in 76% to 90% of women. The much lower prevalence of endometriosis suggests that additional factors determine susceptibility to endometriosis. Once in the peritoneal cavity, the survival and implantation of endometrial cells seem to be mediated by abnormal MMP and TIMP expression, altered immune milieu, aberrant local aromatase activity, and genetic and environmental factors.

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