

Chapter 2

Predisposing and Protective Factors of Endometriosis

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2.1 Predisposing Factors

2.1.1 *Early Menarche, Late Menopause, Low Parity*

A number of risk factors are associated with endometriosis, including early menarche (age ≤ 11 years), short menstrual cycles (< 26 – 27 days), menorrhagia (bleeding > 7 days or 80 mL), [1], nulliparity, low birth weight [2] and obesity [1, 3, 4] have been related to higher risks of endometriosis. Most risk factors are associated either with elevated estrogen levels or prolonged menstruation. This strengthens the estrogen dependence of endometriosis and the association between menstruation and endometriosis.

2.1.2 *Hormonal Factors: High Estrogen and Low Progesterone*

Patients with endometriosis often have high levels of estrogen and low levels of progesterone. The presence of the steroid hormone imbalance enhances the disease severity. Imbalance caused by estrogen excess and a lack of progesterone has been hypothesized to exacerbate endometriosis. Estrogens activate estrogen receptors inside endometriotic cells and regulate their gene expression. The four different types of natural estrogen are estradiol (E2), estrone (E1), estriol, and estetrol. Estradiol (E2) is secreted by the ovary and is the predominant type of circulating estrogen during the reproductive years. Estradiol levels increase around ovulation. Estradiol directly reaches the endometriotic tissue implants in the pelvic region and acts on the estrogen receptors present within them, which thereby increases endometriotic tissue survival. Endometriotic tissue implants contain the enzyme

aromatase, which converts androgens to estrogens, thereby increasing local estrogen concentration and enhancing the growth of endometriotic lesions.

Endometriotic tissue implants also contain receptors for progestins and androgens [5]. The hormone progesterone (P4) is responsible for the development of secretory endometrium, embryo implantation and regulation of various genes. It also suppresses estrogen receptor α [6]. Progesterone is known for its growth limiting action. It can inhibit and even reverse estrogen-induced endometrial growth in human endometrium. Progesterone acts through its receptors PR-A and PR-B. A truncated variant of PR-A isoform also acts as a repressor for PR-B function [7]. Studies have shown down-regulation of PR-B in ectopic endometrial lesions in women with endometriosis compared to their eutopic endometrium [7, 8]. Eutopic endometrium is resistant to progesterone. The enzyme 17 β -hydroxysteroid dehydrogenase type 2 (17 β HSD2) inactivates the conversion of estradiol to estrone in response to progesterone in the eutopic endometrium. However, estradiol levels are enhanced in endometriotic tissue due to the lack of progesterone [9]. The progesterone resistance seen in women with endometriosis can be attributed to the absence of the stimulatory PR-B isoform and the presence of the inhibitory PR-A isoform in the endometriotic tissue [7].

Prostaglandins are locally produced, hormone-like compounds that contribute to the symptoms of endometriosis. In particular, higher levels of prostaglandins E2 and F2 α are present in the endometriotic tissues of women with endometriosis. High levels of these prostaglandins induce pain. Prostaglandin F2 α has vasoconstrictive properties, and increased levels cause excessive uterine contractions leading to the dysmenorrhea seen in women with endometriosis [10].

The enzyme aromatase also plays a role in the pathophysiology of endometriosis. It converts androgens in the peripheral tissue to estrogen. Aromatase is highly expressed in the eutopic endometrium of women with endometriosis and positively correlates with the severity of dysmenorrhea experienced in women with endometriosis [11]. Elevated levels of aromatase mRNA levels were observed in women with ovarian endometrioma [12].

2.1.3 Exposure to Environmental Agents Such as Dioxins

Evidence suggests that women who were exposed in utero to synthetic estrogens such as diethylstilboesterol (DES) and potent environmental toxins had a higher incidence of endometriosis [4].

Growing evidence suggests a possible link between endometriosis and exposure to environmental pollutants. Some environmental pollutants contribute to the pathogenesis of endometriosis and include dioxins, polyhalogenated aromatic hydrocarbons, organochlorine pesticides, phthalates, and bisphenols. Dioxins mainly exert their action through the binding and activation of aryl hydrocarbon receptor (AhR). AhR exists in tissues throughout the body including eutopic and ectopic endometrium. The mechanism by which they cause endometriosis includes a combination

of growth factor activation, gene regulation, immunosuppression, and altered estrogen signaling pathways.

2.1.4 Immunological Dysregulation

CD4 T cells are divided into type 1 (Th1) and type 2 (Th2) helper T cells. Th1 cells secrete interleukin IL-2, IL-12 and interferon γ while type 2 (Th2) cells secrete IL-4, 5, 6, 10, and 13 [13]. In women with endometriosis, Th2 helper cells in the peritoneal fluid suppress cell-mediated immunity by increasing IL-4 and IL10 secretion in the peritoneal fluid [14]. As a result, there is decreased T cell cytotoxicity, allowing endometrial cells to implant in the peritoneum.

Upon extra-uterine implantation, ectopic endometrial tissues release cytokines, activate macrophages, and suppress phagocytosis within the peritoneum [15]. Endometriosis induces a chronic inflammatory state. Elevated cyclooxygenase-2 (COX-2) levels stimulate local activity of aromatase [2]. The peritoneal fluid of endometriosis patients is known to contain elevated levels of cytokines, growth factors, T cells, B cells, and macrophages [16, 17] along with reduced natural killer (NK) cell activity [15]. Ectopic implants also establish a constant blood supply through angiogenic growth factors such as vascular endothelial growth factor (VEGF), transforming growth factor- β (TGF- β) and insulin like growth factor (IGF) [18, 19]. Because endometriosis is a hormonally dependent disease, sites of ectopic implantation are sensitive to estrogen, which fuels the growth of endometrial cells [20].

As mentioned earlier, normal physiologic mechanisms utilize the recruitment of immune cells such as macrophages, NK cells, and lymphocytes to expel excess menstrual tissue and endometrial cells outside the uterine cavity [21]. However, since retrograde menstruation is a common occurrence in most women, those with endometriosis may have a dysregulated immune response [2]. An aberrant immune surveillance mechanism is a plausible cause for the survival of ectopic tissue [22]. Abnormal cell-mediated immunity (CMI, particularly defective functioning of NK cells), may allow for the persistence and implantation of ectopic endometrial tissue, as was first demonstrated in 1991 by Oosterlynck et al. [23] Further, endometriosis may develop from an impaired ability of NK cells to scavenge autologous endometrial cells [17].

ICAM-1, an immunoglobulin involved in cell adhesion, has been detected in ectopic endometrial tissue. Because it is normally present in the endometrium, expression of ICAM-1 in ectopic endometrium and implants may contribute to defective NK cytotoxicity and allow ectopic cells to evade detection by the immune system [24]. The cytotoxicity of NK cells may also be inhibited by endometrial secretion of the s-ICAM-1 (soluble) receptor in peritoneal fluid and its subsequent binding to lymphocyte presenting LFA-1 [25, 26]. Binding of s-ICAM-1 to leukocyte-related ligands causes leukocyte-cell communication to falter, thus weakening natural immune responses [27]. Within the peritoneal fluid of women with endometriosis, Th2 helper cells have been shown to hamper CMI by stimulating

release of IL-4 and IL-10 [13, 14]. This decreased cytotoxicity of T-lymphocytes to autologous endometrial cells may also allow for peritoneal implantation of endometrial cells [28]. These mechanisms of ectopic endometrial tissue escape from the body's normal defense systems and its subsequent survival and implantation outside the uterus can be triggered by persistent retrograde menstruation [29]. As such, dysfunctional immunity likely contributes to the disease.

Endometrial cells, through retrograde menstruation, implant in the pelvis. There they gain access to the peritoneal cavity and lead to an inflammatory reaction followed by angiogenesis, adhesion, neuronal infiltration and oxidative stress [30]. However, almost 95 % of women have retrograde menstruation, and roughly only 10 % of them develop endometriosis [12]. This can partially be explained by differences in the eutopic endometrium and also in the peritoneal fluid among women with and without the disease [31]. An immune dysfunction is one of those differences. Lymphocytes T and NK cells have been described as down-regulated in women with endometriosis, and lymphocyte B is associated with autoantibody production. Mier-Cabrera et al. [32] showed that the cytotoxic response is diminished because of a change in T cell functions and not because of a quantitative difference in the number of cells.

The transcriptional factor NF- κ B also seems to play an important role in the pathogenesis of the disease, as it increases inflammation, invasion and angiogenesis and decreases apoptosis of endometriotic cells [33]. The accumulation of iron, likewise, is related to endometriosis and induces the chronic activation of NF- κ B [34].

Peritoneal macrophages also seem to play an essential role in the pathogenesis of the disease. Their phagocytic capability is reduced in women with endometriosis [35]. Interleukin-1 (IL1), secreted by peritoneal macrophages, promotes inflammation, cell growth, angiogenesis, and cell adhesion. IL 1 is up-regulated in the peritoneal fluid of women with endometriosis and as a result, IL-1, IL-8, TNF-alpha and IFN-gama are elevated. These interleukins stimulate peritoneal macrophages in women with endometriosis [36]. The peritoneal macrophages release prostaglandin E2, responsible for pelvic pain, and VEGF, responsible for neovascularization.

Apoptosis is another important underlying causative factor because eutopic endometrium of women with endometriosis may also have an anti-apoptotic capacity [30].

2.1.5 Genetic Predisposition and Epigenetic Alterations

This disease has a polygenic inheritance. Knowledge about the genetic predisposition of the disease can help us in the diagnosis of endometriosis and also to assess its severity. In 1981, Simpson et al. studied 123 probands who were histologically proven to have endometriosis. They found that among the 123 probands, 10 of them had mothers who were affected by endometriosis; 5.9 % of their female siblings over the age of 18 years had endometriosis. The study also found that

61 % of probands with an affected first degree relative had severe endometriosis when compared to the 23 % of affected probands without an affected first degree relative [37].

Endometriosis has also been strongly linked with heredity, especially between monozygotic twins [38] and first-degree relatives [1, 39, 40], and several identified genetic polymorphisms seem to increase the risk for disease [41].

In addition, women who have first-degree family members with endometriosis appear to have about seven and ten times the risk of developing the disease than those without affected relatives. Daughters and especially sisters of patients with endometriosis are considered to have a significantly higher risk for the disease [1, 39]. Despite numerical discrepancies regarding the risk and prevalence of endometriosis among relatives, several studies show that there is a clear hereditary pattern [1, 42–44].

Endometriosis results from interactions between genetic and environmental factors [45, 46]. The probability of inheriting these genetics factors is 51 % [47]. To define the genes related to endometriosis, several studies were conducted using GWAS (Genome-wide association studies) or DNA mapping technology [47–49]. In familial linkage, this disease does not appear to be inherited by a simple Mendelian heredity, and the inheritance pattern is most probably polygenic/multifactorial [49].

Some evidence suggests that chromosomes 7 and 10 are linked with endometriosis [50].

Epigenetic alterations: Other underlying causes are epigenetic variations. Kawano Y et al. studied a tumor suppressor gene, CCAAT/enhancer-binding protein (C/EBP- α), and found that in endometriotic women, it is silenced by histone de-acetylation. As a result, there is increased proliferation of endometrial tissue and decreased apoptosis. Quantitative RT-PCR was designed to assess C/EBP- α mRNA expression. Immunohistochemical staining was done for C/EBP- α protein. C/EBP- α knockdown was developed with small interfering RNA (siRNA), and quantitative RT-PCR was performed to evaluate the mechanisms of C/EBP- α [51].

Epigenetic changes in transcription factors SF-1 and ER- β also contributes to the pathogenesis of endometriosis. These transcription factors are overexpressed in endometriotic stromal cells due to decreased promoter methylation leading to increased estradiol production, decreased estradiol inactivation and increased progesterone resistance. These epigenetic changes occur due to genetic and environmental factors that cause changes in DNA methylation [16].

2.1.6 Persistent Inflammatory Status

It is believed that the initial trigger of the immune system is the presence of constant irritation in the form of endometrial cells in the peritoneal cavity, thus leading to persistent inflammation. Inflammation is the basic and primary response to an

infection, irritation, or injury in the body [52]. An inflammatory response increases blood flow and initiates the non-specific immune system to send the necessary defense mechanisms (i.e., macrophages, leukocytes, cytokines etc.) to the infection site, increasing local blood flow. This in turn leads to increased swelling and redness in the inflamed area as well as a release of cytokines from the injured epithelial cells [52].

2.2 Protective Factors

Some of the protective factors for endometriosis include parity, oral contraceptive use, NSAID use, tubal ligation, hysterectomy, and prolonged breast feeding. Endometriosis is associated with pelvic inflammation. Studies show that there is elevated local inflammatory activity in women with endometriosis. Procedures such as tubal ligation and hysterectomy bisects the connection between the upper and lower genital tracts and prevent environmental inflammants from reaching the ovarian epithelium, consequently preventing chronic inflammation.

Parity, prolonged breast feeding, and use of NSAIDs and oral contraceptives all suppress ovulation. Whenever there is ovulation, irritation and inflammation occur. Levels of pro-inflammatory cytokines are elevated after ovulation including $\text{TNF-}\alpha$, interleukin-1 and interleukin-6. The cytokines augment cell proliferation, oxidative stress, and vascular permeability and increase levels of leukotrienes and prostaglandins [53].

Given the dependence of endometriosis on estrogen, factors that decrease estrogen in the body such as prolonged amenorrhea (often encountered in female athletes) and exercise [3] demonstrate protective effects. Additionally, increased parity and lactation have exhibited protection against disease occurrence [4]. Women who take combined oral contraceptives are at a decreased risk of developing endometriosis [54].

2.3 Key Points and Summary

The risk factors associated with endometriosis include early menarche, late menopause and other conditions where there are increased episodes of ovulation. During ovulation, secretion of estradiol increases, leading to increased cell proliferation and survival of endometriotic tissue implants. The disease responds to high estrogen and low progesterone levels. The disease has a polygenic inheritance and genetic predisposition with increased incidence of disease seen in first-degree relatives and in monozygotic twins. Exposure to environmental pollutants, immunological dysregulation, persistent inflammatory status, and/or epigenetic alterations also increase the disease risk. Conditions that suppress ovulation indirectly decrease estrogen levels and reduce disease risk.

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