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Unravelling the Complexity of Endometriosis: Insights into its Multifactorial Etiology and Clinical Management

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Abstract

Endometriosis is a multifactorial disease characterized by the presence of endometrial-like tissue outside the uterus. The etiology and pathogenesis of endometriosis involve multiple factors, including genetic, hormonal, immunological, and environmental factors. This review article focuses on the multifactorial aspects of endometriosis and provides a comprehensive overview of the current knowledge in the field. The article discusses the genetic basis of endometriosis, highlighting the role of specific genes and genetic variants in the pathogenesis of the disease. It also reviews the immunological factors that contribute to the development and environmental factors such as toxins, diet, and lifestyle are also discussed concerning their potential impact on endometriosis. Finally, the article examines the clinical management of endometriosis, including current treatments and emerging therapies. In summary, this review article provides a comprehensive and up-to-date overview of the multifactorial aspects of endometriosis, highlighting the need for a multidisciplinary approach to the diagnosis and management of this complex disease.

Keywords: *Endometriosis, inflammatory cytokines, Candidate genes, multifactorial diseases*

1. Introduction

Endometriosis is a chronic inflammatory disease in women of reproductive age and can cause both pain and infertility (Tanbo & Fedorcsak, 2017). According to WHO (2021), "endometriosis is a complex disease that affects some women globally, from the onset of their first period (menarche) through menopause regardless of ethnic origin or social status". Bulun et al. (2019) suggested that Pelvic endometriosis is a complex syndrome characterized by an estrogen-dependent chronic inflammatory process that affects primarily pelvic tissues, including the ovaries. It is the most common cause of chronic pelvic pain in women and is associated with infertility

Nagai et al. (2015) and Morassutto et al. (2016) estimated that, "among studies using non-selected population cohorts, prevalence estimates of endometriosis have ranged from 0.8% to 11%, and incidence estimates have ranged from 4.2 to 35 per 10,000 women-years". In studies done by Schliep et al. (2017) and Eisenberg et al. (2018) reported that, "the mean prevalence of 10% of endometriosis in the pre-menopausal population, with annual incidences in specific populations varying from 0.112% to 0.72%". In 2016, Rajeswari et al. found that, "the general incidence of endometriosis is estimated to be in around 10% of the women of reproductive age group". According to Palshetkar (2019), "worldwide, ≥176 million women are reported to suffer from endometriosis, and around 26 million in India are reported to have endometriosis".

Farland et al. (2015) stated that, "while there is no definitive etiology of endometriosis, there are several hypotheses regarding how endometriotic lesions develop. In 2017, Parasar et al. pointed out that, "one possible mechanism is retrograde menstruation, a feature of the menstrual cycle in women and non-human primates, which is an outflow of the endometrial lining through the patent fallopian

tubes into the pelvic space". Although endometriosis is not a life-threatening disease, it can substantially affect a patient's reproductive health (Namazi et al., 2021). Endometriosis can be both physically and emotionally debilitating. Physically, endometriosis causes chronic pelvic pain, dysmenorrhoea, dyspareunia, dyschezia, and dysuria, which can impair work-related and daily activities (Moradi et al., 2014; Riazi et al., 2014).

In 2010, Hansen and Eyster stated that, "genetic characteristics that are heritable through genes can help to explain familial clustering of disease". Besides the genetic aspect, immunological, hormonal, and inflammatory reactions have been indicated as contributing to the development of ovarian cancer in endometriosis. Shafrir et al. (2017) reported that endometriosis was associated with a greater risk of cardiovascular disease. Fourquet et al. (2010) explained that "chronic symptoms of endometriosis can significantly affect patients' physical and emotional well-being and quality of life". In 2017, Deiana et al. explained that "the scientific community agrees in recognizing a multifactorial etiology of endometriosis, with possible genetic, hormonal, immunological and environmental factors as causes".

The etiology of endometriosis is not fully understood, and various theories have been proposed to explain its development, including retrograde menstruation, lymphatic and vascular metastases, direct implantation, coelomic metaplasia, embryonic remnants, and mesenchymal cell differentiation or induction. Endometrial stem/progenitor cells and a persistent form of embryonic endometriosis may also be involved. Additionally, genetics and oxidative stress, which can lead to inflammation in the peritoneal cavity, have been identified as potential etiological factors (Chopra, 2020).

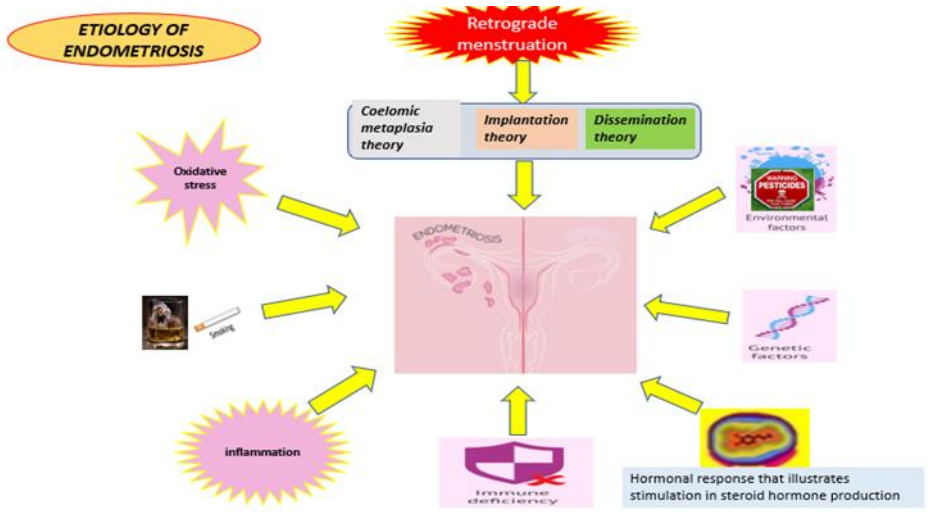

Fig 1: Etiology of endometriosis

Lifestyle

Several research studies pointed out that lifestyle factors have a significant impact on endometriosis. Yen et al. (2019) reported that cigarette smoking is associated with an increased risk of endometriosis in women with surgically confirmed endometriosis from Japan. In a case-control study from Turkey evaluated the interaction between tobacco smoking and glutathione-S-transferase gene polymorphism as a risk factor for endometriosis, an inverse association between smoking and endometriosis was observed (Bravi et al., 2014). Buck et al. (2007) mentioned that "nicotine may prevent the growth of endometriosis since both neovascularization and hyperestrogenism play crucial roles in the development of this condition. Hence, smoking has been found to lower the likelihood that female foetuses may have endometriosis in the future". Besides lifestyle factors, a woman's age is a major factor influencing the spontaneous probability of conception which already starts to decrease by 25–30 years of age (Silvestris et al., 2019). A relation between alcohol drinking and endometriosis risk is biologically plausible since alcohol has been shown to increase levels of endogenous estrogens (Fernandez, 2011). Indeed, a potential association between alcohol intake and the risk of endometriosis has been suggested since the early 1990s (Parazzini et al., 2013). The general results of

this meta-analysis confirm that any alcohol intake is associated with an increased risk of endometriosis compared to no alcohol consumption.

The influence of caffeine on endometriosis was initially reported in a case–control study, conducted in USA and Canada in the early 1990s, where a greater intake of caffeine was found in women with endometriosis than in controls, and the relative risk of endometriosis was statistically significant (Grodstein et al., 1994). A previous review on endometriosis and physical activity (PA) reported an article on the beneficial effects of PA and the interaction between painkillers and PA in women with endometriosis (Bonocher et al., 2014). Cohort and case-control studies that analyzed the association between physical activity (PA) and endometriosis suggested that adult PA decreases endometriosis risk and tends to improve symptoms (Koppan et al., 2011).

Environmental and Dietary factors of endometriosis

Although there are many possible causes of endometriosis, its exact etiology is not well understood. Proposed risk factors include genetic polymorphisms, higher organochlorine body load, lifestyle, reproductive, and dietary variables (Birnbaum & Cummings, 2002; Foster & Agarwal, 2002; Cramer & Missmer, 2002). Foster and Agarwal (2002) pointed out that "researchers have tried to find a link between endometriosis and exposure to environmental toxins, some of which behave as environmental oestrogens because oestrogens are essential to the pathobiology of endometriosis". Bérubé et al. (1998) noted that "obese and alcoholic women are more likely to have endometriosis, as these risk factors encourage higher circulating oestrogen levels". Mayani et al. (1997) reported that "single case-control research comparing 44 women with endometriosis to 35 age-matched women with tubal infertility found a correlation between endometriosis and dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD) exposure". Industrial activities that have been shown to produce dioxin congeners as byproducts include the manufacture of herbicides (such as 2,4,5-trichlorophenoxyacetic acid), wood bleaching with chlorine gas, or plastic incineration (Gilpin et al., 2003). Heilier et al. (2004a, 2005) mentioned that "women with peritoneal endometriosis (PE) and/or deep endometriotic nodules (DEN) had higher blood concentrations of the chemicals polychlorinated dibenzo-p-dioxin (PCDD), polychlorinated dibenzofuran (PCDF), and polychlorinated biphenyl (PCB) than did controls". Khan et al. (2014) stated that "endometriosis risk is increased when certain chemicals are exposed to female foetuses intrauterinally". Herbst et al. (1999) noted that "prior to 1971, when its teratogenic effects were revealed, the medication diethylstilbesterol (DES) was used to prevent preterm labour". Missmer et al. (2004) mentioned that "the Nurses' Health Study's analysis conclusively showed women who had been exposed to DES as foetuses had a higher probability of having endometriosis that had been laparoscopically verified. It is interesting that women who had twin pregnancies also had a higher chance of developing endometriosis, which may have been brought on by the elevated oestrogen levels that are frequently associated with these pregnancies". Nap et al. (2004) found that "endometriosis is known to be increased by congenital uterine abnormalities, which increase 'retrograde menstruation'". The risk of endometriosis in the daughters of pregnant mothers who were exposed to chemicals is similarly increased. This connection is particularly well recognised in situations of exposure to dioxins and polychlorinated biphenyls (Cummings et al., 1999). It was believed that epigenetic changes brought on by TCDD and other dioxin exposure during foetal life might cause endometriosis (Giampaolino et al., 2020). Bérubé et al. (1998) noted that "obese and alcoholic women are more likely to have endometriosis, as these risk factors encourage higher circulating oestrogen levels". Food may have a role in the aetiology of endometriosis by influencing steroid hormone levels; however, few published research has investigated the relationship between diet and endometriosis risk (Trabert et al., 2011). Jurkiewicz-Przondziono et al. (2017) mentioned that "fruits and vegetables, fish oils, calcium and vitamin D-rich dairy products, and Omega-3 fatty acids are all linked to a decreased chance of having endometriosis. Consumption of goods high in trans-unsaturated fatty acids, intake of lipids in general, and consumption of beef and other types of red meat, as well as alcohol, are all risk factors for endometriosis. There are currently no definite links between certain food items and the risk of endometriosis. Trabert et al. (2011) found "an inverse risk of illness with dietary fat and dairy intake, and an increased risk of endometriosis with β-carotene and greater fruit servings, but these findings have not been replicated elsewhere and require additional examination in a prospective study". Endometriosis risk may rise with increased consumption of saturated fats, particularly palmitic acid.

and trans-unsaturated fatty acids. Monounsaturated fats and omega-3 polyunsaturated fatty acids are likely linked to a decreased chance of developing endometriosis and a reduction in disease severity. In food treatment, monounsaturated fats, omega-3 polyunsaturated fatty acids, and an appropriate eicosapentaenoic acid to arachidonic acid ratio can be utilized to enhance the quality of life by lowering pain and inflammation (Marcinkowska & Górnicka, 2023). Harris et al. (2013) found distinct correlations between dietary intakes of total milk, skim/low-fat milk, and magnesium with endometriosis risk among the two endometriosis subtypes. The adverse relationship between anticipated plasma (OH)D levels and endometriosis risk, on the other hand, was highly constant in both women who had never reported infertility and those who had claimed concurrent infertility. This might imply that certain foods and nutrients have distinct roles in persistent pelvic pain symptoms and/or endometriosis causation. Harris et al. (2013) also added "while further research is needed to validate these findings, dairy foods and vitamin D may be among the first modifiable risk factors for endometriosis".

Immunological aspects

Women with endometriosis-associated infertility have an altered intraperitoneal immune cell status compared to women with unexplained infertility (Tariverdian et al., 2009). One of the possible causes of the development of endometriosis might be the immune system, even though endometriosis is generally considered to be a steroid-sensitive disease (Králíčková & Vetvicka, 2015). T regulatory (Treg) cells are altered in endometriosis patients and have been suggested to play a role in the pathogenesis of endometriosis and its associated infertility (Berbic et al., 2010). In monkey and human models of endometriosis, lymphocyte proliferative response and T-cell toxicity are defective (Králíčková & Vetvicka, 2015). Similar to cytotoxic T lymphocytes, the activity of CD+ helper cells in the peritoneal fluid are also decreased, which might correspond to the high concentrations of IL-10 (Ho et al., 1997). Lower numbers of Treg cells have been detected in the eutopic endometrium of a non-human primate endometriosis model (Braundmeier et al., 2012). They are potent suppressors of inflammatory immune responses and are responsible for maintaining antigen-specific T-cell tolerance and immune homeostasis. Even though immunosurveillance seems to have a defect in endometriosis, some aspects of the immune system are upregulated, such as the widespread polyclonal activation of B cells (Lebovic et al., 2001). B lymphocytes produce antibodies against antigens and they seem to contribute to the pathogenesis of endometriosis through autoantibodies secretion (Straub, 2007). In endometriosis, we can observe significant changes in the peritoneal cavity, mostly in the increased number of macrophages and macrophage-derived cytokines (Králíčková & Vetvicka, 2015).

A previous study done by Cruikshank et al. (1995) denoted that, "IL-16 was one of the first characterized cytokines with chemoattractant activity for human T cells and therefore was originally designated as lymphocyte chemoattractant factor (LCF)". In 2014, Richmond et al. mentioned that, "IL-16 is a cytokine originally designated as a lymphocyte chemoattractant factor and is characterized as an essential regulator of various cellular processes, including cell recruitment and activation". In 1955, Laberge et al. pointed out that, "IL-16 is produced by activated CD8-positive (CD8+) T cells and activates CD4+ T cells, monocytes, macrophages and dendritic cells by binding to the CD4 molecular". Conti et al. (2002) suggested that, "other cells, including eosinophils, dendritic cells, mast cells, macrophages, B cells and monocytes, also show high levels of IL-16 secretion under certain conditions". Ponting (1997) stated that, "IL-16 contains PDZ domains in the C-terminal region, which plays a key role in the formation and function of signal transduction and might represent the signature of IL-16 molecules". Mathy et al. (2000) added on that, "to the activation of CD4+ T cells, IL-16 can promote the secretion of inflammatory cytokines such as tumor necrosis factor (TNF) α, interleukin-1β and interleukin-6 (IL-6). In 2012, Lambertsen et al. denoted that, "all of these cytokines are key elements in the ischemic cascade after cerebral ischemia". Mijailovic et al. (2020) reported that "some of them, such as Interleukins (IL-1β), Interleukin-6 (IL-6) and Tumor Necrosis Factor Alpha (TNF- α) are activators of bone resorption through osteoclasts". In 2017, Sell et al. suggested that "these cytokines are also involved in neutrophil chemotaxis, the inflammatory process, and the production of other pro-inflammatory cytokines". Center et al., (2000) mentioned that "IL-16, a chemokine initially described as a chemotactic factor for leukocytes, is produced by some cells, such as T lymphocytes, fibroblasts, and dendritic cells".

Table 1: Selected inflammatory cytokines and their functions

Cytokines	Major Sources	Target Cell	Mode Of Action
Tumour necrosis factor a) TNF – α b) TNF – β	Activated macrophages & monocytes Helper T cells	Macrophages Phagocytes Tumor cells	Tumour cytotoxicity, antiviral effects, endotoxic shock
Interleukins I	Macrophages, B cells & monocytes	B cells, NK cells, T cells	Induce other cytokines. chemotaxis, phagocytosis Stimulation of T cells for the production of IL2 and other Lymphokines.
IL-6	T, B cells, Macrophages fibroblasts	B cells, plasma cells	B-cell proliferation, neutrophils chemotaxis B cells differentiation formation of IL-2 Receptors on T cells
IL-8	Macrophages	neutrophils	Neutrophils chemotactic factor
IL-11	Bone marrow, stromal cells	B cells	Induce acute phase proteins
IL-16	Eosinophils CD8+T cells	CD4+T cells	Chemoattraction of CD4+ cells & activates inflammatory cytokines
IL-17	CD4+T cells	Monocytes Neutrophils	Release of IL-6, IL-8, GCF & PGE2 Recruits' monocytes and neutrophils to the site of infection.
IL-18	Hepatocytes, macrophages, dendritic cells	Monocytes & T cells	Induces interferons γ production, enhances NK cells activity
Interferons a) IFNα b) IFN β c) IFNγ	Macrophages Neutrophils & some somatic cells Fibroblast T cells NK cells	Various Various Various	Antiviral activity Antiviral activity Antiviral, Macrophage activation, increases the cytotoxicity of NK cells

Endocrinolgical aspects

For a sound physiological response, a good hormonal response is inevitable for the fertilization process. Hormones involved in the fertilization process are oestrogen, progesterone, TSH, FSH, and LH. But over activation of different enzyme systems can lead to higher inflammation and oxidative stress. High estrogen production is a consistently observed feature of endometriosis and highlighted the fact that estrogen and its receptors play a key role in the pathophysiology of endometriosis (Chantalat et al., 2020).

Progesterone resistance is one of the causes of endometriosis. It is explicable by the extremely low PR levels in endometriotic tissue. In normal endometrium, levels of PR-A and PR-B progressively increase during the proliferative phase, peaking immediately before ovulation, and diminishing after ovulation, suggesting that E2 stimulates PR levels (Attia et al., 2000). Progesterone normally inhibits estrogen-dependent endometrial proliferation, elicits decidualization of the endometrium, and acts as an anti-inflammatory agent (Kao et al., 2000). Resistance to progesterone in endometriosis was first suggested following in-vitro studies that showed progesterone was unable to induce retinoic acid production (Patel et al., 2017). The absence of retinoic acid production leads to elevated estradiol concentrations in endometriotic lesions, further facilitating growth (Bulun et al., 2006).

Oxidative stress

In the last few years, several studies have demonstrated a possible link between high levels of chronic stress and endometriosis. So far, clinical evidence shows that patients with endometriosis report higher levels of perceived stress, anxiety, and depression than healthy women (Vannuccini et al., 2018). The stress levels measured by PSS can be high or very high in more than 70% of women with endometriosis (Lazzeri et al., 2015 a). The stress intensity is the highest among women with the most severe disease forms and who have been submitted to multiple surgeries (Lazzeri et al., 2015 b).

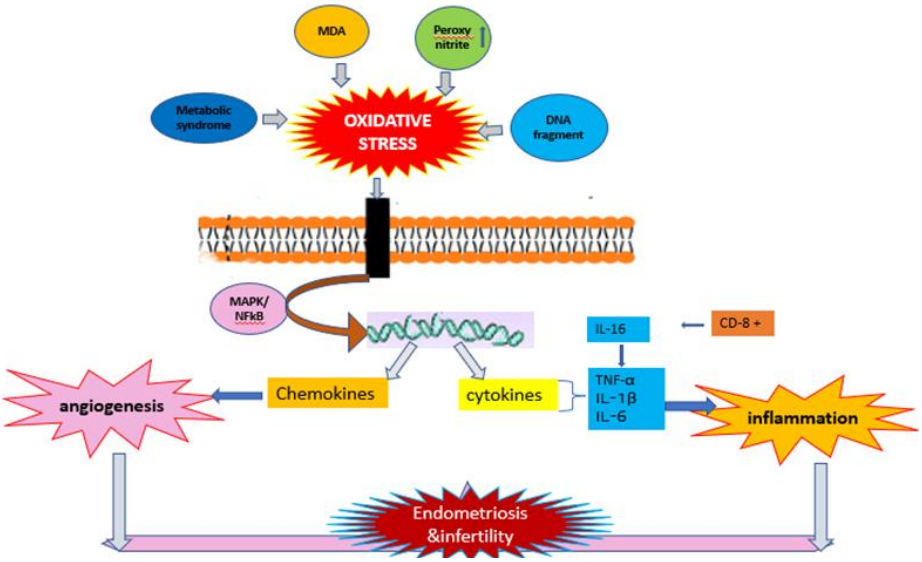

Fig 2: Oxidative stress in endometriosis

Oxidative stress has an essential role in cell proliferation, the inflammatory process, and the apoptosis prevention of the endometriotic cell (Gupta et al., 2015). Some of the research papers hypothesized that endometriosis is may be caused due to ROS and oxidative stress. Infertile females with endometriosis were found to have low antioxidant status (Prieto et al., 2012). The peritoneal fluid of infertile patients has been found to contain higher concentrations of MDA, proinflammatory cytokines, and angiogenic factors as well as oxidized LDL fraction is also elevated so the activation of phagocytosis, and generation of ROS was evident (Rong et al.,2002). Thus, detecting presence of oxidative stress in patients with endometriosis. One of the common features of endometriosis is retrograde menstruation which means the backflow of menstrual blood and endometrial tissue through the fallopian tubes to the peritoneal cavity (Carvalho et al., 2013; Polak & Kotarski, 2010). So massive hemolysis is possible in the peritoneal cavity and leads to the release of iron, so the iron can mediate the production of ROS through the Fenton reaction. The increased presence of iron and the heme around the endometriotic lesions regulates the nitric oxide synthase activity thereby increasing the synthesis of nitric oxide by macrophages resulting in the degradation of DNA. This type of infertile patient blood sample contains elevated levels of lipid peroxides, which suggests the altered redox status and may increase DNA damage (Carvalho et al., 2012).

Genetic aspects

Women with endometriosis show altered endometrial cell behavior, favoring extrauterine adhesion and growth since genetic mutations that cause cell damage are implemented in the progression of endometriosis (Sourial et al., 2014). Altered DNA copy numbers have been detected in endometriosis lesions, by use of comparative genomic hybridization (Gogusev et al., 1999). Several regions of genomic alteration in eutopic endometrium were found in patients with endometriosis compared with unaffected women, which suggests these changes as a pathogenic mechanism (Wang, 2004). Angioni (2017) emphasized that "the genetic component, demonstrating how predisposition generated by certain susceptibility genes plays an important role in the development, maintenance, and recurrence of the disease". Hansen and Eyster (2010) suggested that "another contributing factor of endometriosis may be several different disease processes as evidenced by the differences in peritoneal, ovarian endometriomas and deeply infiltrating endometriosis". The daughters of mothers

with surgically confirmed endometriosis have a more than two times higher risk of developing the disease than daughters of mothers without endometriosis (Dalsgaard et al., 2014). Furthermore, this association can extend beyond first-degree relatives; overall this evidence suggests a distinct genetic contribution to endometriosis (Hull et al., 2002). The higher the proportion of affected relatives, the greater the likelihood of severe endometriosis to be present (Krishnamoorthy, 2017).

Melis et al. (2014) mentioned that, "nonetheless, studies on the genetics of endometriosis are complicated by various factors: the phenotypic heterogeneity of the disease; the still unknown prevalence in the population, burdened by the absence of registries and diagnostic underestimation; the invasiveness of diagnostic methods; and various co-morbidities that can generate bias". Dun et al. pointed out that, "multifactorial or polygenic disorders, such as endometriosis, are determined by multiple genes with allelic variations. And also suggested that endometriosis has a heritable component". Genes for progesterone and estrogen receptors have been found to have an association with endometriosis including CYP17, ER, PR, HSD17B1, and CYP19 (Vigano et al., 2007). Studies identified cases of ovarian cancer associated with endometriosis and demonstrated loss of heterozygosity at 5q, 6q, 9p, 11q, and 22q additional mutations in the PTEN (phosphatase and tensin homolog) tumor suppressor gene located on chromosome 10q23 have also been identified in endometriotic samples (Hansen & Eyster, 2010). Based on epidemiological evidence Heidemann et al. (2014) and Anglesio et al. (2017) reported that "personal history of endometriosis increases the risk of ovarian cancer and clinical evidence that ovarian clear cell and endometrioid carcinomas are associated with endometriosis".

Nodin et al. (2013) explained that "KRAS mutations are commonly found in endometrioid, mucinous, low-grade serous and clear-cell carcinomas". According to Jancik et al. (2010), "a common mutation of the KRAS allele can be seen in the modification of the let-7 single nucleotide polymorphism, and this variant allele is common in women with endometriosis as it leads to an increase in proliferation of invasion within the stromal cells". Dinulescu et al. (2005) demonstrated that, "specific targeting of the KRAS gene in the reproductive tract of mice resulted in the development of endometriosis" Kyo et al. (2020) and Suda et al. (2020) reported that, "representative oncogenes of human cancers, such as KRAS and PIK3CA, are frequently mutated in ovarian endometriosis, deep infiltrating endometriosis, and iatrogenic endometriosis. Moreover, those oncogenes have also been identified in normal endometrium".

Familial aggregation

Endometriosis has long been known to have familial tendencies (Simpson et al., 2003). Endometriosis was found in 9.5% of first-degree relatives of women with endometriosis and just 1% of controls in research by Matalliotakis et al. (2008). Endometriosis in a first-degree relative had an odds ratio of 10.21 (95% CI 2.45-42.5; P 0.001). Women with endometriosis stated that their mother had been diagnosed in 3.9% of instances, and at least one sibling had been diagnosed in 5.6% of cases. The odds ratios for the mother having endometriosis (7.99, 95% CI 1.06-60.1) or at least one sister having (11.55, 95% CI 1.56-85.59) were considerably higher when compared to the control group. According to the findings of Moen et al. (1993), endometriosis was discovered in 3.9% of case moms and 0.7% of control mothers, 4.8% of case sisters and 0.6% of control sisters. In a first-degree relative, the relative risk of endometriosis was 7.2 (95% confidence range 2.1, 24.3). Severe endometriosis manifestations were identified more frequently in patients with a favorable family history than in those without (26% versus 12%, p 0.01). Women with affected siblings had a significantly increased risk of developing endometriosis, with an incidence of 35.45/10,000 person-years. The familial risk of endometriosis was further increased for women with affected twins. Additionally, women with a family history of endometriosis who also smoked, had early menarche, or low BMI had a significantly higher risk of developing endometriosis compared to the general population. The combined effects of smoking and early menarche with a family history of endometriosis were found to be greater than their individual risks. These findings suggest that women with both a family history and additional risk factors may be considered a high-risk group for endometriosis (Kim et al., 2021).

Candidate genes

Galactose-1-phosphate uridyl transferase

Galactose-1-phosphate uridyl transferase (GALT) was the first gene to be studied for association or linkage with endometriosis. The gene is located on chromosome 9 (9p13) and a specific polymorphism, N314D, was initially reported to be associated with endometriosis (Bischoff & Simpson, 2004).

Phase I detoxification genes

Studies have explored the association between endometriosis and various Phase I detoxification genes, including the Ah receptor, CYP1A1, and NAT2. These enzymes act by introducing a functional group into their substrates and may play a role in metabolically activating procarcinogenic compounds. However, no significant association was found between Ah receptor or CYP1A1 gene polymorphisms and endometriosis in Japanese women or in a study of endometriosis patients and control subjects (Watanabe et al., 2001; Hadfield, 2001).

Phase II detoxification genes

The Phase II detoxification genes GSTs and NAT2 are important for detoxifying oxidative stress products, and the null alleles of GSTM1 and GSTT1 may increase the risk for cancer if they do not efficiently metabolize toxic intermediate compounds. Studies on the association between these genes and endometriosis have reported conflicting results. While Baranova et al. (1999) found that the homozygous GSTM1 null allele was more prevalent in endometriosis cases, other studies failed to confirm this association. Additionally, Baranova et al. (1999) reported increased frequency of slow acetylation genotypes for NAT2, but other studies found contradictory results or no differences in NAT2 genotypes between endometriosis cases and controls. However, the active allele of GSTM1 was found to be more prevalent in endometriosis cases compared to controls in some studies.

Steroid-related genes

Several genes related to steroid hormones, including the estrogen receptor (ER) and aromatase gene (CYP19), have been studied in relation to endometriosis. However, the results have been mixed and contradictory. Some studies found an association between ER polymorphisms and endometriosis, while others did not. Similarly, a polymorphism in the aromatase gene (CYP19) did not show any association with endometriosis in one study. Another study found an association between a deletion in the CYP19 gene and endometriosis, but the sample sizes were small. A polymorphism in the CYP17 gene did not show any association with endometriosis. Finally, a progesterone receptor polymorphism (PROGINS) was found to be more frequent in endometriosis cases than controls. However, further research is needed to clarify the role of these genes in the development of endometriosis (Bulun et al., 2000; Kurabayashi et al., 1999; Wieser et al., 2002).

Tumor suppressor genes

Genes of special interest to researchers studying endometriosis in relation to cancer include oncogenes and tumor suppressor genes. TP53 and PTEN are tumor suppressor genes of special interest to researchers. Loss of heterozygosity (LoH) in endometriosis has been found in chromosomal regions 9p, 11q, and 22q, and chromosomal alterations were observed in endometriosis cases associated with carcinoma. Alterations in chromosomal regions 5q, 6q, 9p, 11q, and 22q were observed in 25-30% of endometriosis cases associated with carcinoma. Chromosome 17, specifically BRCA1 and TP53, became a focused candidate gene. Studies indicated that perturbation does not necessarily involve the loss of the entire chromosome 17, but only of the TP53 locus. PTEN mutations have been reported in endometrioid tumors and in an ovarian epithelial tumor that shows a relationship to endometriosis but not to either serous or mucinous epithelial ovarian tumors. Somatic mutations involving PTEN have been observed only in endometrioid tumors, albeit in only 21% of cases (Kosugi et al., 1999; Obata et al., 1998; Sato et al., 2000).

GWAS

GWAS (genome-wide association studies) of endometriosis have identified genetic variants associated with an increased risk of developing the condition, providing insight into the underlying biology of the disease. However, the identified genetic variants explain only a small proportion of the heritability of endometriosis, suggesting the involvement of additional genetic and environmental factors. In various investigations, GWAS have found many genomic areas with high evidence of

correlation with endometriosis risk and excellent replication (Fung et al., 2015; Zondervan et al., 2016). The details of some genomic areas are given below (Table 2).

Table 2: Endometriosis genetic variations revealed by a meta-analysis of eight genome-wide association (Rahmioglu et al., 2014; Sapkota et al., 2015)

SNP	Chromosome	Gene
rs7521902	1	WNT4
rs13394619	2	GREB1
rs7739264	6	ID4
rs12700667	7	Intergenic
rs1537377	9	CDKN2BAS
rs10859871	12	VEZT
rs1250248	2	FN1
rs6542095	2	IL1A
rs7798431	7	Intergenic
rs1333049	9	CDKN2BAS
rs4141819	2	Intergenic
rs6734792	2	Intergenic

pigenetics

The maintenance of proper and uninterrupted organismal development relies heavily on the crucial role played by epigenetics. Deviations in the epigenetic patterns occurring at inappropriate times or locations can lead to the onset of numerous diseases. DNA methylation, histone modifications, and microRNA involvement are the three categories that epigenetic modifications can be divided into, and these mechanisms are interconnected, with their interactions contributing to the observed molecular and clinical outcomes (Esteller, 2002).

Endometriosis is characterized by differences in gene expression and epigenetic modifications between endometriotic and endometrial tissue, resulting in altered molecular profiles and responses to various factors (Esfandiari et al., 2021). Epigenetic research has established the role of epigenetic factors in the etiopathogenesis of endometriosis, with somatic mutations involving oncogenes and suppressor genes found in epithelial cells, and epigenetic modifications found in stromal cells (Anglesio et al., 2017; Li et al., 2014). The stable change in gene expression patterns in eutopic and ectopic endometrium suggests cellular memory involvement in the maintenance of endometriosis, with epigenetic changes responsible for the pathomechanism of the disease and related infertility (Borghese et al., 2017; Guo et al., 2009). The role of epigenetic mechanisms in the development of endometriosis has been underestimated, with increasing evidence pointing towards the importance of hormone-mediated epigenetic modifications in endometrial and mesenchymal stem cells. Excess estrogen exposure and progesterone resistance are crucial factors in the failure of epigenetic homeostasis, leading to altered properties in endometrial and mesenchymal stem cells (Szukiewicz et al., 2022).

Clinical management of endometriosis

Endometriosis is diagnosed based on history and symptoms and indicators, confirmed by physical examination and imaging modalities, and eventually proven by histological investigation of specimens acquired during laparoscopy (Joshi & Aggarwal, 2020)**.** Endometriosis can be treated medically or surgically, both conservatively and aggressively. According to Hansen and Eyster (2011), "oral contraceptives, progestins, gonadotropin-releasing hormone analogues, and danazol are among the medicinal treatments available. All of these medical treatments cause a hormonal steady state, which creates an environment unfavorable to the establishment of endometriosis". They also suggested that, "conservative treatments for endometriosis-related pain include the removal of endometriotic implants and adhesions as well as the restoration of normal anatomy. Radical surgery entails removing the uterus with or without removing the ovaries. Endometriosis basic scientific advances present the prospect of less intrusive diagnostic tests and better therapy".

Medicinal therapy is frequently used as the first line of treatment for endometriosis patients to alleviate symptoms or avoid post-surgical disease recurrence (Ferrero et al., 2018). Pharmacotherapy plays an important role in the treatment of endometriosis, with long-term medications balancing clinical effectiveness with an acceptable safety profile. Many factors influence treatment selection, including age and patient preference, reproductive goals, pain intensity, illness severity, and the occurrence of side effects (Ferrero et al., 2018). Virtually the majority of the known endometriosis treatments decrease ovarian function and are not effective. To alleviate pain sensations, these individuals are frequently given a combination of oral contraceptives and progestins. When first-line medications are inefficient, are not tolerated, or are contraindicated, gonadotropin-releasing hormone agonists are administered. Aromatase inhibitors are recommended for women who have failed previous therapies (Ferrero et al., 2018).

When hormonal therapy is terminated, they are frequently associated with unpleasant side effects, delayed conception, and return of illness and symptoms. For these reasons, new medicines with novel targets are necessary to produce illness and symptom regression while avoiding severe hypo-estrogenic consequences (Elnashar et al., 2015). Linzagolix is a novel GnRH receptor antagonist with minimal pharmacokinetic/pharmacodynamic variability that is being developed. It binds to and inhibits the GnRH receptor in the pituitary gland, leading to a dose-dependent decrease in the production of LH and FSH. This decrease in LH and FSH levels results in a dose-dependent decrease in oestrogen (Donnez et al., 2023). Although various innovative agents are being studied for the treatment of endometriosis, there has been little progress in the discovery of curative rather than suppressive medications. As a result, more efforts are required to create an effective, and hopefully curative, therapy for this chronic, expensive, and overpowering condition (Zajec et al., 2022).

2. Conclusion

In women of reproductive age, endometriosis continues to be a major cause of illness and lowers the quality of life. Endometriosis' origin is yet unknown. In conclusion, endometriosis is a complex disease with multifactorial etiology and its precise pathogenesis remains unclear. The review article highlights various theories regarding the development of endometriosis. Moreover, various factors like genetics, oxidative stress, lifestyle, etc which can lead to inflammation in the peritoneal cavity, have been identified as potential etiological factors. The complexity of the etiology of endometriosis underscores the need for a multidisciplinary approach to diagnosis, treatment, and management. Further research is needed to better understand the underlying mechanisms and develop more effective therapeutic options for this challenging condition. Multidisciplinary treatment becomes a cornerstone to achieve a comprehensive and successful approach to patients with CKD. The collaboration between dentists, doctors, nurses and other specialists contributes to a better result in the treatment and postoperative control of the patient. By working as a team, eventual situations that could significantly affect the patient's health can be prevented and resolved. The progressive increase in the morbidity and prevalence of CKD, according to epidemiological data, highlights the importance of recognizing and understanding the specific signs and symptoms of this systemic pathology. Dental professionals must be prepared to face these challenges and appropriately and responsibly address the nursing procedures necessary in the care of these patients. Efficient and well-informed management is key to providing optimal care to those suffering from this complex kidney disease.

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