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Mechanisms of Decidual Dysfunction and Infertility in Endometriosis: Roles of Prostaglandins and SASP

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ABSTRACT

Background: Endometriosis is a challenging disease to treat and one of the leading causes of infertility. Impaired endometrial receptivity, and particularly inadequate decidualization of endometrial stromal cells (ESCs), is a crucial component. Multiple inflammatory factors disrupt decidualization.

Methods: A comprehensive search of PubMed and Google Scholar (peer-reviewed journals only from 2000 to 2025) was performed in April 2025. The keyword "decidualization" was combined with "endometriosis", "infertility", and "inflammation". We summarize recent findings regarding the mechanisms of endometrial receptivity, focusing on the decidualization of ESCs, and discuss the impact of endometriosis, particularly in relation to PG metabolism and the senescence-associated secretory phenotype (SASP).

Main Findings: Endometriotic lesions demonstrate progesterone (P4) resistance and heightened inflammation due to elevated local estrogen levels and feedback loops involving PGE_2 and steroidogenic enzymes. Oxidative stress secondary to inflammation and menstrual blood in ectopic locations promotes lesion growth. Excessive numbers of senescent cells with SASP contribute to fibrosis in the lesions. Impaired decidualization also occurs in eutopic ESCs, which show epigenetic dysregulation and inflammation, and these have effects through P4 and PGE_2 signaling.

Conclusion: Both endometriotic lesions and eutopic endometrium in endometriosis patients exhibit changes that contribute to infertility, with abnormal inflammation and epigenetic modifications leading to impaired decidualization.

1 | Introduction

Endometriosis is a disease that is refractory to treatment and has a poor prognosis. It predominantly develops in women of reproductive age and is characterized by pelvic pain and dysmenorrhea [1–4]. However, it also induces infertility in approximately 50% of patients. The prevalence of endometriosis is high: it affects 10% of women of reproductive age and is present in 80% of patients with dysmenorrhea, corresponding to an estimated 2.6 million people in Japan [5]. The disease leads to a decline in the physical activity level and quality of life (QOL) of women who are socially active [6]. It is associated with changes in lifestyle, such as fewer births and later marriage, as well as exacerbations of menstruation-related symptoms and the associated uterine conditions [7]. The socioeconomic losses caused by menstruation-related symptoms are significant [8]. Although treatments such as medication and surgical lesion removal are used, it is difficult to achieve a complete cure, and the incidence of recurrence is high. Furthermore, when hormone therapy is administered, treating infertility becomes more challenging. Therefore, there is a growing demand for hormone-free treatments, and the elucidation of the mechanisms underlying the onset and progression of this disease is an urgent issue in the field of obstetrics and gynecology.

Endometriosis induces infertility through mechanisms such as the formation of adhesions between intraperitoneal tissues, which lead to structural changes in the reproductive organs [9, 10]. Thirty to 50% of patients with infertility have endometriosis. The formation of ovarian chocolate cysts and pelvic adhesions are believed to have negative effects on ovulation, oocyte pick-up by fimbriae of fallopian tube, tubal transport capability, sperm motility, and uterine muscle contraction [11, 12]. It has been reported that oocyte and early blastocyst development are impaired in patients [13]. In addition, not only these anatomic changes, but also the presence of ectopic lesions, increase the production of bioactive substances in the pelvis, causing inflammation and activation of the immune system [14–16], suggesting that the histologic and biochemical properties of eutopic endometrium are altered, which impairs fertility. However, current knowledge regarding the effects of ectopic endometriosis lesions on pregnancy is insufficient. Furthermore, the elucidation of pathology of endometriosis itself and the advent of innovative therapeutic drugs have been long awaited.

Pregnancy is established through the growth of fertilized oocytes, blastocyst implantation in the endometrium, and the formation of the placenta. The endometrium is composed primarily of stromal and glandular cells, and acquires the ability to receive the blastocyst, which is essential for implantation. In this review, we summarize the mechanisms underlying the acquisition of endometrial receptivity, particularly focusing on the decidualization of endometrial stromal cells (ESCs), and the impact of endometriosis on decidualization. We emphasize recent findings regarding pro-inflammatory factors and cellular senescence related to prostaglandins (PGs) and the senescence-associated secretory phenotype (SASP), including the results of our basic research. We also discuss the mechanisms involved in the induction of infertility and the effects of endometriosis-associated pathophysiology on eutopic ESCs.

2 | The Current State of Infertility Therapy in Japan and Overview of Pathophysiology of Endometriosis

Infertility is a challenge faced by approximately one in six adult women globally. In Japan, where birth rates and population size continue to decline, medical and social support for infertility patients is gaining attention. In 2024, the number of births fell below 700,000, which is approximately half of the figure of 40 years ago (1982; approximately 1.52 million) [17]. Both a decline in the population of women of reproductive age and the trend toward later marriage and childbirth contribute to this. In general, later marriage is associated with lower fertility because of a decline in ovarian reserve (the number of viable oocytes) and a lower capacity of the endometrium to accept blastocysts. In response to a growing demand for infertility treatment, advanced reproductive medical technologies have been developed. Currently, approximately one in ten children in Japan are born through assisted reproductive technology (ART). Advances in ART have made it possible to select competent high-quality embryos for transfer. However, the pregnancy rate remains around 30% [18], and recurrent implantation failure despite repeated embryo transfer remains the biggest challenge in infertility treatment. Unknown factors, including failures in endometrial implantation, are believed to disrupt the establishment and maintenance of a pregnancy. Therefore, understanding how endometrial receptivity to the blastocyst develops is crucial in reproductive medicine. Analyzing the mechanisms behind implantation failure could lead to diagnostic and therapeutic approaches for infertility.

The fundamental pathophysiologic mechanisms of endometriosis include a deterioration of the microenvironment of inflammatory lesions and dysregulation of hormonal signaling [19, 20]. However, none of the proposed theories-coelomic metaplasia, hematogenous and lymphatic dissemination, or stem cell theory [3, 4] can fully explain the diverse range of associated symptoms. The most widely accepted hypothesis is retrograde menstruation, which suggests that retrograde menstruation flows backward into the peritoneal cavity through the fallopian tubes, allowing endometrial cell masses, including stem cells, to settle on peritoneal organs and form lesions [21, 22]. These cells create a favorable environment for survival and proliferation, triggering angiogenesis, immune cell migration, and ultimately the development of ectopic tissue masses with chronic inflammation [16, 23]. However, despite the frequent occurrence of retrograde menstruation in many women, it remains unclear why only some women develop endometriosis. Endometriosis is estrogen-sensitive, and its lesions exhibit hypoxia, chronic inflammation, epithelial–mesenchymal transition (EMT), fibrosis, and the accumulation of immune cells and senescent cells [16]. These phenotypic aspects change vary with disease progression, leading to distinct pathological characteristics between lesions.

3 | Decidualization: The Mechanism and Its Significance in Pregnancy Establishment

This section explains the mechanisms of decidualization of the endometrium, an indispensable process for the establishment of pregnancy, focusing on endocrine regulation, its significance in pregnancy, and its association with factors such as PGs, cellular senescence, and SASP.

3.1 | Endocrine Regulation in Early Pregnancy: The Role of Sex Hormones in Implantation

During the secretory phase following ovulation, progesterone (P4) secreted by the corpus luteum induces ESC decidualization and endometrial gland maturation. This process is crucial for endometrial receptivity and is necessary for implantation. The blastocyst adheres to the luminal epithelial cells of the endometrium, penetrates the basement membrane, and invades the ESCs layer. Subsequently, the placenta is formed by the outer trophoblast of the blastocyst. Blastocyst contact, adhesion to the endometrial epithelium, and invasion into the stroma are essential processes of implantation.

The period during which the uterus is receptive to the blastocyst is limited and is referred to as “the window of implantation (WOI)” [24, 25] (Figure 1). Successful implantation, marking the establishment of pregnancy, requires both a blastocyst that is competent for implantation and an endometrium that is receptive. The WOI is the limited period during which the activation

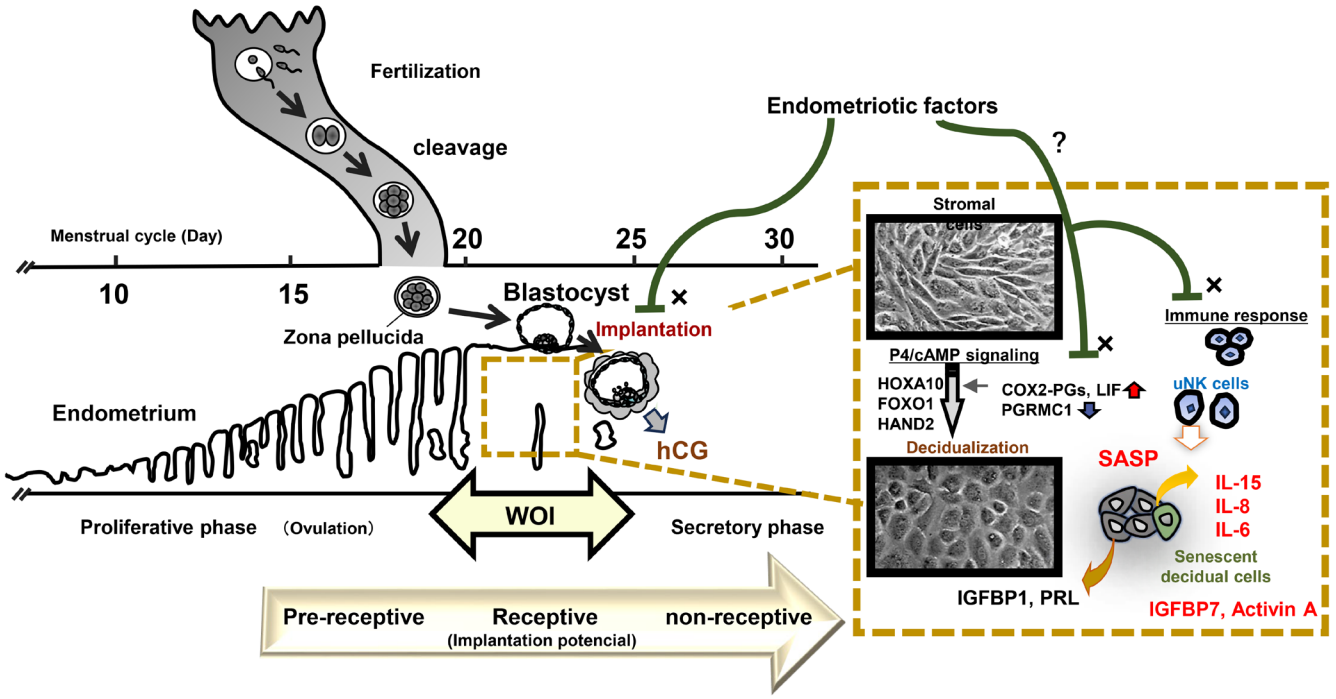

FIGURE 1 | Acquisition of uterine receptivity and possible effects of endometriosis-related pathology during implantation. Implantation and decidualization in the endometrium can only be successful during the appropriate window of implantation (WOI). The decidualization of endometrial stromal cells, which is the process of becoming receptive to the blastocyst, is essential for progesterone (P4)/cAMP signaling. This process involves increases in cyclooxygenase-2 (COX2), prostaglandins (PGs), and leukemia inhibitory factor (LIF), and a decrease in progesterone receptor membrane component 1 (PGRMC1) expression. In addition, some of the decidualized cells transform into senescent decidual cells and display the SASP, which is associated with the secretion of various cytokines that regulate immune cells, such as uterine natural killer cells. These steps may be influenced by abnormalities related to endometriosis, potentially leading to infertility.

of the blastocyst, which is associated with the disappearance of the zona pellucida, overlaps with receptivity of the endometrium. The timing of the WOI is controlled by P4 and estrogen secreted by the corpus luteum and can be divided into three phases: the pre-receptive (early secretory), receptive, and non-receptive phases. The WOI corresponds to the receptive phase. The pre-receptive phase comprises the period between ovulation, triggered by the luteinizing hormone surge, and the start of the receptive phase, which lasts approximately 7 days, and up to 10 days.

The decidualization of ESCs occurs under the influence of P4, which is synthesized and secreted in large amounts by the corpus luteum after ovulation. Decidualization involves cellular reprogramming, which includes cytoskeletal and extracellular matrix (ECM) restructuring, a metabolic stress response, and an inflammatory response. Changes in the expression of the transcription factors homeobox A10 (HOXA10), forkhead box protein O1 (FOXO1), and heart and neural crest derivatives expressed 2 (HAND2) play crucial roles in uterine receptivity [26]. HOXA10 is a transcription factor that regulates the expression of genes essential for endometrial decidualization and embryo implantation [27]. P4 modulates HOXA10 expression, enhancing endometrial receptivity. Furthermore, HOXA10 contributes to P4-mediated immunosuppression, adjusting the immune response in the endometrium during implantation. FOXO1 plays a critical role in the decidual process of ESCs, controlling the transcription of decidual prolactin (dPRL) and insulin-like growth factor-binding protein 1 (IGFBP1) [28, 29]. Additionally, FOXO1 contributes to the structural integrity of endometrial epithelium and the regulation of the P4 receptor expression, thereby influencing P4 signaling [30]. At the implantation sites, FOXO1 facilitates embryonic invasion by promoting differentiation and apoptosis of endometrial epithelial cells. HAND2 is induced in a P4-dependent manner and suppresses the expression of fibroblast growth factors (FGFs) in ESCs, thereby inhibiting estrogen signaling and creating an environment conducive to implantation [31]. HAND2 interacts with the orphan nuclear receptor NR2F2 (nuclear receptor subfamily 2 group F member 2) to regulate the effect of P4 in the endometrium, promoting ESCs differentiation [32]. Dysregulation of the HAND2-NR2F2 axis, akin to HOXA10 and FOXO1 anomalies, can impair endometrial receptivity and contribute to infertility.

When the blastocyst adheres to the endometrial epithelium, it breaks through the epithelium, and decidualized cells migrate to encircle the implanting embryo, protecting it from maternal immunologic rejection and oxidative stress [33]. At the fetal–maternal interface, modulation of the local immune response and the antioxidant stress response to reactive oxygen species (ROS) are triggered by the mobilization of immune cells such as uterine-specific natural killer (uNK) cells that are present in the uterus [34–36]. ROS plays a pivotal role in early pregnancy stress responses; while moderate levels support embryonic development, excessive ROS may induce cellular damage [37, 38]. P4 modulates ROS production and activates antioxidant stress responses, thereby optimizing embryo survival conditions. By stimulating the antioxidant system and mitigating oxidative stress caused

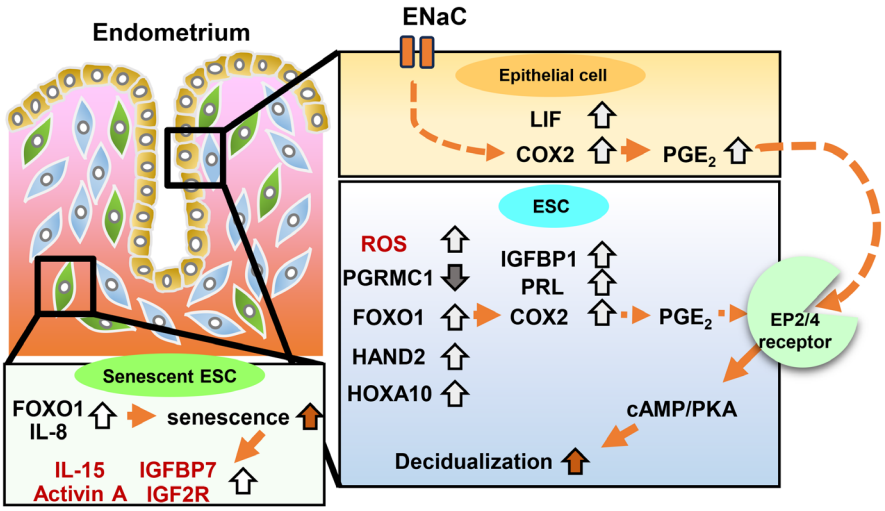

FIGURE 2 | Schematic of the role of PGE_2 and other crucial factors in the decidualization of the endometrium. Prostaglandin E2 (PGE_2), which is produced by endometrial glandular epithelial cells and promotes implantation and decidualization, facilitates decidualization via EP2/4 receptors on stromal cells (ESC) and cAMP signaling. The inhibition of PGRMC1 function promotes PGE_2 production through the expression of cyclooxygenase-2 (COX2) in both epithelial and stromal cells, thereby enhancing decidualization. In addition, senescent ESCs, which increase in number during decidualization, show high expression of IL-15, activin A, Insulin-like growth factor-binding protein (IGFBP)7, and IGF2 receptor (IGF2R).

by excessive ROS, P4 contributes to pregnancy success [39]. P4 regulates immune cell activity within the endometrium to sustain an optimal immune environment [40, 41]. Specifically, it promotes immune tolerance essential for pregnancy maintenance, favoring a Th2-dominant immune response while suppressing Th1-mediated reactions. Additionally, P4 inhibits the production of pro-inflammatory cytokines, preventing excessive inflammation in the endometrium and thus fostering conditions suitable for implantation [42]. A spontaneous decidual reaction occurs in humans that is primarily under the control of sex hormones, regardless of the presence or absence of the blastocyst.

3.2 | Significance of Decidualization in Pregnancy

During early pregnancy, extravillous trophoblast cells infiltrate the basal decidua and replace endothelial cells of the maternal spiral artery, thereby directing blood flow into the intervillous spaces [35, 43]. Decidualized tissue is essential for the formation of the placenta and the maintenance of pregnancy. ECM remodeling, the immune response, the antioxidative response, and angiogenesis are regulated through autocrine and paracrine mechanisms during decidualization [44, 45]. Impaired decidualization may be linked to infertility, recurrent miscarriage, and uteroplacental disorders. Decidual cells function as biosensors, selecting viable embryos during implantation [46]. In co-culture systems, normal decidual cells migrate toward the blastocyst, but react less to abnormal embryos. Impaired migration may lead to the acceptance of abnormal embryos, increasing miscarriage risk. Patients with recurrent miscarriage typically have endometrial cells that interact indiscriminately with embryos [47], suggesting uterine embryo selection. Defective stromal cell biosensing may lead to implantation failure and miscarriage. In addition, abnormal decidualization may contribute to pregnancy disorders involving hypertension. Artificial decidualization, induced in vitro via the medroxyprogesterone (MPA)/cyclic AMP (cAMP) axis, is impaired in ESCs from non-pregnant women with a history of pre-eclampsia, and the medium conditioned by these cells inhibits trophoblast invasion [48]. These abnormalities persist postpartum, potentially contributing to severe hypertensive disorders of pregnancy (HDP). The decidua, as the foundation of the placenta, regulates trophoblast invasion, facilitates fetal immunotolerance, and is expelled with the placenta at birth. Thus, a comprehensive understanding of the mechanisms underlying decidualization is essential for enhancing the success rates of ART and advancing the development of innovative treatments in reproductive medicine.

3.3 | PGs, Cellular Senescence, and SASP in Implantation and Decidualization

3.3.1 | PGs

PGs, lipid mediators synthesized from arachidonic acid via cyclooxygenase (COX1 and COX2), bind to specific G protein-coupled receptors (GPCRs) to regulate diverse cellular functions. In rodents, embryo implantation is mediated by COX-derived PGs [49, 50], and COX2 plays a crucial role in reproductive processes such as ovulation, fertilization, and decidualization, as demonstrated by the infertility of COX2 knockout mice [51]. At implantation sites, vascular permeability increases significantly, triggering an inflammation-like response. COX2 is expressed not only in ESCs, but also in epithelial and perivascular cells of human endometrium [52]. During implantation, the epithelial sodium channel (ENaC)-dependent cAMP-response element-binding protein (CREB)/$COX2/PGE_2$ pathway is activated in epithelial cells. The extracellular PGE_2 release involves multidrug resistance protein 4 (MRP4), a member of the ATP-binding cassette transporter family [53]. The absence of COX2 causes delayed implantation, embryo crowding, and impaired fetal placental development, but also inhibits decidualization. High cAMP concentrations, which are induced by P4 and PGE_2, are essential for

decidualization [54, 55] (Figure 2). Under the influence of P4 and intracellular cAMP signaling, ESCs differentiate from fibroblast-like cells into pavement-like decidual cells, secreting IGFBP1 and dPRL in humans.

Various substances, including androgens, promote decidualization [56–58]. IGFBP1 and PRL facilitate trophoblast growth and invasion, modulate uNK cell survival, prevent immune rejection, and enhance angiogenesis. In mice, PGI_2 plays a critical role in embryo implantation by activating the nuclear receptor peroxisome proliferator-activated receptor (PPAR)δ, rather than a GPCR [59, 60]. PGE_2 and PGI_2 promote decidualization through the prostanoid EP2/EP4 receptor and PPARδ, respectively. The cAMP signaling pathway increases COX2 expression in human endometrial epithelial cells [61, 62]. During early pregnancy, cytosolic phospholipase A2α (cPLA2α), expressed in the uterus, is crucial for regulating PG levels and embryo implantation [63, 64]. Lysophosphatidic acid (LPA) is also essential for embryo implantation, with its receptor, LPAR3, playing a key role in the regulation of inter-embryo spacing. Lpar3-deficient mice show delayed embryonic implantation and irregular uterine spacing, reducing litter size and causing placental sharing [65]. Proper regulation of lipid mediators in the uterine COX–PG axis is vital for successful early pregnancy. Leukemia inhibitory factor (LIF), an essential IL-6 family cytokine for blastocyst implantation, primarily mediates estrogen effects, including the differentiation of endometrial epithelium [66]. LIF expression rises during receptive females. LIF, produced in the endometrial epithelium and stroma, modifies the endometrium to support embryo attachment. In addition, stromal LIF supports subsequent embryonic development, and together, these effects contribute to successful implantation [67].

3.3.2 | Cellular Senescence and SASP-Related Substances

Recent studies have shown that during decidualization, some ESCs undergo irreversible cell cycle arrest, leading to cellular senescence [35, 68, 69] (Figure 1). These senescent decidual cells secrete various proteins, including pro-inflammatory cytokines and chemokines such as interleukin (IL)-6 and IL-8, playing a crucial role in regulating the local cellular environment (Figures 1 and 2). This secretory activity, known as the SASP, influences surrounding cells through autocrine and paracrine signaling. The SASP contributes to immune cell recruitment and chronic inflammation [70], ensuring the clearance of senescent cells while simultaneously influencing tissue remodeling. However, SASP-driven signaling can induce senescence in healthy cells, alter immune function, and promote cancer progression. IL-1 accelerates cellular senescence and impairs decidualization in ESCs through JNK signaling [71]. Furthermore, mice with uterus-specific deletion of the tumor suppressor gene *p53* exhibit abnormal cellular senescence in their decidua, leading to premature birth [72, 73]. This underscores the delicate balance of senescent decidual cells, which regulate immunity and tissue homeostasis while posing risks when dysregulated.

The expression of the decidualization markers IGFBP1 and PRL is positively regulated by FOXO1 [74, 75]. FOXO1 is crucial for the regulation of cellular metabolism, the oxidative stress response, and the cell cycle, and induces senescence in ESCs through the production of IL-8, a SASP-related cytokine [76, 77]. During the receptive phase, sex hormones upregulate IL-15 expression in decidual cells, activating uNK cells to phagocytose senescent ESCs [78, 79]. uNK cells, which make up approximately 70% of endometrial leukocytes during the secretory phase and early pregnancy, contribute to tissue remodeling, angiogenesis, and the regulation of trophoblast invasion [80]. Moreover, ESCs and endometrial glands secrete cytokines like IL-11 and bioactive substances, promoting fetal–maternal immune tolerance essential for embryo acceptance, which maternal cells recognize as foreign.

Oxidative stress refers to a marked increase in ROS, such as superoxide and hydrogen peroxide, beyond physiological levels. ROS are involved in normal cellular metabolism and are also produced in decidual cells. ESCs encase the embryo, shielding it from oxidative damage and mitigating oxidative stress [81, 82]. Decidualized ESCs are more resistant to oxidative cell death than undifferentiated ESCs; however, excessive oxidative stress induces cellular senescence [83]. The generation of ROS is counteracted by the action of antioxidant enzymes such as superoxide dismutase (SOD), which converts ROS to hydrogen peroxide [84, 85]. In cases of spontaneous abortions with vaginal hemorrhage, SOD activity is significantly lower, while lipid peroxide and $PGF_{2\alpha}$ concentrations are higher compared to both normal pregnancies and spontaneous abortions without hemorrhage [86]. Furthermore, ROS can influence endometrial function by regulating $PGF_{2\alpha}$ production by human ESCs [87].

Previous studies, including ours, have identified IGFBP7 as a key factor in decidualization [88–91]. Along with other members of the IGFBP family, it plays a critical role in senescence-related signaling. Siraj et al. [92] found that ROS–PG signaling mediates the release of IGFBP7. Neutralizing antibodies against IGFBP7 reduce SASP-induced senescence, while IGFBP7 exposure drives cells into a senescent state. IGFBP7 can bind to insulin, potentially inhibiting its anti-aging and growth-promoting effects [93]. Additionally, IGFBP7 may enhance IGF2 signaling by blocking the IGF1 receptor and increasing interaction with the IGF2 receptor, thereby promoting senescence [92]. These effects rely on the extracellular signal-regulated kinase (ERK) and AKT signaling pathways. IGFBP7 and activin A appear to regulate each other, suggesting a compensatory mechanism against excessive senescence. IGFBP7 not only inhibits activin A but also interacts with its receptor, potentially inducing senescence via the SMAD pathway. Thus, the mechanisms that regulate cellular senescence are involved in the fate of the stroma and glandular epithelial cells, and their disruption is implicated in infertility and other reproductive disorders. A delicate balance between cell differentiation and senescence is crucial for decidualization, and its disruption may cause abnormalities [69, 94, 95].

P4 is crucial for reproductive function, primarily acting through intracellular classical P4 receptors (PRs) in the uterus and ovaries. PR knockout mice are infertile, and abnormal P4 signaling is associated with endometriosis [96]. However, P4 also binds to non-classical membrane-associated PR (mPR), which triggers cellular responses via genomic and non-genomic signaling cascades. Recent evidence indicates that PR exerts a wide range of effects through mPR. A complex signaling network comprises five mPRs/adipoQ

receptors (PAQRs) and two P4 receptor membrane components (PGRMCs). PGRMC1, a single transmembrane domain protein, is primarily localized to the cell membrane, endoplasmic reticulum, and Golgi apparatus [97]. PGRMC1 mediates the P4-induced inhibition of ovarian granulosa cell apoptosis [98, 99], while uterus-specific PGRMC1 knockout mice exhibit impaired fertility [100]. PGRMC1 also promotes cancer cell proliferation and chemotherapy resistance, independent of P4 binding [101]. It dimerizes via heme and interacts with cytochrome P450 (CYP) and epidermal growth factor receptor, and independently of P4, facilitates glucose uptake via glucose transporters [102]. Human endometrial gene profiling reveals *PGRMC1* downregulation in the secretory phase [103]. In the endometrium, its expression is high in both stromal and epithelial cells during the proliferative phase, but declines in the secretory phase [104, 105]. Treatment of cultured ESCs with dibutyryl cyclic AMP (db-cAMP)/P4 as a decidualization stimulus reduces PGRMC1 expression, and the knockdown or pharmacologic inhibition of PGRMC1 promotes decidualization (Figure 2). Low PGRMC1 expression in cultured ESCs and glandular cells increases COX2 expression and upregulates db-cAMP/P4-induced IGFBP1 and dPRL expression [106]. The inhibition of PGRMC1 induces FOXO1 expression and increases PGE_2 production through COX2, thus contributing to decidualization [76]. In addition, the inhibition of PGRMC1 increases FOXO1 expression and induces cellular senescence, and PGRMC1 knockout mice develop age-related endometrial cysts [100]. Notably, PGRMC1 may suppress cellular senescence in undifferentiated ESCs. Moreover, patients with severe HDP exhibit low expression of COX2 and VEGF in the decidua [107], and the inhibition of PGRMC1 in placental amniotic cells promotes oxidative stress-induced cellular senescence [108]. Thus, PGRMC1 is essential for both decidualization and physiologic cellular senescence, by modulating COX2 expression and PGE_2 production in the endometrium.

In summary, this section has outlined the precise hormonal regulation of decidualization, particularly the role of P4 in supporting early pregnancy and placental formation. Additionally, the involvement of PGs, cellular senescence, and SASP in implantation and decidualization has been highlighted. These insights enhance our understanding of pregnancy establishment and present new possibilities for infertility treatment.

4 | Inflammation, Fibrosis, and Cellular Senescence in Endometriosis Lesions

Inflammation, fibrosis, and cellular senescence are major pathophysiological features in endometriotic lesions. This section outlines the mechanisms of inflammation, epithelial-mesenchymal transition (EMT) associated with ovarian steroid hormones and prostaglandins (PGs), and endometriosis-related epigenetic changes and cellular senescence.

4.1 | Ovarian Steroid- and PG-Related Inflammation

Endometriotic lesions are characterized by P4 resistance, excessive inflammation, impaired cellular differentiation, and prolonged cell survival. These features stem from abnormal ESC differentiation, chronic inflammation induced by excessive estradiol (E2), and aberrant epigenetic regulation. The expression of aromatase (CYP19A1) and steroidogenic acute regulatory protein, a mediator of cholesterol transport into the mitochondrial inner membrane, is high in the lesions, which contributes to an E2-enriched environment [109–111]. This local steroidogenic activity is a hallmark of endometrial lesions, promoting their development and progression through the binding to the estrogen receptors (ERs). In endometriotic tissues, a positive feedback loop involving proinflammatory substances, including PGE_2, may contribute to the upregulation of essential transcription factors that regulate steroidogenic enzyme expression, such as nuclear receptor subfamily 5 group A member 1 (NR5A1; SF-1) and ERβ [112] (Figure 3). Obermajer et al. [113] demonstrated that PGE_2 and COX2 establish a positive feedback loop, amplifying pro-inflammatory substances and transcription factor expression in myeloid-derived suppressor cells. Additionally, the interaction between apoptotic cells and macrophages activates the COX2/PGE_2 pathway through a positive feedback loop, which affects the expression of transcription factors. Expression of CYP19A1 and hydroxysteroid dehydrogenase (HSD)17B1, the enzymes that mediate E2 synthesis, is higher in deep-invasive endometriosis than in eutopic and normal endometrium [114]. This leads to higher levels of local E2 production.

Abnormal ERβ/ERα ratios in ectopic ESCs are associated with the etiology and severity of endometriosis [115, 116]; ERβ is expressed at high levels, whereas ERα expression is low. Since ERα induces PR expression, its reduction leads to P4 resistance. This imbalance creates an estrogen-dominant environment in ectopic endometrial tissues, impairing decidualization in eutopic endometrium via paracrine and systemic mechanisms. As a result, endometriotic stromal cells show heightened estrogen-induced inflammation and excessive PG production due to ERβ hyperactivity. The COX–PGE_2 pathway in endometriotic lesions is closely linked to the CYP19A1–E2–ERβ axis, further exacerbating the pathology (Figure 3).

ROS are produced during the arachidonic acid metabolism that is involved in PG synthesis [117]. Macrophages and neutrophils, responsible for clearing endometrial cells in menstrual blood, release ROS. In endometriosis, ectopic endometrial cells exposed to menstrual blood in the peritoneal cavity experience excessive oxidative stress due to high Fe^{2+} concentrations from hemorrhage, hypoxia, and superoxide released by migrating macrophages. Oxidative stress facilitates the engraftment of ectopic endometrium [118] and correlates with the symptoms of endometriosis severity [118, 119]. Antioxidants like melatonin and resveratrol help alleviate these symptoms. Resveratrol, a natural antioxidant found in red grapes and berries, exhibits potent anti-inflammatory and antioxidant effects, reducing oxidative stress and inflammation, potentially alleviating symptoms. A meta-analysis of dietary antioxidants, including melatonin and resveratrol, found they ameliorate dysmenorrhea and chronic pelvic pain in endometriosis cases [120]. Elevated oxidative stress may also be partially driven by PGE_2 and inflammatory cytokines in menstrual blood. PGs, including PGE_2, regulate inflammation and oxidative stress [121, 122].

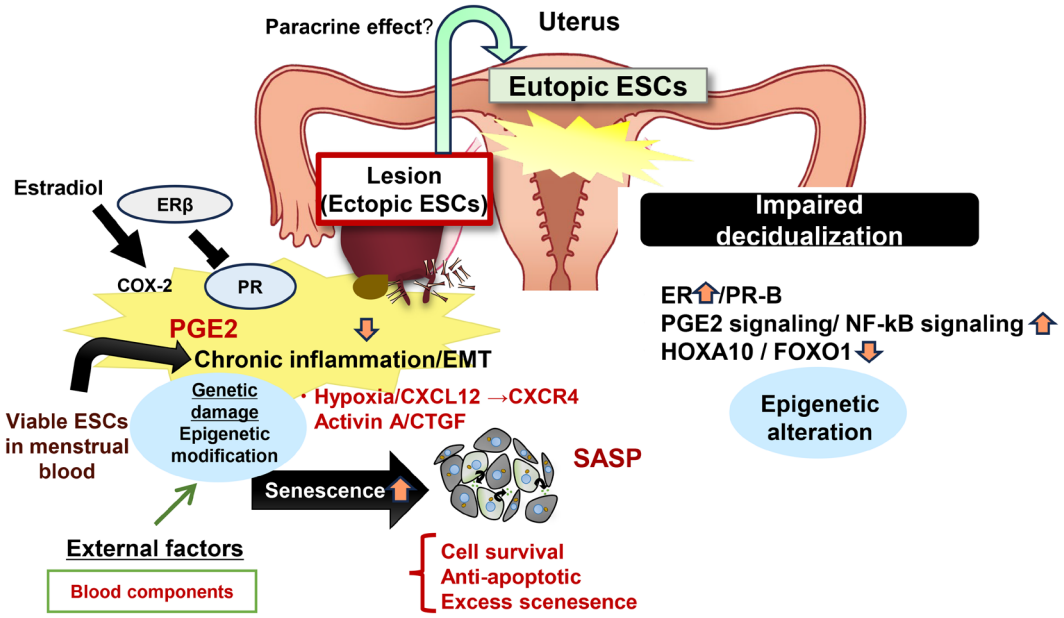

FIGURE 3 | Schematic of the possible effects of endometriosis lesions on the function of eutopic endometrial stromal cells in patients with endometriosis and infertility. Inflammation, fibrosis, and senescence-related pathology in endometriosis lesions may negatively affect the eutopic endometrium through humoral factors. These mechanisms are likely to be intricately intertwined and exacerbate the consequences of genetic susceptibilities via epigenetic alterations and impaired decidualization signaling. COX-2, cyclooxygenase-2; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; CTGF, connective tissue growth factor; EMT, epithelial–mesenchymal transition; ERβ, estrogen receptor β; PR, progesterone receptor.

4.2 | Inflammation and EMT

Multiple studies have explored the role of pro-inflammatory substances, such as PGE_2, in the development and progression of endometriosis [123]. Endometriosis induces chronic inflammation, contributing to pain. Animal models with transplanted human endometrial cells have been developed [124, 125]. We developed a model of endometriosis-like model by implanting endometrial glandular epithelial cells and primary ESCs or stromal cell lines suspended in Matrigel into the peritoneal cavity of ovariectomized mice [126]. This model features endometriosis-like lesion formation at the site of ovarian excision, accompanied by hemorrhage. Histopathologic analysis shows numerous macrophages phagocytosing hemoglobin, suggesting that blood components play a key role in the development of endometriosis. A proteomic analysis of endometriosis-like lesions revealed lesion formation with inflammatory reactions and angiogenesis, indicated by the expression of cytokines. Notably, the protease-activated receptor (the thrombin receptor) has been reported to exacerbate lesion inflammation [127]. Low expression of the serine protease inhibitor alpha1-antitrypsin (SERPINA1), identified through a proteomic analysis, is thought to influence the characteristics of lesion-like tissue. SERPINA1 may play a role in suppressing inflammation [128]. Diminished SERPINA1 expression in endometriosis lesions increases toll-like receptor (TLR) sensitivity, driving chronic inflammation [129] (Figure 3).

Moreover, PGE_2 and thrombin have been reported to contribute to the inflammatory response and EMT in endometriosis lesions [130, 131]. EMT induction and high expression of hypoxia-inducible factors have been observed in these lesions. Evidence suggests that EMT may be involved in the development of endometriosis. Ectopic lesions exhibit an intermediate EMT state, characterized by low E-cadherin expression and high expression of markers of mesenchyme, contributing to inflammation and fibrosis. Endometriotic stromal cells upregulate EMT-related transcription factors and mesenchymal markers, promoting cell survival and migration.

Under hypoxic conditions and upon stimulation with PGE_2/thrombin treatment, the expression of IL-6, IL-8, and C-X-C chemokine receptor type 4 (CXCR4) is increased in both stromal and glandular epithelial cells. Specifically, glandular epithelial cells show low expression of epithelial markers, and high expression of mesenchymal markers and EMT-related transcription factors, enhancing cell migration and invasion. In stromal cells, hypoxia and PGE_2/thrombin increase C-X-C motif chemokine ligand 12 (CXCL12) expression, and this is further amplified by E2. CXCL12 enhances EMT marker expression and cell migration in glandular epithelial cells under hypoxic conditions [130], and high serum CXCL12 concentrations are found in patients with endometriosis. These findings indicate that CXCL12 secreted by hypoxic ESCs binds to CXCR4 in glandular epithelial cells, thus driving the progression of endometriosis by inducing fibrosis and increasing cell migration and invasion via EMT (Figure 3).

In our in vitro model of endometriosis, significant changes occur in TGFβ pathway-related proteins, including greater expression of activin A, a member of the TGFβ family. Activin A induces EMT in ESCs and promotes connective tissue growth factor (CTGF) expression, which, in turn, upregulates myofibroblast markers α-smooth muscle actin, type I collagen, and fibronectin [131]. This suggests that fibroblast-to-myofibroblast

trans-differentiation occurs, leading to fibrosis. It has also been reported that ectopic ESCs show changes in the binding patterns of SMAD4 and H3K27ac during the decidualization process [131], indicating that the effects of TGFβ on transcription are SMAD4-dependent.

4.3 | Endometriosis-Related Epigenetic Alterations and Cellular Senescence

The ESCs that form most endometriosis lesions exhibit extensive epigenetic abnormalities. Epigenetic changes involving DNA methyltransferases (DNMTs), DNA demethylases (TET1), and histone deacetylases (HDACs) have been identified in ectopic endometriosis lesions, suggesting their role in its pathophysiology [132]. Excessive *HOXA10* gene promoter methylation has been observed in women and animal models with endometriosis [133]. The progesterone receptor isoform B (PR-B) gene promoter is also hypermethylated in endometriosis [134], contributing to P4 resistance. Furthermore, significant histone hypoacetylation in the PR-B promoter within the stromal cells of endometriotic lesions highlights the functional importance of HDACs. In ectopic endometrial tissue, PR-A expression is low [135], reducing the PR-B/PR-A ratio [136, 137]. In addition, low PAQR expression has been noted in endometriosis, potentially contributing to the P4 resistance [135].

Ectopic endometriosis lesions exhibit abnormal HDAC expression, including low HDAC mRNA levels and high *HDAC2* expression. Elevated HDAC1 inhibits the inhibition of collagen gene expression through interactions with specific transcription factors, preventing endometrial fibrosis, a process impaired in ectopic lesions.

Long non-coding RNAs (lncRNAs), typically over 200 nucleotides in length, regulate gene expression. Abnormal lncRNA expression is linked to various cancers, neurologic disorders, cardiovascular diseases, diabetes, and endometriosis. lncRNAs primarily act in the nucleus and cytoplasm through several mechanisms. Specific lncRNAs, including HOX transcript antisense RNA (HOTAIR), H19, MALAT1, and MEG3-210, are associated with endometriosis and may serve as diagnostic biomarkers [138, 139]. High expression of HOTAIR expression, correlated with increased HDAC1 expression, activates pro-inflammatory cytokines. Three mechanisms have been proposed: (1) the recruitment of chromatin remodeling and transcription regulators, (2) microRNA sponge function, and (3) the regulation of intracellular signaling pathways. The HOTAIR–miR761–HDAC1 axis may activate signal transducer and activator of transcription 3-related pro-inflammatory cytokines, worsening inflammation [140].

Sirtuins (SIRTs) are NAD-dependent histone deacetylases that regulate epigenetic processes. SIRT1 enhances oxidative stress resistance and delays cellular senescence. In patients with ectopic lesions of endometriosis, it is highly expressed and may promote inflammation and cell proliferation, as well as P4 resistance [122, 141, 142]. Epigenetic changes induced by abnormal transcription factor expression further increase oxidative stress, disrupting epigenetic programming and worsening inflammation in endometriotic stromal cells. Thus, pharmacologic agents that reduce oxidative stress in the lesion microenvironment and modify epigenetic changes may alleviate endometriosis symptoms.

As mentioned above, senescent-like cells also emerge during decidualization. In patients with endometriosis, the SASP-associated cytokine IL-6 is present in high concentrations in the peritoneal cavity and blood. Senescent cells secrete SASP-associated factors, altering surrounding cell characteristics and intensifying local inflammation. Inflammaging is thought to exacerbate inflammation, immune cell migration, fibrosis, and abnormal angiogenesis characteristic of endometriosis lesions. A recent single-cell RNA-sequencing study of endometriosis tissue has shown that ESCs, which comprise the majority of lesions, can be divided into three groups: normal differentiated, senescent, and TGFβ-activated cells [143]. Comparable endometrial cell groups have been detected in menstrual blood from endometriosis patients. Variations in cell group proportions in menstrual blood may impact the pathogenesis of endometriosis.

In our human endometrial cell transplantation model, PGE_2/thrombin treatment induces endometriosis-like cyst formation and increases the number of senescent cells in lesions. Recent studies suggest that activin A is a SASP-related protein [144], implying close associations among cellular senescence, EMT, and fibrosis. Thus, senescent cells help regulate the differentiation of surrounding endometrial cells. Pro-inflammatory factors in menstrual blood, such as activin A, induce senescent cell accumulation, potentially driving the onset and progression of endometriosis. We reported that selectively eliminating senescent ESCs with senolytic agents significantly enhances the ability of endometrial cell differentiation [145]. Delenko et al. [146] showed that quercetin induces ESC apoptosis by inhibiting the AKT and ERK1/2 pathways while stabilizing p53, ultimately targeting senescent cells. Thus, quercetin-activated pathways limit cell proliferation and survival, potentially slowing the progression of endometriosis.

In summary, the section discussed how ovarian steroids and PGs promote inflammation in endometriotic lesions, the mechanisms linking inflammation to EMT and fibrosis, and the potential role of epigenetic abnormalities and cellular senescence in lesion progression. These pathologies are thought to interact intricately and may exacerbate the condition of endometriosis.

5 | Changes in the Eutopic Endometrium in Endometriosis: The Significance of Inflammation and Epigenetic Changes for Infertility

Both ectopic and eutopic ESCs secrete lower levels of IGFBP1 and dPRL after decidual stimulation, indicating impaired decidualization [147]. Decidualization is suppressed in normal ESCs exposed to cytokine-rich peritoneal fluid from endometriosis patients (Figure 3). Zou et al. [148] reported that immune cells in the peritoneal fluid, including macrophages and natural killer dendritic cells, may contribute to the persistence of invaded menstrual debris. Thus, alongside genetic predisposition, a pro-inflammatory microenvironment likely impairs eutopic endometrial function in endometriosis. ESCs derived from eutopic endometrium of patients with endometriosis exhibit a

pro-inflammatory transcriptional profile [149, 150], and high concentrations of pro-inflammatory mediators in the endometrium contribute to the defective decidualization that characterizes endometriosis. Low FOXO1 expression, along with decidual defects, has been reported in the eutopic endometrium of endometriosis patients [151, 152]. Elevated NEK2 expression in eutopic endometrium phosphorylates FOXO1, destabilizing it and impairing decidualization. Notch signaling pathway dysregulation, along with increased AKT1 phosphorylation, leads to FOXO1 phosphorylation and degradation, thereby inhibiting decidualization in endometriosis patients [153, 154].

The expression of ERα and ERβ is higher in the endometrium of endometriosis patients compared to both ectopic endometrial tissue and the endometrium of healthy individuals [116, 155]. The expression of PR isoforms is regulated by promoter-specific DNA methylation. DNA methylation, a key epigenetic modification, directly affects the expression of implantation-related genes in the eutopic endometrium of patients with endometriosis. The methylation of the PR-B promoter is higher in the endometrium of endometriosis patients than in unaffected women during the secretory phase [156, 157]. Elevated DNA methylation correlates with reduced PR-B expression, potentially impairing endometrial receptivity and function in endometriosis patients. DNMT3A expression is significantly higher in the eutopic endometrium of endometriosis patients compared to healthy women [132, 158]. Furthermore, the expression of PR-B in the eutopic endometrium of patients with endometriosis is lower than that of healthy women during the mid-to-late secretory phase [159]. Expression of all the subtypes of PAQR, membrane-type P4 receptors, is also low [135], indicating potential impairment of decidualization due to PR signaling disruption. Further studies are required to assess PAQR and PGRMC1 dysregulation in the eutopic endometrium of endometriosis patients.

In the normal endometrium, HOXA10 expression increases throughout the menstrual cycle, whereas its expression is lower in the eutopic endometrium of endometriosis patients. During the secretory phase, HOXA10 expression in the normal endometrium is upregulated by increased H3K9ac levels [160]. In patients with endometriosis, there is lower H3K9ac, but higher H3K9me3 of the *HOXA10* promoter. Low expression of protein arginine methyltransferase 5 (PRMT5), which is essential for endometrial decidualization, is another feature. Transcriptomic analysis reveals that reduced PRMT5 activity enhances nuclear factor κB signaling by promoting nuclear p65 translocation, a hallmark of endometriosis-affected tissue. PRMT5 overexpression restores IGFBP1 and dPRL expression in the ectopic ESCs of endometriosis patients [161], suggesting that the dysregulation of PRMT5 in eutopic tissue may impair decidualization.

Treatment with a combination of MPA, E2, and db-cAMP increases DNMT3B mRNA and protein expression in ESCs during decidualization [162]. In addition, the eutopic endometrium of patients exhibits histone methylation patterns at H3K4, H3K9, and H3K27 that are distinct from those of the endometrium of healthy women [142, 163]. These histone modifications fluctuate throughout the menstrual cycle and may contribute to impaired decidualization and infertility associated with endometriosis. Elevated levels of H3K9me3 and H3K27me3 have been reported in the patients [164, 165]. PGE_2 signaling via the EP2 and EP4 receptors regulates key transcriptional programs in decidualization. Selective inhibition of these receptors reduces H3K9me3 and H3K27me3, while increasing H3K4me3, H3K9ac, and H3K27ac in the epithelial and stromal cells in endometriosis lesions [166]. These findings suggest that PGE_2 signaling disrupts decidualization in the eutopic endometrium of women with endometriosis, leading to pregnancy failure.

Elevated HDAC1 expression marks the eutopic endometrium of patients [163]. HDAC1 interacts with specific transcription factors to suppress collagen gene expression, thereby preventing endometrial fibrosis [132]. Similarly, elevated HDAC2 expression enhances endometrial tissue proliferation and invasiveness [167, 168]. SIRT1 is also highly expressed in the eutopic endometrium, interacting with PR-A and potentially inducing P4 resistance [141, 169]. Cell cycle dysregulation in the eutopic endometrium of endometriosis patients, linked to aging, may involve HDAC and SIRT activation. Epigenetic dysregulation may induce DNA promoter methylation, histone modifications, and nucleosome structure changes, affecting sex hormone receptors, NR5A1, and HOXA10 expression, thereby driving inflammation, E2 dominance, P4 resistance, and EMT in endometriosis.

Collectively, decidualization disturbances driven by a pro-inflammatory transcriptional profile, excessive AKT1 phosphorylation, and Notch signaling pathway dysregulation critically contribute to endometriosis-related infertility. Epigenetic modifications further disrupt this balance. Increased DNA methylation at the PR-B promoter reduces PR-B expression, while histone modifications such as H3K9me3 and H3K27me3 suppress key implantation-related genes like HOXA10, further impairing implantation. Moreover, increased HDAC1/2 expression disrupts collagen gene regulation, potentially contributing to endometrial fibrosis and functional impairment. Collectively, these epigenetic alterations create a hostile implantation environment, emphasizing the need for targeted therapeutic interventions.

6 | Conclusion

Endometriosis is one of the leading causes of infertility, and its pathophysiology is closely associated with impaired endometrial receptivity, particularly defective decidualization of ESCs. Decidualization is a crucial process for acquiring the receptivity essential for successful implantation. Dysfunction in this process leads to abnormalities in the “window of implantation” (WOI), ultimately resulting in infertility. This review focuses on the roles of PGs and SASP such as IL-15 and activin A in decidualization impairment and summarizes their involvement in the infertility mechanisms of endometriosis. Endometriotic lesions exhibit P4 resistance and excessive inflammation due to a high estrogenic environment and a feedback loop involving PGE2 and steroidogenic enzymes. Additionally, oxidative stress and menstrual blood influence ectopic cells, promoting lesion proliferation and increasing senescent cells with SASP, which contribute to fibrosis. These ectopic lesions may exert systemic or local effects on the eutopic endometrium, leading to decidualization defects even in morphologically normal endometrial tissue. The dysfunction of the eutopic endometrium arises from epigenetic dysregulation and inflammation, impacting the P4 and PGE2 signaling pathways. Inflammatory mediators such as PGs

contribute both directly and indirectly to disease progression and impaired decidualization. Senescent cells with SASP secrete pro-inflammatory factors, not only promoting lesion expansion but also altering the eutopic endometrial microenvironment, negatively affecting the decidualization process. Understanding these mechanisms could facilitate the development of novel diagnostic and therapeutic approaches for endometriosis-associated infertility. In summary, infertility caused by endometriosis is primarily attributed to decidualization impairment resulting from inflammation and epigenetic dysregulation in both ectopic lesions and the eutopic endometrium.

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Conflicts of Interest

The authors declare no conflicts of interest.

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