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Genetic Predisposition and Pathogenesis in Endometriosis

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Abstract: ***Endometriosis is a chronic, estrogen-dependent inflammatory disorder defined by the growth of endometrial-like tissue outside the uterus, leading to pain, infertility, and reduced quality of life. Although retrograde menstruation remains the prevailing theory of pathogenesis, it does not fully explain why only some individuals develop the condition. Accumulating evidence highlights a substantial genetic component, with heritability estimates suggesting that approximately 51% of the risk of endometriosis is genetically driven. Genome-wide association studies (GWAS) have identified more than a dozen risk loci, including WNT4, GREB1, FN1, CDKN2B-AS1, and ESR1, which are involved in reproductive tract development, hormone signalling, immune modulation, and cell adhesion. This review synthesizes findings from genetic, epigenetic, and molecular studies to provide an updated understanding of the pathophysiology of endometriosis. In addition to inherited variants, recent discoveries have included epigenetic alterations, such as DNA methylation and microRNA regulation, which influence gene expression in key pathways related to cell proliferation and differentiation. Moreover, somatic mutations found in eutopic endometrial cells and chromosomal instability within lesions suggest a neoplastic-like progression, especially in advanced stages of the disease. Newly validated GWAS loci and polymorphisms in vascular remodelling and oxidative stress-related genes (e.g., VEGF, MMPs, NAT2) further underscore the multifactorial nature of endometriosis. The purpose of this review is to investigate how genetic predisposition, somatic alterations, and epigenetic mechanisms interact to contribute to lesion development, persistence, and symptom severity. By examining these interconnected pathways, we highlight the current limitations in diagnosis and treatment, and emphasize the urgent need for personalized approaches in clinical care. These insights pave the way for future research to identify biomarkers for earlier diagnosis and to develop individualized therapeutic strategies. A more comprehensive understanding of endometriosis at the molecular level is crucial for advancing precision medicine and enhancing outcomes for women affected worldwide.***

Keywords: Endometriosis, Genetic Predisposition, Aetiology, Risk Loci

Abbreviations:
GWAS: Genome-Wide Association Studies
SNP: Single Nucleotide Polymorphism
LOH: Loss of Heterozygosity
FSH: Follicle-Stimulating Hormone
FSHB: Follicle-Stimulating Hormone Beta
ESR1: Estrogen Receptor 1
VEGF: Vascular Endothelial Growth Factor
MMP: Matrix Metalloproteinase
PAI-1: Plasminogen Activator Inhibitor-1
HOXA: Homeobox A gene cluster
ID4: Inhibitor of DNA binding 4
IL1A: Interleukin 1 Alpha
RND3: Rho Family GTPase 3
CDKN2B-AS1: Cyclin-dependent kinase inhibitor 2B antisense RNA
WNT4: Wingless-type MMTV integration site family member 4
GREB1: Growth regulation by estrogen in breast cancer 1
FN1: Fibronectin 1
ARL14EP: ADP-ribosylation factor-like protein 14 effector protein
SYNE1: Spectrin repeat-containing nuclear envelope protein 1
ETAA1: Ewing's Tumour-Associated Antigen 1
NAT2: N-acetyltransferase 2
miRNA: microRNA
HPG: Hypothalamic-Pituitary-Gonadal axis

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I. INTRODUCTION

Endometriosis, a prevalent condition encountered by gynecologists, refers to the occurrence of stromal tissue and endometrial glands outside the uterine cavity [1]. This ectopic tissue triggers a chronic inflammatory process regulated by estrogen. Up to 10% of women are affected by endometriosis in their reproductive years. Patients typically exhibit symptoms such as pain, subfertility, or a combination thereof, often prompting suspicion during pelvic examination or imaging studies. Initial attention in both investigation and treatment should be aimed at alleviating these presenting symptoms [2]. However, given the chronic and recurring nature of endometriosis, clinicians must establish a comprehensive, long-term management plan tailored to each patient's symptoms and fertility aspirations, as well as their desired quality of life [3]. The predominant pathogenic theory, backed by substantial evidence, revolves around the concept of retrograde menstruation. In this process, functional endometrial fragments pass through the fallopian tubes, potentially driven by pressure imbalances caused by abnormal uterine contractions. These pieces can adhere, proliferate, and infiltrate pelvic tissues within the peritoneal cavity. Various reproductive and menstrual factors, including early onset of menarche or prolonged menstrual periods, can increase the likelihood of pelvic contamination by refluxed endometrium, thereby influencing the epidemiological aspect. Moreover, molecular-level alterations that facilitate the sequential steps of cell implantation and growth at ectopic sites play a significant biological role in this process [4].

Dysfunction of immune mechanisms in eliminating ectopic tissue and abnormal

differentiation of endometriotic tissue have been suggested as potential underlying mechanisms. This includes a stromal-cell defect marked by increased estrogen and prostaglandin production, coupled with progesterone resistance. Changes in estrogen signalling have been linked to the growth of ectopic endometrial tissue, which is stimulated by estrogens. Usually, progesterone induces a response in uterine endometrial tissue characterised by the development of glandular secretions, the suppression of estrogen-driven epithelial cell proliferation, and the differentiation of stromal cells into specialised decidual cells. Inflammation associated with endometriosis may induce resistance to progesterone by disrupting the progesterone signalling pathway. Cytokines, chemokines, and prostaglandins are overproduced when there is ectopic tissue in the peritoneal cavity. When macrophages infiltrate these ectopic lesions, they exhibit indicators of alternative activation, which promotes angiogenesis and lesion expansion. Additionally, non-protein-bound catalytic iron enhances the generation of reactive oxygen species, further facilitating the progression of endometriosis [5]. There have been numerous biological candidate gene studies on endometriosis; however, like other complex diseases, they have largely been unsuccessful, with few results consistently replicated. It is commonly known that candidate gene studies generally fail to uncover genetic mechanisms in complex diseases because they are based on biological hypotheses that may not be correct, they usually only look at one or a small number of genes within a relevant biological pathway, they only test a small number of gene variants without fully covering the gene, the definitions of cases and controls are frequently vague or inconsistent, and the sample sizes are typically too small to find the expected effect sizes of variants influencing complex traits. Due to these limitations, the cellular or molecular origins of this disease remain uncertain. However, in this review paper, we aim to explore the potential origins of this disease, shedding light on the current understanding and the ongoing research efforts in this area [6].

II. GENETIC FACTORS OF ENDOMETRIOSIS

The familial clustering is documented in primates, including humans [7]. Numerous genetic variations and environmental factors interact to cause this disease, which has a complex genetic background. With an estimated 51% heritability, genetic factors explain roughly half of the variation in endometriosis risk [8]. Recent meta-analyses of GWAS conducted in recent years have identified fourteen risk loci strongly associated with endometriosis. These include *WNT4, CDKN2B-AS1, GREB1, FN1, ID4, IL1A, NFE2L3, RND3, VEZT, ETAA1, SYNE1, FSHB, ARL14EP*, and *ESR1* [9].

A. WNT4 - Wingless-type MMTV Integration Site Family Member 4

WNT4 is essential for the steroidogenesis and development of the female reproductive tract [4]. The variant rs7521902 is positioned approximately 21 kb upstream or downstream of *WNT4* [10]. In female mice with *WNT4* deficiency, the Müllerian duct and its derivatives are absent [11]. A prior study examined the expression of genes, such as WNT4, crucial for female reproductive tract development in peritoneal tissue from patients with endometriosis and controls [12]. Their findings indicated that *WNT* genes are expressed in both the endometrium and the normal peritoneum, suggesting that endometriosis may arise through metaplasia, which leverages the developmental processes involved in the embryonic genesis of the female reproductive tract. As previously stated, Wnt signalling is crucial for communication between epithelial and stromal cells in the endometrium. It is likely necessary for the development, differentiation, and implantation of embryos within the endometrium. Moreover, the rs7521902 variant, which is associated with endometriosis, has been linked to bone mineral density at a genome-wide level, making this variant a potential locus with pleiotropic effects [6].

B. CDKN2B-AS1 - Cyclin-Dependent Kinase Inhibitor 2B Antisense RNA

The *CDKN2B-AS1* gene is located in a gene-dense region of the human genome, known for its predicted enhancers. It produces a long noncoding RNA situated in the antisense direction of the CDKN2B and CDKN2A gene cluster, which encodes p15, p16-INK4a, and p14ARF, all of which are tumour suppressor proteins [4]. The variants rs10965235, rs1333049, and rs1537377 are situated in the intron between exons 16 and 17, 48 kb upstream of the gene, and inside the 3′ UTR region, respectively [6]. The CDKN2B-AS1 gene encodes cyclin-dependent kinase inhibitor 2B antisense RNA [13]. This gene is located in the same linkage disequilibrium block as tumour suppressor genes that code for the previously mentioned proteins, and CDKN2B-AS1 is involved in controlling their expression [6]. In cases of endometriosis and endometrial cancer, CDKN2A has been observed to be inactivated due to either loss of heterozygosity or hypermethylation of its promoter [14]. Single-nucleotide polymorphisms (SNPs) within or near the gene locus have been linked to numerous additional characteristics and conditions, several of which are in linkage disequilibrium with SNPs associated with endometriosis. Given these diverse associations, the function of *CDKN2B-AS1* remains an area of active investigation for many researchers [6].

C. GREB1 - Growth Regulation by Estrogen in Breast Cancer 1

In *GREB1*, rs13394619 is situated in an intronic region that lies between exons 9 and 10 [15]. It contributes to the hormone-dependent progression of breast cancer and codes for an early response gene associated with the estrogen regulatory system [16]. Its significance in estrogen-driven development in endometriosis is suggested by its increased expression in peritoneal eutopic endometriotic lesions as opposed to eutopic endometrium. It is still unknown, however, exactly what biological process it uses to support hormone-responsive tissues, including the estrogen-stimulated cell proliferation associated with endometriosis [17]. This region contains numerous other SNPs that have been reported to be associated with various traits and conditions at a genome-wide level, including obesity-related traits. However, none of these SNPs, including rs13394619, are in linkage disequilibrium [6].

D. FN1 - Fibronectin 1

In FN1, rs1250248 is situated in an intronic region positioned between exons 10 and 11 [17]. Numerous cellular functions, including cell adhesion and migration, which are essential for immunological defence, wound healing, embryogenesis, blood coagulation, and metastasis, depend on this gene [18]. Studies have demonstrated that one of the primary regulators of cell migration in ovarian cancer is *SOX2*, a gene that encodes a transcription factor targeting *the fibronectin receptor (FN1)* [19]. Additionally, *FN1* has been shown to modulate cytokine production in macrophages through the CpG motif-dependent pathway, thereby suppressing immune responsiveness via the TLR9 pathway. The *FN1* region has been linked to various traits in genome-wide association studies (GWASs); however, none of them are in linkage disequilibrium with the rs1250248 SNP [6].

E. ID4 - Inhibitor of DNA Binding 4

Located 52 kb downstream of ID4 is rs7739264 [20]. This gene is known as an ovarian oncogene that is absent in healthy ovaries, fallopian tubes, and other tissues but is overexpressed in the majority of primary ovarian malignancies. It is typically overexpressed in ovarian, endometrial, and breast cancer cell lines and has also been linked to breast carcinogenesis through methylation-related regulatory mechanisms [21]. *ID4* may cause transformation by controlling HOXA9 and CDKN1A, which coordinate transcriptional programs that disrupt the normal regulation of cell differentiation and proliferation [22]. It has been demonstrated that HOXA genes play a crucial role in determining the regional differentiation of the Müllerian duct into the oviduct, uterus, cervix, and vagina [23]. The genomic region encompassing the endometriosis-associated SNP rs7739264 includes a substantial number of SNPs that have been identified as linked to various characteristics and medical conditions in genome-wide association studies. However, none of them are in linkage disequilibrium with the rs7739264 SNP [6].

F. IL1A - Interleukin 1 Alpha

The IL1A gene encodes the interleukin-1 cytokine family member IL-1α. This gene is located 2.3 kb upstream of the rs6542095 variant. IL-1α is crucial in controlling the synthesis of chemokines and proinflammatory cytokines, thereby exacerbating inflammation [24]. Inflammatory mediator levels in serum and peritoneal fluid are elevated in endometriotic lesions, as numerous studies have highlighted [25]. GWAS have shown a positive association between endometriosis and the *IL1A* rs6542095 SNP, and it has been positively linked with stage III/IV endometriosis in both European and Japanese ethnic groups [26].

G. NFE2L3 - Nuclear Factor Erythroid 2-Like Factor 3

The NFE2L3 gene encodes a transcription factor belonging to the cap'n'collar basic-region leucine zipper family. The downstream locations of the rs12700667 and rs7798431 SNPs are 290 kb and 331 kb from the gene, respectively. This transcription factor is known to regulate cell differentiation, inflammation, and carcinogenesis [24]. In stage III/IV, women with the rs12700667 mutant allele (A) are more likely to develop endometriosis [27]. However, no correlation was found between endometriosis and the rs7798431 SNP [28].

H. RND3 - Rho Family GTPase 3

A member of the small GTPase protein superfamily is encoded by the RND3 gene, which is situated 280 kb downstream of the rs6734792 SNP [6]. Lacking GTP hydrolytic activity, this atypical Rho-GTPase is believed to negatively regulate cytoskeletal architecture, hence contributing to a loss of cell adhesion. It also functions as a general modulator of tumour proliferation and migration [29]. RhoA, which RND3 antagonises, exhibits a progressive rise in the normal endometrial stromal cells of healthy individuals compared to those from eutopic and ectopic sites in patients with endometriosis. These findings suggest that Rho GTPase inhibitors may offer a novel approach to treating endometriosis [27]. However, no association has been identified between endometriosis and the rs6734792 variant [24].

I. VEZT - Vezatin

The location of rs10859871 is 17 kb upstream of *VEZT*. A transmembrane protein that attaches to myosin VIIA in adherens junctions is encoded by this gene. In endometrial tissue samples, it demonstrates its increased expression levels and transcriptional silencing, which indicate that it may be a target for the endometriosis progression [30]. The *VEZT* rs10859871 SNP has been positively linked to endometriosis when the risk allele (C) is present. Additionally, there has been evidence of elevated *VEZT* expression in the endometrium and blood [31].

J. ETAA1 - Ewing's Tumour-Associated Antigen 1

The *ETAA1* gene is situated 227 kb downstream of the rs4141819 SNP [20]. *ETAA1* is responsible for encoding a novel repair protein that recruits replication protein A (RPA) to stop replication forks, thereby aiding their restart [32]. Additionally, in Ewing's family tumours, this gene acts as a cell surface antigen unique to tumours, thereby providing an extra diagnostic marker. The *ETAA1* rs4141819 variant is associated with a higher risk of developing stage III/IV endometriosis [27].

K. SYNE1 - Spectrin Repeat-Containing Nuclear Envelope Protein 1

A significant genotype–phenotype correlation has been identified for *SYNE1*. *SYNE1* encodes the Nesprin1 protein, a structural protein responsible for connecting the actin cytoskeleton and nuclear envelope. Patients with endometriosis carrying damaging variants within this gene exhibit severe endometriosis-related symptoms. Recently, this gene has been linked to the most common pain complaints related to endometriosis, including menstrual migraine, cyclic pelvic pain, dyspareunia, and dysmenorrhea. Delving deeper into the role of *SYNE1* variants in endometriosis-associated pain could prove crucial in unravelling the complex mechanisms underlying symptom severity and variability. This exploration may lead to the discovery of new molecular indicators for the future clinical treatment of patients with SYNE1 variants, enabling more effective clinical therapy. Personalised treatment plans can be activated to enhance the quality of life for patients [33].

L. FSHB - Follicle-Stimulating Hormone Subunit Beta

The FSH β-subunit is encoded by the *FSHB* gene, which forms the FSH heterodimer in association with an α-chain. FSH is crucial for many of the human reproductive processes and is involved in the HPG axis [34]. The anterior pituitary is where FSH is produced. FSH increases granulosa cell proliferation, follicle formation, estrogen synthesis, and the development of the androgen-converting enzyme aromatase in women when it binds to its G-protein-coupled receptor (FSHR) [35]. The pituitary's production and release of FSH are positively regulated by gonadotropin-releasing hormone (GnRH). By inhibiting GnRH and modulating activin-involved processes, estrogen, progesterone, and testosterone can control the transcription of the *FSHB* gene [36]. An increased risk of endometriosis may result from the stimulation of aberrant endometrial development by elevated FSH levels, either directly or indirectly [37].

M. ARL14EP - ADP-Ribosylation Factor-Like Protein 14 Effector Protein

Endometriosis has been associated with the 11p14.1 region, which contains the *ARL14EP* gene [38]. *ARL14EP* demonstrates robust expression in various tissues, including the brain, endometrium, ovary, lymph nodes, thyroid, and adrenal glands, among others [39]. The protein that *ARL14EP* encodes interacts with MYO1E, ACTB, and ARL14 to regulate the export of MHC II molecules [40]. Further targeted studies are now necessary to better understand the gene and its relationship to endometriosis [35].

N. ESR1 - Estrogen Receptor 1

The *ESR1* gene encodes estrogen receptor alpha, the most prevalent type of estrogen receptor present in the healthy endometrium. Therefore, genetic abnormalities in ESR1 may lead to abnormal gene expression and be linked to the aetiology and progression of endometriosis [41]. Several gene polymorphisms have been investigated for potential links to endometriosis, including rs9340799, rs2234693, rs3138774, rs3020348, rs1884052, and rs1159327. All infertile women with endometriosis in stages I/II and III/IV showed a substantial increase in *ESR1* transcripts, in contrast to fertile women [42].

Table-I: Genetic Factors Associated with Endometriosis and Their Functional Roles

Gene	Full Name	Associated SNP(s)	Function / Role	Relevance to Endometriosis
WNT4	Wingless-type MMTV integration site family member 4	rs7521902	Essential for female reproductive tract development and steroidogenesis	Linked to reproductive tract formation and metaplasia; variant associated with bone mineral density [4, 6, 11, 12]
CDKN2B-AS1	Cyclin-dependent kinase inhibitor 2B antisense RNA	rs10965235, rs1333049, rs1537377	Regulates tumor suppressors (p15, p16, p14ARF)	Involved in tumour suppression and epigenetic regulation; SNPs associated with endometriosis [4, 6, 14]
GREB1	Growth regulation by estrogen in breast cancer 1	rs13394619	Estrogen-responsive gene	Expressed in endometriotic lesions; linked to estrogen signalling and hormone-responsive growth [16, 17]
FN1	Fibronectin 1	rs1250248	Cell adhesion, migration, and immune response	Impacts immune response via TLR9 pathway; regulated by SOX2 [18, 19]
ID4	Inhibitor of DNA binding 4	rs7739264	Regulates HOXA9 and CDKN1A, oncogene	Overexpressed in gynaecological cancers; linked to Müllerian development [20, 21, 22, 23]
IL1A	Interleukin 1 Alpha	rs6542095	Regulates inflammation via cytokines	SNP associated with stage III/IV endometriosis; promotes proinflammatory state [24, 25, 26]
NFE2L3	Nuclear factor erythroid 2-like factor 3	rs12700667, rs7798431	Transcription factor for inflammation and differentiation	rs12700667 linked to stage III/IV endometriosis; rs7798431 not associated [24, 27, 28]
RND3	Rho Family GTPase 3	rs6734792	Modulates the cytoskeleton and cell adhesion	Altered expression in endometrial cells; potential therapeutic target, but SNP not directly linked [24, 29]
VEZT	Vezatin	rs10859871	Transmembrane protein in cell adhesion	Overexpressed in endometrial tissue; SNP associated with risk allele (C) [30, 31]
ETAA1	Ewing's Tumour-Associated Antigen 1	rs4141819	DNA replication stress response	SNP associated with increased stage III/IV risk [20, 27, 32]
SYNE1	Spectrin repeat-containing nuclear envelope protein 1	Not specified	Links the actin cytoskeleton to the nuclear envelope	Variants tied to severe endometriosis symptoms and pain phenotypes [33]
FSHB	Follicle-stimulating hormone subunit beta	Not specified	Controls FSH in the HPG axis	Elevated FSH is linked to abnormal endometrial growth [34, 35, 36, 37]
ARL14EP	ADP-ribosylation factor-like protein 14 effector protein	Not specified	Regulates MHC II export	Located in risk locus 11p14.1; expression noted in reproductive tissues [35, 38, 39, 40]
ESR1	Estrogen Receptor 1	rs9340799, rs2234693, rs3138774, rs3020348, rs1884052, rs1159327	Estrogen receptor alpha	Overexpressed in infertile women with endometriosis; tied to hormone signalling [41, 42]

As summarized in Table 1, multiple genetic loci have been associated with endometriosis, each contributing to various aspects of its pathophysiology. In addition to these previously established genetic factors, recent research has expanded our understanding of the disease by identifying new genetic, epigenetic, and molecular mechanisms. These include somatic mutations in eutopic endometrial tissue, epigenetic regulation

through microRNAs, and newly validated risk loci identified via genome-wide association studies (GWAS). Such findings underscore the complexity of endometriosis and highlight emerging diagnostic and therapeutic targets. A summary of these insights is presented in Table 2.

O. Epigenetic Mechanisms and MicroRNA Regulation

Epigenetic changes, including alterations in DNA methylation and histone modification, play a crucial role in the pathogenesis of endometriosis. MicroRNAs are particularly influential in regulating the expression and methylation of key genes, such as *WNT4* and *HOXA*, which are involved in endometrial proliferation and metaplasia. These regulatory mechanisms are potential diagnostic markers and therapeutic targets [43].

P. Somatic Mutations in Eutopic Endometrium

Recent evidence suggests that eutopic endometrial epithelial cells in women with endometriosis frequently harbour somatic mutations. These genetically altered progenitor cells may be responsible for initiating the development of ectopic lesions [44].

Q. Chromosomal Instability and Loss of Heterozygosity (LOH)

Cytogenetic analyses of endometriotic lesions reveal chromosomal anomalies and frequent LOH, particularly in cases progressing toward malignancy [45]. These findings suggest that endometriosis may follow a neoplastic-like progression pathway [46].

R. Expanded GWAS Insights

While GWAS have identified over 190 loci associated with endometriosis, replication remains limited. Nonetheless, several polymorphisms—such as rs13394619 (*GREB1*), rs7521902 (*WNT4*), and rs1250248 (*FN1*)—have been consistently validated, reinforcing their importance in disease susceptibility [47].

S. Polymorphisms in Vascular and Tissue Remodelling Genes

Genetic variations in angiogenesis and remodelling pathways have been associated with an increased risk of endometriosis [48]. Specifically, polymorphisms in *VEGF*, *MMP-1*, *MMP-3*, and *PAI-1* genes influence tissue invasion and lesion stability [49].

T. Oxidative Stress and Genetic Interplay

Genes involved in detoxification and redox balance, such as *NAT2*, have been associated with both endometriosis severity and infertility [50]. These genetic predispositions may increase vulnerability to oxidative stress, compounding inflammatory and pathological outcomes [51].

Table-II: Summary of Genetic Insights for Endometriosis

Genetic Feature	Role in Endometriosis	Notable Variants/Genes
Epigenetic Regulation	Controls gene expression (e.g., WNT4, HOXA, CDKN2A)	microRNAs, methylation changes [43].
Somatic Mutations	Alters epithelial progenitors, promotes ectopic growth	PTEN, KRAS mutations [44].
GWAS-confirmed SNPs	Established genetic risk	rs13394619 (GREB1), rs7521902 (WNT4), rs1250248 (FN1) [47].
Chromosomal Instability	Supports the neoplastic transformation model	LOH, chromosomal anomalies [45, 46].
Vascular/Tissue Remodelling Genes	Contribute to lesion formation and invasion	VEGF, MMPs, PAI-1 [48, 49].
Oxidative Stress Genes	May worsen infertility and disease severity	NAT2, GSTM1 [50, 51].

III. DISCUSSION

Genetic predisposition plays a central role in the development of endometriosis, with heritability estimates suggesting that approximately 51% of the disease risk can be attributed to inherited factors. Genome-wide association studies (GWAS) have consistently identified several key loci, including *WNT4*, *CDKN2B-AS1*, *GREB1*, *FN1*, and *ESR1*, implicating genes involved in reproductive tract development, hormone regulation, immune response, and cell adhesion. Notably, the *WNT4* gene, essential for Müllerian duct development, and the *CDKN2B-AS1* region, known for regulating tumour suppressor pathways, demonstrate how disruptions in developmental and cell cycle regulation pathways may contribute to ectopic endometrial growth. Similarly, *GREB1* and *ESR1* underscore the significance of estrogen-responsive mechanisms in disease progression, while FN1 and IL1A highlight their roles in inflammation and extracellular matrix remodelling. Recent findings have expanded this framework by revealing epigenetic and somatic genetic contributions. Epigenetic regulators, particularly microRNAs, influence key genes such as HOXA and WNT4, providing insight into how gene expression is dynamically altered in endometrial tissues. Somatic mutations in eutopic endometrial epithelial cells suggest that localised genetic changes may initiate the formation of lesions. Additionally, chromosomal instability and loss of heterozygosity in endometriotic lesions support a neoplastic-like model of disease progression in severe cases. Polymorphisms in vascular and remodelling genes, such as VEGF, MMPs, and PAI-1, further support the theory that aberrant angiogenesis and matrix degradation are crucial for lesion establishment. Moreover, detoxification genes like *NAT2* indicate that genetic susceptibility to oxidative stress may exacerbate inflammation and infertility in endometriosis patients. Together, these findings highlight the complex and multifaceted nature of endometriosis, which involves both inherited genetic risk and epigenetic modifications, as well as somatic alterations. Understanding these layers offers promising avenues for developing targeted diagnostics and personalized therapeutic strategies.

IV. CONCLUSION

In brief, effectively managing endometriosis requires a comprehensive approach that acknowledges its complex nature. Although the concept of backwards menstrual flow remains prominent and well-supported, understanding the detailed cellular and molecular processes underlying the condition is an ongoing pursuit. Genetic studies have identified various risk factors associated with endometriosis, highlighting the interaction between genetic elements and external factors in determining vulnerability to the disease. Nevertheless, turning these discoveries into customized treatment plans requires more investigation. Looking ahead, teamwork across different fields and the use of creative research approaches are crucial for deepening our understanding of endometriosis and improving patient treatment.

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After aggregating input from all authors, I must verify the accuracy of the following information as the article's author.

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