Molecules and Cells

Minireview

Female reproductive disease, endometriosis: From inflammation to infertility

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ABSTRACT

Despite the fact that endometriosis is a common gynecological disease that occurs in 10% of women of reproductive age, the pathogenesis and treatment strategy are not clear to date. Endometriosis patients are commonly characterized by adhesions in the pelvis or ovaries, which leads to prolonged inflammation in the abdominal cavity. To handle the chronic inflammation, changes of immune cells, including T cells, NK cells, and macrophage, are accompanied. Therefore, diverse cytokines and adhesions of the abdominal cavity lead to poor quality of ovarian follicles, inappropriate response to the hormone, and infertility. This review will guide researchers to summarize the molecular changes and identify new treatment strategies for endometriosis-mediated inflammation and pregnancy failure.

Keywords: Endometriosis pathology, Immune responses, Implantation failure, Inflammatory environment

INTRODUCTION

Endometriosis is characterized by the growth of ectopic endometrial tissue outside the uterus (Park et al., 2023). Approximately 10% of women of reproductive age suffer from endometriosis. Although various studies have been conducted, the exact cause of endometriosis remains unclear (Saunders and Horne, 2021). However, inflammatory, immunological, or hormonal changes are frequently observed in endometriosis patients (Angioni, 2017). Current treatment strategies focus on managing these symptoms rather than addressing the underlying causes. Since endometriosis is closely related to estrogen response in the menstrual cycle, hormone therapy and surgical removal of ectopic lesions are commonly employed (Chen et al., 2020). However, for patients who wish to become pregnant, only cytokine-inhibiting drugs or nonsteroidal anti-inflammatory drugs are typically prescribed, despite their limited effectiveness (Zhang et al., 2023).

In endometriosis, immune dysregulation with inflammatory cytokines damages the ovaries and pelvic tissue, leading to the disruption of uterine function. These systemic changes cause an abnormal pelvic environment, characterized by chronic pelvic pain and implantation failure (Boucher et al., 2022). The average spontaneous pregnancy rate in endometriosis patients is 60% lower than in healthy women of reproductive age (Daniilidis et al., 2022). Many studies have suggested that the proper balance of inflammatory mediators and immune cell dynamics plays a critical role in recurrent miscarriage and implantation failure (Dai et al., 2023; Lin et al., 2024).

Therefore, understanding the mechanisms of immune responses and inflammatory reactions during the development of endometriosis is crucial for improving reproductive outcomes. This review focuses on infertility related to inflammation and immune cell activity in endometriosis, as well as the use of assisted reproductive techniques (ARTs) to enhance pregnancy outcomes. It includes mechanistic studies involving T cells, natural killer (NK) cells, macrophages, and cytokine changes in endometriosis. These findings may provide insights into overcoming endometriosis-mediated female infertility.

ENDOMETRIOSIS DEVELOPMENT

Pathogenesis of Endometriosis Revealed to Date

Endometriosis, characterized by the presence of endometrial tissue outside the uterus, poses a challenge in identifying its exact cause, despite several proposed theories (Koninckx et al.,

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2021). The Retrograde Menstruation Theory suggests that during menstruation, endometrial tissue refluxes into the pelvic cavity through the fallopian tubes, subsequently implanting pelvic organs and leading to endometriosis (Bulun, 2022). Meanwhile, the Hormonal Imbalance Theory proposes that disruptions in estrogen and progesterone levels play a role in its development (Marquardt et al., 2019). Additionally, the Immune System Dysfunction Theory posits that abnormalities in immune function fail to prevent the ectopic implantation of endometrial tissue. Genetic factors are also implicated, as the Genetic Factor Theory suggests that genetic predispositions influence susceptibility to endometriosis (Yang et al., 2023). Lastly, the Environmental Factor Theory implicates external factors or toxins in inducing endometriosis (Polak et al., 2021). Together, these theories offer insights into the multifaceted nature of endometriosis pathogenesis, highlighting the need for further research to unravel its complexities.

Pathological Characteristics of Endometriosis

Peritoneal endometrial tissue typically forms small, well-circumscribed nodules or plaques, often located beneath or on the surface of the mesothelium. The cells usually have round-to-oval nuclei and typically contain scant, indistinct cytoplasm. Moreover, prominent vascularity is often observed, with erythrocytes frequently found within the blood vessels (McCluggage, 2020). The histological diagnosis of endometriosis is typically straightforward; however, challenges may arise due to variations or the absence of tumorous components. Hormonal and metaplastic changes, nuclear abnormalities, and hyperplasia can alter the appearance of tumorous constituents. Additionally, endometriosis may manifest in various locations, such as the ovarian surface, cervix, vagina, or intestines, making prediction difficult. Furthermore, vigilance is warranted for findings that may be mistaken for endometriosis, including pseudoxanthomatous nodules, polypoid growths, substantial lesions, and venous, lymphatic, or perineural invasion, among others (Clement, 2007).

Complications of Endometriosis

Endometriosis can increase the risk of pregnancy complications, including miscarriage, preterm birth, premature rupture of membranes, placenta previa, pre-eclampsia, pregnancy-induced hypertension, gestational diabetes, gestational cholestasis, fetal growth restriction, postpartum hemorrhage, placental abruption, and fetal malformations (Breintoft et al., 2022; Drummond et al., 2023; Matsuzaki et al., 2021a, 2021b; Minebois et al., 2017; Porpora et al., 2020). While some studies suggest that endometriosis may not significantly affect pregnancy outcomes, limited evidence indicates that the surgical removal of endometriosis may not reduce the risk of these complications. Additionally, common pathogenic mechanisms have been identified, including abnormal activation of inflammation, structural and functional alterations in the junctional zone, and aberrant uterine peristalsis (Figure 1).

INFLAMMATION IN ENDOMETRIOSIS

Inflammation is a central pathophysiological mechanism of endometriosis, playing a role in pain, lesion implantation, fibrosis, and angiogenesis (Bulun et al., 2019). Inflammation contributes to infertility in endometriosis patients by compromising ovarian function and embryo implantation (Lee et al., 2020). Additionally, chronic inflammation can promote the malignant transformation of endometriosis (Leenen et al., 2021). Several clinical observations have demonstrated that chronic inflammation and suppression of the immune response are key contributors to the pathophysiology of endometriosis. The elevation of proinflammatory cytokines in the peritoneal fluid has been widely observed in patients with endometriosis, strongly indicating the role of local inflammation in endometriosis progression (Fan et al., 2018). The implantation of endometrial tissue in the peritoneum induces the recruitment of lymphocytes, including neutrophils and macrophages, leading to the secretion of inflammatory and angiogenic factors such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, and vascular endothelial growth factor (Ahn et al., 2015). Various types of lymphocytes are involved in the survival, proliferation, and adhesion of ectopic endometrial tissues (Osuga et al., 2011) (Figure 2).

Role of T Cells in Progression of Endometriosis

In both the peritoneal cavity and endometriosis lesions, regulatory T cells (Tregs) are significantly increased in patients with endometriosis compared with women without the condition (Králíčková et al., 2018b). In endometriosis patients, elevated estrogen (E2) levels induce an increase in Tregs and consequently reducing immune surveillance (Králíčková et al., 2018a; Wang et al., 2017). Additionally, the Th1/Th2 balance has been suggested to play a role in the pathogenesis of endometriosis (Olkowska-Truchanowicz et al., 2021). Specifically, the Th2 immune response is predominant in endometriosis (Chen et al., 2012, 2016).

In endometriosis patients, the level of IFNγ, which is Th1-type inflammatory cytokine, is elevated, suggesting that inflammation is continuously induced by lymphocytes (Podgaec et al., 2007). On the other hand, anti-inflammatory cytokine IL-10 and Th2-type T cells that produce it have been also increased in peritoneal environments of endometriosis patients (Podgaec et al., 2010). This indicates that the condition of endometriosis involves a complex immune reaction, including Th2-mediated anti-inflammatory response. This complicated T-cell immune response is closely associated with an imbalance between Th1 and Th2 responses in endometriosis, suggesting that dominance of Th2-type T cells might contribute to chronic inflammation. Still, the role of T cells in endometriosis remains controversial, elucidating the role of anti-inflammatory cytokines in an inflammatory environment would help to identify the function of T cells in the context of endometriosis.

Role of NK Cells in Progression of Endometriosis

A defective function of NK cells may contribute to the survival of endometrial cells in the peritoneal cavity. Some reports suggest that NK cells exert antiproliferative activities and modulate

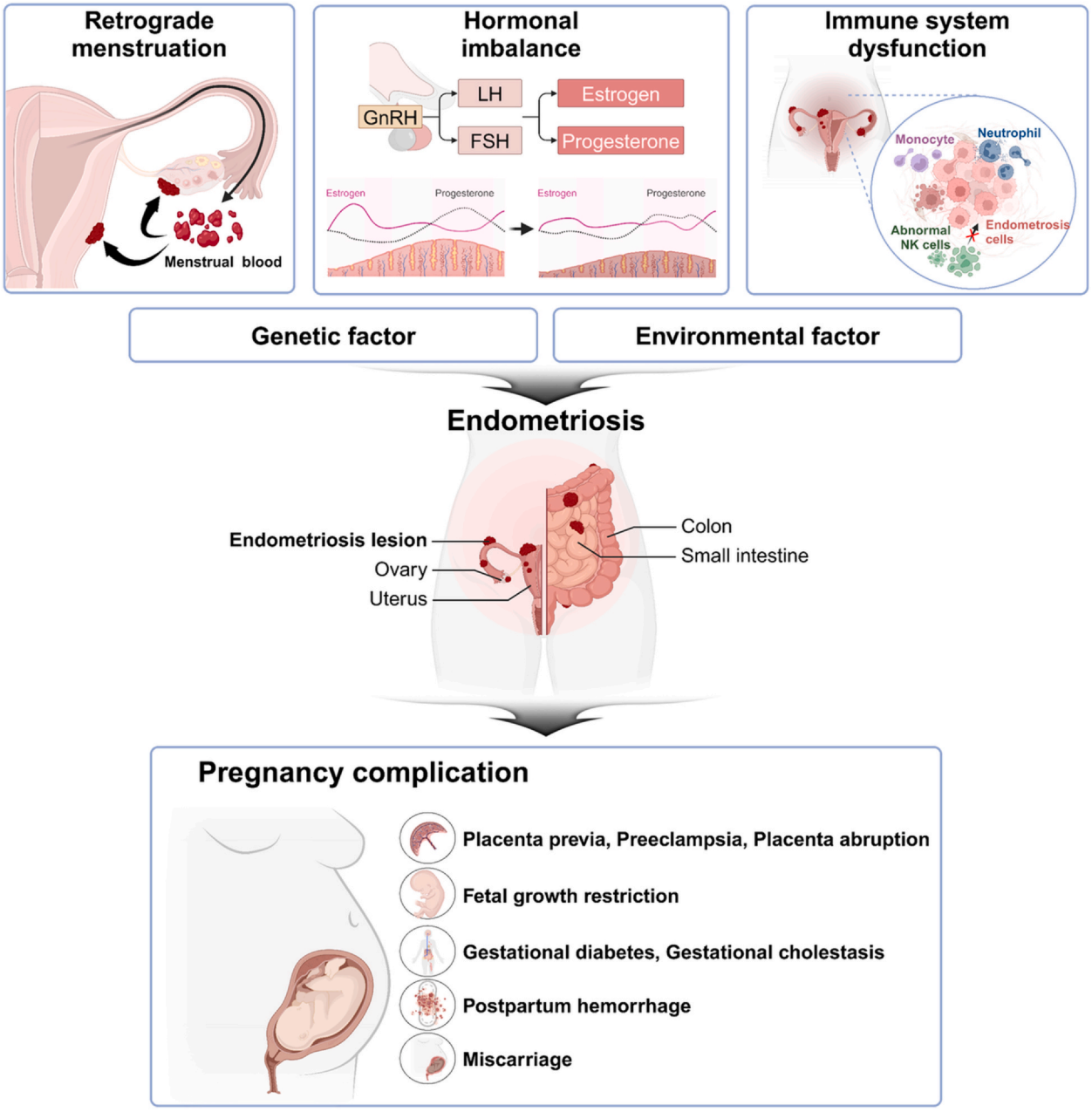

Fig. 1. Illustration provides information on the mechanism and complications of endometriosis. The 5 hypotheses are considered to be the main causes of endometriosis: (1) reflux of endometrial tissue by retrograde menstruation and transplantation to abnormal locations, (2) growth of endometrial tissue by hormonal imbalance, (3) induction of excessive inflammatory environment by abnormal functions of immune cells, (4) genetic factors, and (5) environmental factors. These pathogeneses might form lesions in various intraperitoneal organs such as ovaries, uterus, small intestine, and colon. In addition, endometriosis might be triggered by various pregnancy-related complications, such as maternal metabolic disorders, abnormal placenta, and small fetus.

inflammatory responses in various diseases (Bai et al., 2024; Cho et al., 2022; Heo et al., 2023). The number and activity of NK cells have been reported to be reduced in endometriosis patients (Ścieżyńska et al., 2019). Ectopic endometriosis lesions, particularly stromal cells, are involved in the impairment of NK cell-mediated cytotoxicity (Maeda et al., 2012; Yu et al., 2016). Particularly, increased IL-10 levels, which show an intricate immune microenvironment of endometriosis, have been reported to suppress both viability and cytotoxic activity of NK cells (Yang et al., 2017). Indeed, the binding of IL-10 to IL-10R on NK cells activates STAT3 and leads to the down-regulation of cytotoxic cytokine secretion, such as GM-CSF (Cameron and Kelvin, 2003). Although several observations suggest that local dysfunction of NK cells contributes to the

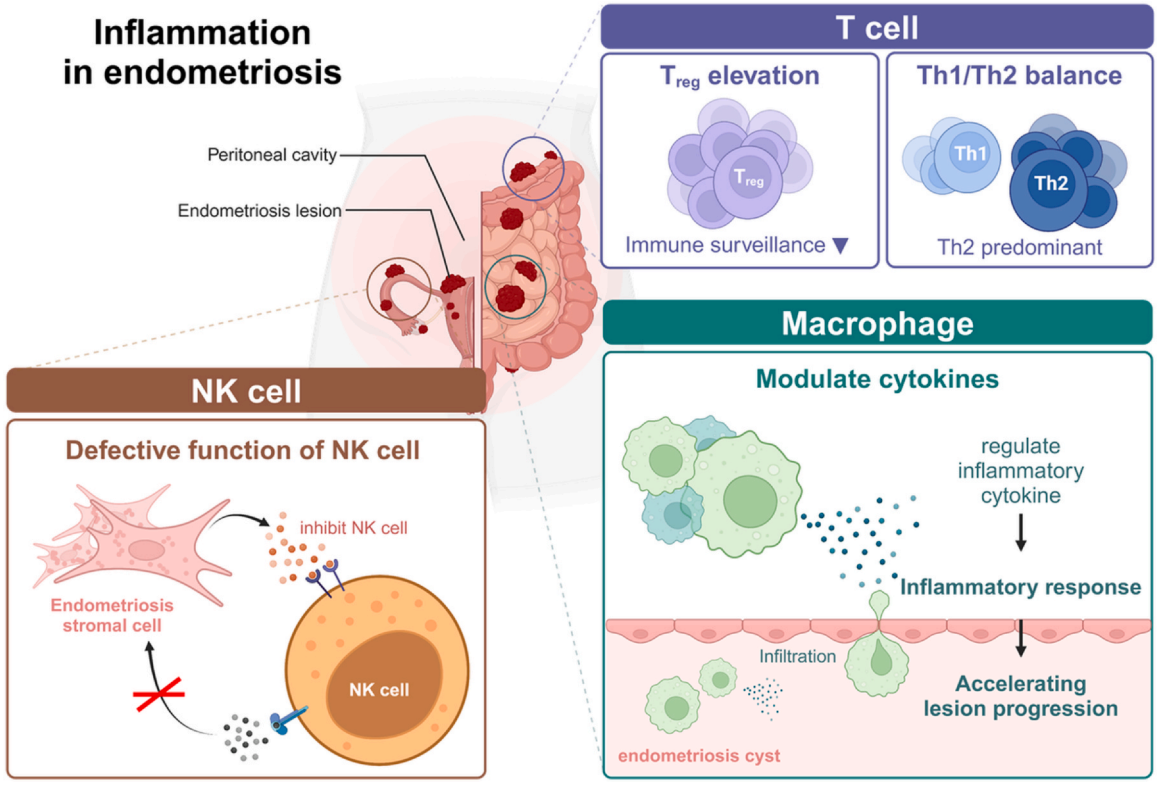

Fig. 2. An inflammatory environment of endometriosis is caused by dysregulated immune cells. (1) Alteration of T-cell subpopulation in peritoneal and endometriotic lesions is identified. Increased T_{reg} cells contribute to the survival of endometriosis cells by reducing immune surveillance. In addition, Th1/Th2 balance switches to Th2 predominant direction. (2) The cytotoxicity of natural killer (NK) cells was inhibited by endometriosis stromal cells. The defected function of NK cells might induce survival of endometriosis cells. (3) Macrophages, the predominant immune cells in the peritoneal cavity, regulate various inflammatory cytokines and induce an inflammatory response. This activated inflammatory response accelerates the progression of endometriosis lesions.

development of endometriosis (Thiruchelvam et al., 2015), the mechanisms initiating these immunological alterations in NK cells require further explanation.

Role of Macrophage in Progression of Endometriosis

Macrophages are predominant immune cells in the peritoneal cavity and modulate cytokines or T cells (Hornung et al., 2003; Kim et al., 2022, 2023a; Liu et al., 2022b). They are also the primary inflammatory cells that infiltrate endometriotic cysts (Kusunoki et al., 2021). An upregulation of macrophages has been observed in the peritoneum of patients with endometriosis (Ramírez-Pavez et al., 2021). This increase in macrophages is a potential source of inflammatory cytokines, which contribute to endometriosis growth and pregnancy failure (Hogg et al., 2020). Differentiated peritoneal macrophages express estrogen receptor allowing E2 to induce a proinflammatory response (Calippe et al., 2008; Khan et al., 2015). Furthermore, macrophages are known to play a crucial role in angiogenesis and innervation, thereby accelerating lesion progression (Forster et al., 2019). Therefore, a deeper understanding of the role of macrophages in endometriosis may provide insights into the systemic progression of peritoneal inflammation and endometriosis development (Taylor et al., 2021).

Recent studies have shown that phagocytosis by macrophages induces the release of heme, leading to increased iron levels. This increase in iron has been suggested to contribute to an inflammatory environment (Wyatt et al., 2023). In addition, it has been proposed that the accumulation of iron in the peritoneum promotes the development of endometriosis lesions by increasing the expression of IL-8 and vascular endothelial growth factor A, which are involved in angiogenesis (Yi et al., 2022). Therefore, although the role of macrophages in the development of endometriosis has been actively studied, their detailed regulatory mechanisms remain elusive. Further investigation is needed to determine which specific macrophage subtypes influence the cytokine profile in the peritoneal environment (Figure 3).

ENDOMETRIOSIS-MEDIATED INFERTILITY AND TREATMENT

Relationship Between Endometriosis and Infertility

Infertility is generally defined as the inability to achieve pregnancy after 1 year of unprotected sexual intercourse during the fertile phase of the menstrual cycle (Ray et al., 2012). The diagnostic process for infertility involves various evaluations of reproductive function. However, approximately 30% of infertile

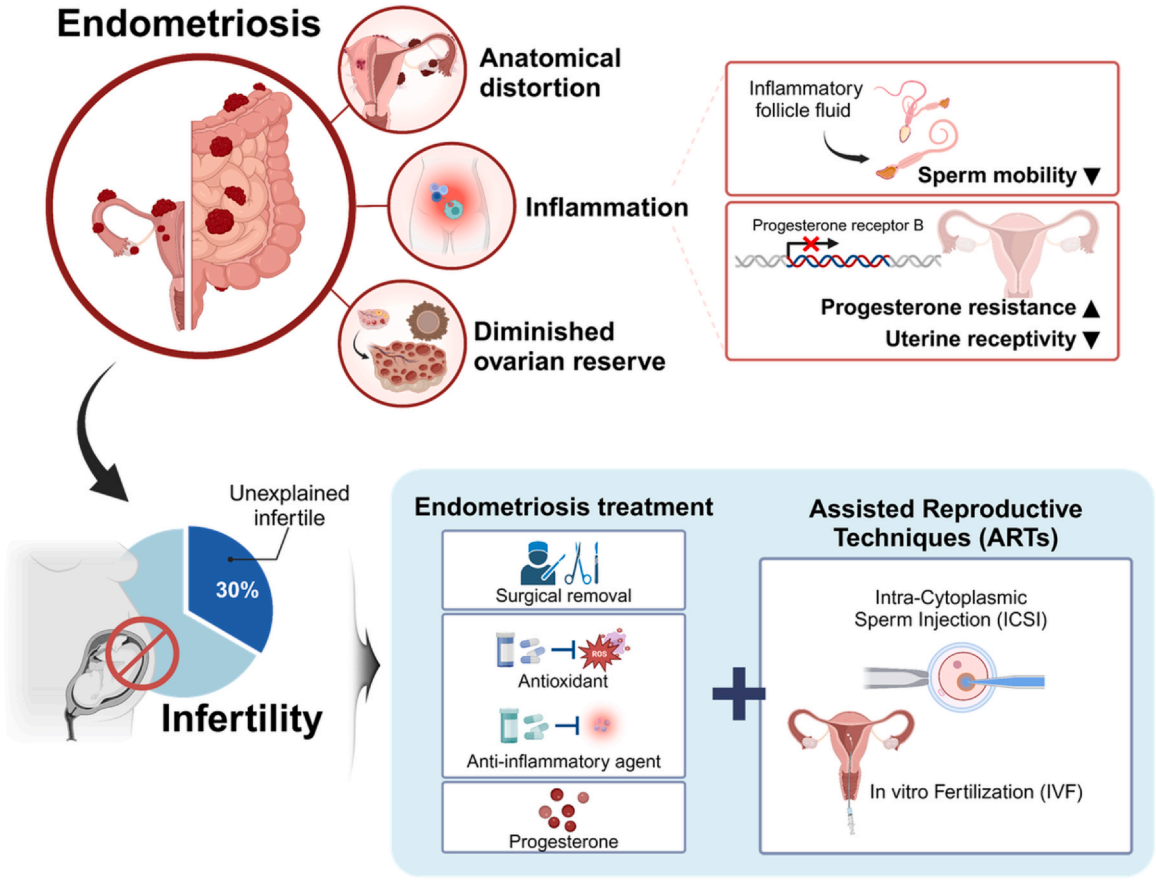

Fig. 3. The effects of endometriosis on infertility and the treatment options of infertility with endometriosis are schematically illustrated. Endometriosis causes anatomical distortion of the female reproductive system and problems, such as the inflammation and reduction of ovarian reserves. In particular, the inflammatory environment of female reproductive system reduces sperm mobility and uterine receptivity through induction of progesterone resistance in the endometrium. Endometriosis may contribute to unexplained infertility. Infertility patients with endometriosis should consider the following treatment methods for endometriosis before ART to improve ART outcomes: (1) surgical removal of endometriosis, (2) pharmacological treatment (antioxidants or anti-inflammatory drugs), and (3) hormone therapy.

couples are classified as having unexplained pregnancy failure, where no specific problem is identified (Kim et al., 2023b; Quaas and Dokras, 2008).

Endometriosis is proposed as a potential cause of infertility (Nezhat et al., 2024; Practice Committee of the American Society for Reproductive, 2012; Prescott et al., 2016). Although the exact pathophysiological mechanisms by which endometriosis contributes to pregnancy failure remain unclear, several potential causes have been suggested. Aberrant endometriotic lesions can lead to the formation of adhesions and anatomical distortions in the female reproductive system, including the ovaries and fallopian tubes (Tanbo and Fedorcsak, 2017). Additionally, various functional abnormalities related to fertility have been identified in women with endometriosis, including decreased ovarian reserve, reduced oocyte quality, and impaired endometrial receptivity (Large and DeMayo, 2012; Tan et al., 2022).

Relationships Between Inflammatory Environment and Fertility

The increase in inflammatory cytokines and the induction of systemic inflammatory responses in women with endometriosis are considered primary causes of the pathophysiological symptoms associated with the condition. These inflammatory environments are also expected to reduce fertility in women. Based on the relationship between the inflammatory environment and infertility caused by endometriosis, various studies are being conducted to elucidate the underlying mechanisms.

Follicular fluid in women with endometriosis exhibits higher levels of inflammatory cytokines compared to that in women without the condition. This inflammatory follicular fluid may potentially reduce ovarian reserve and oocyte production due to the inflammatory responses affecting the ovaries (Fan et al., 2023; Latif and Saridogan, 2023; Suryavanshi et al., 2023). Especially, C-C motif chemokine 2 (CCL2) and IL-8 levels in follicular fluid were found to be higher in endometriosis patients than in normal women (Fan et al., 2023). These cytokines recruit neutrophils and promote inflammation in the lesion (Vilotić et al., 2022). The direct influence of inflammatory cytokines on follicular development is known to involve the NF-κB pathway activation in granulosa cells induced by IL-1β or TNF-α (Li et al., 2019). Abnormal activation of NF-κB in granulosa cells can lead to inhibit follicular development and induce follicular atresia (Yamagata et al., 2002). Since TNF-α levels have been shown

to be significantly increased in the peritoneal cavity and follicular fluid of women with endometriosis (Bullimore, 2003), IL-1β and TNF-α might directly impair reproductive function by suppressing follicular development in endometriosis patients. In addition, although the precise molecular mechanisms require further investigation, it is noteworthy that activated neutrophils secrete TNF-α (Tecchio et al., 2014). Thus, the increased recruitment of neutrophils driven by CCL2 and IL-8 might be a potential source of elevated TNF-α. This highlights the need for a deeper understanding of the regulatory pathways governing TNF-α secretion in neutrophils in the context of endometriosis.

Additionally, sperm exposed to this inflammatory follicular fluid show decreased motility, suggesting that the inflammatory environment associated with endometriosis adversely affects fertility (Suryavanshi et al., 2023). Chronic inflammation associated with endometriosis also affects the expression of aromatases and steroid receptors in the uterine endometrium. Particularly, the expression of progesterone receptor B (PR-B) is suppressed due to inflammatory reactions (Peters et al., 2017). During a typical pregnancy, PR-B suppresses excessive inflammatory reactions, maintaining normal implantation and pregnancy (McGlade et al., 2022). However, excessive chronic inflammation caused by endometriosis can inhibit PR-B expression in the uterus, leading to issues related to uterine receptivity, such as increased progesterone resistance, which contributes to pregnancy failure (Hon et al., 2023).

In endometriosis, specific types of immune cells, which are involved in the increased expression of PR-B, have not yet been identified. However, a correlation between increased macrophage infiltration and decreased PR expression in endometriosis lesions has been demonstrated, contributing to the unregulated proliferation of the lesion tissues (Jiang et al., 2013). These findings suggest the potential role of immune cells in PR regulation. In addition, proinflammatory macrophage has been observed to be increased in eutopic endometrium of endometriosis patients. This interaction needs further investigation as a potential mechanism contributing to infertility in the pathological context of endometriosis. The inflammatory environment associated with endometriosis can adversely affect various aspects of normal pregnancy, ultimately leading to implantation failure. Understanding the mechanisms underlying these inflammation-mediated reproductive disorders can help in developing additional treatments to improve the success rate of assisted reproductive technologies in infertile women with endometriosis.

Assisted Reproductive Technology for the Treatment of Infertility Induced by Endometriosis

Treatment options for patients with endometriosis generally include natural pregnancy after the surgical removal of endometrial lesions or attempts of ARTs, such as in IVF and intracytoplasmic sperm injection. However, recent studies suggest that surgery for endometriosis may not significantly improve the success rate of ARTs (Nickkho-Amiry et al., 2018; Rubod et al., 2023). Additionally, the inflammatory environment associated with endometriosis may negatively affect IVF outcomes, potentially due to mechanisms that interfere with endometrial receptivity and embryonic development (Salmeri et al., 2023).

Indeed, the retrospective study on the performance of IVF in endometriosis patients found that pregnancy and implantation rate per transfer were lower in women with endometriosis compared with women without endometriosis (Alson et al., 2024; Budak et al., 2007). This was attributed to the reduced quality of oocytes and embryos, as well as reduced ovarian reserve (Kuroda et al., 2012). In the follicles of women with endometriosis, the levels of IL-8 and IL-12 were abnormally increased, indicating impairment of oocyte and embryo quality (Singh et al., 2016). In addition, treatment with dexamethasone demonstrated a recovery effect on mouse embryos whose development was impaired by the peritoneal fluid of endometriosis patients (Heitmann et al., 2015). This suggests that pretreatment with supplements like dexamethasone, which reduces inflammatory mediators, could improve embryo quality and potentially enhance ART success rates in women with endometriosis.

Several methods have been explored to improve the results of ARTs in patients with endometriosis. Short-term treatment with the antioxidant rapamycin has been shown to elevate IVF outcomes, including embryo transfer success and fertility rates (Fan et al., 2024). Similarly, the use of the anti-inflammatory cytokine TNF-α antagonist etanercept has been reported to increase the pregnancy rate in IVF (Onalan et al., 2018). Additionally, a protocol using progesterone during the pre-IVF ovarian stimulation phase to inhibit early ovulation has demonstrated positive effects, such as decreased expression of inflammatory cytokines and increased expression of various amino acids critical for oocyte and blastocyst development (Guo et al., 2023).

Taken together, inflammatory cytokines, such as IL-8, IL-12, and TNF-α, lower ART success rates in endometriosis patients by directly damaging oocytes and embryos and indirectly interfering with endometrial receptivity. These findings provide crucial insights into the uterine environment not only in endometriosis but also in cases of unexplained infertility. Therefore, identifying cytokines that directly affect oocyte maturation and embryo quality and developing effective inhibitors are considered the most critical strategies for successful ART.

CONCLUSION AND PERSPECTIVES

In conclusion, inflammation plays a major role in the pathophysiology of endometriosis. Although extensive studies are underway to identify regulatory factors associated with immune response and inflammation, reliable biomarkers or therapeutic targets are still lacking. Therefore, a thorough understanding of the immunological mechanisms in endometriosis, including whether peritoneal inflammation is a cause or consequence of the condition, is required to prevent endometriosis and related gynecological complications. Many studies have focused on identifying the cause of the inflammatory environment, and recent findings suggest that elevated iron levels in endometriotic lesions and peritoneal fluid are major contributors to the inflammatory state (Liu et al., 2022a). Thus, lots of results suggest targets for novel therapeutics, including iron chelators

(Wyatt et al., 2023). Nevertheless, various strategies to alleviate inflammation and oxidative stress associated with endometriosis have been developed, improving oocyte quality and IVF outcomes. These approaches have the potential to enhance fertility outcomes for patients with endometriosis.

AUTHOR CONTRIBUTIONS

Wonhyoung Park: Writing—original draft, visualization, and data curation. **Whasun Lim:** Writing—original draft, data curation, and conceptualization. **Miji Kim:** Writing—original draft, vsualization. **Hyewon Jang:** Writing—original draft, visualization. **Soo Jin Park:** Data curation. **Gwonhwa Song:** Writing—review and editing, supervision, and conceptualization. **Sunwoo Park:** Writing—review and editing, supervision, and funding acquisition.

DECLARATION OF COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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