Mechanistic insights into inflammatory cytokines in adenomyosis-induced infertility (Review)

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Abstract. Adenomyosis (AM), an estrogen-dependent chronic inflammatory disease with a rising incidence, has emerged as a major cause of infertility and reduced clinical pregnancy rates in reproductive-aged women, severely impairing reproductive health and quality of life. The core pathological mechanisms of AM are closely linked to aberrant local expression of inflammatory cytokines, including interleukin (IL)-6, C-X-C motif chemokine ligand 8 (CXCL8), IL1B, tumor necrosis factor-α, NF-κB, cyclooxygenase-2 and TGF-β, which disrupt the immune barrier at the endometrial-myometrial junction. This disruption further breaks the critical balance between proinflammatory and anti-inflammatory cytokines, ultimately fostering an immune microenvironment hostile to embryo survival. Concurrently, inflammatory cytokine-activated cellular processes, including proliferation, invasion, tissue injury and repair, epithelial-mesenchymal transition and fibrosis, further induce pathological neovascularization and impair blood perfusion in the junctional zone. These pathological changes, in turn, compromise endometrial receptivity and inhibit decidualization, ultimately resulting in implantation failure. Based on these mechanisms, key inflammatory cytokines such as IL-6, CXCL8, IL1B and IL-10 hold potential as diagnostic biomarkers for AM-related infertility and provide a theoretical basis for developing fertility-preserving therapies targeting the inflammatory cascade (such as IL-6 receptor monoclonal antibodies and TGF-β inhibitors). These findings offer new approaches to achieve the dual goals of lesion control and fertility preservation in clinical practice.

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Contents

1. Introduction

Adenomyosis (AM) is a gynecological disorder characterized by the infiltration of endometrial tissue into the myometrium, clinically manifesting as dysmenorrhea, menorrhagia and infertility (1). Epidemiological data indicate an incidence of ~21.9% (2), with 5-25% of cases occurring in women under the age of 39. Although advances in imaging techniques such as transvaginal ultrasound and magnetic resonance imaging (MRI) have significantly improved the diagnostic rate of AM in women of reproductive age (3), the increasing trend of delayed childbearing has made the disease a major contributing factor to secondary infertility, with chronic inflammatory response and immune dysregulation emerging as the core drivers linking the pathological progression of AM to reproductive impairment. Moreover, due to its insidious nature, early-stage and mild cases are often underdiagnosed, suggesting that the actual prevalence may be underestimated.

Numerous studies have confirmed that women with infertility frequently present with sonographic features of AM and exhibit significant immune dysfunction (4,5). AM has increasingly become a critical factor impacting both female fertility and the outcomes of assisted reproductive technology (ART) (6,7). The abnormal infiltration of tissue-specific immune cell subsets, such as macrophages, natural killer (NK) cells and mast cells, combined with an imbalance between pro-inflammatory cytokines [such as interleukin (IL)-6, IL1B and C-X-C motif chemokine ligand 8 (CXCL8)] and anti-inflammatory cytokines (such as IL-4 and IL-10), contributes to pathological angiogenesis, impaired endometrial decidualization and reduced endometrial receptivity (ER). These changes ultimately lead to embryo implantation failure (8), thereby resulting in adverse pregnancy outcomes. Elevated levels of inflammatory markers in both serum and peritoneal fluid confirm that chronic inflammation and immune dysregulation are not isolated local phenomena but systemic disruptions of the immune-inflammatory network in AM (9). Therefore, elucidating the unique immunoregulatory network centered on chronic inflammation and immune dysregulation in AM, identifying diagnostic inflammatory cytokines and developing targeted intervention strategies are essential to improving reproductive outcomes in affected patients.

2. Pathogenic mechanisms and clinical evidence of AM-associated reproductive impairment

AM-induced reproductive dysfunction arises from the interplay of three interconnected pathological dimensions: Structural derangements of the uterus and fallopian tubes, functional impairments of ovarian and myometrial physiology and molecular dysregulation of the endometrial microenvironment, with persistent inflammatory signaling serving as the core mediator that links these dimensions into a self-reinforcing pathological loop (10). Studies have consistently confirmed that these multifaceted abnormalities collectively compromise both natural conception and ART outcomes (11), as elaborated below.

Pathogenic mechanisms. The pathogenesis of AM-related infertility begins with structural anomalies that disrupt the physiological architecture of the reproductive tract. Structural assessments through hysterosalpingography reveal significantly higher uterine cavity distortion rates in patients with AM compared with controls: 78% in diffuse AM and 54% in focal AM vs. 37% in non-AM populations (6). Anatomical distortion of the uterine wall, characterized by myometrial hypertrophy and endometrial invagination into the myometrium, not only destroys the spatial integrity required for embryo implantation but also exerts mechanical traction on the fallopian tubes, impairing their transport dynamics (11). Using T2-weighted MRI and hysterosalpingoscintigraphy, Kissler *et al* (12) demonstrated a significantly higher incidence of impaired tubal transport in patients with diffuse AM compared with those with focal AM and healthy controls. This tubal dysfunction compromises the timely meeting of gametes and the subsequent transport of embryos to the uterine cavity, directly hindering fertilization. Concurrently, the structural derangement of the uterus exacerbates functional impairments: Aberrant myometrial contractility patterns (marked by increased frequency and uncoordinated contractions) disrupt embryo positioning within the uterus and reduce blood perfusion to the junctional zone (JZ), a critical region for implantation (13). Additionally, reduced ovarian responsiveness in patients with AM is closely linked to local and systemic inflammatory cytokines [such as tumor necrosis factor-α (TNF-α) and IL-6], which interfere with granulosa cell function and folliculogenesis, diminishing oocyte quality and quantity (11).

Underpinning these structural and functional abnormalities is molecular and immunological dysregulation, with the persistent inflammatory microenvironment acting as a central driver. Spatial transcriptomic analyses have revealed that during ectopic endometrial invasion in AM, $SFRP5^+$ epithelial cells promote endometrial proliferation and angiogenesis through activation of the Indian hedgehog signaling molecule signaling pathway, initiating basal layer invagination, while $ESR1^+$ smooth muscle cells (SMCs) facilitate invasive tract formation via collagen degradation (13). These processes not only reinforce uterine structural distortion but also sustain inflammation, which further suppresses implantation-related molecular pathways. Specifically, elevated levels of pro-inflammatory cytokines (such as IL-6 and TNF-α) and oxidative stress markers in the adenomyotic microenvironment downregulate key implantation genes such as Homeobox (HOX)A10, HOXA11 and leukemia inhibitory factor (LIF), compromising ER and inhibiting decidualization (6). A genomic study has further confirmed the dysregulation of 34 fertility-associated genes during the implantation window, including imbalances in the matrix metalloproteinases (MMPs)/tissue inhibitors (TIMPs) system, an essential regulator of decidualization and trophoblast invasion (14).

Notably, these pathological processes are mutually reinforcing; structural distortion amplifies inflammatory signaling by disrupting tissue integrity, while inflammation exacerbates structural and functional damage through fibrosis (driven by

$CNN1^+$ stromal fibroblasts) and sustained tissue injury (13). This loop ultimately creates an intrauterine environment hostile to embryo survival and implantation.

Clinical evidence. Clinical data consistently validate the link between the pathological features of AM and poor reproductive outcomes, with severity-dependent effects clearly observed. In terms of ART outcomes, meta-analysis data has revealed that patients with AM have a clinical pregnancy rate of 40.5% following *in vitro* fertilization (IVF)/intracytoplasmic sperm injection compared with 49.8% in controls [risk ratio (RR), 0.72; 95% confidence interval (CI), 0.55-0.95], coupled with significantly elevated miscarriage rates (31.9 vs. 14.1%; RR, 2.12; 95% CI 1.20-3.75) (15). Further supporting this severity-dependent effect, a prospective multicenter study by Mavrelos *et al* (16) demonstrated a stepwise decline in clinical pregnancy rates: 42.7% (95% CI, 37.1-48.3) in women without sonographic AM features, 22.9% (95% CI, 13.4-32.6) in those with four features and further to 13.0% (95% CI, 2.2-23.9) in those with all seven features, indicating a strong association between disease severity and reduced fertility. Epidemiological data further highlight the role of AM in reproductive failure: The prevalence of AM is 24.4% among infertile populations, rising to 38.2% in recurrent miscarriage cohorts and 34.7% in recurrent implantation failure (RIF) groups (17), a finding consistent with the notion that persistent inflammatory and molecular dysregulation disproportionately affects women with repeated reproductive losses. Even in oocyte recipient cycles, AM independently increases early miscarriage risk and lowers term pregnancy rates, likely due to JZ dysfunction impairing trophoblast development and early placentation (18). Collectively, this confirms that intrauterine pathological changes (rather than ovarian factors alone) drive poor reproductive outcomes (11).

Synthesizing the aforementioned mechanisms and clinical evidence, we consider that while anatomical derangements and myometrial dysfunction represent relatively fixed pathological endpoints, the aberrant inflammatory milieu (functioning as the core mediator of the pathological loop) constitutes a tractable therapeutic target. Elucidating the key signaling pathways and immunomodulatory networks underlying inflammation-driven damage could inform the development of novel interventional strategies to disrupt this pathological loop, restore ER and ultimately improve fertility outcomes in patients with AM. This framework also directs future translational research toward validating these targets in clinical trials.

3. Abnormal expression of inflammatory cytokines in AM promotes infertility

Pro-inflammatory cytokine IL-6 enhances proliferation and invasion of the eutopic endometrium. IL-6, predominantly secreted by activated macrophages (19), exhibits elevated expression in endometrial stromal cells (ESCs) in macrophage co-culture systems (20). Spatial transcriptomics analysis has identified an IL-6-centered protein-protein interaction subnetwork within adenomyotic lesions, forming a synergistic pro-inflammatory axis with cytokines such as CXCL8 and TNF-α, which activates local inflammatory cascades via the Toll-like receptor (TLR)4/NF-κB signaling pathway (21). Mechanistically, canonical IL-6 signaling involves complex formation with the soluble IL-6 receptor and gp130 co-receptor (22), triggering Janus kinase (JAK)2/signal transducer and activator of transcription (STAT)3 pathway activation characterized by STAT3 phosphorylation and nuclear translocation (23). Dysregulation of the IL-6/JAK2/STAT3 pathway has been implicated in the pathogenesis of autoimmune diseases, chronic inflammation and certain malignancies (24). In AM, endometrial cell-derived exosomes have been shown to activate this signaling pathway, thereby promoting ESC proliferation, migration and cell cycle progression. Tocilizumab, an IL-6 receptor inhibitor, was able to effectively reverse these effects (25). Moreover, IL-6 trans-signaling activates the PI3K/AKT/mTOR pathway, which suppresses the autophagic death of ectopic endometrial cells, thereby promoting lesion establishment (26). Concurrently, activation of the RAS/RAF/MEK/ERK pathway enhances cellular motility, accelerating disease progression in AM (27).

In reproductive physiology, IL-6 plays key regulatory roles in embryo implantation, fetal development and other pregnancy-associated processes (28). Experimental evidence demonstrates that blastocyst development is impaired in IL-6 knockout mice, thereby adversely affecting pregnancy outcomes. IL-6 not only induces the secretion of monocyte chemoattractant protein-1 (MCP-1) by decidual stromal cells, promoting macrophage recruitment and the formation of a localized inflammatory response that impairs embryo implantation (20), but also disrupts ER and affects embryo implantation through activation of the JAK/STAT3 signaling pathway (29). Furthermore, IL-6 mediates vascular and immune dysregulation at the maternal-fetal interface (placenta/decidua) and has been proposed as a potential diagnostic or biomarker candidate for endometriosis (EMs)-associated infertility (30).

Pro-inflammatory cytokine CXCL8 induces proliferation and angiogenesis in the eutopic endometrium. As a key member of the α-chemokine family, CXCL8 mediates neutrophil chemotaxis and activation via specific interactions with cognate receptors CXCR1 and CXCR2. In patients with AM, CXCL8 mRNA and protein expression are markedly upregulated in both ectopic lesions and the eutopic endometrium (31), paralleled by proliferative-phase upregulation of CXCR1/CXCR2 receptors on endometrial epithelial cells (32). Through paracrine signaling, the CXCL8-CXCR1 axis is activated, thereby promoting the invasive growth of ectopic endometrial tissue (33).

Physiologically, CXCL8 expression in normal endometrium peaks during the late secretory phase, facilitating neutrophil recruitment and stromal proliferation to prepare for menstruation (32). However, in AM pathophysiology, loss of CXCL8 cyclical rhythmicity results in defective postmenstrual repair and pathological angiogenesis within the eutopic endometrium. Activation of the TLR4/p38/ERK pathway can induce CXCR1 expression and promote CXCL8 secretion (34). Clinical analyses reveal diminished CXCL8 concentrations in the cervical mucus of patients with AM-associated infertility (35), while elevated serum CXCL8 levels and autoantibody positivity highlight its potential as a diagnostic biomarker for immune-mediated infertility (36). Singh *et al* (37) demonstrated inverse correlations between

CXCL8 levels and both oocyte maturity and embryo quality. A further study has confirmed the dual role of CXCL8 in regulating early pregnancy outcomes through endometrial paracrine signaling and mediating embryo implantation via CXCR1 binding in patients with AM (38).

IL1B regulates inflammatory cascades, immune homeostasis and hormonal crosstalk in AM-associated infertility. IL1B, a prototypical pro-inflammatory cytokine, initiates biological responses through binding to IL-1 receptor type I (IL-1R1) and recruiting IL-1 receptor accessory protein (IL-1RAcP) to form a high-affinity receptor complex (39). IL1B undergoes canonical activation by lipopolysaccharide (LPS) binding to TLRs. This binding event induces TLRs to recruit the adaptor protein MyD88 via their intracellular Toll/IL-1 receptor domain, culminating in IL1B transcriptional activation (40). Elevated IL1B expression is consistently observed in the eutopic and ectopic endometrium of patients with AM (19), where it serves as a critical initiator of pathological inflammatory cascades. MyD88 can also activates IRAK kinases and the IκB kinase (IKK) complex, leading to inhibitor of NF-κB (IκB) degradation and NF-κB nuclear translocation (41), thereby initiating downstream inflammatory cascades via the classical NF-κB pathway.

Furthermore, upregulation of IL1B has been implicated in disrupting the T helper cell 17 (Th17)/regulatory T cells (Treg) balance, leading to immune intolerance at the maternal-fetal interface, which is a key mechanism underlying implantation failure (42). The function of regulatory factors involved in embryo-maternal communication, such as IL-1RAcP and IL-1R antagonist (IL-1RA), may also be impaired. The ratio of IL-1RA to IL1B has been proposed as a potential predictive marker for adverse pregnancy outcomes in patients with AM (43).

In addition, Wang *et al* (44) demonstrated a significant positive correlation between IL1B expression and serum levels of estradiol (E2), progesterone and endometrial thickness ($P<0.05$), suggesting that IL1B may synergize with E2 and progesterone to improve ER and could serve as a predictive indicator of pregnancy outcomes. Lastly, IL1B has been reported to impair sperm binding to the zona pellucida in EMs (45), suggesting that this mechanism may also contribute to infertility in patients with AM.

Anti-inflammatory cytokine IL10 facilitates immune tolerance in ectopic endometrial tissues. As a representative anti-inflammatory cytokine, IL-10 exerts its effects by forming a functional heterodimeric receptor complex composed of IL-10 receptor 1 and IL-10 receptor 2 (46). On one hand, IL-10 suppresses immune responses by inhibiting Th1 cell activity and disrupting the Th1/Th2 balance; on the other hand, it can also enhance immune responses by stimulating the functions of $CD8^+$ T cells, NK cells and B cells (47).

Multiple studies have confirmed that IL-10 expression is significantly elevated in both the eutopic and ectopic endometrial epithelial tissues of patients with AM compared with normal endometrium (48-50). Mechanistically, ectopic endometrial tissues in AM exhibit tumor-like invasive and immune escape properties as they must evade host immune surveillance to colonize and proliferate within the myometrium (51). This process is highly consistent with the immunosuppressive function of IL10. In tumor cells, IL-10 has been shown to inhibit antigen-presenting cell function and T cell activation by inducing the expression of human leukocyte antigen-G (HLA-G) and downregulating the levels of classical MHC class I and II antigens, thereby reducing pro-inflammatory cytokine production and achieving immune escape (52). This suggests that IL-10 may play a similar role in AM, promoting immune escape and enabling ectopic endometrial cells to invade the myometrium and establish local immune tolerance (53).

At the maternal-fetal interface, IL-10 critically maintains immune tolerance through STAT3/HOXA10-mediated regulation of ER (54). During the implantation window, IL-10 contributes to the establishment of a tolerogenic immune microenvironment by reducing the proportion and functional activity of uterine NK (uNK) cells at the decidual-placental interface. Abnormally low IL-10 levels in the endometrium or placental tissues have been observed in pregnancy-related complications such as recurrent miscarriage and preeclampsia (55). During the implantation window, significantly reduced local endometrial IL-10 levels have been observed in patients with AM, which may represent a key factor contributing to their lower embryo implantation rates compared with women with normal endometrium (20).

Role of other inflammatory cytokines in AM-related infertility

COX-2 mediates cell proliferation, angiogenesis and multifaceted pathways to drive AM-associated reproductive dysfunction. COX-2 is a key enzyme involved in the conversion of arachidonic acid into various endogenous prostaglandins. While typically undetectable in normal tissues, COX-2 can be induced by inflammatory stimuli, earning it the label of a 'stress gene' (56). In AM, elevated COX-2 expression has been observed in both the eutopic and ectopic endometrium; it contributes to disease pathogenesis by regulating inflammatory pathways linked to cell proliferation, angiogenesis and immune suppression (57). Moreover, COX-2 has been proposed as a potential molecular biomarker or therapeutic target for dysmenorrhea in patients with early-stage AM (58). An *in vitro* study has shown that COX-2 inhibitors significantly suppress the migration and invasion of endometrial mesenchymal stem cells (59), supporting its potential as a novel therapeutic target in AM.

COX-2 exacerbates AM-associated infertility through multiple mechanisms. First, its upregulation increases prostaglandin E2 (PGE2) production, driving chronic inflammation that leads to ovarian apoptosis, pelvic adhesions, fallopian tube dysfunction and luteal phase defects. Second, COX-2-derived PGE2 activates aromatase, boosting local estrogen biosynthesis and creating a positive feedback loop between estrogen and inflammation that accelerates ectopic lesion growth. In addition, the COX-2/PGE2 signaling pathway downregulates progesterone receptor (PR) expression, inducing progesterone resistance and impairing endometrial decidualization (60). Furthermore, COX-2 may disrupt the function of stromal telocytes, compromising structural integrity at the utero-tubal junction and affecting gamete transport and the embryo implantation microenvironment (61). Through these coordinated effects on hormonal balance, tissue structure and

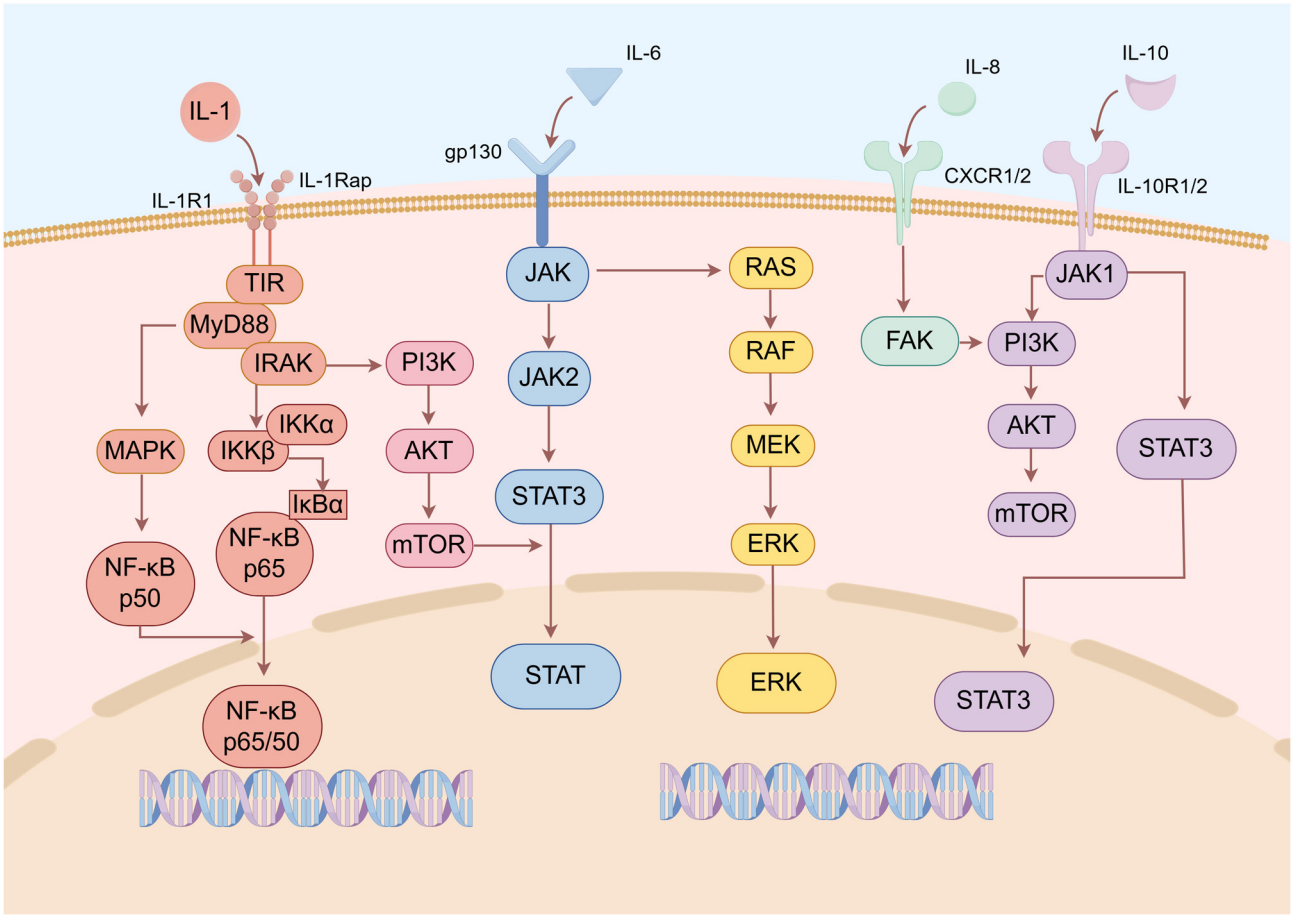

Figure 1. Main inflammatory pathways through which inflammatory cytokines promote the occurrence and development of adenomyosis. IL-1, IL-6, CXCL8 and IL10 are the inflammatory cytokines mainly described in the present review. Their promotion of the establishment and development of adenomyosis mainly involves signal pathways such as JAK/STAT, PI3K/AKT/mTOR, RAS/RAF/MEK/ERK and NK-κB. AKT, protein kinase B; CXCR1/2, C-X-C chemokine receptor 1/2; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; gp130, glycoprotein 130; IKKa/b, IκB kinase a/b; IκBa, inhibitor of nuclear factor κB a; IL, interleukin; IL-1R1, interleukin-1 receptor 1; IL-1Rap, interleukin-1 receptor accessory protein; IRAK, interleukin-1 receptor-associated kinase; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor κ-light-chain-enhancer of activated B Cells; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma viral oncogene homolog; STAT3, signal transducer and activator of transcription 3; TIR, Toll/interleukin-1 receptor domain.

immune-endocrine crosstalk, COX-2 acts as a central regulator of reproductive dysfunction in AM.

NF-κB mediates the pathogenesis of AM via regulating inflammatory cytokine networks, immune tolerance and progesterone resistance. NF-κB serves as a central regulator of inflammatory responses. Upon stimulation by pro-inflammatory factors such as LPS, TNF-α or IL-1, IKKβ mediates the phosphorylation of IκB, leading to the release of the active p50/p65 heterodimer. This complex translocates into the nucleus and initiates the transcription of pro-inflammatory cytokines such as IL-6, TNF-α and CXCL8, as well as COX-2 (62). A preclinical study has validated the pathogenic role of NF-κB in AM, where endometrial microenvironmental aberrations sustain NF-κB activation, generating cytotoxic inflammation that impairs embryonic viability and endometrial epithelial integrity, ultimately diminishing implantation rates, effects reversible through NF-κB inhibition in murine AM models (63).

In terms of pregnancy, the TLR4/NF-κB pathway regulates maternal-fetal immune tolerance by modulating the Th17/Treg cell ratio. This balance is crucial for proper trophoblast invasion and angiogenesis at the placental interface, which are essential for ensuring adequate fetal blood supply, nutrient delivery and successful pregnancy outcomes (64). Furthermore, NF-κB engages in reciprocal crosstalk with PR isoforms: Chronic inflammatory signaling induces constitutive NF-κB activation that selectively downregulates PR-B expression, fostering progesterone resistance. This molecular disruption impairs endometrial decidualization and creates a non-receptive implantation milieu. Fig. 1 illustrates the regulatory networks of multiple inflammation-related cytokines (including IL-1, IL-6, IL-8 and IL-10) and their downstream signaling pathways (such as NF-κB and STAT3) involved in the aforementioned processes (65).

Immune cell-derived inflammatory cytokines lead to infertility. Immune cells serve as the primary source of inflammatory cytokines, and their dysregulated activation and crosstalk disrupt the endometrial immune microenvironment and maternal-fetal interface homeostasis, ultimately contributing to AM-associated infertility.

Macrophages. Macrophages are critical regulators of tissue inflammation and repair, and their phenotypic and functional abnormalities are closely linked to AM pathogenesis. Studies consistently demonstrate significantly elevated macrophage density in both the eutopic and ectopic endometrial tissues of patients with AM compared with normal endometrium (66,67), with a phenotypic shift: Pro-inflammatory M1 macrophages decrease, while anti-inflammatory M2 macrophages increase, this shift creates an immunosuppressive microenvironment that favors ectopic lesion survival.

The pathogenic effects of M2 macrophages in AM are multifaceted: First, excessive M2-derived cytokines (such as IL-10 and TGF-β) promote angiogenesis, accelerate ectopic endometrial cell proliferation and induce pathological tissue fibrosis. Second, M2 macrophages activate the STAT3 signaling pathway in ectopic endometrial cells, further enhancing their growth and invasive capacity (68), Third, the accumulation of M2 macrophages alters myometrial contractility, disrupting embryo transport through the fallopian tube and impairing the stability of the implantation microenvironment (69).

Mechanistically, an *in vitro* study has confirmed that AM-derived ESCs secrete chemokine CCL2, which recruits monocytes via the estrogen receptor β (ERβ)/NF-κB signaling pathway (70); these recruited monocytes then undergo excessive M2 polarization under the influence of the CCL2-CCR2 axis. In addition, ESCs release exosomal microRNA (miRNA/miR)-301a-3p, which mediates M2 polarization via the PTEN/PI3K pathway (71), forming a vicious cycle. Upregulated Legumain pseudogene 1 not only promotes M2 polarization but also serves as a non-invasive biomarker for predicting lesion recurrence (72). The resultant M1/M2 disequilibrium disrupts implantation-phase inflammatory homeostasis at the maternal-fetal interface, impairing embryo attachment competence (73).

NK cells. uNK cells are the most abundant lymphocyte subset in the endometrium, accounting for 30-50% of endometrial lymphocytes and 70% of decidual lymphocytes. Under physiological conditions, uNK cells play indispensable roles in regulating ER, trophoblast invasion and placental vascular remodeling, functions mediated by their secretion of cytokines such as TNF-α, IL-10, IL-1β and LIF (74). The number and function of uNK cells exhibit dynamic changes throughout the menstrual cycle: Their counts remain low during the proliferative phase, increase significantly after ovulation and peak during early pregnancy (75). In the secretory phase, uNK cells participate in spiral artery remodeling; after embryo implantation, they promote early placental development by facilitating trophoblast invasion and optimizing spiral artery dilation, thereby ensuring efficient maternal-fetal exchange of nutrients and oxygen (76). Additionally, uNK cells eliminate infected maternal decidual cells during early pregnancy, maintaining local immune surveillance without damaging the embryo (77). Abnormal uNK cell function has been implicated in multiple reproductive disorders, including recurrent miscarriage and repeated implantation failure, highlighting their critical role in reproductive success (78).

Although current studies have not confirmed significant differences in NK cell expression in women with AM, one key study has reported increased uNK cell counts in the eutopic endometrium of patients with severe AM (diffuse or adenomyoma type). More notably, regardless of quantity, the functional defect of uNK cells in AM [specifically, reduced expression of killer immunoglobulin-like receptors (KIRs)] is a major factor impairing embryo implantation (79). Furthermore, uNK cells collaborate with other endometrial/decidual immune cells to establish a Th2-dominant immune environment, a hallmark of maternal-fetal immune tolerance. In AM, abnormal uNK cell subsets or dysregulated uNK-derived cytokine networks disrupt this Th2-dominant state, increasing the risk of maternal immune rejection of the embryo and impeding successful pregnancy (80).

Mast cells and T cells. Aberrant activation of immune cells such as mast cells and T cells adversely affects reproductive function by modulating the inflammatory microenvironment. Table SI summarizes the key immune cell subsets (including mast cells, T cells and other relevant populations), their associated pro-inflammatory/profibrotic mediators and downstream pathological effects on the endometrium and reproductive outcomes. Specifically, activated mast cells release profibrotic mediators such as TGF-β1 and fibroblast growth factor (FGF), which accelerate endometrial fibrosis (81); this not only distorts the endometrial structure (compromising ER) but also enhances the invasive capacity of ectopic lesions. Moreover, mast cell-derived inflammatory mediators (such as histamine and prostaglandins) disrupt endometrial epithelial integrity and alter local blood flow, creating an unfavorable microenvironment for embryo implantation (82).

T cell subsets (particularly Th17 cells and Treg cells) play a central role in maintaining immune homeostasis at the maternal-fetal interface. In AM, this balance is severely disrupted: The number of pro-inflammatory Th17 cells increases, while the number and functional activity of immunosuppressive Treg cells decrease (83), This Th17/Treg imbalance intensifies local endometrial inflammation (such as elevated IL-17 secretion) and impairs maternal-fetal immune tolerance.

Inflammatory microenvironment in AM affects pregnancy outcomes. The tumor microenvironment, often referred to as the 'soil' for malignant tumor growth, plays a critical role in coordinating tumor invasion and immune evasion through inflammatory mediators, immune cell infiltration, angiogenesis and matrix remodeling. Notably, a highly analogous dynamic system exists in AM. Although considered a benign condition, AM lesions exhibit several hallmarks of malignancy. Specifically, ectopic endometrial cells are capable of degrading the basement membrane via MMP-2 and MMP-9, infiltrating the myometrium in an asymmetric pattern, disrupting the vascular and lymphatic systems and facilitating the implantation of endometrial tissue within the myometrial layer, processes that closely resemble the local invasion behavior of malignant tumors (84). Furthermore, lesion cells can evade apoptosis by upregulating the anti-apoptotic protein Bcl-2 through the activation of NF-κB signaling (85). In addition, persistent activation of hypoxia-inducible factor-1α (HIF-1α) drives a shift toward glycolytic metabolic reprogramming, resulting in excessive lactate production. This not only supports cellular energy homeostasis but also creates an acidic microenvironment similar to that observed in tumors, thus establishing a vicious cycle that confers survival

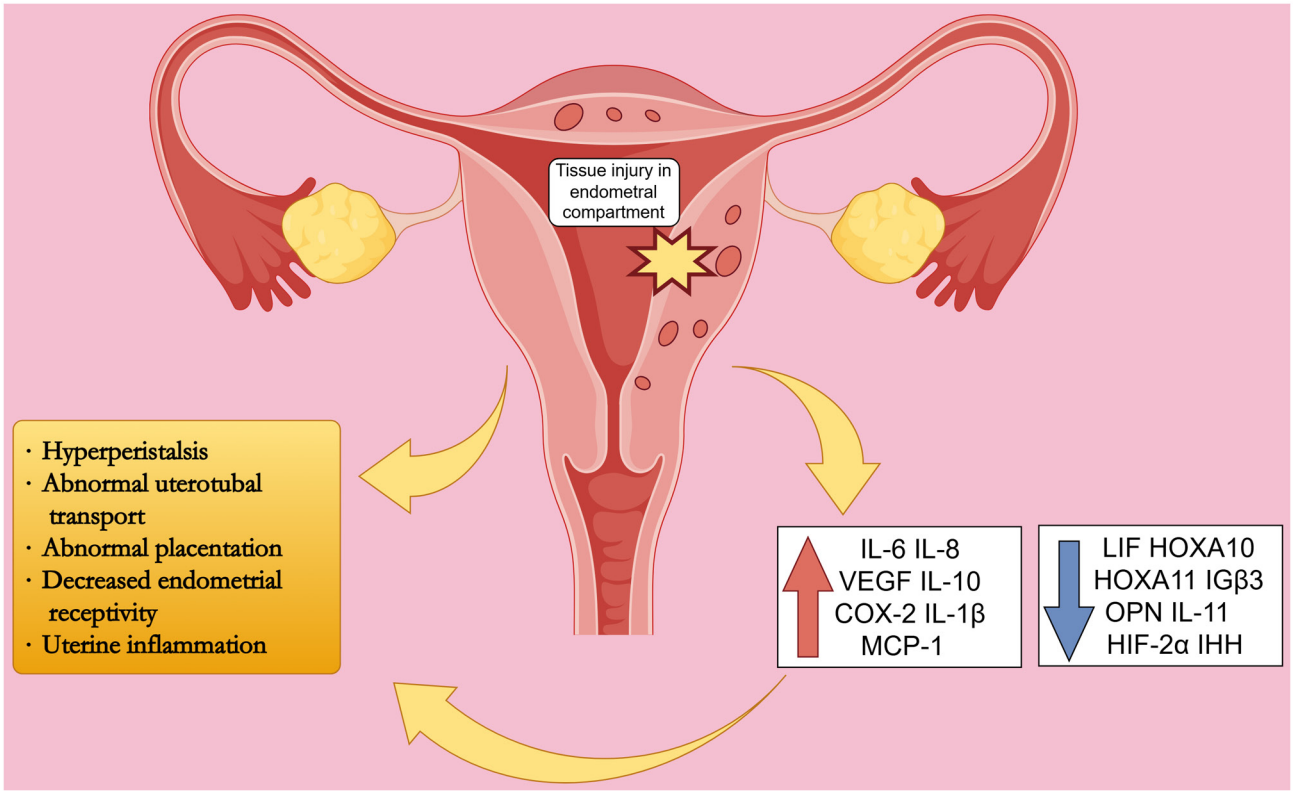

Figure 2. Abnormal aggregation of inflammatory cytokines affects the inflammatory microenvironment and interferes with multiple stages of embryo implantation. Tissue damage at the endometrium-myometrium interface is the key trigger for abnormal aggregation of inflammatory cytokines. Among them, IL-6, CXCL8, VEGF, IL10, COX-2, IL1B and MCP-1 are upregulated, while LIF, HOXA10, HOXA11, IGβ3, OPN, IL11, HIF-2α and IHH are downregulated. The abnormal inflammatory microenvironment leads to hyperperistalsis of the uterus, decreased fallopian tube transport function, abnormal placental formation and decreased endometrial receptivity. COX-2, cyclooxygenase-2; HIF-2α, Hypoxia-Inducible Factor-2α; HOXA10, homeobox A10; HOXA11, homeobox A11; IHH, Indian hedgehog; IGβ3, integrin β3; IL, interleukin; LIF, leukemia inhibitory factor; MCP-1, monocyte chemoattractant protein-1; OPN, osteopontin; VEGF, vascular endothelial growth factor.

advantages (86). Notably, chronic inflammatory stimulation has been shown to induce the expression of epithelial-mesenchymal transition (EMT) markers such as Snail and vimentin, which enhances the invasive potential of lesion cells and significantly increases the risk of malignant transformation of ectopic endometrial lesions (87).

The immune dysregulation associated with AM markedly contributes to infertility; it impairs ovulatory function, induces tubal dysfunction or adhesions and disrupts the transport of sperm and embryos (88). Additionally, the immunosuppressive microenvironment, characterized by the secretion of immunoinhibitory factors, interferes with the immune support required for normal embryo development, leading to pregnancy failure (Fig. 2) (89). Some patients may also produce autoantibodies against endometrial tissue or embryos (such as antiphospholipid antibodies and anti-endometrial antibodies), directly damaging the endometrium or targeting the embryo, thereby impairing implantation (90). Moreover, abnormal expression of chemokines and adhesion molecules may disrupt embryo-endometrial signaling, reducing ER. A recent single-cell RNA sequencing study has revealed altered intercellular communication among epithelial cells, stromal cells, perivascular cells, endothelial cells and immune cells within ectopic lesions. These alterations lead to changes in pathways associated with cell proliferation, angiogenesis and immune responses, underscoring the dynamic remodeling of the AM microenvironment. This spatiotemporal dysregulation ultimately impairs embryo implantation (91).

4. Mechanisms of inflammatory cytokine regulation in myometrial peristalsis, tissue damage and repair and EMT in AM

Inflammatory cytokines disrupt uterine peristalsis by altering the immune microenvironment. Under physiological conditions, the JZ (a transitional region between the endometrium and myometrium) serves two core functions; it exhibits periodic contractile patterns to regulate menstrual shedding, gamete transport and embryo implantation (92), while also acting as a physiological immune regulatory barrier that maintains genital tract microbial homeostasis and optimizes the embryo implantation microenvironment via immune cells (such as macrophages and NK cells) and cytokine networks (93).

In MRI diagnostics, JZ thickening (>12 mm) is explicitly a pathognomonic feature of AM (94). Maubon *et al* (95) confirmed a threshold-dependent association between JZ thickness and implantation rate: Implantation rates of 45% when JZ thickness is <10 mm, a sharp decline to 16% at 10-12 mm, and a further reduction to 5% in cases with JZ thickness >12 mm. They further summarized that MRI-quantified JZ thickness is the primary negative predictor of implantation failure; specifically, beyond the critical threshold of 7 mm, the risk of

implantation failure increases exponentially (95). This inverse thickness-implantation relationship persists across diagnostic modalities. Notably, Tellum *et al* (96) emphasized that JZ morphological heterogeneity, particularly focal asymmetric thickening secondary to myometrial cysts or adenomyoma formation, should be incorporated into the differential diagnostic criteria for AM.

JZ dysfunction in patients with AM impairs placentation. Impaired decidual transformation leads to trophoblast retention within the JZ, hindering spiral artery remodeling and causing defective deep placentation (17). Single-cell RNA sequencing has further confirmed a reduced number of uNK cells and an insufficient secretion of angiogenic factors in JZ-thickened regions, which directly limits the depth of trophoblast invasion and exacerbates defective deep placentation (16). Therefore, the abnormally thickened JZ observed in AM may hinder embryo transport and preimplantation positioning, while also disrupting the microenvironmental homeostasis at the endometrial-myometrial junction (EMJ) during decidualization (12).

Physiologically, uterine peristalsis exhibits phase-specific dynamics. Antegrade peristaltic waves mediate menstrual shedding during the proliferative phase, retrograde contractions facilitate sperm migration during the ovulatory window and quiescent contractions in the luteal phase create a favorable microenvironment for embryo implantation (97). Thus, physiological uterine peristalsis is indispensable for coordinating intrauterine sperm and embryo translocation. In patients with AM, speckle-tracking transvaginal ultrasonography reveals characteristic pathological contractile patterns, including a disorganized contractile direction during the ovulatory phase and hypercontractility in the luteal phase (98). The core mechanism underlying this pathological contractility is linked to the excessive local production of prostaglandin F2α (PGF2α) and IL-6 in the JZ (99). These factors collectively drive luteal-phase uterine hyperperistalsis, impairing embryo positioning and adhesion. Chronic hypercontractility further exacerbates JZ microtrauma, sustains inflammatory cascades and establishes an 'inflammation-estrogen' feedforward loop that accelerates AM pathogenesis. Clinically, these dysregulations manifest as obstetric sequelae, including uterine atony, retained placenta and postpartum hemorrhage, highlighting the central role of JZ dysfunction in both the pathological mechanisms and clinical consequences of AM (100).

Mechanisms of tissue injury and repair (TIAR). The TIAR hypothesis is a central framework for explaining AM pathogenesis, as it highlights inflammation and immune dysregulation as key drivers of disease initiation and progression, with elevated inflammatory mediators and a disrupted endometrial immune niche ultimately impairing embryo implantation (101). This subsection systematically elaborates on the triggers of TIAR, its mediated pathological cascades and the subsequent amplifying loops that sustain AM development.

TIAR activation in AM arises from two primary sources of mechanical stress. Endogenously, supraphysiological uterine peristalsis and increased intrauterine pressure (a hallmark of AM) directly damage myocytes and fibroblasts within the JZ, a critical physical barrier between the endometrium and myometrium (102), and this mechanical damage initiates the TIAR cascade. Exogenously, iatrogenic injuries (such as curettage, childbirth, induced abortion and cesarean section) impose supraphysiological mechanical strain on the uterus, directly inducing COX-2 and CXCL8 expression in fibroblasts (4). Even mild mechanical stretching of cultured fibroblasts has been shown to activate COX-2, promote PGE2 and CXCL8 production and thereby trigger TIAR (4). Notably, iatrogenic damage often impairs the JZ (103); as the JZ serves as a barrier to prevent endometrial invasion, its disruption further facilitates endometrial penetration into the myometrium and increases AM risk following intrauterine procedures (104).

Once triggered, the TIAR cascade drives AM progression through a sequential pathological process. First, TIAR-induced microtrauma leads to myometrial fissures, enabling the ectopic displacement of endometrial fragments (105). These ectopic fragments are recognized by the immune system as damaged tissue-initiating lesion-specific inflammatory priming characterized by IL1B/IL-6 upregulation, platelet aggregation and HIF-1α stabilization, which propagates local-to-systemic inflammatory cascades (102). At the molecular level, IL1B plays a central role in amplifying inflammation; it activates COX-2 transcription via a mitogen-activated protein kinase (MAPK)-dependent pathway, which enhances COX-2 binding to the cAMP response element, recruiting immune cells and further amplifying the inflammatory cascade (106), and it activates the ERK1/2 and NF-κB signaling pathways to induce COX-2 expression; elevated COX-2 then promotes PGE2 synthesis (9), which in turn upregulates IL-6 and CXCL8 expression, creating a positive feedback loop to sustain inflammation.

Beyond inflammatory amplification, the TIAR-mediated response interacts with estrogen metabolism to form a vicious cycle that accelerates AM chronicity. PGE2 upregulates the expression of steroidogenic acute regulatory protein and CYP19A1 to enhance local E2 biosynthesis (67); E2 further activates estrogen receptors (ERα/ERβ) to promote cell proliferation while simultaneously trans-activating the COX-2 gene, thus increasing PGE2 production and perpetuating inflammation. Notably, ectopic lesions (predominantly localized to the anterior/posterior uterine walls and fundal-cornual regions with concentrated mechanical stress) exacerbate uterine hyperperistalsis, which reinforces this TIAR-inflammation-estrogen loop and in turn drives disease progression (107).

EMT, fibroblast-to-myofibroblast transdifferentiation (FMT) and fibrosis: Pathogenic roles in AM and impacts on pregnancy. EMT is a biological process in which epithelial cells lose polarity and intercellular junctions, gaining mesenchymal characteristics, including enhanced motility and invasiveness (108). Hallmarks of EMT include downregulation of E-cadherin and upregulation of N-cadherin and vimentin, resulting in the loss of epithelial polarity and increased invasive potential. In AM, EMT serves as a key driver of ectopic lesion formation by enabling endometrial cells to traverse the EMJ and establish adenomyotic lesions (67), while also exacerbating disease progression by promoting fibrosis and uterine dysfunction.

Multiple cytokines and signaling pathways orchestrate EMT in AM. CXCL8 activates the FAK/PI3K/AKT pathway to enhance the proliferation, migration and invasiveness

of eutopic ESCs (34), supporting their survival in ectopic environments (59). Macrophage-induced IL-6 overactivation in human endometrial cells suppresses E-cadherin promoter activity and upregulates N-cadherin/vimentin via the JAK2/STAT3 pathway, directly inducing EMT (67). IL1B activates the Wnt/β-catenin pathway, a key regulator of EMT, with COX-2 further amplifying this effect to drive AM progression (109,110). Hypoxic conditions in the ectopic microenvironment also induce HIF-1α expression, which upregulates IL-6, CXCL8 and CXCL12. CXCL12 promotes angiogenesis via its receptor CXCR4, while IL-6 and CXCL8 amplify inflammatory and pro-fibrotic signals (103).

Additionally, Notch1 is upregulated in ectopic endometrium and indirectly promotes EMT by modulating pathways such as NF-κB, leading to N-cadherin/Snail/Slug upregulation and E-cadherin loss; downregulation of Numb, a negative regulator of Notch, may further exacerbate EMT-driven fibrosis and lesion invasion (111). Although the direct role of IL-10 in AM-associated EMT remains unstudied, its EMT-promoting effects in cancer and renal cells suggest potential relevance (112); notably, thymus-expressed chemokine derived from embryonic stem cells and macrophages upregulates Tregs in the ectopic microenvironment, promoting IL-10/TGF-β1 secretion that suppresses NK cell cytotoxicity and Th1-type immunity, creating an immunosuppressive niche that protects ectopic endometrial cells from clearance (113). Beyond driving ectopic lesions, EMT collaborates with fibrosis to worsen AM pathogenesis, as fibrosis in AM arises from dysregulated wound healing. Unlike the regenerative phase of normal tissue repair (where injured cells are replaced without scarring), AM is characterized by a fibrotic phase in which parenchymal tissue is replaced by fibrotic connective tissue, accompanied by excessive extracellular matrix (ECM) deposition and remodeling imbalance (114).

EMT and FMT are central to this process, driving lesion stabilization and myometrial thickening (115), while ectopic ESCs directly interact with the myometrium to induce SMC fusion and abnormal expansion, altering uterine morphology and function. As key fibrotic regulators, macrophages orchestrate EMT, FMT and SMC modulation via M1-M2 polarization and activation of the canonical TGF-β/Smad3 pathway, synergistically promoting ECM collagen synthesis; during phagocytic clearance of cellular debris, they also regulate ECM turnover via the dynamic balance between MMPs and their TIMPs, mediating the degradation-deposition cycle of ECM reconstruction (84,116), a pathway that further cross-talks with PI3K/AKT and MAPK signaling to amplify pro-fibrotic effects. Under TIAR mechanisms, ectopic endometrial cells undergo cyclic hemorrhage-induced chronic inflammation, triggering EMT, FMT and SMC modulation to form fibrotic scars, with fibrosis markers such as α-smooth muscle actin and type I collagen positively correlating with uterine volume, linking fibrosis severity to disease progression (114).

From a reproductive perspective, EMT and fibrosis disrupt AM-associated reproductive function via multiple pathways: They cause structural disruption at the EMJ, interfering with embryo implantation and placental development; induce uterine hyperperistalsis, impairing embryo and gamete transport (117); and promote excessive scar formation that increases intrauterine adhesion risk, ultimately contributing to infertility (118). The integrated regulatory network linking these key pathogenic processes (inflammatory cytokine signaling, TIAR cascades, EMT, FMT and fibrosis) to AM-related reproductive dysfunction is systematically summarized in Fig. 3.

5. Impact of inflammatory cytokines on pregnancy outcomes in AM

Impact of neovascularization on pregnancy. In AM, aberrantly elevated pro-angiogenic factors, such as VEGF and FGF, and reduced anti-angiogenic activity drive excessive neovascularization. This not only provides nutritional support for ectopic lesions [facilitates their invasion, survival and proliferation to form a vicious cycle (119)] but also causes structural abnormalities in neovessels. These fragile vessels are prone to rupture, leading to abnormal uterine bleeding, disrupted endometrial homeostasis and impaired ER (120). The aberrant vascular network further interferes with embryo positioning and adhesion, contributing to implantation failure.

Pathological angiogenesis in AM is primarily triggered by TIAR, closely linked to vascular damage from cyclical endometrial bleeding (121). Under physiological conditions, endometrial repair follows a four-phase process: Hemostasis, inflammation, proliferation and remodeling (122). This ordered process ensures proper tissue recovery without persistent damage. However, in pathological states, this repair process is disrupted. The disorganized repair leads to vascular structures, which in turn exacerbate local inflammation and fibrosis and perpetuate a vicious cycle of tissue injury and dysregulated repair.

In the initial phase of repair, activated platelets drive hemostasis (123) and release bioactive molecules [such as thromboxane A2, 5-hydroxytryptamine, PDGF and epidermal growth factor (EGF)] that upregulate pro-inflammatory genes including VEGF, COX-2 and MMP-9, thereby creating a pro-angiogenic microenvironment (124). Notably, VEGF, a key specific marker of angiogenesis, not only directly promotes endothelial cell proliferation but is also elevated in the follicular fluid of patients with EMs, and clinically increased VEGF levels are significantly associated with poor ovarian response, reduced oocyte maturation rates and higher miscarriage risk (125).

Moreover, platelets secrete platelet-derived growth factor, EGF and FGF to directly stimulate endothelial proliferation and recruit macrophages and neutrophils to the lesion site; these immune cells subsequently release inflammatory cytokines (such as IL-6, IL-10, CXCL8, TGF-β, IL-22 and NF-κB) to amplify the local inflammatory response (Fig. 4) (126,127). Platelets also upregulate tissue factor, which binds to circulating factor VIIa to activate the coagulation cascade. The resultant thrombin generation promotes sustained platelet activation, forming a 'coagulation-inflammation' positive feedback loop (128). Salim *et al* (129) confirmed the upregulation of these angiogenesis- and inflammation-related factors in adenomyotic lesions, supporting increased pathological neovascularization. Growing evidence indicates that platelets are not merely hemostatic cells but also key immunoregulatory agents (130) whose interaction with ectopic lesions fosters a microenvironment supporting lesion progression and fibrosis (131).

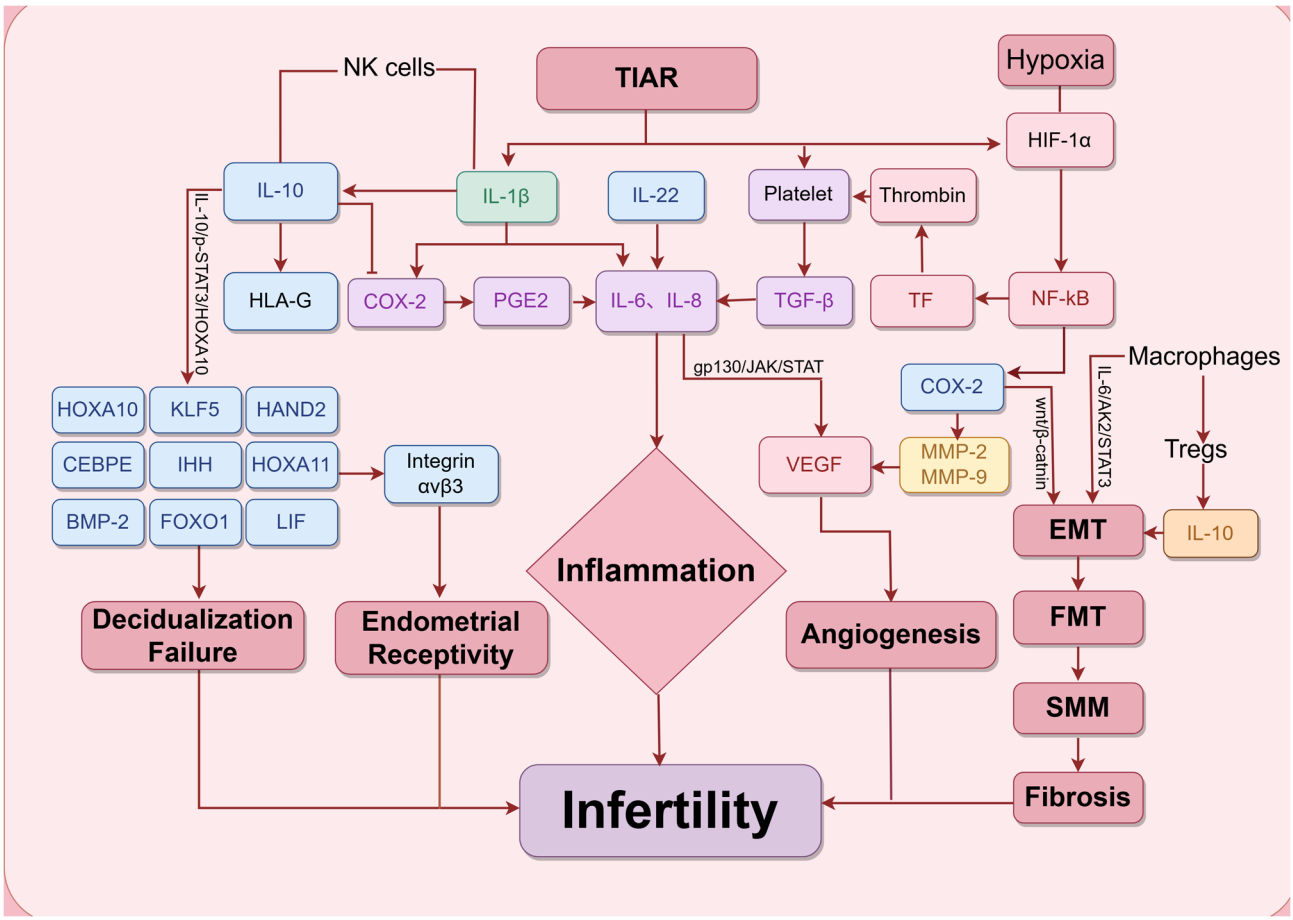

Figure 3. Overview of interactions between inflammatory cytokines in adenomyosis-related infertility in the present review. However, these interactions do not necessarily represent the actual or complete biological pathways. NF-κB, nuclear factor κB; HIF1A, hypoxia-inducible factor 1α; VEGF, vascular endothelial growth factor; TGF-β, transforming growth factor β; MMP, matrix metalloproteinase; HLA-G, human leucocyte antigen-G; COX2, cyclooxygenase2; PGE2, prostaglandin E2; TF, tissue factor; BMP-2, bone morphogenetic protein-2; CEBPE, CCAAT/enhancer-binding protein ε; EMT, epithelial-mesenchymal transition; FMT, fibroblast-myofibroblast transition; FOXO1, forkhead box O1; HAND2, heart and Neural Crest Derivatives Expressed 2; HOXA10, homeobox A10; HOXA11, homeobox A11; IHH, Indian hedgehog; IL, interleukin; JAK, Janus kinase; KLF5, Kruppel-like factor 5; LIF, leukemia inhibitory factor; NK cells, natural killer cells; gp130, glycoprotein 130; SMM, smooth muscle metaplasia; STAT, signal transducer and activator of transcription; TIAR, tissue injury and repair; Tregs, regulatory T cells.

The interplay between angiogenesis, immune cells and inflammation is well-recognized (132). Angiogenesis is modulated by immune cells and inflammatory mediators (133-135) and reciprocally influences immune responses. Wei *et al* (136) demonstrated that IL-6 promotes pathological angiogenesis by upregulating VEGF via activating the STAT3 signaling pathway. Clinical data reveal a strong positive correlation between serum IL-6 levels and lesion microvessel density, indicating the potential of IL-6 as a biomarker for disease progression (137). Thymic stromal lymphopoietin (TSLP) induces CXCL8 secretion in cervical cancer cells via the ERK1/2 pathway to stimulate human umbilical vein endothelial cell proliferation and angiogenesis, and this mechanism appears to be recapitulated in the ectopic endometrium of AM, suggesting TSLP as a potential therapeutic target (138,139). IL1B enhances CXCL8 and VEGF expression to promote invasive migration of ESCs and facilitate immune cell extravasation by upregulating ICAM-1 and VCAM-1, thereby driving tissue remodeling (140). Silencing the COX-2 gene significantly reduces VEGF and MMP-9 expression in ectopic endometrium, underscoring the pivotal role of COX-2 as an upstream regulator in AM (141). Additionally, clinical specimens show a strong correlation between COX-2 positivity, dysmenorrhea severity and lesion volume (58). As a central transcription factor, NF-κB directly regulates COX-2, VEGF, MMPs and the plasminogen activator system (142,143), and mediates endothelial inflammation induced by IL1B and TNF-α (144), highlighting the central role of the COX-2/NF-κB axis.

Compared with normal endometrium, IL-10 expression in adenomyotic tissues is reduced by 62%, which impairs its regulatory effect on COX-2, MMP-2 and MMP-9 and contributes to uncontrolled angiogenesis (145); this dysregulation is closely associated with impaired ER due to an abnormal IL-10/IL-6 ratio during the implantation window. IL-22, a member of the IL-10 cytokine family, enhances stromal cell invasiveness by upregulating VEGF, IL-6 and CXCL8 expression (146), and clinical data show that serum IL-22 levels are significantly elevated in infertile patients and inversely correlated with embryo implantation rates during IVF cycles (147). Fischer *et al* (148) confirmed by immunohistochemistry that eutopic endometrial cells in AM exhibit heightened sensitivity

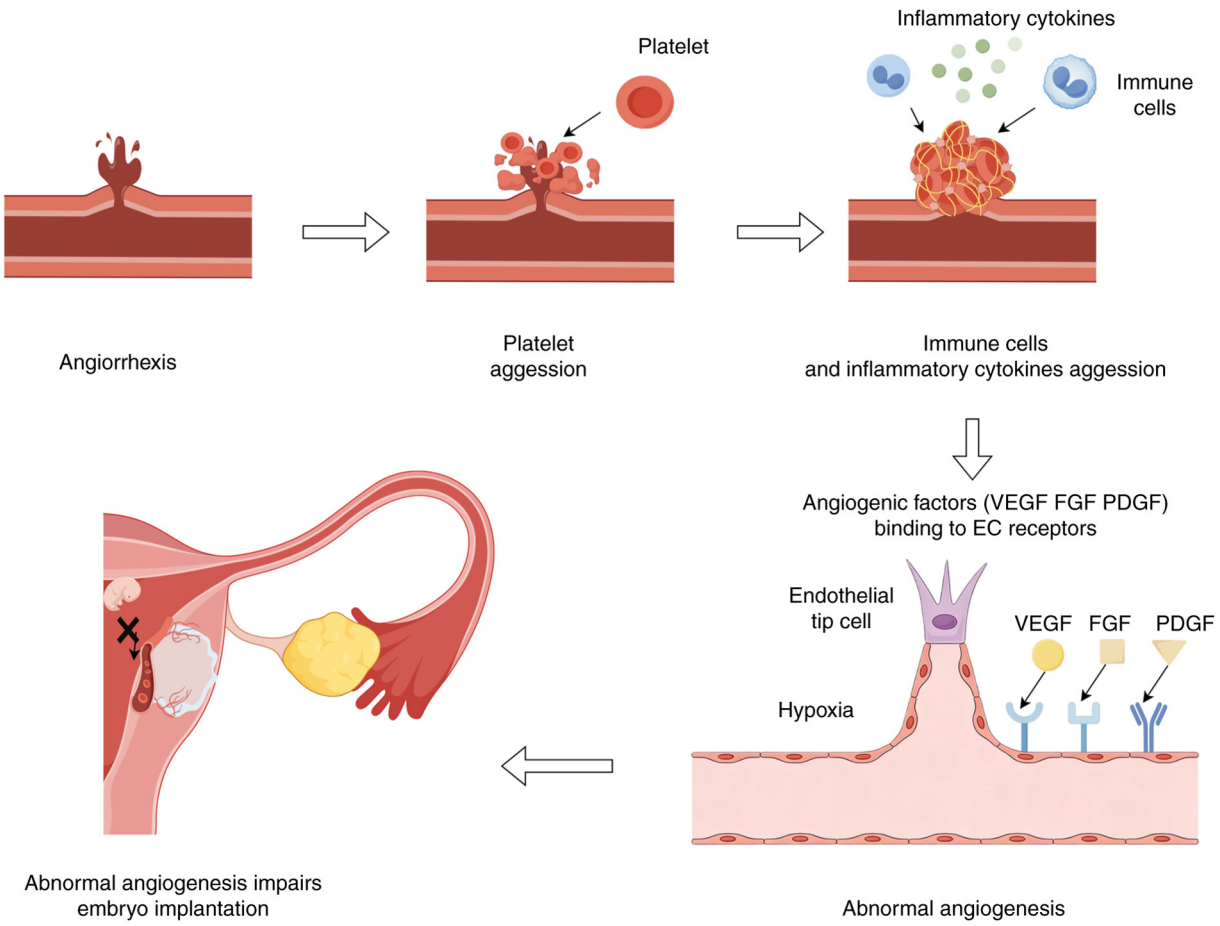

Figure 4. Main process of angiogenesis. First, endometrial bleeding occurs periodically as a sign of tissue damage. Second, platelet adhesion and aggregation participate in hemostasis. Third, platelets attract inflammatory cytokines and immune cells to gather at the wound. Fourth, inflammatory cytokines act as angiogenic factors to induce neovascularization of ectopic endometrium and upregulate factors directly related to angiogenesis such as VEGF, FGF and PDGF. Among them, hypoxia is a crucial inducing factor. Fifth, abnormal angiogenesis leads to decreased endometrial receptivity and affects embryo implantation. EC, endothelial cell; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

to IL-1, with increased expression of CXCL8, CXCL8 receptor and VEGF, indicating that excessive neovascularization impairs ER. The expression of angiogenic markers in both eutopic and ectopic endometrium suggests that angiogenesis not only facilitates invasion of normal endometrial tissue but also supports the maintenance of ectopic lesions, thereby serving as a critical factor in implantation failure (128).

Furthermore, tissue injury-induced vascular hyperpermeability, extravasation of blood components and increased interstitial fluid volume (149) may contribute to common clinical symptoms in patients with AM such as abnormal uterine bleeding and infertility (150). Perfusion loss and subsequent hypoxia from vascular injury activate the HIF-1α/NF-κB pathway, which robustly upregulates VEGF expression (151) and drives the COX-2-PGE2-P450 aromatase positive feedback loop, leading to abnormal uterine peristalsis; clinical data show a strong correlation between COX-2 and VEGF expression (152). During this process, upregulated PGE2 activates P450 aromatase to promote local estrogen synthesis, which in turn induces EMT and increases vascular permeability, driving ectopic endometrial cells into a pro-angiogenic state (67,153). Additionally, extravasated platelets may provide a protective barrier for ectopic stromal cells, shielding them from physical clearance and immune surveillance (133).

Regulation of ER impairment in AM

Regulatory basis of normal ER and hormonal-immune imbalance in AM. Embryo implantation depends on the dynamic hormonal-immune balance established at the maternal-embryo interface (154). The ability of the endometrium to support normal embryo implantation, referred to as ER, is primarily governed by the precisely timed and transient window of implantation (WOI) during the mid-secretory phase. During this period, an immunosuppressive state dominated by NK cells helps prevent maternal immune rejection of the semi-allogeneic embryo (155). However, in patients with AM, this hormonal-immune balance is disrupted, characterized by aberrant expression of pro-inflammatory cytokines, chemokines and immunoregulatory factors. This disruption leads to impaired ER and reduced sensitivity to progesterone (156). Furthermore, delayed embryo implantation beyond the WOI is perceived as embryo malposition by the maternal system, increasing the risk of placenta previa, abnormal placentation and placental insufficiency, all of which can result in preterm birth, intrauterine growth retardation and even preeclampsia (157).

Immune-cytokine alterations and key gene dysregulation in the AM endometrium. Both in natural and stimulated cycles, the endometrium of patients with AM demonstrates

characteristic alterations in immune cell infiltration and cytokine profiles, including increased macrophage infiltration, elevated IL-6 expression and reduced expression of IL-11 and its receptor, key regulators of implantation (158). Notably, IL-6 receptors are widely expressed on blastocyst trophectoderm and endometrial epithelial cells, indicating that chronic local inflammation may impair embryo-endometrium crosstalk and directly compromise receptivity (159). Moreover, COX-2 is markedly upregulated in perivascular regions of the endometrium; it aggravates inflammation via the induction of IL-6 and CXCL8, while also promoting aberrant angiogenesis, collectively disrupting the microenvironment required for implantation. These findings position COX-2 as a potential biomarker of impaired ER (160). Immune tolerance during the WOI also depends on adequate IL-10 secretion; however, significantly reduced IL-10 levels have been observed in the decidua of patients with AM and this deficiency has been associated with recurrent miscarriage and preeclampsia (161). Additionally, uNK cells exhibit functional abnormalities, including decreased secretion of VEGF and placental growth factor, which may impair trophoblast migration and angiogenesis at the implantation site (162). Other inflammatory mediators, such as IL1B and corticotropin-releasing hormone, are also abnormally elevated in the endometrium of affected patients, further contributing to implantation failure (19).

Beyond immune cell and cytokine dysregulation, intrinsic molecular regulators of ER, specifically homeobox genes, are also significantly disrupted in AM. Homeobox genes HOXA10 and HOXA11 serve as essential regulators of ER; they promote embryo adhesion by regulating β3-integrin expression and the formation of stromal cell pinopodes (163). A clinical study has shown that patients with implantation failure often exhibit downregulation of HOXA10 and HOXA11 expression (164). In AM, both HOXA10 and HOXA11 are significantly downregulated, while HIF-2α is upregulated. Pharmacological inhibition of HIF-2α has been shown to restore HOX gene expression (165), suggesting that a hypoxic microenvironment impairs ER through the HIF-2α-HOX axis (166). Notably, this link between HOX genes and ER is further supported by animal studies. Specifically, Hoxa10/A11-deficient mice exhibit reduced endometrial gland formation and decreased LIF secretion (164).

LIF, a member of the IL-6 cytokine family, is essential for blastocyst development, decidualization and trophoblast differentiation (167) and it regulates implantation via the STAT3/ERK signaling pathway (168). In AM, aberrant LIF expression levels, together with dysregulated IL-11, contributes to impaired gp130-mediated signal transduction (157). Furthermore, disruption of the IL-10/phosphorylated-STAT3/HOXA10 signaling axis has been strongly linked to infertility and early pregnancy loss (54). The IL-33/ST2 pathway also regulates HOXA10 expression and participates in the decidualization process (156). Additionally, the expression of β3-integrin and its ligand osteopontin (OPN), both essential for blastocyst adhesion, is significantly reduced in the endometrium of patients with AM (169). This reduction may be driven by IL-6/CXCL8-mediated downregulation of αvβ3 integrin expression (170). HOXA10 directly promotes β3-integrin expression, while OPN binds to CD44 receptors to enhance blastocyst adhesion. Impaired function of both molecules further exacerbates implantation failure.

ER-related signaling pathway dysregulation and potential therapeutic targets. Aberrant activation of the NF-κB signaling pathway in AM induces the production of TNF-α, IL1B and IL-6, molecules that damage the endometrial epithelium and reduce implantation rates (171). In animal models, NF-κB activation during the WOI has been shown to interfere with LIF expression, thereby impairing ER and adversely affecting pregnancy outcomes (172). Although the direct connection between ER and endometrial fibrosis remains unclear, a preclinical study has highlighted a potential therapeutic direction: Treatment with anti-TGF-β1 improves both fibrosis and pregnancy outcomes in AM models (173). This suggests that TGF-β1 may serve as a potential therapeutic target for restoring receptivity as it can modulate both fibrosis and the immune microenvironment (174).

Abnormal decidualization of the endometrium

Normal decidualization process and core defects in AM. Decidualization is a critical process for embryo implantation and placental development (175); it refers to the transformation of ESCs into specialized decidual cells with secretory functions under progesterone regulation, which further establishes an immunotolerant microenvironment, participates in embryonic nutrient supply and maintains maternal-fetal interface homeostasis (157). Physiologically, decidualization follows a two-phase dynamic progression: The early acute inflammatory phase relies on chemokine-mediated immune cell recruitment to support stromal remodeling, while the subsequent anti-inflammatory phase establishes maternal-fetal immune tolerance (157). Transcriptomic analyses by Salker *et al* (176) showed that during the initiation phase (day 2) of decidualization, 70 cytokines/receptors were significantly upregulated, whereas only 12 key regulators (including IL-11Rα and LIFR) remained highly expressed in the terminal differentiation phase (day 8).

However, in patients with AM, decidualization is frequently impaired, primarily driven by pathological factors such as chronic inflammation, oxidative stress and immune dysregulation, all of which are core mechanisms underlying infertility and adverse pregnancy outcomes (177). A hallmark pathological feature of AM, uterine JZ disruption, induces upregulation of pro-inflammatory cytokines (such as IL-6, IL1B and CXCL family chemokines) and accumulation of reactive oxygen species (ROS); this disrupts the pro-inflammatory/anti-inflammatory balance essential for normal decidualization (178,179). Notably, the aforementioned temporal dysregulation of cytokine expression further exacerbates decidualization defects in AM.

Key pathogenic mechanisms of decidualization impairment in AM. Abnormalities in inflammatory mediators are central to AM-associated decidualization defects. IL-6 is highly expressed in decidual cells of adenomyotic tissues (180); it promotes ectopic endometrial proliferation via the gp130/JAK/STAT3 axis while suppressing progesterone-induced decidualization genes such as KLF5 and FOXO1, thereby inhibiting stromal cell differentiation (181). The STAT3 pathway, critical for embryo adhesion, decidual transformation (68), ovarian steroidogenesis, follicular

development, endometrial decidualization and early events of embryo implantation (182), exhibits aberrant activation in AM, potentially reducing fertility and increasing miscarriage risk (183). IL1B is physiologically required for embryo implantation by upregulating integrin αvβ3 and mediating adhesion through the COX-2/PTGS2/PGE2 axis, but it is abnormally elevated in AM (184,185). This elevation triggers NF-κB-driven hyperinflammation, which impairs early decidual-trophoblast and chorionic-decidual interactions (186), reduces ER and contributes to placental insufficiency, a mechanism that also links EMs to adverse pregnancy outcomes (187). Additionally, chemokines such as MCP-1, CXCL1/2/3 and MIP-3α are aberrantly upregulated in AM (188). This upregulation induces excessive uNK cell infiltration and disrupts T-cell polarization, which in turn impairs embryo selection and implantation failure (189). MCP-1, in particular, acts as a major immune effector in this process (66).

Beyond abnormal inflammatory mediators, the expression of multiple key genes regulating decidualization is significantly downregulated in the endometrium of patients with AM. Reduced expression of embryo implantation-related genes such as FOXO1, KLF5, CEBPB and HAND2 directly impairs decidual cell differentiation and lowers ER (180). Diminished bone morphogenetic protein 2 secretion decreases the expression of HOXA10 and LIF in ESCs, affecting embryo positioning and trophoblast invasion (190). Inadequate expression of EGF and heparin-binding EGF-like growth factor (HB-EGF) impairs β3 integrin expression, weakens EMT and disrupts paracrine regulation during the early phase of decidualization (191). Moreover, co-culture of decidualized human ESCs with developmentally arrested embryos reduces the secretion of key implantation modulators (including IL1B, HB-EGF, IL-6 and IL-10) (192). Since decidual factor secretion is critical for screening viable embryos, this finding suggests that patients with AM and recurrent miscarriage may lack the ability to select viable embryos.

Immune homeostasis imbalance at the maternal-fetal interface is another key mechanism underlying impaired decidualization in AM. Trophoblast cells lack classical MHC-I antigens to avoid maternal T-cell attack, but this renders them susceptible to surveillance by decidual uNK and lymphokine-activated killer cells (193). In AM, reduced infiltration of decidual Treg cells disrupts immune balance, enhancing the activity of cytotoxic T cell and NK cells (194) and increasing the risk of recurrent miscarriage. uNK cells, which are essential for regulating trophoblast invasion into the JZ and spiral artery remodeling (195), rely on HLA-C/KIR interactions for maternal recognition of the semi-allogenic fetus (193). Decidualization defects in AM alter HLA-C expression and disrupt the ligand-receptor balance, thereby impairing immune tolerance. Additionally, cytokines critical for decidualization and immune regulation (such as IL-11, IL-15 and IL-33) are abnormally expressed in AM (176,196,197). Dysregulation of IL-11 impairs the decidualization process, while upregulated IL-15 drives abnormal uNK cell proliferation and exacerbates inflammation at ectopic endometrial lesions (198). The imbalance between MMPs and their TIMPs in the decidua of patients with AM also contributes to infertility and decidualization defects (199).

Additionally, elevated thrombin levels, which are observed in patients with AM and menorrhagia, are also closely associated with impaired decidualization. Thrombin exerts multiple deleterious effects on decidualization; it upregulates pro-inflammatory chemokines, induces endothelial dysfunction and hyperpermeability, promotes platelet aggregation, suppresses prolactin secretion (a marker of decidualization) and alters the morphology of decidualized stromal cells (200). Thrombin also activates genes involved in ECM degradation and chemokine production, further exacerbating decidualization defects. This effect is part of the broader multi-pathway regulatory network (encompassing tissue injury and repair cascades, macrophage polarization, EMT, angiogenesis dysregulation and reduced endometrial receptivity) that converges to drive infertility in AM, as systematically summarized in Fig. 5.

6. Clinical medications targeting inflammatory cytokines for the treatment of AM-related infertility

Non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs exert therapeutic effects in AM primarily by inhibiting COX activity and subsequently reducing prostaglandin synthesis (201). Studies have demonstrated that NSAIDs can decrease the depth of endometrial infiltration into the myometrium, inhibit the migration and invasion of ESCs and induce apoptosis (202,203). In addition, NSAIDs suppress key pathological processes such as fibrosis, angiogenesis and EMT (204). Therefore, NSAIDs are considered promising pharmacological candidates for the clinical management of AM.

Celecoxib, a highly selective COX-2 inhibitor, significantly reduces inflammatory responses and the depth of lesion infiltration in EMs by suppressing the expression of pro-inflammatory cytokines such as IL1B, IL-6 and TNF-α, as well as the transcription factor NF-κB (205). Studies have suggested that in ART, localized inflammatory responses may impair embryo implantation by inducing abnormal uterine contractility and reducing ER via prostaglandin-mediated mechanisms (10,206). Theoretically, NSAIDs may improve ART outcomes by mitigating the detrimental effects of prostaglandins; however, this hypothesis requires further experimental validation (207).

Hormonotherapy

Gonadotropin-releasing hormone (GnRH). GnRH is a hypothalamic peptide hormone that acts on the anterior pituitary via the hypophyseal portal system to regulate the synthesis and pulsatile secretion of follicle-stimulating hormone and luteinizing hormone. A study by Zippl *et al* (89) reported no significant differences in endometrial immune characteristics between women with AM and those with recurrent pregnancy loss or RIF. The study also found that GnRH-a suppress the production of inflammatory cytokines such as TNF-α and IL1B by modulating the mononuclear phagocyte system, thereby inhibiting inflammation and angiogenesis. Similarly, Khan *et al* (208) demonstrated that GnRH-a treatment downregulates the secretion of cytokines (such as IL1B, MCP-1 and VEGF) from adenomyotic endometrial cells, attenuates the immune response of von Willebrand factor and improves the inflammatory microenvironment, ultimately enhancing ER.

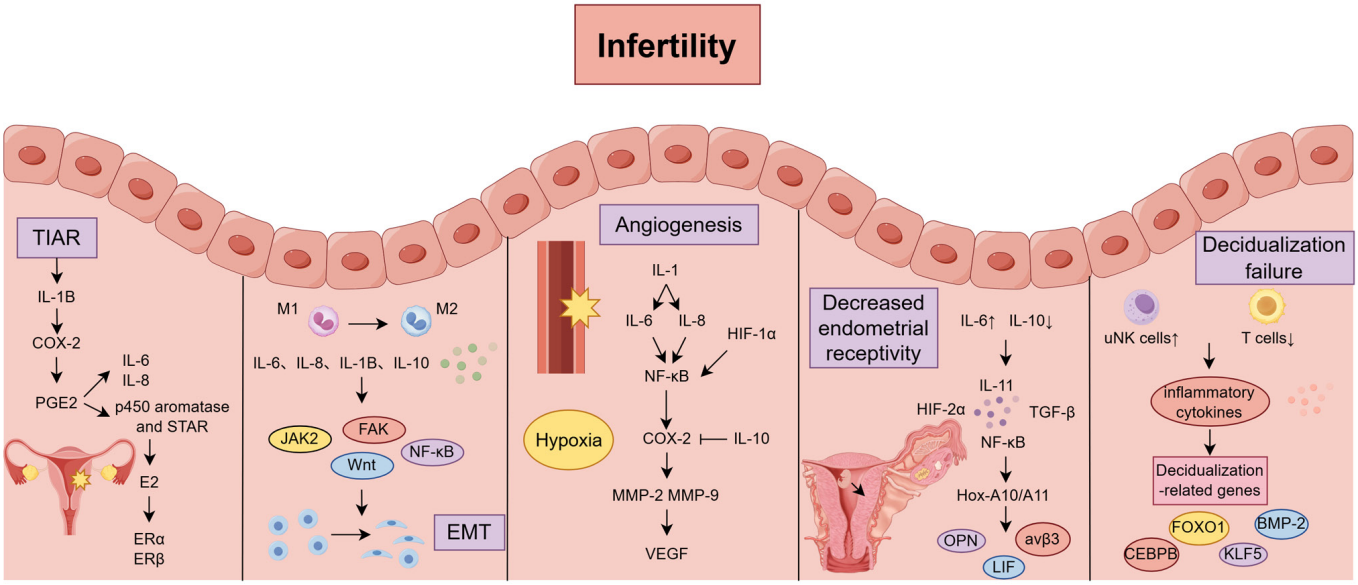

Figure 5. Main pathogenesis of adenomyosis-related female infertility. Inflammatory cytokines mainly promote the occurrence and development of adenomyosis by promoting TIAR and EMT and interfere with the normal embryo implantation process by promoting angiogenesis, leading to decreased endometrial receptivity and impaired decidualization. BMP-2, bone morphogenetic protein-2; CEBPB, CCAAT/enhancer-binding protein β; COX-2, cyclooxygenase-2; E2, estradiol; EMT, epithelial-mesenchymal transition; ERα, Estrogen Receptor Alpha; ERβ, Estrogen Receptor β; FAK, Focal Adhesion Kinase; FOXO1, Forkhead Box O1; HIF-1α, hypoxia-inducible factor-1α; Hox-A10/A11, homeobox A10/A11; IL, interleukin; JAK2, Janus kinase 2; KLF5, Kruppel-like factor 5; LIF, leukemia inhibitory factor; MMP, matrix metalloproteinase; OPN, osteopontin; PGE2, prostaglandin E2; STAR, steroidogenic acute regulatory protein; TGF-β, transforming growth factor-β; TIAR, tissue injury and repair; uNK cells, uterine natural killer cells; VEGF, vascular endothelial growth factor.

Furthermore, GnRH-a therapy has been shown to upregulate the expression of key receptivity markers in the endometrium, including HOXA10, HOXA11, integrin β3 and LIF, thereby promoting embryo implantation (209). Several case reports have confirmed successful pregnancies in previously infertile women with AM following GnRH-a treatment (210,211). Notably, the combination of GnRH-a with surgical intervention appears to yield superior outcomes. In a large prospective study, 55 out of 165 women with AM conceived after surgery alone or surgery followed by GnRH-a therapy, achieving a clinical pregnancy rate of 77.5%, with 69.0% delivering successfully by the end of a 2-year follow-up period (212).

GnRH antagonists (GnRH-As). GnRH-As exert their effects by competitively blocking GnRH receptors in the pituitary gland, thereby directly inhibiting the secretion of gonadotropins. Compared with GnRH-a, GnRH-As offer the advantage of avoiding the initial 'flare-up effect' (a transient surge in gonadotropins at the onset of treatment) and allow for a more rapid recovery of ovarian function after drug withdrawal, making them particularly suitable for patients desiring fertility preservation (213). Currently available GnRH-As include elagolix, relugolix and linzagolix. A clinical study has shown that the administration of GnRH-A prior to ART procedures or surgical intervention may improve embryo transfer outcomes and increase surgical success rates (209).

Lessey *et al* (214) demonstrated that treatment with elagolix for 2 months led to the upregulation of several anti-inflammatory mediators, including IL-10, IL-13, CCL18 and TWIST2. Simultaneously, miRNA-mediated downregulation of inflammatory components such as NOTCH1, NF-κB, T cells and NK cells was observed, suggesting that elagolix significantly modulates the systemic inflammatory milieu. Moreover, elagolix has been associated with higher pregnancy and live birth rates compared with oral contraceptive pills, although further research is warranted to confirm these findings (215).

Dienogest (DNG). DNG is a progestin with high selectivity for PRs that exerts mild ovulation-inhibiting effects; it can directly suppress the proliferation of AM stromal cells and induce apoptosis. As the primary target of DNG, the activation of the PR also regulates inflammation in the endometrium (216). A prospective study confirmed that dienogest and danazol can alleviate the production of TNF-α-induced IL-6 and CXCL8 in endometriotic stromal cells by inactivating NF-κB (217). Oral administration of dienogest also increases the number of infiltrating NK cells in ectopic endometrial glands, benefiting pregnancies that occur after cessation of treatment in terms of embryo implantation and fetal protection (218).

Immunomodulators. Immunomodulators represent a promising therapeutic strategy for preserving fertility as they target inflammatory responses, modulate the immune microenvironment and inhibit the growth of ectopic lesions. Most notably, these agents can improve tubal patency, enhance oocyte quality and restore the pelvic microenvironment without interfering with estrogen secretion or ovulatory cycles, making them an optimal choice for patients seeking to retain reproductive potential (219).

IL-targeted therapies. A study has demonstrated that tocilizumab, an IL-6 receptor antagonist, can effectively inhibit ectopic lesion cell proliferation and migration induced by endometrial cell-derived exosomes (220). Tocilizumab induces G1/S cell cycle arrest and significantly suppresses activation of the IL-6/JAK2/STAT3 signaling axis, thereby exerting potent anti-inflammatory and antiproliferative effects (25).

AMY109, a long-acting circulating antibody targeting CXCL8, has shown promising antitumor activity by reducing

fibrosis and immunosuppression in cancer models (221). In a non-human primate model of EMs, AMY109 significantly reduced the volume of nodular lesions and improved fibrosis and adhesions; its mechanism is associated with the inhibition of neutrophil recruitment and MCP-1 production, and notably, it does not impair ovarian function (222).

The classic antidiabetic drug metformin has demonstrated therapeutic potential in AM (223); it exerts beneficial effects by modulating oxidative stress, inflammation and apoptosis. Specifically, metformin downregulates pro-inflammatory cytokines (including IL-6 and CXCL8), angiogenic factors (including VEGF and MMP-9), and simultaneously upregulates LIF and HOXA10, thereby enhancing ER and supporting implantation (224). A clinical study has confirmed that the combination of high-intensity focused ultrasound and metformin significantly reduces uterine volume and lowers recurrence rates in AM, largely due to the suppression of inflammatory mediators (225).

Anakinra, an IL-1 receptor antagonist that competitively binds to IL-1R1, has been shown in a clinical study to significantly reduce visual analogue scale (VAS) pain scores and improve quality of life in patients with EMs, without adversely affecting ovulatory function or menstrual regularity during treatment (226).

Lipoxin A4, an anti-inflammatory and pro-resolving lipid mediator, significantly reduces the size of endometriotic lesions by downregulating pro-inflammatory cytokines (including IL1B and IL-6) and inhibiting the expression of COX-2 and PGE2 in both lesions and peritoneal fluid cells (227). Additionally, it suppresses the expression of angiogenic factors (such as VEGF, HIF-1α and MMP-9), thereby inhibiting neovascularization, and regulates TGF-β isoform expression, reducing adhesion and invasive properties of endometriotic cells (228). These effects collectively contribute to lesion regression and potential improvements in fertility.

NF-κB inhibitors. Disulfiram, a derivative of thiamine, has recently been shown to exert anti-endometriotic effects. An animal study has demonstrated that disulfiram significantly reduces serum TNF-α and IL1B levels and inhibits angiogenesis within ectopic lesions by downregulating VEGF-A and MMP-2 expression via suppression of NF-κB nuclear translocation (229). Moreover, disulfiram alleviates postoperative inflammatory adhesions associated with EMs, thereby helping to prevent infertility caused by adhesion formation (230).

Animal experiments have also shown that melatonin exerts therapeutic effects in AM by blocking the NF-κB signaling pathway. Melatonin downregulates ROS and pro-inflammatory cytokines such as TNF-α and IL1B, while upregulating VEGF, thereby improving the endometrial microenvironment, reducing apoptosis of endometrial cells and restoring ER. These effects ultimately improve pregnancy outcomes in AM mouse models (231). Furthermore, melatonin alleviates uterine oxidative stress and improves uteroplacental hemodynamics, creating a favorable environment for embryo implantation and development (232).

TNF-α inhibitors. Etanercept, a TNF inhibitor, effectively blocks TNF-α/β-mediated NF-κB activation (233). Experimental studies have shown that administration of etanercept in baboon models of EMs significantly reduces both the number and volume of endometriotic lesions (234). In mouse models, treatment with etanercept results in reduced lesion size along with downregulation of VEGF, IL-6 and TNF-α levels (235). A retrospective study involving 68 infertile women with EMs reported that a single intramuscular injection of 50 mg etanercept on day 2 of the menstrual cycle in the treatment group (n=19) led to improved clinical pregnancy and embryo implantation rates (236).

Pentoxifylline, a non-selective phosphodiesterase inhibitor, has been shown to suppress the secretion of pro-inflammatory cytokines such as TNF-α and IL1B, while also downregulating key angiogenic factors (237). A randomized controlled trial confirmed that postoperative treatment with pentoxifylline significantly reduced VAS pain scores and improved long-term outcomes in patients with EMs (238). Another randomized controlled trial demonstrated that in patients with mild or asymptomatic EMs, the pregnancy rate in the pentoxifylline-treated group was twice as high as that in the control group (239).

Emerging technologies

Specialized targeted materials. Intralipid, an intravenous lipid emulsion derived from soybean polyunsaturated fatty acids and egg yolk phospholipids, has gained significant attention in reproductive medicine due to its immunomodulatory properties. Basic research indicates that intralipid exerts broad anti-inflammatory and immune homeostasis effects by specifically suppressing NK cell activity (240). In patients with RIF complicated by NK cell hyperactivity, intralipid treatment has been associated with live birth rates ranging from 33 to 42%, while clinical observations in patients with recurrent pregnancy loss report even higher live birth rates of 75 to 91%, markedly improving adverse pregnancy outcomes (241). Consequently, lipid-based intralipid administration could be considered as a novel delivery route for patients with AM (242).

Recent advances in nanoparticle-based precision diagnostics and therapeutics have shown breakthrough potential. A digital droplet enzyme-linked immunosorbent assay system constructed with SiO_2 nanoparticles achieved femtomolar sensitivity for detecting inflammatory markers such as OPN, IL-6 and IL-10 in menstrual blood, unveiling for the first time the molecular-level immune-inflammatory signatures in patients with EMs and providing reliable non-invasive biomarkers (243). Furthermore, 10 nm magnetic iron oxide nanoparticles enable *in situ* visualization and localization of ectopic lesions via MRI, markedly enhancing diagnostic accuracy (244).

Outer membrane vesicle-modified poly (lactic-co-glycolic acid) nanoparticles have been developed to deliver IL-4 plasmids specifically to macrophages, successfully reversing M2 polarization and markedly inhibiting lesion progression without compromising ovarian reserve (245). In addition, cerium dioxide nanoparticles have been shown to reduce oxidative stress and inhibit angiogenesis, thereby alleviating induced endometrial lesions in mouse models while preserving both the quantity and quality of oocytes (246).

Precision therapeutics targeting non-coding RNAs (ncRNAs). miRNAs, small ncRNAs that suppress target gene translation by binding mRNAs, regulate angiogenesis and inflammatory responses during EMs pathogenesis. Elevated levels of angiogenic and inflammatory factors such as VEGF-A, IL-6 and CXCL8 in ectopic lesions are closely

linked to aberrant activation of miRNA regulatory networks, including miR-21 and miR-135b (247). Notably, miR-199a targets and suppresses IKKβ in ESCs, inhibiting NF-κB activation and CXCL8 production, thereby attenuating ESC adhesion, migration and invasiveness (248), miR-25-3p, delivered via EMs-derived extracellular vesicles (EMs-EVs), targets the PTEN/AKT pathway, inducing collagen deposition and inhibiting decidualization, ultimately decreasing ER (220). The U.S. FDA has approved RNA interference therapeutics such as patisiran, which employs lipid nanoparticles to silence pathogenic RNAs in lesions (249). Additionally, exosomes have been explored as natural carriers for therapeutic ncRNAs (such as miR-141-3p or let-7b), enabling targeted delivery to ectopic lesions and enhancing local uptake (250). Patients with AM exhibit aberrant expression of 21 fertility-related miRNAs in EMs-EVs secreted by the endometrium, potentially underlying infertility mechanisms (251). Small-molecule drugs targeting EMs-associated miRNAs (such as inhibitors of miR-135 or miR-196) have entered phase II clinical trials, highlighting ncRNA-based therapies as promising novel strategies for fertility preservation in patients with EMs.

Artificial intelligence (AI)-driven novel target identification. The AI-powered drug target discovery platform PandaOmics (https://pandaomics.cn/access) has recently made breakthrough progress in EMs research. Through intelligent algorithmic screening, the platform identified two novel immune-regulatory therapeutic targets, guanylate binding protein 2 Gene (GBP2) and hemopoietic cell kinase (HCK). Key validation experiments demonstrated that gene silencing of GBP2 or HCK significantly inhibited EMs cell proliferation and induced apoptosis, confirming their potential as therapeutic targets (252). Therapeutically, outer membrane vesicle-functionalized poly(lactic-co-glycolic acid) nanoparticles precisely targeting macrophages modulate the immune microenvironment, markedly suppressing lesion progression without impairing ovarian reserve, offering a novel non-hormonal treatment option for reproductive-aged patients (245).

Traditional Chinese Medicine (TCM). Comprehensive TCM therapies, including oral herbal formulations, acupuncture and topical applications, have been shown to reduce inflammatory cytokine levels and demonstrate unique advantages in the diagnosis and treatment of AM. For instance, Shaoyao-Gancao decoction and its active ingredient paeoniflorin significantly decrease PGE2 and PGF2α levels, alleviating AM-associated dysmenorrhea (253).

Resveratrol, a polyphenolic compound, has both anti-inflammatory and antioxidant properties. Animal studies have demonstrated that it can effectively inhibit myometrial infiltration and alleviate pain-related characteristics without disrupting hormonal homeostasis (254). Clinical trials have demonstrated that a daily dose of 30 mg resveratrol combined with oral contraceptives significantly reduces the expression of COX-2 and aromatase expression, potentially via suppression of prostaglandin biosynthesis pathways, thereby diminishing the invasive potential of ectopic endometrial tissue (255).

Oleuropein, a novel natural product, selectively inhibits ERβ activity without affecting ERα. As ERβ can activate the NLRP3 inflammasome, potentiate IL-1β-mediated proliferation and modulate signaling cascades such as TNFα/NF-κB, ROS and IL-6/JAK/STAT3, selective inhibition by oleuropein may impede disease progression (256). Experiments have further indicated that oleuropein restores defective endometrial decidualization and attenuates excessive inflammatory responses, ultimately improving pregnancy rates in EMs models (257).

Quercetin, a natural flavonoid polyphenol, exhibits antioxidant, anti-inflammatory, antiproliferative and antitumor activities; it dose-dependently suppresses the migration and invasion of ectopic ESCs by downregulating invasion-related proteins including Fascin, Ezrin and MMP-2/MMP-9 (110), aligning with the natural bioactive compound-based interventions featured in the multi-modal therapeutic framework of Fig. 6.

Furthermore, sodium tanshinone IIA sulfonate inhibits platelet aggregation and suppresses the TGF-β1/Smad3 and NF-κB signaling pathways, thereby attenuating fibrosis (258). Oral emodin dose-dependently inhibits IL1B-induced NF-κB expression and Wnt/β-catenin signaling activation to treat AM (109). Berberine significantly reduces LPS-induced endometrial invasion and downregulates IL-6 and CXCL8 expression, promoting apoptosis of proliferative ESCs (259). Collectively, a growing body of evidence supports these findings. Guided by TCM principles of syndrome differentiation and individualized therapy, patients can achieve symptomatic relief and improved fertility, with robust clinical efficacy. These TCM-derived bioactive components are included in Table SII, which comprehensively summarizes the full spectrum of medications for AM treatment. These agents target inflammatory cytokines while preserving female reproductive capacity.

7. Discussion

AM is commonly regarded as a chronic inflammatory immune disease. We consider that chronic inflammation acts as the upstream inducer of immunological abnormalities in AM, with the subsequent imbalance between proinflammatory and anti-inflammatory signals, serving as a downstream pathological consequence; together, this cascade constitutes the critical core factors affecting fertility in affected women. Notably, this pathogenic process originates from persistent TIAR at the EMJ: Repeated menstrual microtrauma at the EMJ triggers sustained release of proinflammatory cytokines, which in turn initiates chronic inflammation. This chronic inflammatory milieu further induces EMT in eutopic endometrial cells, enhancing their invasiveness to infiltrate the myometrium, while simultaneously disrupting local immune homeostasis to cause immune dysregulation, establishing a reciprocal amplification loop between inflammation and immune dysfunction that underpins AM pathogenesis.

Inflammatory cytokines, key immunological markers, abnormally accumulate in endometrial lesions, serum and peritoneal fluid and play a central role in AM-related infertility. Driven by chronic inflammation and synergized by immune dysregulation, their dysregulated expression exerts multi-stage reproductive impairment. On the one hand, they sustain an abundant blood supply to ectopic lesions by promoting neovascularization and the inflammatory changes

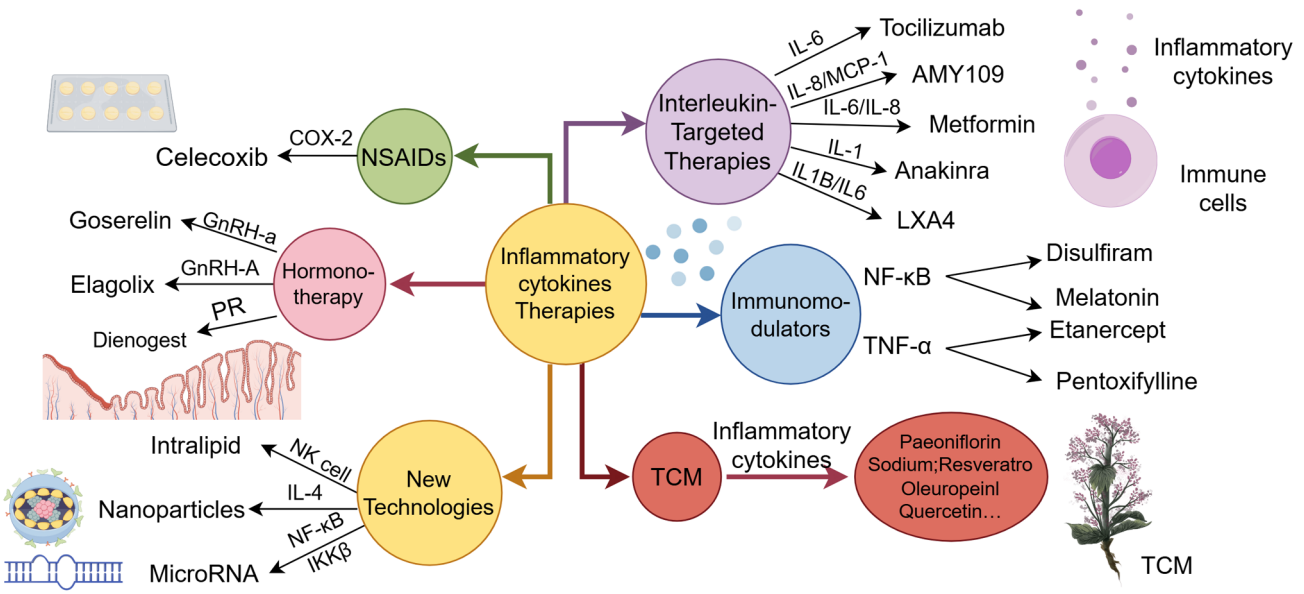

Figure 6. Main therapeutic strategies for adenomyosis-related female infertility. Taking inflammatory cytokines as the core regulatory target, this figure covers multiple therapeutic modalities including NSAIDs, hormonal therapy, interleukin-targeted therapies, immunomodulators, TCM and emerging therapeutic technologies and displays the corresponding specific drugs and their action targets for each modality. These therapeutic strategies can modulate inflammatory cytokines, thereby ameliorating adenomyosis-associated pathological processes, further enhancing endometrial receptivity and reversing decidualization dysfunction, which contributes to improving the infertility outcomes in women with adenomyosis. TCM, Traditional Chinese Medicine; GnRH-a, gonadotropin-releasing hormone agonist; GnRH-A, gonadotropin-releasing hormone antagonist; IKKβ, IκB kinase β; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; NSAIDs, non-steroidal anti-inflammatory drugs; PR, progesterone receptor.

at the EMJ (exacerbated by EMT-mediated tissue remodeling) lead to reduced ER and impaired decidualization. On the other hand, immune dysregulation disturbs the maternal-fetal immune tolerance required for embryo implantation.

Together, these effects ultimately hinder embryo implantation, causing infertility, IVF failure and recurrent pregnancy loss. In addition, disturbances in inflammatory cytokine levels are associated with adverse immune environments during childbirth and postpartum, contributing to risks such as preterm birth, postpartum hemorrhage and premature rupture of membranes. Other symptoms of AM, including menorrhagia and dysmenorrhea, are also rooted in this chronic inflammation-immune dysregulation cascade, as proinflammatory factors sensitize pain pathways and disrupt endometrial hemostasis.

At present, the clinical diagnosis of AM relies primarily on non-invasive methods, such as transvaginal ultrasound or MRI, with CA-125 as the only routinely measured biomarker. However, CA-125 has limited diagnostic potential, with insufficient sensitivity for detecting early and mild AM, and lacks the capacity for timely diagnosis and prevention of chronic pain and infertility associated with AM (260). Therefore, the development of novel serum biomarkers is essential for patients with AM who have long-term fertility plans. Research has demonstrated that inflammatory cytokines possess diagnostic sensitivity and specificity (261), with IL-6, CXCL8 and IL1B showing the most notable potential for clinical translation. Serum IL-6 is a reliable marker for the early diagnosis of infertility related to EMs. CXCL8 may serve as a specific predictor for evaluating embryo and oocyte quality in patients with AM undergoing IVF and can independently assess pretransfer embryonic developmental potential (238). Elevated IL1B levels may also act as a highly sensitive and specific potential indicator for early AM diagnosis (262). Additionally, the neutrophil-to-lymphocyte ratio in peripheral blood has been recognized as a valuable marker for infertility in women with EMs, while increased levels of anti-inflammatory cytokines, such as IL10, IL4 and IL-1RA, have been linked to the disease prognosis (263). Endometrial autoantibodies also offer a novel, non-invasive diagnostic approach (264). However, to enable effective diagnosis or treatment of AM based on inflammatory cytokines, high-sensitivity cytokine arrays and multivariable statistical analyses (accounting for inter-individual phenotypic variability) are necessary, highlighting the need for optimized diagnostic tools. When multiple biomarkers are evaluated, multivariable statistical analyses are needed, with careful consideration of the phenotypic variability of EMs across different individuals. Thus, further advancements in diagnostic tools and techniques are crucial.

The present review also discussed recent advances in pharmacological therapies targeting inflammatory cytokines such as IL1B, IL-6, CXCL8, IL-10, NF-κB and COX-2. As treatment strategies for AM often depend on the specific patient's symptoms, a number of medications effective for dysmenorrhea and menorrhagia may compromise fertility, with some significantly compromising reproductive function (242). Therefore, prior to treatment, individualized assessment of the inflammatory and immune status of the patient is essential for determining the most appropriate therapeutic approach, which may support the development of more effective, safer management options for AM-associated infertility.

Future research should focus on three specific priorities to advance the field: First, large-scale prospective studies should be conducted to validate the diagnostic cut-off values of IL-6 and IL1B for early AM and AM-related infertility and establish combined biomarker panels to improve diagnostic

accuracy; second, clinical trials should be launched to evaluate the efficacy of IL-6-targeted therapies (such as tocilizumab) for improving IVF implantation rates in patients with AM and explore the synergistic effects of combining NF-κB inhibitors with IL1B antagonists; third, the crosstalk mechanism between chronic inflammation-induced EMT and immune dysregulation at the EMJ should be clarified, to identify new intervention nodes that simultaneously target lesion invasion and immune tolerance for fertility preservation.

In conclusion, chronic inflammation-driven immune dysregulation is the core pathogenic link underlying AM-related reproductive impairment and IL-6, CXCL8 and IL-1β represent the most promising targets for diagnostic optimization and therapeutic innovation. Further research into these directions will provide critical support for improving reproductive outcomes in patients with AM.

8. Conclusion

The present review summarizes the role of inflammatory cytokines in the pathogenesis of AM-related infertility, particularly highlighting that the pathological progression and fertility impairment of AM are largely dependent on the regulation of inflammatory cytokines. These cytokines directly or indirectly affect the fertility of patients with AM by modulating multiple signaling pathways to regulate critical physiological processes, including cell proliferation and invasion, EMT, TIAR, angiogenesis and ER. Given their irreplaceable and core role in disease progression, these inflammatory cytokines hold great promise as important biomarkers for the early diagnosis and targeted treatment of AM-related infertility. However, current research on their clinical application value is still in the exploratory stage. Further studies are needed to conduct targeted investigations to further explore their potential in optimizing diagnosis methods and therapeutic strategies.

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Authors' contributions

BY wrote the manuscript and constructed the tables and figures. YS, FL, JJ and GC provided critical insights and contributed to the manuscript writing. ZW and MN refined the research ideas, reviewed the initial draft and revised the final manuscript. ZL and WS reviewed and provided critical feedback for the manuscript. All the authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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