

Review

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Review

Precision Therapeutic and Preventive Molecular Strategies for Endometriosis-Associated Infertility

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Abstract: Endometriosis, a chronic estrogen-dependent disorder defined by ectopic endometrial-like tissue growth, causes pelvic pain and infertility in reproductive-age women. Despite its prevalence, underlying mechanisms driving lesion persistence and reproductive impairment remain unclear. This review synthesizes recent pathophysiological advances, highlighting how hormonal dysregulation, immune dysfunction, epigenetic alterations, and oxidative stress collectively foster lesion persistence and treatment resistance. Critically, these molecular disturbances disrupt critical reproductive functions—including oocyte quality, endometrial receptivity, and embryo implantation. We further explore emerging non-hormonal therapeutic strategies, including MAPK and PI3K/AKT inhibitors as well as epigenetic agents targeting HOXA10 methylation and microRNA modulation, which offer fertility-sparing alternatives to conventional hormonal suppression. To enhance clinical translation, we propose a multi-level prevention framework—encompassing primary risk reduction, secondary biomarker-guided intervention, and tertiary fertility preservation—to anticipate disease progression and personalize reproductive care. By delineating shared pathways between endometriosis and infertility, this work advances precision medicine approaches for affected patients.

Keywords: Endometriosis-associated infertility; Epigenetics; biomarkers; prevention; Therapeutics

1. Introduction

Endometriosis—a chronic inflammatory disorder driven by estrogen-dependent growth of ectopic endometrial tissue—remains a formidable clinical challenge, profoundly impacting the physical, psychological, and reproductive health of 190 million women worldwide [1,2]. Despite affecting approximately 10% of reproductive-age women and up to 50% of infertility cases, its elusive pathogenesis results in diagnostic delays averaging 7-10 years and limited therapeutic efficacy beyond symptomatic control [3]. Crucially, molecular dysregulation lies at the heart of this disease. Aberrant estrogen signaling, progesterone resistance, and immune dysfunction collaborate to create a self-sustaining microenvironment that promotes lesion survival, angiogenesis, and therapeutic evasion [4,5]. These same mechanisms directly impair key reproductive functions and contribute to infertility: not merely through anatomical distortion, but by disrupting oocyte competence, endometrial receptivity, and embryo-maternal crosstalk. Even minimal disease can inflict molecular scars that compromise pregnancy chances.

This review deciphers how endometriosis hijacks reproductive biology at the molecular level. We first unravel the pathogenic triad (hormonal, immune, and epigenetic disturbances) fueling lesion persistence. We then expose their direct fallout on fertility—from folliculogenesis to implantation. By connecting these dots, we highlight actionable therapeutic windows and advocate for precision care tailored to women's reproductive aspirations.

2. Molecular Mechanisms of Endometriosis

The pathogenesis of endometriosis is driven by a complex interplay of hormonal, immune, oxidative, and epigenetic dysregulations. Estrogen excess and progesterone resistance sustain lesion growth, while chronic inflammation—mediated by interleukin (IL) -1 β and tumor necrosis factor (TNF)- α —amplifies tissue injury. Impaired natural killer (NK) cell activity, oxidative DNA damage, angiogenic remodeling, and epithelial-to-mesenchymal transition (EMT) further promote immune evasion and invasiveness. Together, these processes form a self-reinforcing molecular loop that underpins lesion persistence and reproductive dysfunction. The following subsections dissect the key pathways contributing to this pathogenic cascade.

2.1. Hormonal Dysregulation

Endometriotic implants acquire biochemical autonomy, transforming into miniature endocrine organs that escape the timing and magnitude of ovarian cycles. This autonomy is driven by an interplay of enzyme induction, receptor reconfiguration, and epigenetic dysregulation, resulting in local estrogen excess and progesterone resistance [6]. Estrogen production is amplified on two fronts. First, prostaglandin-E₂ (PGE₂) stimulates steroidogenic factor-1 (SF-1), enhancing Cytochrome P450 19A1 (CYP19A1) and aromatase expression and creating a feedback loop with estradiol and cyclooxygenase-2 [7–9]. Second, a recently documented sulfatase pathway supplements de-novo synthesis: steroid sulfatase liberates estrone from the abundant circulating reservoir of estrone-sulfate that is imported via the transporter Solute Carrier Family 10 Member 6 (SLC10A6), ensuring precursor availability even under low androgen conditions [10–12]. Simultaneously, reduced 17 β -hydroxysteroid dehydrogenase type 2 (17 β -HSD2) activity limits estradiol inactivation [13,14], amplifying local estrogenic effects.

Estrogen sensing is also altered. A dominance of Estrogen Receptor (ER) β over ER α in stromal cells promotes inflammation and reduces apoptosis, supporting lesion persistence [15–19]. Notably, ER β also activates NACHT, LRR and PYD Domains-Containing Protein 3 (NLRP3) inflammasome *via* caspase-1, increasing interleukin-1 β and linking estrogen signaling directly to sterile inflammation [20–22]. At the same time, cytoplasmic ER β disrupts TNF- α -mediated apoptosis by forming complexes with Apoptosis Signal-Regulating Kinase 1 (ASK1), Serine/Threonine Kinase Receptor-Associated Protein (STRAP), and 14-3-3 proteins [23–25]. Membrane-anchored G-protein-coupled estrogen receptor (GPER, also known as GPR30) accelerates estrogenic signaling by mobilizing cAMP and trans-activating SF-1, further boosting aromatase transcription [26–29]. This pathway may explain lesion responsiveness to environmental xenoestrogens like bisphenol A (BPA) and the Selective Estrogen Receptor Modulator (SERM) tamoxifen.

Hormonal dysregulation is closely tied to aberrant epigenetic regulation. Promoter hypermethylation and histone deacetylase (HDAC)-mediated repression of the progesterone receptor gene reduce progesterone receptor isoform B (PR-B) expression, a hallmark of progesterone resistance [30–33]. Estrogen enhances these changes by upregulating DNA methyltransferase 1 (DNMT1), promoting Runt-related transcription factor (RUNX3) hypermethylation and silencing [34]. BPA contributes through a WD repeat domain 5 (WDR5)/ten-eleven translocation methylcytosine dioxygenase 2 (TET2) axis that increases ER β transcription [35]. Metabolic–epigenetic crosstalk has recently emerged as a further amplifier. The cellular prion protein (PrPC) has emerged as an estrogen-responsive gene that represses peroxisome proliferator-activated receptor- α (PPAR- α), driving intracellular cholesterol accumulation and fuelling additional aromatase activity [36]. Estradiol, in turn, up-regulates PrPC, closing a vicious metabolic loop [37–39].

Collectively, enhanced enzymatic activity, altered receptor signaling, and epigenetic reprogramming shape an estrogen-dominant, progesterone-resistant environment that initiates and sustains downstream cellular dysregulation.

2.2. Epigenetic Reprogramming and Non-Coding RNAs

Endometriotic chromatin is marked by stable yet dynamic epigenetic alterations that reshape transcription long before lesions become clinically apparent. Recent methylome and histone-mark surveys confirm that DNA methylation and post-translational modifications cooperate to reprogram gene expression [40]. CpG hypermethylation at the promoters of Homeobox Protein A10 (HOXA10) and PR-B silences genes crucial for endometrial receptivity, reinforcing progesterone resistance and impaired decidualization [30,40–43]. These changes are strengthened by histone deacetylation—particularly via sirtuins and class-I/II HDACs—which enforce a transcriptionally repressive chromatin conformation. Superimposed on this epigenetic framework, non-coding RNAs exert an agile layer of gene regulation. MicroRNAs (miRNAs) such as miR-135a/b and miR-135b repress HOXA10 [44,45], mirroring its epigenetic silencing, while others (miR-29c, miR-194-3p) modulate immune response, stromal proliferation, and extracellular matrix dynamics [46–50]. These miRNAs, often upregulated by inflammatory cytokines, act as both sensors and amplifiers of lesion inflammation. Regulation becomes still more intricate with long non-coding RNAs (lncRNAs; >200 nt) and circular RNAs (circRNAs; covalently closed transcripts that resist exonuclease degradation) [51]. The lncRNA H19 sequesters multiple miRNA, facilitating EMT and immune evasion [52–54]. Parallely, circ_0007331 captures miR-200c-3p, stabilizing hypoxia-inducible factor-1 α (HIF-1 α) and promoting both steroid resistance and angiogenesis [55,56]. These lncRNAs and circRNAs engage in competing endogenous RNA (ceRNA) networks, modulating transcript abundance through shared miRNA interactions.

2.3. Intracellular Signaling Pathways

On top of the epigenetically altered chromatin landscape, endometriotic cells engage multiple constitutively active intracellular signaling pathways that drive their survival, invasion, and proliferation. The phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) and Wntless-related integration site (Wnt)/ β -catenin pathways are central to this dysregulated network, enhancing cellular fitness while promoting hormonal and immune escape [57–61]. Hyperactivation of PI3K–AKT–mTOR heightens glucose uptake, stimulates aerobic glycolysis and neovascularization, and impairs immune surveillance, thus granting ectopic foci a tumor-like resilience [62–64]. Activated AKT further diminishes progesterone-receptor activity, tightening the hormonal resistance already established by epigenetic modifications [65]. Simultaneously, dysregulated Wnt signaling facilitates nuclear translocation of β -catenin, which complexes with T-cell factor (TCF)/Lymphoid Enhancer-binding Factor (LEF) transcription factors to drive the expression of EMT markers, motility genes, and matrix-remodeling proteases such as matrix metalloproteinases (MMP)-2 and MMP-9 [60,66]. These pathways intersect with the transforming growth factor- β (TGF- β) signaling axis, an upstream conductor of EMT and fibrogenesis. Upon activation, (S) homologues of Mothers Against Decapentaplegic (SMAD) complexes cooperate with β -catenin and phosphorylated AKT to upregulate Snail Family Transcriptional Repressor 1 (SNAIL), Snail Family Transcriptional Repressor 2 (SLUG), and Zinc Finger E-box-Binding Homeobox 1 and 2 (ZEB1/2), repress E-cadherin, and induce vimentin and N-cadherin, thereby reducing cell–cell adhesion and promoting deep tissue invasion—hallmarks of advanced endometriosis [67].

Together, PI3K/AKT/mTOR, Wnt/ β -catenin, and TGF- β form a tightly linked, self-reinforcing network that integrates hormonal, inflammatory and metabolic signals. This robust molecular machinery converts endometrial cells into a semi-transformed phenotype that is plastic, invasive, and resistant to endocrine regulation—sustaining lesion persistence even in adverse peritoneal conditions.

2.4. Inflammation, Immune Cell Recruitment, and Neuro-Immune Crosstalk

Intracellular hyperactivation alone does not explain how ectopic tissue persist under mechanical stress and immune surveillance. The same signals that activate PI3K/AKT/mTOR and Wnt/ β -catenin pathways also ignite chronic inflammation, which recruits innate and adaptive immune cells and wires pain circuitry into lesions. Peritoneal fluid from affected women contains abundant macrophages, dendritic cells, neutrophils, mast cells, and both CD4⁺ and CD8⁺ lymphocytes. These cells accumulate in ectopic sites and amplify cytokine production [68–70]. Recent single-cell RNA sequencing (scRNA-seq) has identified a macrophage subset within lesions that mimics "foamy" tumor-associated macrophages. These cells suppress cholesterol-efflux pumps ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1), accumulate lipids, and hyperactivate IL-1 β /IL-6 inflammasomes and PGE₂ synthesis [71]. This links metabolic overload to the cytokine–pain axis and highlights ABCA1/ABCG1 and their upstream Liver X Receptor–Peroxisome Proliferator-Activated Receptor (LXR–PPAR) regulators as promising therapeutic targets.

Danger signals like hypoxia and oxidized cell debris drive the release of IL-1 β , IL-6, IL-8, TNF- α and IL-17A through Th17 differentiation. These cytokines are linked to immune dysfunction, angiogenesis and neuroinflammation [72–74]. IL-17A, in particular, promotes vascular endothelial growth factor (VEGF) transcription, enhances MMP production, and when neutralized, reduces vascularization and lesion size in models [75]. IL-1 β and TNF- α sustain this inflammatory state by upregulating cyclo-oxygenase-2 (COX2) and reinforcing the PGE₂-estrogen loop [29,76–78]. Complement activation further exacerbates the environment. Complement C5a receptor (C5aR1)-positive macrophages and Schwann cells heighten amplify inflammasome activity and mechanical allodynia [79]. Mast-cell infiltration also contributes. Tryptase-positive mast cells accumulate in deep infiltrating endometriosis, activating Protease-Activated Receptor 2 (PAR-2), promoting fibrosis and sustaining neurogenic inflammation [80]. All these cues converge on the TGF- β axis. Activated SMAD complexes work with β -catenin and phosphorylated AKT to upregulate SNAIL, SLUG and ZEB1/2, repress E-cadherin and promote fibroblast-to-myofibroblast transition, key events in matrix stiffening and fibrosis [81,82]. TGF- β also promotes immune tolerance by expanding Forkhead Box P3-Positive (FOXP3⁺) regulatory T cells and suppressing cytotoxicity [83–85]. Neuro-immune crosstalk closes the circle. Pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) induce nerve-growth factor (NGF) and brain-derived neurotrophic factor, which stimulate nerve fiber sprouting and lower nociceptor thresholds [86]. The resulting peritoneal niche is thus proinflammatory, neurotrophic, and angiogenic—conditions that support lesion growth, invasion, and pain.

2.5. Oxidative Stress and Peritoneal Toxicity

Retrograde menstruation and lesion hemorrhage expose the peritoneal cavity to hemolyzed erythrocytes. Macrophage-mediated clearance releases ferrous iron, overwhelming iron-binding proteins and triggering Fenton reactions that produce hydroxyl radicals. Elevated ferritin, transferrin, and free iron in peritoneal fluid coincide with oxidative damage markers, including lipid peroxides and protein carbonyls [87–91]. This oxidative stress disrupts mitochondrial membrane potential and electron transport, leading to cytochrome c release and impaired DNA repair [92–94]. Damaged macromolecules act as danger signals, attracting and activating macrophages and reinforcing inflammation [95]. Reactive oxygen species (ROS) also modulate gene expression by altering DNA methylation at antioxidant loci via Ten-Eleven Translocation dioxygenase (TET) enzymes, sustaining pro-survival transcriptional programs [96]. Systemically, ROS damage granulosa cells, impair mitochondrial distribution [97], reduce glutathione stores, and compromise meiotic spindle stability, factors that affect oocyte quality [98]. In the peritoneal niche, oxidative damage remodels the extracellular matrix by modifying structural proteins and activating redox-sensitive proteases, facilitating the invasive processes discussed in the next section.

2.6. Extracellular Matrix Remodeling, EMT, and Fibrogenesis

Oxidative and inflammatory cues initiate a cascade of structural remodeling in the extracellular-matrix (ECM). MMPs, particularly MMP-2 and MMP-9, drive ECM degradation and are elevated in serum, peritoneal fluid and lesion tissue [99,100]. Their role has now been confirmed by a 2024 meta-

analysis of over 1,000 patients [101]. Spatially divergent levels of tissue inhibitors of metalloproteinases (TIMPs) create gradients of proteolytic activity that guide directional invasion [102–104]. The urokinase-type plasminogen activator (uPA) system further enhances matrix remodeling. Overexpression of uPA and its receptor (uPAR) facilitates plasmin generation, which activates latent MMPs and degrades fibrin and fibronectin [105–107]. TGF- β -induced PAI-1 signaling through uPAR has been linked to endothelial senescence and fibrosis [108]. Concurrently, epithelial cells undergo EMT, losing polarity and epithelial markers like E-cadherin while gaining mesenchymal traits including vimentin and N-cadherin. These changes, driven by TGF- β , oxidative stress, hypoxia, and cytokines, are more pronounced in advanced disease stages [109,110]. Fibrogenesis is completed through TGF- β /SMAD-mediated conversion of fibroblasts into myofibroblasts, which deposit dense collagen I, fibronectin and laminin. Enzymes such as lysyl oxidase (LOX) stiffen this matrix, correlating with pain intensity, disease severity and surgical difficulty [111]. Redox-sensitive LOX-like proteins and angiotensin II/Angiotensin II Type 1 Receptor (AT1R) signaling further potentiate fibrosis [106]. In sum, ECM degradation, EMT, and fibrogenesis form a reinforcing loop that embeds endometrial cells within a fibrotic, immune-evasive niche.

2.7. Aberrant Vascular Remodeling and Non-Canonical Angiogenic Pathways

Endometriotic angiogenesis diverges markedly from physiological endometrial vascularization. Hypoxia and oxidative stress stabilize Hypoxia-Inducible Factor-1 α (HIF-1 α), which cooperates with inflammatory cytokines to drive a burst of VEGF-A. However, resulting vessels are disorganized, leaky, and poorly supported by pericytes [112,113]. Non-canonical angiogenic signals further shape the aberrant vasculature. The Slit guidance ligand 2 (Slit2)/Roundabout guidance receptor 1 (Robo1) guidance system disrupts vessel branching and stability [114,115], while prokineticin-1 (PROK1) and its receptor PROKR1 axis enhances endothelial proliferation and permeability. Importantly, PROK1 also interfaces with Nuclear Factor κ -Light-Chain-Enhancer of Activated B Cells (NF- κ B)-driven transcriptional programs, reinforcing the molecular crosstalk between angiogenesis, inflammation, and estrogen signaling [116]. Additionally, suppression of Notch/Delta-like ligand 4 (Dll4) signaling—normally a regulator of tip-cell formation—exacerbates vascular disorganization and excessive sprouting [117]. Collectively, these alterations generate a structurally unstable yet functionally permissive microvascular network that facilitates stromal invasion, immune cell infiltration, neural ingrowth and pain. Recognition of these VEGF-independent mechanisms opens new avenues for precision-based anti-angiogenic therapies

Together, these interwoven pathways—hormonal, inflammatory, oxidative, and structural—create a reinforcing network that sustains endometriotic lesions and impairs reproductive function.

3. Molecular Bridges Between Endometriosis and Infertility

Infertility associated with endometriosis unfolds as a progressive, system-wide injury that shadows every milestone of the reproductive journey—from initial follicle recruitment in the ovary to the moment a competent blastocyst meets a receptive endometrium. Lesion-derived cytokines, iron-driven oxidative bursts, endocrine disequilibrium and epigenetic drift leak far beyond ectopic implants, rewriting the molecular script of tissues that can appear perfectly normal on ultrasound or at laparoscopy. Recent single-cell atlases, high-resolution metabolomics and spatial transcriptomics now allow these hidden injuries to be traced with unprecedented precision, revealing a common signature of inflammatory, oxidative and hormonal stress across the ovary, fallopian tube and uterus [118]. Below, six interconnected facets illustrate how this ripple effect steadily erodes reproductive competence (Figure 1).

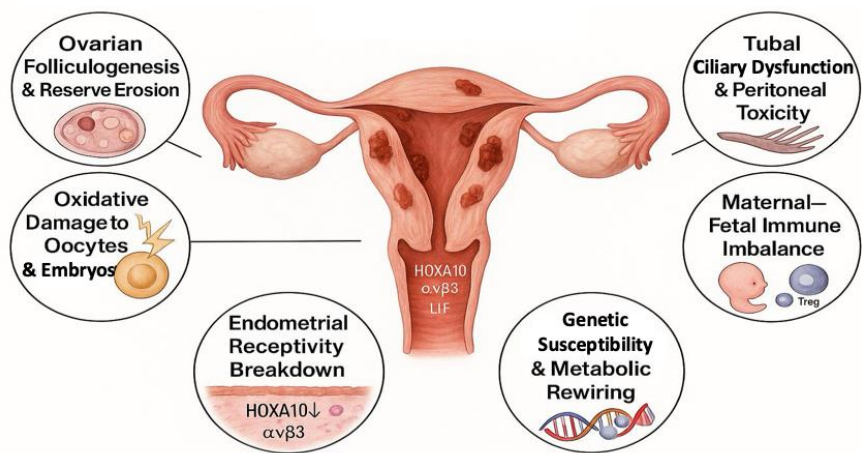


Figure 1. Interconnected mechanisms driving infertility in endometriosis.

3.1. Ovarian Folliculogenesis and Reserve Erosion

The ovarian environment in endometriosis is subject to persistent inflammatory and oxidative stress, which undermines folliculogenesis and progressively diminishes ovarian reserve. Key pro-inflammatory cytokines, including TNF- α and IL-1 β , have been shown to impair granulosa cell function, notably by downregulating essential genes such as the FSH receptor (FSHR) and aromatase (CYP19A1)—two critical mediators of follicle growth and estrogen synthesis [119–123]. The presence of endometriomas—ovarian cysts lined with ectopic endometrial tissue—exerts both mechanical and biochemical insults on adjacent ovarian cortex. The cyst fluid, often enriched with free iron, proteolytic enzymes, and ROS, contributes to stromal fibrosis, follicular apoptosis, and the premature activation of primordial follicles, which over time exhausts the follicular reserve. Clinically, these effects are reflected by lower serum anti-Müllerian hormone (AMH) levels and reduced antral follicle counts, both of which serve as biomarkers of diminished ovarian reserve [124]. While surgical excision of endometriomas is often necessary—particularly for large, symptomatic lesions—it carries the risk of unintentional removal of healthy cortical tissue, further compromising ovarian reserve. This trade-off highlights the importance of careful preoperative assessment, particularly in women of reproductive age, and supports the adoption of fertility-preserving strategies, including cyst-sparing techniques, ovarian tissue cryopreservation, or adjunctive medical suppression before and after surgery [125].

3.2. Oxidative Damage to Oocytes and Early Embryos

The same oxidative siege compromises oocyte integrity. Exposure of human oocytes to pathophysiological ROS ($\approx 150\text{ }\mu\text{M H}_2\text{O}_2$) disrupts mitochondrial distribution, fragments actin-microtubule scaffolds, and misaligns kinetochores, reducing fertilization [126–132]. Down-stream, early embryos from women with endometriosis display higher rates of fragmentation and developmental arrest, consistent with the carry-over of oxidative and spindle damage [133].

3.3. Tubal Ciliary Dysfunction and Peritoneal Toxicity

In endometriosis, the chronic inflammatory milieu extends beyond the pelvic lesions and profoundly affects the fallopian tubes and peritoneal environment, disrupting key steps in fertilization and early embryo transport. Elevated levels of pro-inflammatory cytokines, particularly IL-6 and TNF- α , have been shown to impair both ciliary activity and smooth muscle contractility, two essential mechanisms for gamete capture and embryo transit [134–136]. Chronic exposure to cytokines and prostaglandins damages the ciliated epithelium and impairs smooth muscle contractility, disrupting coordinated gamete and embryo transport [136,137]. Simultaneously, peritoneal adhesions resulting from fibrosis and scarring can form physical barriers that hinder

sperm-oocyte interaction and embryo migration. Additionally, the peritoneal fluid in endometriosis is enriched in pro-inflammatory cytokines, proteases, and ROS, which together create a toxic microenvironment detrimental to fertilization and early embryonic development [138–140].

3.4. Endometrial Receptivity Breakdown

Because the embryo reaches the uterus just a few days after fertilization, the brief “window of implantation” acts as the earliest decisive link between fertilization, blastocyst development, and uterine attachment. Disruption at this juncture can swiftly lead to infertility. Adequate endometrial receptivity remains indispensable for implantation [141], yet in women with endometriosis, key receptivity markers are epigenetically silenced [142,143]. Among these, HOXA10 is central to stromal differentiation and integrin expression, and its silencing results in reduced levels of integrin $\alpha\beta 3$, leukemia inhibitory factor (LIF), and glycodelin—all of which are critical for embryo adhesion [43,144,145]. Transcriptomic analyses show that over-expression of miR-135a/b reinforces HOXA10 silencing, tightening this epigenetic brake on receptivity [44]. Concurrently, diminished PR-B expression limits stromal decidualization and contributes to progesterone resistance [146,147]. These changes are reinforced by aberrant activation of PI3K/AKT and mitogen-activated protein kinase (MAPK) pathways, which further impair endometrial receptivity [148,149].

3.5. Maternal–Fetal Immune Imbalance and Implantation Failure

Once the blastocyst attaches to a receptive endometrium, the maternal immune system must swiftly shift from surveillance to tolerance at the maternal–fetal interface; in endometriosis, disruption of this transition forms the second critical bottleneck leading to implantation failure [150,151]. Dysfunctional uterine natural killer (uNK) cells exhibit altered cytokine secretion and reduced angiogenic potential, impairing spiral artery remodeling and early placental development [152]. Concurrently, a deficiency in regulatory T cells (Tregs) disrupts maternal immune tolerance, increasing the risk of embryo rejection [153,154]. A skew toward pro-inflammatory Th17 cells—driven by an up-regulated IL-23/Th17 axis—exacerbates oxidative stress and destabilizes the implantation micro-environment [155]. Clinical studies in women with repeated implantation failure confirm an elevated Th17/Treg ratio and heightened endometrial inflammation [156], underscoring the immunologic hurdle to successful nidation.

3.6. Genetic Susceptibility and Metabolic Rewiring

Even after fertilization and a provisional immune truce, inherited genetic variants and metabolic reprogramming can still compromise embryonic development and placentation—highlighting the substantial contribution of genetic predisposition to both endometriosis and infertility [157]. Genome-wide association studies (GWAS) have identified susceptibility loci such as Wnt family member 4 (WNT4), Vezatin Adherens junctions Transmembrane protein (VEZT), and cyclin dependent kinase inhibitor 2B antisense RNA 1 (CDKN2B-AS1) that influence uterine development, endometrial function, and cellular proliferation [158–160]. Metabolic reprogramming in endometriotic lesions—including altered tryptophan and arginine metabolism—perturbs immune regulation, redox balance, and local inflammation [161–163]. Targeted metabolomics has further uncovered dysregulated sphingolipid and ceramide pathways in follicular fluid from women with endometriosis, correlating with poorer *in vitro* fertilization (IVF) outcomes [164]. At the transcriptome level, compromised LIF- Signal Transducer and Activator of Transcription 3 (STAT3) signaling and progesterone response have been demonstrated in the eutopic endometrium of patients with repeated implantation failure [165], closing the loop between metabolic, inflammatory, and hormonal insults that collectively undermine reproductive success.

4. Emerging Therapeutic Targets in Endometriosis-Associated Infertility

Recent advances in the molecular understanding of endometriosis have catalyzed the development of targeted therapies aimed not only at symptom management but also at preserving and restoring fertility. This represents a shift away from traditional symptom-oriented treatments toward mechanistically driven interventions that directly address the biological underpinnings of

lesion persistence and reproductive dysfunction [166]. Several emerging non-hormonal approaches now focus on key molecular pathways—such as inflammation, oxidative stress, angiogenesis, and immune imbalance—central to the disease’s pathogenesis (Figure 2).

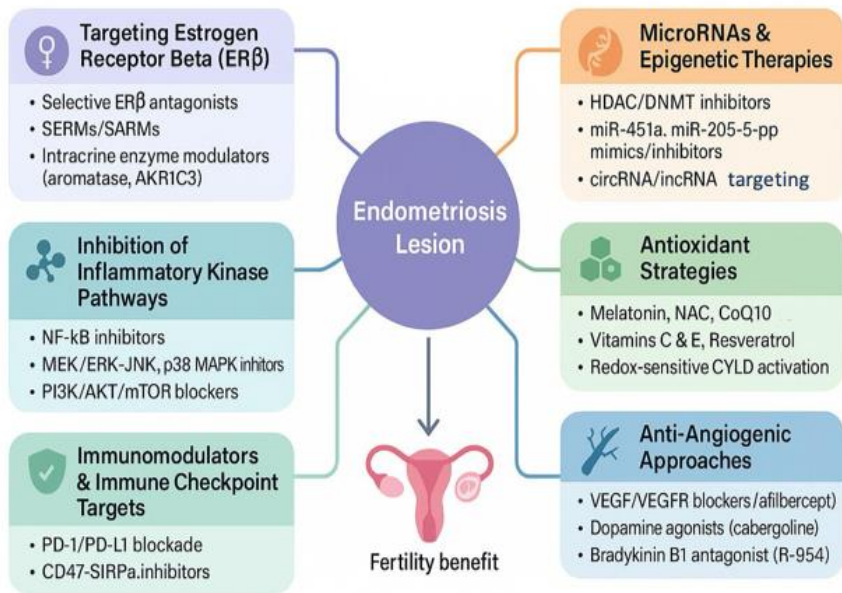


Figure 2:

Molecular landscape of non-hormonal therapies in endometriosis.

4.1. Targeting Estrogen Receptor Beta (ERβ) Signaling.

Endometriotic lesions consistently exhibit dysregulated estrogen receptor profile, marked by a heightened ERβ-to-ERα ratio. This receptor imbalance fosters a microenvironment marked by sustained inflammation, apoptotic resistance, progesterone insensitivity, and enhanced angiogenesis. Through transcriptional reprogramming, ERβ activation promotes lesion survival and impairs endometrial receptivity. Selective ERβ antagonists have demonstrated promising results in preclinical models, reducing lesion growth and partially restoring progesterone responsiveness [167,168]. Unlike systemic estrogen suppression, these compounds allow targeted modulation of local estrogen signaling without compromising ovulation, making them particularly attractive for fertility-preserving interventions. In parallel, attention has turned to intracrine steroidogenesis and receptor subtype modulation to recalibrate the hormonal landscape of the endometrium. Selective estrogen receptor modulators (SERMs), selective androgen receptor modulators (SARMs), and selective androgen receptor degraders (SARDs) are currently being explored for their capacity to restore endocrine balance and enhance receptivity without systemic suppression. These compounds frequently converge on metabolic enzymes such as aromatase, steroid sulfatase, and Aldo-Keto Reductase family 1 member C3 (AKR1C3), which regulate local estrogen and androgen biosynthesis within stromal and epithelial compartments. By modulating cross-talk among hormonal, immune, and vascular networks, these agents aim to reestablish a receptive endometrial microenvironment and improve fertility outcomes [169].

Altogether, ERβ-targeted therapies represent a compelling alternative to traditional hormonal suppression. Their ability to selectively modulate the pathological features of endometriotic tissue while preserving systemic reproductive function places them at the forefront of emerging fertility-friendly treatments.

4.2. Inhibition of inflammatory Kinase Pathways

Recent advances in the molecular profiling of endometriosis have highlighted several intracellular kinase pathways as central orchestrators of lesion persistence, chronic inflammation, and hormonal resistance. Among these, the NF- κ B pathway is one of the most consistently activated in ectopic endometrial tissue. Its sustained activation drives the transcription of pro-inflammatory cytokines, enhances anti-apoptotic signaling, and promotes an immune-tolerant lesion microenvironment [170,171]. The MAPK cascade — including extracellular signal-regulated kinases 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38— is similarly hyperactivated in endometriotic cells. This pathway promotes epithelial proliferation, matrix degradation, and immune cell recruitment. Moreover, the PI3K/AKT/mTOR signaling axis, which has been extensively characterized in oncology, supports stromal cell growth, neovascularization, and insensitivity to progesterone-based therapies [172,173].

Pharmacological inhibition of these kinase pathways has shown encouraging results in preclinical studies. For example, Mitogen-Activated Protein Kinase kinase (MEK) inhibitors (e.g., U0126) and NF- κ B pathway blockers (e.g., BAY11-7082) have been shown to significantly reduce lesion volume, epithelial proliferation, and inflammatory infiltration in rodent models. These agents also downregulate markers associated with proliferation (Proliferating Cell Nuclear Antigen (PCNA)) and invasion (MMP9), indicating a multi-layered effect on lesion pathophysiology [174]. The mTOR pathway has attracted significant interest due to its dual role in cell metabolism and immunomodulation. Inhibitors such as everolimus and rapamycin—already in clinical use for oncology and transplant medicine—are now being evaluated in endometriosis models. Beyond suppressing lesion growth, mTOR inhibition appears to improve implantation rates, reduce miscarriage risk, and preserve ovarian reserve in preclinical studies [175]. Additionally, when combined with hormonal therapies, mTOR blockade may help overcome progesterone resistance, thereby enhancing the efficacy of conventional treatments. Emerging evidence also implicates oxidative stress in the activation of kinase cascades within endometriotic lesions. The deubiquitinase cylindromatosis (CYLD), a redox-sensitive negative regulator of NF- κ B, has been proposed as a key modulator of inflammation in this context [176]. This highlights a mechanistic link between redox imbalance and sustained inflammatory signaling—an avenue that will be further explored in the section on antioxidant strategies.

Taken together, these findings support the repurposing of kinase inhibitors—originally developed for cancer and autoimmune diseases—as promising non-hormonal therapies in endometriosis. Their ability to target lesion growth, modulate inflammation, and restore reproductive function makes them attractive candidates for fertility-preserving treatment strategies.

4.3. Non-Hormonal Immunomodulation and Immune Checkpoint Targets

Immune dysfunction is a hallmark of endometriosis, characterized by chronic inflammation, impaired immune clearance, and local immune tolerance that permits ectopic tissue survival. In this context, immune checkpoint molecules such as programmed cell death protein 1 (PD-1) and its ligand PD-L1 have emerged as novel targets to restore immune surveillance and enhance endometrial receptivity. Although still in early stages of investigation, modulating PD-1/PD-L1 signaling holds promise for correcting immune escape and dampening lesion-associated inflammation [177,178]. Another promising axis involves the CD47–signal-regulatory protein alpha (SIRP α) pathway, through which ectopic stromal cells evade macrophage-mediated phagocytosis. CD47 is overexpressed in endometriotic lesions and binds to SIRP α on macrophages, delivering a “don’t eat me” signal. Experimental blockade of CD47 has been shown to promote phagocytic clearance and trigger apoptosis in ectopic cells, offering a dual mechanism to reduce lesion viability [179]. Additionally, several non-hormonal immunomodulatory agents are being explored to address the immune imbalance in endometriosis. TNF- α inhibitors such as etanercept and infliximab have demonstrated efficacy in reducing lesion volume and pelvic pain in animal models. Notably, recombinant human TNFRSF1A (r-hTBP1) significantly reduced lesion burden and inflammatory markers in primate models, without suppressing estrogen signaling—an advantage for fertility preservation [180–182]. IL-8, a chemokine involved in leukocyte recruitment and tissue remodeling, is also a target of interest. In a Phase 1 trial, the anti-IL-8 antibody AMY109 showed a favorable safety

and pharmacokinetic profile in both healthy women and patients with endometriosis. Crucially, it did not disrupt menstrual cycling, suggesting its potential compatibility with fertility goals [183]. However, not all cytokine-targeting interventions yield positive results. For example, interferon- α 2b was associated with increased recurrence rates postoperatively and lacked clear immunological benefit, highlighting the need for context-specific, precisely targeted immunotherapies [184].

4.4. Epigenetic Therapies and Non-Coding RNA Modulators

Epigenetic dysregulation is increasingly recognized as a central contributor to progesterone resistance and impaired endometrial receptivity in endometriosis-associated infertility. Key transcriptional regulators such as HOXA10 and the PR-B are frequently silenced via aberrant DNA methylation and histone deacetylation mechanisms. HDACs and DNA methyltransferases have been implicated in this repression, impairing stromal decidualization and progesterone responsiveness [33,185–187]. Pharmacological inhibitors of HDACs have demonstrated the ability to reverse these epigenetic marks, restoring transcriptional activity of implantation-related genes and offering a potential therapeutic pathway for patients unresponsive to hormonal therapies. For instance, treatment with the DNA demethylating agent 5-azacytidine (5-Aza) successfully reactivated HOXA10 expression in endometrial stromal cells, validating the role of promoter methylation in gene silencing [188].

Beyond chromatin-modifying enzymes, non-coding RNAs, particularly miRNAs, have emerged as powerful post-transcriptional regulators of gene networks involved in inflammation, hormone signaling, and extracellular matrix remodeling. Dysregulated miRNAs in endometriosis, including let-7b, miR-135a/b, and miR-29c, modulate key pathways relevant to implantation and lesion progression [189]. Therapeutic delivery of miRNA mimics or inhibitors (antagomirs) offers a highly specific strategy to reprogram pathological signaling. For example, inhibition of miR-451a in mouse models resulted in reduced lesion size and downregulation of multiple targets including 14-3-3 protein zeta/delta (YWHAZ), MAPK1, β -catenin (CTNNB1), and IL-6, underscoring its multifaceted action [190]. Similarly, targeting the circ_0007331/miR-200c-3p/HIF-1 α axis reduced angiogenesis and lesion invasiveness in vivo [191]. Fibrosis—a defining feature of deep infiltrating endometriosis—can also be modulated through miRNA-based interventions. Exosomal delivery of miR-214 suppressed connective tissue growth factor (CTGF) and collagen type I alpha 1 chain (COL1A1), reducing fibrosis in cell and xenograft models [192]. Moreover, miR-205-5p was found to inhibit stromal invasion by targeting angiopoietin-2 (ANGPT2) and repressing AKT/ERK signaling, with its expression inversely correlating with disease severity in patient samples [193].

4.5. Antioxidant-based Strategies and Redox Modulation

Oxidative stress is increasingly recognized as a key contributor to the reproductive complications observed in endometriosis, including oocyte damage, impaired fertilization, and embryo development arrest. Elevated levels of ROS disrupt mitochondrial function, impair chromosomal alignment, and activate inflammatory pathways like MAPK and NF- κ B, aggravating hormonal resistance [94]. In this context, antioxidant supplementation has been explored as a strategy to counteract redox imbalance. Vitamins C and E have been associated with improved oocyte quality and reduced oxidative markers in early studies [194]. Such interventions may be particularly relevant in assisted reproductive technologies (ART), where oxidative stress is amplified. Reviews have highlighted antioxidant potential to improve fertility outcomes in endometriosis patients [94,195]. Coenzyme Q10, by supporting mitochondrial bioenergetics and scavenging ROS, has shown benefits in oocyte maturation and embryo development under oxidative stress competence [194]. Melatonin, another potent antioxidant, improves mitochondrial function and reduces inflammation in preclinical endometriosis models [196–198]. N-acetylcysteine (NAC), a glutathione precursor, has demonstrated efficacy in reducing lesion size and inflammation while enhancing oocyte quality and fertilization in IVF cycles [199]. Plant-derived polyphenols exhibit a broad spectrum of bioactive properties, including antioxidant, anti-inflammatory, antiproliferative, and anti-angiogenic effects across various disease contexts, including cancer and reproductive disorders [200–202]. Among them, resveratrol has shown promise in improving endometrial receptivity and reducing lesion

vascularization, contributing to better implantation outcomes [202–204]. Although findings are encouraging, larger clinical trials are needed to confirm the impact of antioxidants on fertility outcomes in endometriosis [205]. Meanwhile, antioxidant therapies may serve as supportive options for patients experiencing oxidative stress-related reproductive impairment.

4.6. Anti-Angiogenic and Vascular Normalization Therapies

Pathological angiogenesis is a hallmark of endometriotic lesion development, supplying ectopic tissue with the vascular support necessary for survival, proliferation, and invasion. These lesions are marked by increased microvascular density, largely driven by overexpression of VEGF and its receptor VEGFR2, which orchestrate neovascularization in the peritoneal environment [206]. Inhibition of the VEGF/VEGFR axis has thus emerged as a promising non-hormonal strategy to suppress lesion progression. In preclinical models, VEGF inhibitors such as aflibercept—a recombinant VEGF-trap that sequesters VEGF-A—have demonstrated significant reductions in lesion size, VEGF expression, and CD31-positive microvessel density, outperforming leuprolide acetate in various histological parameters [207]. In parallel, the bradykinin B1 receptor antagonist R-954 has shown efficacy in reducing VEGF/VEGFR expression, cyst formation, cytokine production, and cellular infiltration in murine models, without disturbing estrous cyclicity, thereby supporting its compatibility with reproductive goals [208,209]. Dopaminergic compounds have also been evaluated for their anti-angiogenic effects. Dopamine receptor agonists such as cabergoline and quinagolide inhibit the VEGF/VEGFR2 cascade, limiting vascular expansion critical for ectopic lesion maintenance. Clinical evidence supports the relevance of this strategy: in women with endometriosis-associated hyperprolactinemia, quinagolide significantly reduced lesion vascularization and total lesion volume [210,211]. Collectively, these findings underscore a therapeutic paradigm shift toward vascular normalization, aimed at selectively impairing pathological angiogenesis while preserving endocrine function and endometrial receptivity.

Such approaches may provide valuable fertility-preserving alternatives to conventional hormonal suppression, particularly for patients actively seeking conception [212]. Table 1 summarizes the most promising candidates currently under investigation, detailing their mechanisms of action, stage of development, and potential impact on fertility outcomes.

Table 1. Promising molecular targets and their impact on infertility in endometriosis.

| Therapeutic Strategy | Molecular Target/ Mechanism | Effects on Endometriosis/Fertility | Development Phase | References |
|---|---|---|--------------------------------|-------------------|
| Selective ERβ antagonists | ERβ-mediated inflammation and progesterone resistance | Reduce lesion survival; restore PR-B signaling; preserve ovulation | Preclinical | [16,17,167,168] |
| Kinase inhibitors (MEK, mTOR, p38, JNK) | NF-κB; MAPK/ERK1/2; PI3K/AKT/mTOR pathways | Decrease lesion growth & inflammation; overcome progesterone resistance | Preclinical | [166,171,173–175] |
| Immune-checkpoint blockade | PD-1/PD-L1 and CD47-SIRPα axes | Restore immune clearance; lower lesion burden; enhance tolerance | Preclinical | [23,177–179] |
| Anti-TNFα therapy | TNFα-driven inflammatory pathways | Reduce pain, inflammation, and lesion size | Preclinical and early clinical | [166,180,181] |
| Anti-IL-8 therapy (AMY109) | IL-8 mediated chemotaxis and fibrogenesis | Suppress fibrosis and lesion expansion without disrupting cycles | Phase I clinical trial | [183] |

| | | | | |
|---|--|---|---|-------------------|
| Epigenetic modulators (HDACi, DNMTi) | HDACs & DNMTs at HOXA10 and PR-B promoters | Restore decidualization and uterine receptivity | Preclinical | [16,185–188] |
| Antioxidants (Vit C/E, CoQ10, NAC, melatonin, resveratrol) | ROS; MAPK & NF-κB activation | Improve oocyte/embryo quality; mitigate oxidative injury & inflammation | Preclinical and early clinical | [194,205,213,214] |
| Anti-angiogenic/vascular-normalisation agents | VEGF/VEGFR2 cascade; dopamine D2 agonists (cabergoline, quinagolide); bradykinin B1 | Reduce microvessel density; maintain endocrine function & fertility | Preclinical and Phase 2 clinical trial | [206–212] |
| miRNA-based therapy (miR-135a/b, miR-451a, miR-214, miR-205-5p) | Post-transcriptional control of HOXA10, VEGF, CTGF, ANGPT2, CTNNB1, etc. | Reprogram gene networks; suppress angiogenesis, invasion, and fibrosis | Preclinical | [44,190–193] |
| SERMs/SARMs/SARDs | ER-subtype balance; intracrine steroidogenesis (aromatase, steroid sulfatase, SLC10A6, AKR1C3) | Re-calibrate local hormones; improve endometrial receptivity | Preclinical and early-to-advanced clinical (Phase II–III) depending on compound | [169] |

Abbreviations (in alphabetical order): **AKR1C3** (Aldo-Keto Reductase Family 1 Member C3); **ANGPT2** (Angiopoietin-2); **CD47** (Cluster of Differentiation 47); **CoQ10** (Coenzyme Q10); **CYLD** (Cylindromatosis Deubiquitinase); **CTGF** (Connective Tissue Growth Factor); **CTNNB1** (Catenin Beta 1); **DNMTi** (DNA Methyltransferase Inhibitor); **ERβ** (Estrogen Receptor Beta); **ERK1/2** (Extracellular Signal-Regulated Kinase 1/2); **HDACi** (Histone Deacetylase Inhibitor); **HOXA10** (Homeobox A10); **IL-8** (Interleukin-8); **JNK** (c-Jun N-Terminal Kinase); **MAPK** (Mitogen-Activated Protein Kinase); **MEK** (Mitogen-Activated Protein Kinase Kinase); **miR** (microRNA); **MMP9** (Matrix Metalloproteinase-9); **mTOR** (Mammalian Target of Rapamycin); **NAC** (N-Acetyl-L-Cysteine); **NF-κB** (Nuclear Factor κ-Light-Chain-Enhancer of Activated B Cells); **PCNA** (Proliferating Cell Nuclear Antigen); **PD-1** (Programmed Cell Death Protein 1); **PD-L1** (Programmed Death-Ligand 1); **PI3K** (Phosphoinositide 3-Kinase); **PR-B** (Progesterone Receptor Isoform B); **ROS** (Reactive Oxygen Species); **SARM** (Selective Androgen Receptor Modulator); **SARD** (Selective Androgen Receptor Degradar); **SERM** (Selective Estrogen Receptor Modulator); **SIRPα** (Signal-Regulatory Protein Alpha); **SLC10A6** (Solute Carrier Family 10 Member 6); **TNF-α** (Tumor Necrosis Factor Alpha); **VEGF** (Vascular Endothelial Growth Factor); **VEGFR2** (Vascular Endothelial Growth Factor Receptor 2); **p38** (p38 Mitogen-Activated Protein Kinase).

While novel molecular approaches offer compelling therapeutic avenues, several obstacles continue to hinder their clinical implementation. Challenges include suboptimal pharmacokinetics, concerns about drug delivery systems, long-term safety and off-target effects [215], especially for RNA-based therapies [216–218]. Regulatory frameworks pose further barriers which demand extensive toxicological and immunogenicity profiling before clinical approval [219,220]. Finally, the high development costs combined with persistent underfunding of non-hormonal endometriosis research constrain the pace of innovation and hinder large-scale, fertility-focused clinical trials [221,222]. Bridging these translational gaps will require integrated efforts in research funding, regulatory strategy, and design of trials that prioritize reproductive endpoints.

5. From Risk Reduction to Fertility Preservation: Biomarker-Guided Strategies in Endometriosis Care

Although considerable molecular progress has been made in understanding endometriosis, preventive strategies—particularly those focused on fertility preservation—remain inadequately developed. Integrating biomarkers into the framework of preventive care represents a promising paradigm shift, offering the possibility to identify at-risk individuals, initiate earlier interventions, and optimize reproductive outcomes [223]. To date, no single biomarker has demonstrated sufficient accuracy or specificity to function as a standalone diagnostic or triage tool in clinical settings. Many of the candidate molecules identified thus far lack disease specificity and are also elevated in other inflammatory or physiological conditions, resulting in false positives and limiting their clinical applicability. However, recent advances in high-throughput omics technologies—including proteomics, transcriptomics, and metabolomics—have accelerated the identification of promising biomarker candidates with potential clinical relevance [224]. This section explores the emerging role of such biomarkers across three complementary levels of prevention. By supporting risk stratification before symptom onset (primary prevention), guiding ovarian preservation in early-stage disease (secondary prevention), and personalizing assisted reproductive protocols following surgical intervention (tertiary prevention), these approaches offer a path toward breaking the cycle of disease progression, recurrence, and infertility [225].

5.1. Primary Prevention: Risk Stratification and Early Identification

Primary prevention aims to reduce disease onset in asymptomatic individuals, particularly those with familial or genetic susceptibility. Well-known risk factors include early menarche, short menstrual cycles, nulliparity, and a family history of endometriosis—all contributing to prolonged estrogen exposure and retrograde menstruation [226,227]. Preventive strategies such as regular physical activity, early use of combined oral contraceptives, and minimizing chronic inflammation may attenuate hormonal and immunological drivers during adolescence.

Given the rapid evolution of the field, this section highlights a selection of recent studies—particularly those involving large patient cohorts or rigorous validation frameworks. However, we acknowledge that this is not an exhaustive review, and that numerous other promising genomic, epigenetic, proteomic, and miRNA biomarkers are currently under active investigation. A growing number of studies are seeking optimal combinations of markers with improved specificity and clinical utility, particularly for early diagnosis and patient stratification [228,229]. The coming years are expected to yield a significant expansion in the availability of validated, non-invasive biomarkers for endometriosis. Recent studies suggest that integrating molecular biomarkers into screening tools may allow for stratified risk assessment in asymptomatic individuals—especially first-degree relatives of affected women. Several GWAS have identified single-nucleotide polymorphisms (SNPs) in *WNT4*, Growth Regulation by Estrogen in Breast Cancer 1 (*GREB1*), and *VEZT*—genes implicated in genital tract development, hormonal signaling, cell proliferation, and tissue remodeling [230–233]. Recent large-scale, multi-ancestry GWAS, supported by transcriptome-wide (TWAS) and proteome-wide association studies (PWAS), have identified over 45 susceptibility loci for endometriosis, including ancestry-specific signals such as *POLR2M* in African-ancestry populations. These integrative -omics analyses revealed novel genes such as R-spondin 3 (*RSPO3*) (PWAS) and confirmed others like *GREB1*, *WNT4*, and Cell Division Cycle 42 (*CDC42*) (TWAS), implicating dysregulated Wnt signaling, immune pathways, and altered endometrial cell differentiation and migration [234]. These findings provide a genetic and molecular basis for developing polygenic risk scores and early screening strategies tailored to ancestry and molecular subtype.

In parallel, epigenetic alterations—particularly DNA methylation—are under investigation as predictive indicators. *HOXA10* promoter hypermethylation, a key regulator of endometrial receptivity, has been consistently found in eutopic and ectopic tissues. Although promising for diagnosis and prognosis, its sensitivity in early disease remains variable [42]. More recently, circulating cell-free DNA (cf-DNA) has emerged as a minimally invasive biomarker. Elevated serum cf-DNA—up to 3.9-fold in women with endometriosis—along with altered methylation patterns in genes such as Ribosomal RNA-Processing Protein 1 (*RRP1*), Disco-Interacting Protein 2 Homolog C (*DIPC2*), Ubiquitin-Specific Peptidase 1 (*USP1*), and *DNMT1*, highlights its potential for early-stage detection [235]. Beyond DNA methylation, circulating miRNAs are gaining attention as early

stratification tools. A five-miRNA panel (miR-17-5p, miR-20a-5p, miR-199a-3p, miR-143-3p, and let-7b-5p) distinguished cases from controls with 96% sensitivity and 79% specificity [236], while another six-miRNA signature (miR-125b-5p, miR-150-5p, miR-342-3p, miR-451a, miR-3613-5p, and let-7b) achieved an AUC of 0.94 for early-stage disease detection [237]. Several recent studies also identified additional miRNAs that regulate inflammation, fibrosis, and hormonal signaling, reinforcing their relevance in non-invasive detection [238,239]. Additional miRNAs with diagnostic potential continue to be identified, and future research is expected to refine and expand these panels for broader clinical application.

Proteomic approaches have yielded complementary insights. A large scale study involving over 800 women identified and validated a 10-proteins plasma panel—including Selenoprotein P, Neuropilin-1, Complement C9, and Vitamin K-dependent protein S—that discriminated endometriosis from both healthy and symptomatic controls with an AUC up to 0.997 [240]. These proteins reflect immune dysregulation, oxidative stress and, coagulation anomalies. In a separate prospective cohort, blood samples collected up to nine years before clinical diagnosis showed elevated levels of innate immunity proteins such as S100 Calcium-Binding Protein A9 (S100A9), Intercellular Adhesion Molecule 2 (ICAM2), DNA Topoisomerase I (TOP1), and CD5 Molecule-Like (CD5L), suggesting that systemic immune perturbations may precede clinical manifestation [241]. Proteomics remains an expanding area, with numerous candidate biomarkers currently being validated in longitudinal and multi-cohort studies.

Although traditional inflammatory markers like IL-8 and CA-125 lack adequate sensitivity and specificity for early-stage disease [242], they may gain clinical utility when combined with omics-based signatures [243,244]. Notably, circulating endometrial cells (CECs) have recently demonstrated superior diagnostic performance [245,246]. One study reported an 89.5% detection rate in endometriosis patients—significantly outperforming CA-125 and especially effective in early-stage detection [247]. Moreover, recent findings by Guder et al. demonstrate that elevated circulating Stress-inducible heat shock protein 70 (Hsp70) levels and mHsp70-expressing CECs (which share features with tumor cells) could serve as non-invasive diagnostic markers for endometriosis, particularly in extra-uterine cases, suggesting a pathogenic role of mesenchymal stem-like cells [248].

Beyond molecular diagnostics, mitigating modifiable environmental exposures remains key. Endocrine-disrupting chemicals (EDCs)—including dioxins, phthalates, and BPA—can epigenetically reprogram endometrial tissue, compromising receptivity and implantation [30,249–252]. Reducing exposure during gestation and adolescence represents a feasible public health strategy to lower long-term disease risk [253–255]. Additionally, diets rich in omega-3 fatty acids and antioxidants may help modulate oxidative and inflammatory pathways implicated in disease initiation [213,256,257].

In summary, primary prevention in endometriosis is evolving from generalized health recommendations to biomarker-guided, personalized risk stratification. Combining genomic, epigenetic, and proteomic data into predictive models may enable earlier intervention and improved fertility outcomes in high-risk, asymptomatic populations.

5.2. Secondary Prevention: Halting Disease Progression and Preserving Ovarian Function

Secondary prevention in women already diagnosed with endometriosis focuses on halting disease progression and preserving ovarian reserve before irreversible damage occurs. This approach emphasizes timely interventions guided by molecular biomarkers and personalized strategies to maintain fertility and prevent long-term reproductive sequelae [258,259]. Among the earliest indicators of ovarian compromise is a decline in serum AMH, which may precede reductions in antral follicle count or menstrual irregularity. AMH decline, alongside elevated FSH, has been consistently associated with diminished ovarian reserve in endometriosis patients [259–262]. More recently, insulin-like peptide 3 (INSL3) has emerged as a complementary marker reflecting ovarian stromal aging and functionality, although clinical validation is ongoing [263].

Epigenetic alterations also provide insight into disease activity and therapeutic targets. Hypermethylation of the HOXA10 gene, pivotal for endometrial receptivity, has been associated with progesterone resistance and aberrant Wnt/ β -catenin signaling. This methylation is frequently

observed in eutopic but not ectopic tissue, correlating with impaired implantation potential. Therapeutic agents such as Gonadotropin-Releasing Hormone (GnRH) analogs, letrozole, and metformin have been shown to restore HOXA10 expression, positioning it as a dual diagnostic and therapeutic candidate [42].

In parallel, miRNAs offer promising avenues for diagnosis, therapy, and fertility management. They serve as valuable biomarkers for disease activity and severity, with circulating and peritoneal miRNA profiles reflecting inflammatory and angiogenic dynamics [264–266]. Beyond their diagnostic utility, certain miRNAs, such as miR-451a, may enable non-hormonal therapeutic strategies targeting multiple pathways [190]. Moreover, recent studies have highlighted the role of miRNAs in fertility, identifying lesion-derived miRNAs in serum extracellular vesicles that may aid in optimizing assisted reproduction timing [267]. Notably, a saliva-based miRNA signature has demonstrated high diagnostic accuracy for infertility in endometriosis, opening the door to non-invasive and personalized fertility assessment [268,269]. While these results are compelling, many other miRNAs with predictive value are currently under investigation. The rapid expansion of miRNA-based studies is expected to yield optimized diagnostic and prognostic panels in the near future.

Oxidative stress is another central factor in oocyte quality and IVF success. Elevated follicular 8-hydroxy-2'-deoxyguanosine (8-OHdG) and imbalanced Glutathione (GSH)/Glutathione disulfide (GSSG) ratios reflect oxidative DNA damage and reduced embryo viability, making antioxidant therapy a rational preventive strategy [140,260,270]. Concurrently, follicular fluid miRNA profiles correlate with oxidative markers and oocyte competence, underscoring their value as integrated prognostic indicators for ART [271].

The endometrial microbiome has emerged as a key modulator of implantation, immune tolerance, and endometrial receptivity [272]. *Lactobacillus*-dominant profiles (LDM) are associated with higher pregnancy and live birth rates, while non-*Lactobacillus*-dominant microbiomes—rich in *Gardnerella*, *Prevotella*, or *Acinetobacter*—have been linked to implantation failure and poor endometrial receptivity [273,274]. Dysbiosis in women with repeated implantation failure (RIF) correlates with reduced expression of receptivity markers such as LIF, HOXA11, and VEGF. Recent clinical data support microbiota-targeted interventions in endometriosis. Transvaginal *Lactobacillus* supplementation has been shown to improve pregnancy rates in women with prior ART failure [275], while *Lactobacillus gasseri* reduced lesion growth in animal models by enhancing IL-2 production and NK cell responses [276]. A broader review also highlights the contribution of urogenital dysbiosis in sustaining chronic inflammation and promoting lesion recurrence [277,278]. Although current treatments for bacterial dysbiosis remain limited in the clinical practice, emerging strategies such as the use of pro- and prebiotics or microbial transplants, hold considerable promise for modulating the uterine microbiota. Nonetheless, randomized controlled trials are still required to evaluate their clinical efficacy, identify the most beneficial probiotic strains, and clarify their role in ART outcomes and fertility preservation. Future research should also focus on characterizing the composition of the upper female reproductive tract microbiota and elucidating the mechanisms underlying its relationship with endometriosis pathophysiology.

Multi-omic approaches continue to offer critical insights for individualized care. While discussed in detail in Section 5.1, their integration at this stage allows dynamic monitoring of biological activity and early detection of therapeutic windows [279]. This supports the move toward precision-based monitoring and fertility-preserving interventions in women with active disease. In summary, secondary prevention in endometriosis is moving toward a precision-medicine framework, integrating molecular, epigenetic, and microbial biomarkers to guide early therapeutic interventions. By stratifying patients based on biological activity rather than symptoms alone, clinicians can implement fertility-preserving strategies before significant ovarian compromise occurs—shifting the paradigm from reactive to proactive care.

5.3. Tertiary Prevention: Preventing Recurrence and Individualizing Long-Term Fertility Planning

Tertiary prevention in endometriosis focuses on reducing recurrence risk and supporting long-term fertility planning following surgical or medical management. Given the chronic and often relapsing nature of the disease, maintenance therapy is critical for sustaining remission, optimizing

reproductive outcomes, and preserving quality of life [258]. Hormonal maintenance, using combined oral contraceptives, progestins, or levonorgestrel-releasing intrauterine systems (LNG-IUS), remains the cornerstone post-surgery and is effective in reducing recurrence and preserving ovarian function [280–284]. These agents suppress ovulation and cyclic estrogen fluctuations, reducing inflammation and the potential for lesion reactivation. For patients with ovarian endometriomas, long-term hormonal suppression also mitigates the risks of inflammation-induced follicular damage and surgical insult to the ovarian cortex. Current strategies advocate for individualized regimens based on clinical phenotype, reproductive goals, and safety considerations, including the choice of hormone type and route of administration. Incorporating emerging molecular markers of disease activity into follow-up may further enhance early detection of recurrence and timely intervention [29,166]. Molecular diagnostics—such as miRNA panels, angiogenic markers like VEGF-A and miR-486-5p, and inflammatory mediators (IL-6, IL-8)—may allow for more precise risk stratification and longitudinal monitoring of residual or reactivating disease [265].

Fertility preservation remains a core component of tertiary prevention, particularly in women delaying conception. Cryopreservation of oocytes or embryos is increasingly recommended before repeat surgery, especially in cases of declining AMH, bilateral ovarian involvement, or diminished reserve [285–288]. Longitudinal assessment of AMH, Insulin-Like Peptide 3 (INSL3), and follicular fluid biomarkers (e.g., oxidative stress markers, follicular miRNAs) can help determine optimal timing for ART or preservation procedures [258,263,289]. In addition to hormonal and surgical considerations, patient education and clinician awareness are essential to maintaining reproductive health. Reducing diagnostic delay and promoting early initiation of maintenance therapy may have profound impacts on long-term outcomes. Multidisciplinary care models that incorporate reproductive endocrinologists, pain specialists, and fertility counselors are increasingly advocated.

In essence, tertiary prevention marks a transition from episodic treatment to a continuum of long-term, patient-centered care, integrating maintenance therapy, biomarker surveillance, reproductive counseling, and personalized follow-up to break the cycle of recurrence and protect reproductive health.

6. Conclusions and Perspectives

Endometriosis epitomizes a multifactorial and systemic disorder that transcends pelvic confinement, rooted in the complex interplay of hormonal dysregulation, chronic inflammation, epigenetic reprogramming, oxidative stress, immune dysfunction, and metabolic remodeling. Far beyond its physical manifestations, the disease disrupts the molecular architecture of both eutopic and ectopic tissues, compromising ovarian reserve, endometrial receptivity, embryo viability, and maternal–fetal immunotolerance. The present review underscores how estrogen dominance, progesterone resistance, and aberrant activation of signaling pathways (e.g., PI3K/AKT, MAPK) jointly sustain lesion survival, angiogenesis, and fibrotic remodeling, while also perturbing fertility-related processes at multiple levels. Importantly, infertility in endometriosis is no longer viewed as a mere consequence of anatomical distortion but is increasingly recognized as the result of deeply embedded molecular dysfunctions affecting gametogenesis, implantation, and systemic homeostasis.

Advances in high-throughput technologies have unveiled a wide spectrum of therapeutic targets—including ER β modulation, inflammatory kinase inhibition, epigenetic therapies, immune checkpoint regulators, miRNA-based strategies, and redox modulators—that collectively pave the way for personalized, fertility-preserving interventions. Several of these approaches, although still in the preclinical or early clinical phase, demonstrate tangible potential to move beyond hormone suppression, offering non-hormonal avenues for patients desiring conception. Simultaneously, the emergence of circulating biomarkers, polygenic risk scores, cfDNA methylation patterns, and proteomic signatures has begun to redefine the landscape of early detection and disease monitoring. This molecular arsenal supports the integration of stratified prevention into clinical care—from risk reduction in asymptomatic individuals (primary prevention), through fertility-preserving interventions in early disease (secondary prevention), to recurrence surveillance and reproductive planning after treatment (tertiary prevention). Taken together, these insights advocate for a paradigm shift toward translational precision medicine in endometriosis, where diagnostic, therapeutic, and

preventive strategies are molecularly guided and patient centered. To achieve this shift, clinical implementation will require the development of supportive infrastructure, including the integration of molecular diagnostics and longitudinal biomarker monitoring into assisted reproduction and gynecology care settings. Bridging fundamental mechanisms with clinical practice will not only improve reproductive outcomes but also transform endometriosis care into a proactive, multidisciplinary, and personalized continuum.

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Abbreviations

- The following abbreviations are used in this manuscript:
- 17β-HSD2 17β-Hydroxysteroid Dehydrogenase Type 2
 - 8-OHdG 8-Hydroxy-2'-Deoxyguanosine
 - ABCA1 ATP-Binding Cassette Transporter A1
 - ABCG1 ATP-Binding Cassette Transporter G1
 - AKR1C3 Aldo-Keto Reductase Family 1 Member C3
 - AKT Protein Kinase B
 - AMH Anti-Müllerian Hormone
 - ANGPT2 Angiopoietin-2
 - ASK1 Apoptosis Signal-Regulating Kinase 1
 - AT1R Angiotensin II Type 1 Receptor
 - BPA Bisphenol A
 - C5aR1 Complement C5a Receptor 1
 - CD5L CD5 Molecule-Like
 - CDKN2B-AS1 Cyclin-Dependent Kinase Inhibitor 2B Antisense RNA 1
 - CDC42 Cell Division Cycle 42
 - ceRNA Competing Endogenous RNA
 - CECs Circulating Endometrial Cells
 - circRNA Circular RNA
 - COL1A1 Collagen Type I Alpha 1 Chain
 - COX-2 Cyclo-Oxygenase-2
 - CTGF Connective Tissue Growth Factor
 - CTNNB1 Catenin Beta 1 (β-Catenin)
 - CYLD Cyldromatosis (Deubiquitinase)
 - CYP19A1 Cytochrome P450 19A1
 - DIPC2 Disco-Interacting Protein 2 Homolog C
 - Dll4 Delta-Like Ligand 4

| | |
|--------------------|--|
| DNMT1 | DNA (Cytosine-5) Methyltransferase 1 |
| EDC | Endocrine-Disrupting Chemical |
| ER | Estrogen Receptor (generic) |
| Er α | Estrogen Receptor Alpha |
| ER β | Estrogen Receptor Beta |
| ERK/ERK1/2 | Extracellular Signal-Regulated Kinase 1/2 |
| ESC | Endometrial Stromal Cell |
| FOXP3 ⁺ | Forkhead Box P3-Positive Regulatory T Cell |
| FSHR | Follicle-Stimulating Hormone Receptor |
| GnRH | Gonadotropin-Releasing Hormone |
| GREB1 | Growth Regulation by Estrogen in Breast Cancer 1 |
| GPER | G-Protein-Coupled Estrogen Receptor |
| GPR30 | G-Protein-Coupled Receptor 30 |
| GSH | Glutathione (reduced) |
| GSSG | Glutathione Disulfide (oxidized) |
| GWAS | Genome-Wide Association Study |
| HIF-1 α | Hypoxia-Inducible Factor-1 Alpha |
| HOXA10 | Homeobox A10 |
| ICAM2 | Intercellular Adhesion Molecule 2 |
| IL | Interleukin |
| INSL3 | Insulin-Like Peptide 3 |
| IVF | In Vitro Fertilization |
| JNK | c-Jun N-Terminal Kinase |
| LIF | Leukemia Inhibitory Factor |
| LNG-IUS | Levonorgestrel-Releasing Intrauterine System |
| lncRNA | Long Non-Coding RNA |
| LOX | Lysyl Oxidase |
| LXR | Liver X Receptor |
| MAPK | Mitogen-Activated Protein Kinase |
| MAPK1 | Mitogen-Activated Protein Kinase 1 |
| MEK | Mitogen-Activated Protein Kinase Kinase |
| miRNA | MicroRNA |
| mTOR | Mammalian Target of Rapamycin |
| MMP | Matrix Metalloproteinase |
| NAC | N-Acetyl-L-Cysteine |
| NLRP3 | NACHT, LRR and PYD Domains-Containing Protein 3 |
| NGF | Nerve Growth Factor |
| NF- κ B | Nuclear Factor κ -Light-Chain-Enhancer of Activated B Cells |
| NK | Natural Killer (Cell) |
| PAR-2 | Protease-Activated Receptor 2 |
| PCB | Polychlorinated Biphenyl |
| PCNA | Proliferating Cell Nuclear Antigen |
| PD-1 | Programmed Cell Death Protein 1 |
| PD-L1 | Programmed Death-Ligand 1 |
| PI3K | Phosphoinositide 3-Kinase |
| PPAR | Peroxisome Proliferator-Activated Receptor |
| PPAR- α | Peroxisome Proliferator-Activated Receptor Alpha |
| PR-B | Progesterone Receptor Isoform B |
| PROK1 | Prokineticin-1 |
| PROKR1 | Prokineticin Receptor 1 |
| PrPC | Cellular Prion Protein |
| PWAS | Proteome-Wide Association Study |
| r-hTBP1 | Recombinant Human TNFRSF1A |

| | |
|--------|---|
| ROS | Reactive Oxygen Species |
| RRP1 | Ribosomal RNA-Processing Protein 1 |
| RSPO3 | R-Spondin 3 |
| RUNX3 | Runt-Related Transcription Factor 3 |
| S100A9 | S100 Calcium-Binding Protein A9 |
| SARM | Selective Androgen Receptor Modulator |
| SARD | Selective Androgen Receptor Degradar |
| SERM | Selective Estrogen Receptor Modulator |
| SF-1 | Steroidogenic Factor 1 |
| SIRPα | Signal-Regulatory Protein Alpha |
| Slit2 | Slit Guidance Ligand 2 |
| SMAD | (S)-Homologues of Mothers Against Decapentaplegic |
| SNAIL | Snail Family Transcriptional Repressor 1 |
| SNP | Single-Nucleotide Polymorphism |
| STAT3 | Signal Transducer and Activator of Transcription 3 |
| STRAP | Serine/Threonine Kinase Receptor-Associated Protein |
| TET | Ten-Eleven Translocation Dioxygenase |
| TET2 | Ten-Eleven Translocation Methylcytosine Dioxygenase 2 |
| TGF-β | Transforming Growth Factor Beta |
| TIMPs | Tissue Inhibitors of Metalloproteinases |
| TOP1 | DNA Topoisomerase I |
| TNF-α | Tumor Necrosis Factor Alpha |
| Tregs | Regulatory T Cells |
| TWAS | Transcriptome-Wide Association Study |
| uNK | Uterine Natural Killer Cell |
| uPA | Urokinase-Type Plasminogen Activator |
| uPAR | Urokinase-Type Plasminogen Activator Receptor |
| USP1 | Ubiquitin-Specific Peptidase 1 |
| VEGF | Vascular Endothelial Growth Factor |
| VEZT | Vezatin Adherens Junctions Transmembrane Protein |
| WDR5WD | Repeat Domain 5 |
| Wnt | Wingless-Related Integration Site (Wnt) Family |
| WNT4 | Wnt Family Member 4 |
| YWHAZ | 14-3-3 Protein Zeta/Delta |
| ZEB1/2 | Zinc Finger E-Box-Binding Homeobox 1 & 2 |

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