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HORMONAL AND GENETIC MECHANISMS OF ENDOMETRIOSIS: GENE POLYMORPHISMS AND EXPRESSION OF ESR1/ESR2, PGR, FSHR, AND LHCGR (A LITERATURE REVIEW)

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Abstract

Endometriosis is a chronic, estrogen-dependent inflammatory disease characterized by the presence of endometrium-like tissue outside the uterine cavity, affecting up to 10–15% of women of reproductive age worldwide [24, 14]. It is among the leading causes of chronic pelvic pain and remains one of the most common gynecological disorders, associated with a marked decline in quality of life and a substantial socio-economic burden [24, 14].

Despite a certain decrease in incidence reported in some regions, endometriosis continues to represent a major medical and public health challenge due to delayed diagnosis, pronounced clinical and molecular heterogeneity, and the limited effectiveness of currently available therapeutic approaches. Diagnostic delay often reaches 7–10 years, thereby facilitating disease progression, chronicity of inflammation, and the development of resistance to hormonal therapy [14, 12].

Contemporary concepts of endometriosis pathogenesis have evolved considerably—from isolated anatomical theories to an understanding of the condition as a systemic disorder driven by a complex interplay of hormonal dysregulation, immune inflammation, oxidative stress, and genetic and epigenetic alterations [17, 14]. A central element of this multi-level pathogenic cascade is local hyperestrogenism, resulting from autonomous estrogen synthesis within endometriotic lesions and altered sensitivity of target tissues to steroid hormones.

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A key component of endometriosis pathogenesis is impaired receptor-mediated responses to sex steroids. Altered expression of estrogen receptors (*ESR1/ESR2*) and progesterone receptors (*PGR*) shifts the balance between proliferative and apoptotic signaling, enhances inflammatory activity, and promotes progesterone resistance—one of the central molecular phenotypes of the disease [21, 12]. These disturbances contribute to the persistence of endometriotic tissue, maintenance of a chronically inflamed microenvironment, and reduced responsiveness to hormonal therapy.

An additional contribution to endometriosis pathogenesis arises from dysregulation of the hypothalamic–pituitary–ovarian axis, including changes in gonadotropin secretion and the functional consequences of polymorphisms and altered expression of the follicle-stimulating hormone and luteinizing hormone receptor genes. Such alterations may modify the hormonal milieu, folliculogenesis, and steroidogenesis, thereby shaping inter-individual variability in clinical presentation and disease course [17, 9].

Taken together, these data indicate that endometriosis develops and progresses not only as a consequence of anatomical factors but also through profound molecular remodeling of hormonal, receptor, and downstream signaling pathways. This underlines the relevance of a comprehensive review of the literature on hormonal and genetic mechanisms of endometriosis, aimed at identifying key molecular determinants of the disease and substantiating personalized diagnostic and therapeutic strategies.

Aim of the Study

This review aims to systematize current evidence on the hormonal and genetic mechanisms underlying endometriosis by analyzing polymorphisms in key genes involved in steroidogenesis and receptor regulation; additionally, it considers their potential role in clinical heterogeneity and reproductive outcomes.

Material Selection Methods

This study was conducted as a narrative review of the literature. Sources were identified through searches of PubMed/MEDLINE, Scopus, Web of Science, and

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Google Scholar covering the period 2010–2025. The search strategy used combinations of terms related to the disease, candidate genes, and genetic study design (endometriosis; *ESR1*, *ESR2*, *PGR*, *FSHR*, *LHCGR/LHR*; SNP, polymorphism, genotype, haplotype, gene expression, inflammation).

Eligibility criteria were as follows: (1) reporting data on polymorphic variants of the specified genes and/or their expression; (2) clinical and/or morphological verification of endometriosis; (3) specification of the genetic model and statistical measures of association (OR/95% CI or equivalent); and (4) publication in a peer-reviewed journal. Exclusion criteria comprised reports lacking a description of genotyping and/or expression analysis methods, review articles without primary data (with the exception of systematic reviews and meta-analyses), and duplicate publications.

A qualitative synthesis was performed: findings were grouped by gene and by outcome type (risk, severity, and phenotypic characteristics), with an assessment of consistency across populations and individual studies.

Contribution of *ESR1/ESR2* Polymorphisms to the Development of Endometriosis. The *ESR1* and *ESR2* genes encode the nuclear estrogen receptors ERα and ERβ, which mediate the biological effects of estradiol and determine hormonal sensitivity in the eutopic endometrium and endometriotic lesions. *ESR1* (ERα) is located on the long arm of chromosome 6 at 6q25.1, whereas *ESR2* (ERβ) maps to 14q23.2. Both genes exhibit substantial genetic variability, including single-nucleotide substitutions and repeat sequences, which has made them widely investigated as candidate genes for endometriosis [24].

Expression studies consistently indicate that endometriosis is accompanied by qualitative remodeling of the estrogen receptor profile. In endometriotic heterotopias—and, in some cases, in the eutopic endometrium—*ESR1* expression is decreased and *ESR2* expression is increased, resulting in a shift of the ERα/ERβ ratio toward ERβ [13, 24]. This receptor redistribution is considered one of the key molecular mechanisms supporting proliferation, inhibiting apoptosis, and amplifying inflammatory activity within endometriotic tissue.

Among ESR1 variants, the most extensively studied intronic SNPs are PvuII (*rs2234693*, T>C) and XbaI (*rs9340799*, A>G). Although these polymorphisms

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do not alter the amino acid sequence of the receptor, they may influence transcriptional regulation, alternative splicing, and overall gene expression levels. For ESR2, the most frequently analyzed variants include *rs4986938* (located in the 3′ untranslated region) and *rs1256049* (within the coding region), along with several less-studied SNPs examined predominantly in Asian populations [24].

In clinical genetic association studies, links between *ESR1* polymorphisms and endometriosis have shown marked population- and phenotype-specific heterogeneity. Paskulin et al. (2013), in a Brazilian cohort of infertile women, reported that carriage of the GG genotype of *rs9340799* (XbaI) was significantly associated with the presence of endometriosis; after adjustment for age, the odds ratio was 4.67 (95% CI 1.84–11.83). The authors also noted an association between this genotype and unfavorable outcomes of assisted reproduction, underscoring the potential clinical relevance of this variant in a reproductive context [15].

However, when evidence was aggregated in larger datasets, the conclusions became less consistent. In a meta-analysis by Zhao et al. (2016) spanning multiple populations, no robust association was identified between ESR1 *rs2234693* and *rs9340799* and overall endometriosis risk. Nevertheless, stage-stratified analyses suggested that the PvuII variant (*rs2234693*) may be associated with endometriosis at earlier stages (I–III) under a recessive genetic model, with an odds ratio of 1.53 (95% CI 1.05–2.21) [29]. These findings highlight the importance of accounting for clinical heterogeneity when interpreting genetic associations.

For ESR2, association results likewise remain conflicting. Several primary studies—particularly in Asian populations—have linked *rs4986938* to increased endometriosis risk or more severe disease forms, yet reproducibility has been limited. In a meta-analysis by Guo et al. (2014), pooled evidence did not support a statistically significant association between *ESR2* variants *rs4986938* or *rs1256049* and endometriosis risk in the overall population; the authors emphasized potential limitations related to small sample sizes and differences in study design [8].

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Experimental evidence on estrogen receptor regulation offers an important framework for interpreting the inconsistent reproducibility of genetic associations. Several studies have shown that reduced *ESR1* expression in endometriotic tissue may be linked to hypermethylation of *ESR1* promoter regions, whereas increased ESR2 expression appears to arise from combined transcriptional and epigenetic mechanisms [13, 24]. This suggests that polymorphic variants in *ESR1/ESR2* exert their effects within a complex regulatory network that includes epigenetic remodeling and tissue-specific reprogramming of hormonal responses in endometriosis.

Overall, available data indicate that endometriosis is characterized by a sustained disruption of estrogen receptor balance, with ERβ predominance over ERα, whereas associations between individual *ESR1/ESR2* polymorphisms and disease risk or clinical manifestations remain variable and depend on population background, disease stage, and reproductive phenotype. The most persuasive evidence concerns *ESR1 rs9340799* in the context of endometriosis accompanied by reproductive impairment [15], whereas for *ESR2*, the major contribution appears to reflect functional upregulation of receptor expression within endometriotic lesions rather than the effect of a single SNP [8, 24].

Role of PGR Gene Polymorphisms in the Development of Endometriosis. The *PGR* gene encodes the nuclear progesterone receptor, a key mediator of progesterone's anti-proliferative, anti-inflammatory, and differentiating effects in the endometrium. *PGR* is located on the long arm of chromosome 11 at 11q22–q23 and is expressed as two major isoforms, PR-A and PR-B, generated through alternative promoter usage. The balance between these isoforms is essential for normal endometrial receptivity and an adequate progesterone response [7, 16].

Experimental and clinical studies consistently demonstrate that endometriosis is characterized by progesterone resistance, manifested by reduced *PGR* expression and impaired progesterone-dependent transcription in both the eutopic endometrium and endometriotic lesions. Shved N.Y. et al. (2019) reported that *PGR* expression in endometriotic foci and in the endometrium of patients with external genital endometriosis shows substantial inter-individual variability and,

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in a subset of cases, is significantly reduced compared with controls, supporting the molecular basis of progesterone resistance in this condition [21].

Among *PGR* variants, the most extensively investigated in relation to endometriosis is the PROGINS haplotype, which comprises an Alu insertion within intron G together with linked single-nucleotide substitutions, most commonly tagged by rs1042838. This haplotype has been considered functionally relevant because experimental models suggest it may be associated with reduced receptor stability and attenuation of progesterone signaling [18, 1].

Association studies examining PROGINS and endometriosis have produced conflicting results. Several early reports described a higher frequency of PROGINS among women with endometriosis compared with controls, interpreted as a genetic predisposition to an altered progesterone response [18]. However, subsequent studies across different populations have not consistently replicated these findings. In a large population-based analysis, Trabert et al. (2011) found no strong independent association between *PGR rs1042838* and endometriosis risk, although *PGR* was considered within a broader hormonal pathway potentially involved in disease pathogenesis [26].

An attempt to synthesize the available evidence was undertaken in the meta-analysis by Hu et al. (2012), which assessed the association between PROGINS and endometriosis across ethnic groups. The authors observed a trend toward increased endometriosis risk among PROGINS carriers; however, the pooled estimate did not reach strict statistical significance (OR 1.43; 95% CI 0.99–2.08), suggesting a modest effect and potential dependence on population background and study design [10].

Despite the ambiguity of genetic associations, functional studies underscore the central role of *PGR* in endometriosis pathogenesis. Several reports indicate that decreased *PGR* expression—particularly reduced PR-B—is associated with impaired decidualization, heightened inflammatory responses, and reduced endometrial sensitivity to progestins [16, 5]. These alterations are considered a key molecular mechanism underlying the lack of efficacy of progestin therapy in a subset of patients with endometriosis.

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Overall, the evidence suggests that *PGR* contributes to endometriosis pathogenesis primarily through functional disruption of progesterone signaling and the development of progesterone resistance. Associations between individual polymorphisms, including the PROGINS haplotype, and endometriosis risk appear modest and not uniformly reproducible; nevertheless, when integrated with expression and functional data, they support the concept of endometriosis as a disorder characterized by an impaired hormonal response to progesterone [10, 26, 5].

FSHR in Endometriosis. The *FSHR* gene encodes the follicle-stimulating hormone receptor, a member of the G protein–coupled receptor family that mediates FSH actions in ovarian granulosa cells. Through activation of the adenylate cyclase–cAMP pathway, *FSHR* regulates folliculogenesis, steroidogenesis, aromatase expression, and estradiol synthesis. The gene is located on the short arm of chromosome 2 at 2p21, comprises 10 exons, and harbors several functionally relevant single-nucleotide polymorphisms that may modulate ovarian sensitivity to *FSH* [22, 11].

The most extensively studied *FSHR* variants are the nonsynonymous polymorphisms *rs6165* (Thr307Ala) and *rs6166* (Asn680Ser), which are in strong linkage disequilibrium and define the major receptor haplotypes. Although these variants do not disrupt receptor structure, they influence functional activity and surface expression density, as supported by both experimental and clinical studies [23, 11].

In the context of endometriosis, *FSHR* is viewed not as a primary susceptibility gene but rather as a modifier of the hormonal phenotype, capable of influencing clinical course and reproductive manifestations. In a study by Schmitz et al. (2015) involving women with endometriosis-associated infertility, genotype distributions for *FSHR rs6166* differed from those in controls, and carriage of the Ser680 allele was associated with reduced sensitivity to endogenous FSH and impaired ovulatory response [19].

Similar conclusions have been reported in clinical studies addressing outcomes of controlled ovarian stimulation. Bianco et al. (2021) showed that, among

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patients with endometriosis, the Ser/Ser genotype at rs6166 was associated with higher basal FSH levels, a reduced number of retrieved oocytes, and a less robust response to stimulation in assisted reproductive technology (ART) cycles. The authors emphasized that this polymorphism may partly explain variability in ovarian response among women with endometriosis who otherwise share comparable clinical characteristics [3].

In a review by Tanase et al. (2020) on genetic determinants of female infertility, *FSHR rs6165/rs6166* variants were consistently linked to changes in hormonal profiles and ovarian reserve; in the presence of endometriosis, their impact may be amplified by the co-existence of chronic inflammation and local hyperestrogenism. The authors highlighted that, in this setting, *FSHR* primarily determines individual sensitivity to hormonal stimulation rather than serving as an independent risk factor for endometriosis [25].

Additional evidence was provided by Conforti et al. (2022), who, based on a pooled analysis of clinical studies, reported that carriage of the Ser680 variant was associated with an increased risk of poor ovarian response to stimulation, with this effect persisting in subgroups of patients with endometriosis. The functional relevance of rs6166 was attributed to reduced FSH signal transduction, which may have clinical implications for selecting ovarian stimulation protocols and optimizing hormonal therapy [6].

Overall, available evidence indicates that *FSHR* contributes to the hormonal and reproductive phenotype in endometriosis primarily by modulating ovarian sensitivity to follicle-stimulating hormone. The *rs6166* (Asn680Ser) polymorphism appears to be the most clinically relevant *FSHR* variant, associated with variability in hormonal responsiveness and ovarian function in women with endometriosis, whereas a direct association between *FSHR* and overall disease risk has not been consistently demonstrated [19, 3, 6].

LHR (LHCGR) in Endometriosis. The *LHCGR* gene (also referred to as *LHR*) encodes the luteinizing hormone/choriogonadotropin receptor, a transmembrane G protein–coupled receptor that mediates the effects of LH and hCG in the ovary and other target tissues. Activation of *LHR* triggers the cAMP/PKA and MAPK

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signaling cascades, which regulate ovulation, luteinization, progesterone synthesis, and maintenance of corpus luteum function. *LHCGR* is located on the long arm of chromosome 2 at 2p21, comprises 11 exons, and harbors several functionally relevant polymorphisms that may modulate gonadotropin sensitivity [22, 2].

The best-studied *LHCGR* variant in relation to endometriosis and reproductive impairment is insLQ, an insertion of three amino acids (Leu–Gln) in the N-terminal extracellular domain of the receptor. This variant does not appear to impair ligand binding but may alter signaling efficiency and receptor activation kinetics, as supported by functional studies [23]. In addition, SNPs such as *rs2293275* (Asn312Ser) and *rs12470652* have been investigated; however, insLQ has received the greatest clinical attention.

Expression and functional data suggest that endometriosis may be associated with dysregulation of the hypothalamic–pituitary–ovarian axis, including alterations in the LH–LHR system. Reviews emphasize that chronic inflammation and local hyperestrogenism can modify ovarian responsiveness to LH, providing a biological context in which *LHCGR* genetic variants may shape the clinical phenotype of the disease [5].

Clinical genetic studies indicate that *LHCGR* is not a classical susceptibility gene for endometriosis; rather, its polymorphic variants are linked to endometriosis-associated reproductive disorders. In a Brazilian population study, Schmitz et al. (2013) reported that carriage of the insLQ variant was significantly more frequent in women with endometriosis and infertility than in fertile controls. The odds ratio for endometriosis-associated infertility among insLQ carriers was 3.05 (95% CI 1.40–6.64), suggesting a clinically meaningful effect size [20].

In a later study, Schmitz et al. (2015) simultaneously evaluated *LHCGR* and *FSHR* polymorphisms and showed that the combination of insLQ *LHCGR* with specific *FSHR* genotypes further exacerbated adverse reproductive phenotypes in women with endometriosis. The authors emphasized that the contribution of *LHCGR* becomes apparent primarily in the setting of established disease and is mediated through impaired ovulatory processes and luteal function rather than by increasing the risk of endometriosis per se [19].

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Evidence regarding the role of single-nucleotide polymorphisms such as *rs2293275* and other *LHCGR* SNPs is less consistent. Several population-based studies have not demonstrated significant differences in their distribution between women with endometriosis and control groups, supporting the concept that *LHCGR* exerts a secondary, modifying influence on disease manifestations [23, 25].

Collectively, these findings suggest that *LHCGR* acts as a modifier of the reproductive phenotype in endometriosis. The most compelling data involve the insLQ variant, which has been associated with endometriosis-related infertility and disturbances of ovulatory–luteal function. Unlike genes involved in steroidogenesis and sex-steroid receptor signaling, *LHCGR* appears to influence clinical outcomes not by promoting lesion formation but by altering ovarian responsiveness to LH in the context of chronic inflammation and hormonal imbalance [20, 19, 5].

Conclusion

Collectively, evidence on *ESR1/ESR2* and *PGR* indicates that the hormone-dependent component of endometriosis pathogenesis does not arise from isolated "defects," but rather from mutually reinforcing shifts, including local hyperestrogenism, altered receptor sensitivity, and attenuation of progesterone-mediated restraint of inflammatory–proliferative cascades. At the tissue level, this is reflected by marked variability in the expression of key hormonal targets, such that women within the same clinical category may exhibit fundamentally different molecular profiles. This heterogeneity—across both eutopic endometrium and ectopic lesions—and the lack of a single "typical" *ESR1/PGR* expression pattern support the rationale for molecular stratification and treatment personalization [21].

Within the estrogen receptor system, the most consistent finding across studies is a shift toward ERβ predominance: in endometriotic lesions, *ESR2*/ERβ expression is higher, whereas *ESR1*/ERα and *PGR*/PR (including PR-B) are lower than in normal endometrium [27, 28, 24]. This observation is clinically meaningful because receptor architecture determines how local estradiol excess

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is translated into downstream biological effects. Under ERβ dominance, estrogen signaling is more readily coupled to inflammatory mediators, prostaglandin circuitry, and anti-apoptotic programs, while reduced ERα and PR weaken physiological mechanisms of cyclic differentiation. Importantly, inter-study differences in *ESR2* levels are frequently attributed to epigenetic regulation of the promoter (CpG methylation) rather than inherited variants alone, which may partly explain the heterogeneity of SNP-association results across populations [27, 24].

Reduced progesterone sensitivity in endometriosis should be regarded as a nodal mechanism linking hormonal imbalance to chronic inflammation and therapeutic resistance. The classical model of progesterone resistance emphasizes PR-B deficiency and overall low PR expression in endometriotic tissue, leading to impaired stromal differentiation and insufficient inactivation of estradiol [4]. More recent clinicopathogenetic reviews similarly describe endometriosis as a state of PR deficiency within endometriotic stroma that underlies resistance to progesterone [5]. In this context, *PGR* polymorphisms (including the PROGINS haplotype) appear more plausibly as modifiers of susceptibility and treatment response rather than universal "risk genes," whereas a more robust biological marker is the tissue PR status and the PR-A:PR-B ratio [17].

Finally, the gonadotropin receptor block (*FSHR* and *LHCGR*) connects endometriosis to variability in ovarian responsiveness and folliculogenesis quality. The biological roles of *FSHR* and *LHCGR* as GPCRs governing follicular growth, ovulation, and luteinization are well established in foundational reviews [22, 2]. Clinically oriented studies and reviews highlight that SNPs in *FSHR* and *LHR/LHCGR* may be associated with ovulatory disturbances, and that within the inflammatory and hormonal milieu of endometriosis their phenotypic impact may become more pronounced [17]. This aligns with the "phenotype modifier" framework: such variants need not increase the risk of endometriosis itself, yet they may influence reproductive profile, ovarian reserve, and stimulation response—clinical parameters that directly shape prognosis and treatment strategy. In an ERβ-dominant, PR-deficient environment, even modest reductions

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in FSH/LH sensitivity or altered signaling dynamics may translate into clinically meaningful deterioration of folliculogenesis quality and luteal function [17].

Overall, the gene set reviewed here converges into a coherent causal framework: *ESR1/ESR2* determine the direction and "tone" of estrogen responsiveness (with ERβ predominance); decreased *PGR* expression and altered PR-A:PR-B balance establish progesterone resistance and remove physiological constraints on inflammation and proliferation; and *FSHR* and *LHCGR* modulate individual ovarian sensitivity to gonadotropins, thereby contributing to variability in reproductive phenotype and treatment response. The central message of this review is therefore not the identification of a single "key" polymorphism, but the necessity of interpreting hormonal–genetic factors as a network of interrelated modifiers that operate through tissue-level expression, epigenetic regulation, and the clinical heterogeneity of endometriosis [21, 24, 17].

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