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Review

Endometriosis: An Immunologist's Perspective

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Abstract: Endometriosis, a complex inflammatory disease, affects a significant proportion of women of reproductive age, approximately 10–15%. The disease involves the growth of endometrial glands and stroma outside the uterine cavity, leading to tissue remodeling and fibrosis. Hormonal imbalances, accompanied by local and general inflammation and pain, are key features of endometriosis. Endometriotic lesions are associated with the overproduction of cytokines, metalloproteinases, prostaglandins, reactive oxygen radicals, and extracellular vesicles. Genetic predisposition and cytokine gene polymorphisms have been documented. Macrophages, dendritic cells, mast cells, Th1 in the early phase, Th2 in the late phase, and T regulatory cells play a crucial role in endometriosis. Reduced NK cell function and impaired immune vigilance contribute to endometrial growth. The strong inflammatory condition of the endometrium poses a barrier to the proper implantation of the zygote, contributing to the infertility of these patients. Cytokines from various cell types vary with the severity of the disease. The role of microbiota in endometriosis is still under study. Endometriosis is associated with autoimmunity and ovarian cancer. Hormonal treatments and surgery are commonly used; however, recent interest focuses on anti-inflammatory and immunomodulatory therapies, including cytokine and anti-cytokine antibodies. Modulating the immune response has proven critical; however, more research is needed to optimize treatment for these patients.

Keywords: endometriosis; cytokines; inflammation; autoimmunity; cancer; therapy

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1. Introduction

Endometriosis is a prevalent chronic inflammatory condition affecting 10 to 15% of women of reproductive age, which incurs substantial healthcare costs [1,2]. This disorder is characterized by the growth of endometrial tissue outside the uterus, resulting in inflammation and fibrosis. The displaced tissue experiences cyclical changes akin to those of normal endometrial tissue. Multiple risk factors contribute to the onset of endometriosis, including familial history of the disease, nulliparity (the condition of never having given birth), early onset of menstruation (menarche), and exposure to various environmental influences. The condition predominantly affects women aged 25 to 45 [3] and is associated with elevated rates of obstetric complications [4,5] and a diminished quality of life [6].

The diagnosis of endometriosis is often delayed, with a typical gap of 7 to 12 years from the onset of symptoms to a surgical diagnosis [7,8]. The condition is systemic, affecting 50–80% of women with pelvic pain, and is a common cause of unexplained infertility [9].

It disrupts the function of the fallopian tubes and interferes with embryo transport, with 25–50% of women undergoing fertility treatments being treated for this condition [9]. Additionally, endometriosis impacts liver and adipose tissue metabolism, which leads to systemic inflammation and altered brain gene expression and contributes to pain sensitization and mood disorders [9].

Chronic inflammation, immune cell phenotype, and function changes are associated with endometriosis [3,5,10]. There are disturbances in neutrophils, monocytes/macrophages, dendritic cells, natural killer (NK) cells, B cells, and T cells [11]. While benign, endometriosis exhibits cancer-like behaviors, including hyperplasia and invasive growth [11,12]. The eutopic endometrium in affected women exhibits molecular abnormalities, which activate oncogenic pathways and increase the production of estrogen, cytokines, prostaglandins, and metalloproteinases, thereby supporting endometrial implant survival [11,12]. Autoimmunity is also observed in patients with endometriosis [13].

In this review, we discuss the immune system's involvement in endometriosis, the critical role of cytokines, the mechanisms of inflammation and pain, and a brief overview of anti-inflammatory, cytokine, and anti-cytokine treatments.

2. Endometriosis

The hypothesis of endometriosis encompasses several mechanisms, including retrograde menstruation, metaplasia, and genetic susceptibility [13–18]. The Sampson theory explains that during menstruation, endometrial cells can survive and invade pelvic structures through tubal reflux, leading to ectopic lesions. However, it does not fully explain the mismatch between the high incidence of reflux of menstrual blood (90%) and the lower incidence of endometriosis (10%) [17]. No single theory comprehensively accounts for the various clinical presentations and lesions of endometriosis, including those outside the abdominal cavity or in men [18]. Research has also highlighted proangiogenic factors, such as VEGF, IL-1β, and TNF-α, which play a crucial role in the vascularization of endometriosis [19]. Furthermore, patients with carbohydrate antigen 125 levels ($\geq$35 U/mL) have a higher risk of pelvic adhesions and more extensive lesions [20].

Endometrial tissue growing outside the uterus causes symptoms like chronic pelvic pain, menstrual pain, painful sex, and infertility in 50% of patients [2,11]. The development of endometriosis may involve factors such as retrograde menstruation, immune response issues, and inflammation triggered by adipokines like leptin [21]. Diet and gut microbiota also play a role in influencing symptoms [22]. Endometrial implants depend on estrogen for growth, and there is often an imbalance between estrogens and progestogens, along with progesterone resistance [23]. Inflammation plays an essential role in the pathophysiology of endometriosis. Inflammation is responsible for pain, tissue remodeling, lesion formation, fibrosis, and infertility (decreased ovarian reserve, reduced oocyte quality, impaired endometrial receptivity) and can promote malignant transformation [5,24,25]

There are three types of endometriosis: superficial peritoneal disease (15–50% of patients), ovarian endometrioma (2–10%), and deep infiltrating endometriosis (20%) [26]. Deep endometriosis features nodules deeper than 5 mm and is the most aggressive form, linked to more significant pain and infertility [15,27]. Symptoms may relate to lesion appearance, and treatment response varies by lesion type, with undifferentiated lesions usually being deep infiltrating [28].

Endometriosis and adenomyosis, while benign, exhibit malignant traits like rapid growth and invasiveness. Transitioning from adenomyosis to a premalignant tumor involves genetic and epigenetic changes [29,30]. Integrin β3 (ITGB3) is upregulated in ectopic endometrial stromal cells from endometriosis patients, promoting cell proliferation and invasion [31–33]. ITCH, a ubiquitin E3 ligase involved in endometriosis, is downregulated in

this condition and, when overexpressed, enhances the ubiquitination of ITGB3, affecting the proliferation and invasion capabilities of ectopic cells [31–33]. The opposing expressions of ITCH and ITGB3 suggest that dysregulation of the ubiquitin process may play a crucial role in endometriosis pathogenesis [33]. Additionally, *HOTAIR* lncRNA influences the invasion and migration of endometrial stromal cells via the miR-519b-3p/PRRG4 pathway [12].

Table 1 summarizes the clinical phenotypes associated with endometriosis, highlighting its relationship with pain, infertility, and potential comorbid medical conditions. Diagnosing this condition can be complex due to its similarities with other clinical entities, lack of awareness among healthcare professionals, normalization of symptoms in society, and variability in clinical presentation.

Table 1. Spectrum of the clinical phenotypes in endometriosis based on the literature [2–4,9–11,13,15,16,34].

Lesion	Clinical Characteristics	Possible Coexisting Medical Conditions
Pelvic Superficial peritoneal [9,13] Focal (adenomyoma) or diffuse (adenomyosis) lesions within the myometrium [9,13] Ovarian endometriosis [9,13] Deep endometriosis Lesions > 5 mm [13,15] Common in the rectovaginal septum It may involve the large intestine, bladder, ureters, and appendix [13,15]	**Pelvic pain** Dysmenorrhea [9,13] Dysuria [9,13] Dyschezia [9,13] Dyspareunia [13]	**Pelvic** Cystitis/painful bladder [9,13] Irritable bowel syndrome [13] Anal bleeding [13] Chronic endometritis [9,13] Inflammatory bowel disease [9,10,13] Polycystic ovary syndrome [9,10,13] Ovarian cancer [9,13] Uterine Fibroids (leiomyomata) [9,13] Vulvodynia [13] Possible link with recurrent vaginal infections [9,13]
Extra pelvic Thoracic [9,13,15] Diaphragm, lungs, pleura, pericardium Liver and spleen [9,13,15] Abdominal wall [9,13,15] Lymph nodes [9,10,13] Brain [9,13,15] Kidney [9,13,15]	**Infertility** Implantation failure [2,4,9,13] Spontaneous miscarriage [4,9,13] Alterations of tubal structures [4,9,13] Diminished ovarian reserve [9,13] Placenta previa [9] Premature delivery [9]	**Extra pelvic** Fatigue [2,4,9,13] Fibromyalgia [13] Joint disorders [13] Migraine [2,9,13] Systemic [2,4,9,13] Systemic autoimmune diseases (Lupus, Sjögren's syndrome, Rheumatoid arthritis) [2,13,16,34] Tissue-specific autoimmune diseases (Thyroiditis, Crohn's disease, Addison's disease) [2,13,16,34], Immune-related conditions (allergies, chronic inflammation) Thyroid disorders [13,16,34] Mental health conditions (depression, anxiety) [2,9,13]

The table shows a difference between autoimmune diseases encountered in patients with endometriosis. The most frequent systemic autoimmune diseases are lupus erythematosus, Sjögren's syndrome, and rheumatoid arthritis [13]. However, there are also patients with tissue-specific autoimmune diseases, thyroid diseases, Crohn's disease, and Addison's disease, which have very different characteristics [11,13]. The connection between endometriosis and autoimmune disease is discussed later in the text.

2.1. Genetic and Epigenetic Changes in Endometriosis

Endometriosis has genetic and environmental causes with polygenic inheritance. Relatives of affected individuals are seven times more likely to develop the disease. A twin study indicates that about 52% of disease variance is genetic, and six genetic markers linked to endometriosis have been identified.: CISD2, EFRB, GREB1, IMMT, SULT1E1, and

UBE2D3 [35]. Additional analyses have pinpointed associations with loci on chromosomes 7p15.2, 2p25.1 (GREB1), and 12q22 near VEZT [35]. A recent Genome-Wide Association Study (GWAS) and integrative-omics analyses highlight the role of immunopathogenesis and key signaling pathways (Wnt, NOTCH, TGFβ) in regulating endometrial cell behaviors in endometriosis [36].

Endometriosis increases the risk of epithelial ovarian carcinoma, including clear cell, endometrioid, and low-grade serous types [37–39]. Carcinogenesis is linked to an imbalance of reactive oxygen species, antioxidants, and systemic inflammation. Endometriotic cysts have high free iron levels, leading to oxidative stress [39]. Abnormal microscopic features of endometriosis, such as atypical cytology and architecture, can be either benign or malignant and have been observed in patients with ovarian cancer [40]. A clear connection between endometriosis, ovarian cancer, and genetic predisposition is observed [41–48]. An integrated analysis of DNA profiles was used to analyze candidate genes for ovarian endometriosis. Lei and coworkers [41] were able to show that the most relevant genes for ovarian endometriosis are TMEM184A, GREM2, SFN, KIR3DX1, HPGD, ESR1, BST2, PIK3CG, and RNASE1. Some of these gene candidates are also associated with cancer: TMEM184A is a prognostic marker in cervical squamous cell carcinoma and endocervical adenocarcinoma [41]; GREM2 inhibits cancer progression and is associated with the inhibition of adipogenesis [42], SFN [41], KIR3DX1 [41], HPGD [43], ESR1 [44], BST2 [45]; PIK3CG [41], and RNASE1 [41].

Mutations in ARID1A, PIK3CA, and PTEN may drive the progression from benign endometriosis to cancer [46,47]. Additionally, these cancers may display mutations in K-RAS and β-catenin/Wnt, along with microsatellite instability, indicating shared genetic susceptibility [48,49]. Exome sequencing revealed that 79% of deep endometriosis patients had somatic mutations; nevertheless, these mutations alone are insufficient for malignant transformation [49].

Chou and coworkers [50], studying the genetics of killer inhibitory receptors (KIRs) in Chinese patients with endometriosis, reported an increase in the number of patients with centromeric A/A haplotypes and a decrease in KIR2DL2, an inhibitory gene of the B haplotype. On the other hand, Marin et al. [51] reported a significant association of KIR2DL2 with the risk of deep endometriosis in Euro-descendants [51]. KIR2DL2 is associated with impaired NK cytotoxic activity and clearance of ectopic endometrial cells [50,51]. A Japanese study found a lower frequency of activating KIR3DS1 and a higher frequency of the inhibitory KIR3DL1+/HLA-Bw4+ combination [52]. It can be concluded that extensive studies are required to define the relationship between KIRs and endometriosis.

The NOD-like receptor (NLR) pathway fundamentally regulates interleukins, proinflammatory cytokines, and NF-κB activity. Single-nucleotide polymorphisms (SNPs) of the NOD1 and PYDC2 genes were associated with endometriosis, whereas SNPs of the NOS2 and PYDC1 genes were not [53]. Other studies have identified additional cytokine gene polymorphisms associated with the disease, including IL1A rs2856836 and rs2856836 [54]; rs11575812, rs2069772, and rs2069762 [55]; IL-10 (rs1800872) and IFN-γ a13 allele [56]; IL-12B rs3212227 [57,58], IL-16 rs11556218, rs4778889 [59], and rs4778889 [60]; IL-17A rs2275913 [61]; IL-18 SNP rs1946518 [62]; association with severity (TNF, rs1800629); IL-1beta (IL1B, rs1143634) and IL1-Ra (rs2234663) [63]; and macrophage migration inhibitory factor (MIF) rs755622 [64]. IL-8 SNP rs4073 has been related to pelvic pain in endometriosis [65]. These reports show a clear association with disease and disease severity. However, most studies focused on only one target cytokine, and integrative studies are required.

The epigenetic changes associated with endometriosis include DNA methylation and phosphorylation, modifications to histones and non-coding RNA, and chromatin re-

modeling and organization [66]. Specific epigenetic abnormalities have been described in endometriosis that alter the expression of key transcription factors. For example, hypomethylation of the GATA-binding factor-6, accompanied by overexpression, transforms an endometrial stromal cell into an endometriotic phenotype [66]. Steroidogenic factor-1 overexpression causes excessive estrogen production, which drives inflammation via pathologically high levels of estrogen receptor-β [67].

Some miRNAs serve as biomarkers for endometriosis and could be targets for therapy [68,69]. Some of these miRNAs are shared between endometriosis and atherosclerosis, both diseases are linked [70]. The most relevant miRNA-detected changes in plasma and serum are (1) increased miRNA 122, 199a, 125 b-5p, 150-5p, 342-3p, and 451a, and (2) decreased miRNA Let-7b, Let-7d, Let-7f, 17-5p, 20c, 20a-5p, and 3613-5p [67–71]. Studies on non-coding and circular RNA and endometriosis are ongoing [72].

Impaired endometrial decidualization reduces fertility in endometriosis. Transcriptomic profiling shows alterations in pathways, including defective BMP/SMAD4 signaling, oxidative stress response, and retinoic acid signaling [70]. Constitutive NF-κB activation in endometriotic lesions promotes inflammation, invasion, and angiogenesis while inhibiting apoptosis [73–75]. Active endometriosis lesions become fibrous, resulting in the adherence of tissues and organs [76].

High levels of BCL-6 (a transcription factor) in women with endometriosis are associated with decreased activation of progesterone receptors, resulting in progesterone resistance in the endometrium [77]. The BCL6 gene is significantly upregulated in ectopic tissues compared to tissue from healthy controls [78]. mRNA levels of estrogen-related receptors β and γ (ERRβ and ERRγ) were substantially lower in ectopic tissues from patients with severe endometriosis than in the eutopic endometrium of healthy controls [79].

The activation of mutated K-RAS in donor endometrial epithelium and stroma promotes lesion growth in a murine model of endometriosis but is insufficient for cancer transformation [80]. Essential factors for the progression from endometriosis to endometriosis-associated ovarian cancer include somatic mutations in ARID1A, K-RAS, PTEN, and microsatellite instability [81,82]. Overall, there is a link between genetic predisposition and polymorphism for endometriosis, along with other factors under investigation: signal transduction modulation, miRNA, long coding, and circular RNA.

2.2. Extracellular Vesicles

Extracellular vesicles (EVs) are membrane-bound particles that transport regulatory molecules like proteins, miRNAs, and lipids. They consist of small EVs (sEVs), such as exosomes, and large EVs (lEVs), also known as macrovesicles, which are released from various cellular compartments [83]. Gram-positive and Gram-negative bacteria can generate apoptotic bodies and extracellular vesicles (BEVs) [84]. BEVs can be formed from the microbiota in the endometrial fluid and can induce the secretion of TNF, IL-6, and IL-17, which are involved in endometriosis [84].

Vesicles of different sizes are found in follicular fluid and affect follicle size, oocyte function, promote granulosa cell proliferation, and cell survival under stress [83,85]. Small and large EVs differ in number, morphology, specific membrane markers, and miRNAs [83,84]. Large EVs influence steroidogenesis by affecting enzyme mRNA levels, stimulating estradiol secretion via the PI3K/AKT pathway [83,85]. Newly identified mitochondria-derived EVs that contain mitochondrial proteins have a potential role in fertilization [83].

Nazri et al. [86] reported the isolation of exosomes from peritoneal fluid. The concentration varied by cycle phase and disease stage. Proteomic analysis revealed specific proteins in exosomes from endometriosis patients that were absent in healthy controls. Five proteins found exclusively in the endometriosis groups are PRDX1, H2A type 2-C,

ANXA2, ITIH4, and tubulin α-chain [87]. Moreover, tissue-derived exosomes downregulated NKG2D-mediated cytotoxicity by containing NKG2D ligands MICA/B and ULBP1-3 and the proapoptotic molecules FasL and TRAIL [87]. The presence of these ligands impairs the immune response against endometrial tissue.

Patients with endometriosis exhibited a higher percentage of particles testing positive for platelet biomarkers than the total number of EVs [88,89]. Platelets create a procoagulative state in endometriosis patients and transport miRNA, including miRNA15b-5p and 65 [90]. These findings suggest a potential role for platelets in the development of endometriosis. They are found in lesions, contribute to fibrosis in damaged tissue [75,88,89], and are associated with extracellular vesicles [91]. Nevertheless, the impact of platelets on endometriosis still requires more research.

2.3. Microbiota and Endometriosis

Microbiota plays a role in establishing and progressing endometriosis [92,93]. The gut microbiota may influence estrogen production and local immune inflammation, promoting endometrial cell proliferation [92–96]. Estrogen metabolism entails a comprehensive three-phase process that includes hepatic conjugation, microbial deconjugation, and subsequent excretion [93,94]. Within the liver, estrogen undergoes conjugation to form water-soluble metabolites, such as estrone sulfate and estradiol glucuronide, which facilitate biliary excretion into the gastrointestinal tract [94]. The gut microbiota plays a crucial role in this process, particularly through specific bacteria such as *Clostridium*, *Escherichia*, *Bacteroides*, and *Lactobacillus*, which produce the enzyme β-glucuronidase [94]. This enzyme deconjugates estrogen metabolites, permitting their reabsorption into the systemic circulation. This phenomenon, called enterohepatic recirculation, is essential for regulating estrogen bioavailability and maintaining hormonal homeostasis [94–96]. Dysbiosis, characterized by an imbalance in gut microbial composition, can significantly disrupt estrogen metabolism [94]. Reducing β-glucuronidase-producing microbes may hinder estrogen reabsorption, potentially resulting in systemic estrogen deficiency, adversely affecting reproductive and metabolic functions [94–96]. Conversely, an overabundance of these bacteria may lead to excessive estrogen recirculation, which has been linked to estrogen-dependent conditions such as breast cancer, endometriosis, and infertility [94–96].

The endometrial environment and peritoneal cavity microbiota have been linked to endometriosis [97–102]. Increased levels of *Gardnerella*, *Streptococcus*, *Escherichia*, *Shigella*, and *Ureaplasma* were noted in the cervical microbiota of endometriosis patients [98]. Distinct microbial communities were found in feces and peritoneal fluid, with increased pathogens in peritoneal fluid and reduced protective microbes in feces [88,89]. Endometriosis patients exhibited lower alpha and beta diversity in gut microbiota compared to controls, with significant differences in the abundance of several bacterial classes [101]. The Firmicutes/Bacteroidetes ratio, indicative of dysbiosis, was also higher in endometriosis patients, alongside notable differences in various taxa [101]. The relationship between endometritis and endometriosis has been documented [102–104]. Clinical trials targeting dysbiosis and endometrial lesions could benefit cases of recurrent implantation failure and pregnancy loss [104].

Modulating gut microbiota could potentially slow endometriosis progression. Sobstyl et al. [105] noted that interactions among microbiota and dysbiosis may activate immune cells, producing proinflammatory cytokines that disrupt stem cell homeostasis and affect estrogen levels. Certain gut bacteria, like *Bacteroides* and *Lactobacillus*, secrete enzymes that elevate free estrogen levels [106]. An increase in *Escherichia coli* has been observed in the feces of endometriosis patients, but the interactions between gut, vaginal, and endometrial microbiota remain unclear [104,107].

Patients with chronic pain and endometriosis had lower alpha diversity than controls, showing increased levels of vaginal *Streptococcus anginosus* and rectal *Ruminococcus* [106,107]. Guo et al. [108] speculated that different Gram-negative bacteria, such as *Escherichia coli*, residing in the vagina could be involved in the pathogenesis of endometriosis in humans. In addition, gut microbiota promotes the progression of endometriosis by influencing peritoneal immune cell populations. Then, the onset and development of endometriosis may be related to the abnormal immune response caused by gut dysbiosis [108].

3. Immune Response in Endometriosis

3.1. Pattern-Recognition Receptors (PRRs), Pathogen-Associated Molecular Patterns (PAMPs), Damage-Associated Molecular Patterns (DAMPs), and Endometriosis

PRRs can be classified into five families: Toll-like receptors (TLRs), C-type lectin receptors (CLRs), NOD-like receptors (NLRs), retinoic acid-inducible gene I-like receptors (RLRs), and AIM2-like receptors (ALRs) [109–111]. Their activation leads to proinflammatory cytokine, interferon production, phagocytosis, and cell death [109–111]. PAMPs include lipopolysaccharides, flagellin, viral RNA, and fungal cell walls [109–111]. DAMPs are various molecules, such as proteins (e.g., amyloid beta, HSP70), metabolites (e.g., ATP, uric acid), ions (Ca^{2+}, K^{+}), and nucleic acids (self RNA, DNA) [112].

Endometriosis may develop in two distinct phases. The initial wave occurs with an infection and TLR activation. The second wave is characterized by sterile inflammation resulting from oxidative stress and receptor activation by DAMPs [111–113].

Increased TLR2 B cells and myeloid dendritic cells correlate with severe endometriosis [111–114]. Individuals with endometriosis have significantly higher TLR2 and TLR9 concentrations in peritoneal fluid than healthy controls [115]. In a mouse model, *Ureoplasma urealyticum* infection promotes endometriosis by enhancing inflammatory mediators and MMP-2 expression via TLR2 signaling [115]. Additionally, ectopic endometriotic lesions show heightened TLR3 and TLR4 mRNA expression compared to eutopic tissues [116–118].

Inflammasomes are multi-protein complexes, particularly the NLRP3 inflammasome, which activate inflammatory caspases [119]. NLRP3 binds to procaspase-1, activating caspase-1, which cleaves pro–IL–1β and pro–IL–18 into their active forms [119,120]. This mechanism has been linked to endometriosis's pathogenesis, with increased caspase-1, IL-18, and NLRP3 expression observed in ectopic endometrial tissue [121,122]. Granulosa cells from women with endometriosis show elevated levels of the NLRP3 inflammasome and increased IL-1β and IL-18 in follicular fluid, contributing to infertility [123,124]. NLRP3 expression is significantly higher in ovarian endometriosis, and using an NLRP3 inhibitor has effectively reduced ovarian endometriosis lesions in animal models [125,126].

Interactions between macrophages and endometrial stromal cells via NLRP3 signaling enhance stromal cell migration and endometriosis progression [127]. NLRP3-deficient mice had smaller endometrial lesions, but this was reversed with wild-type macrophages [127]. Ectopic endometrial tissues showed elevated IL-18, IL-6, and IL-1β mRNA levels compared to eutopic endometrium and controls [128,129]. NLRP3-mediated pyroptosis is associated with fibrosis via TGF-β1, and inhibiting it may reduce fibrosis in endometriosis [124,130]. TRIM24 potentially facilitates endometriosis progression through the NLRP3/caspase-1/IL-1β pathway [131,132]. High estrogen receptor β levels in endometriotic lesions correlate with increased IL-1β, promoting cell adhesion and proliferation [132]. Progesterone inhibits NLRP3 activation in normal stromal cells via autophagy, but this effect is reduced in endometriotic cells [133].

NLR family CARD domain-containing 5 (NLRC5) acts as a negative regulator in endometriosis by inhibiting inflammation [134,135]. Its overexpression increases autophagy in ectopic endometrial stromal cells, while inhibition decreases it [135]. NLRC5 levels

are higher in the ectopic and eutopic endometria of endometriosis patients compared to those with leiomyoma, peaking in the ectopic endometrium, and it suppresses IL-6 and TNF-α [136]. This suggests that NLRC5 overexpression inhibits estrogen receptor β-mediated development and inflammatory responses in endometriosis [134–136].

C-type lectin receptors (CLRs) play a key role in the innate immune system by recognizing carbohydrates [137]. In patients with endometriosis, peritoneal fluid exhibited increased CLR MR2 and DAP12 mRNAs, alongside decreased galectin levels [137–139]. The mannose receptor C, type 2 (MRC2), was found to be lower in ectopic endometrial stromal cells compared to normal ones, whereas peritoneal dendritic cells in endometriosis showed heightened mannose receptor expression [139]. Additionally, the receptor for advanced glycation end products (RAGEs) is associated with endometriosis and infertility [140], with soluble RAGEs (sRAGEs) potentially impacting in vitro fertilization success [140]. The functions of RAGEs and CLRs continue to be explored.

3.2. Innate Immune Response in Endometriosis

Tables 2 and 3 provide a general overview of endometriosis's innate and adaptive immune involvement. The aim is to give the reader a summary of the most critical issues in endometriosis.

The innate immune cell response comprises several protein elements, with the complement pathway and defensins being the most relevant. The complement system, a component of innate immunity, contains over 50 proteins that aid in eliminating pathogens, removing immune complexes and apoptotic debris, and participating in processes such as inflammation, adaptive immunity, coagulation, metabolism, tissue regeneration, and host–microbiota symbiosis [141,142]. Table 2 shows several pathway components that have been related to endometriosis. On the other hand, defensins produced by Paneth cells, neutrophils, and epithelial cells have not been involved in endometriosis (Table 2).

Macrophages are crucial in endometriosis physiopathology. Chronic macrophage stimulation and high iron levels in the peritoneal cavity elevate reactive oxygen species in women with endometriosis [143–145]. Estrogen prompts peritoneal macrophages to secrete cytokines and prostaglandins through estrogen receptor-β, which decreases MMP-9 activity and inhibits phagocytosis [25]. Upon cell activation, NF-κB p65 phosphorylation induces the transcription of proinflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8), proangiogenic factors VEGF, growth factors like FGF-2, and adhesion molecules [146,147], and COX-1 and 2. COX-2 is responsible for the increased concentrations of PGE2 in the peritoneal fluid [148]. The co-culture of macrophages with endometrial stromal cells enhances the proliferation and invasiveness of these endometrial stromal cells [149].

Proinflammatory peritoneal fluid in women with endometriosis elevates FasL expression in regurgitated endometrial cells, enhancing Fas-mediated cell death of activated immune cells and aiding immune evasion by endometrial cells [150,151]. Macrophages initiate a regenerative program vital for lesion growth. In patients with endometriosis, peritoneal macrophages exhibit higher iron storage than controls [146,152] and have difficulty managing elevated hemoglobin levels in the peritoneal fluid [153–156]. In women with endometriosis, peritoneal macrophages show heightened proinflammatory markers of the M1 phenotype, while M2 macrophages often shift toward M1 [154–156]. The presence of two subpopulations of macrophages in the lesion was reported using single-cell analysis [156] and the role of M2a in fibrogenesis [157]. In the advanced stages of the disease, there is an increase in M2 macrophages and a decrease in the M1 type; the opposite occurs in the initial stages (I–II) [145,158]. Macrophages activated by IL4 can induce epithelial-to-mesenchymal transition and fibroblast-to-myofibroblast transdifferentiation through the production of TGF-β1 [145,152].

Uterine NK (uNK) cells express CD56 but no other classical NK cell or T cell markers. The number of uNK cells changes during the menstrual cycle, pregnancy, and various endometrial pathologies [159]. There is an increase in uNK in the mid-secretory phase [151]. CD56+ cells remain high during early pregnancy and comprise 70% of the lymphocytes at the interface between maternal decidua and the invading trophoblast [159]. Approximately 10% of uNK are CD56+ CD16+, while 90% of the population has the CD56+ CD16− phenotype [159]. In the peripheral blood, 90% of NK cells are CD56+ CD16+ (pNK); CD56+ CD16+ and CD56+ CD16− uNK cells exhibit functional differences. CD16+ cells are cytolytic, whereas CD16− uNK cells secrete cytokines [159]. Activated uterine natural killer (uNK) cells regulate trophoblast invasion into the decidua [159]. The elevation of CD56+ cells is higher in infertile women and pregnancy loss and appears to be directly correlated with pelvic endometriosis [160].

Limited information exists on the roles of neutrophils and eosinophils in the endometrium [161] since they are not commonly observed in the endometrium or vagina except for infectious diseases. Nonetheless, mast cells are therapeutic targets for treating endometriosis, inflammation, infertility, and pain. A recent review [162] describes the different experimental treatments involving mast cells in animal models.

Myeloid-derived suppressor cells (MDSCs) are a diverse group of immature myeloid cells, including dendritic cells, granulocytes, and monocyte/macrophage precursors, known for their immunosuppressive properties [163]. They play a significant role in the progression of immunological disorders, such as chronic inflammation and cancer. MDSCs can be categorized into two primary types: polymorphonuclear (PMN) MDSCs, also referred to as granulocyte (G) MDSCs, and monocytic (M) MDSCs. The significant outcome of MDSC expansion is immunosuppression, which may lead to angiogenesis and the secretion of cytokines or growth factors, potentially exacerbating the progression of conditions such as endometriosis [163–166].

While the proportion of PMN-MDSCs in both peripheral blood and peritoneal fluid was significantly higher in patients with endometriosis, the proportion of M-MDSCs did not differ between control subjects and those with endometriosis [166,167]. On the contrary, an abnormal expansion of M-MDSCs in peripheral blood and peritoneal fluid of patients with endometriosis [167]. Additionally, MDSCs are more abundant in ectopic endometrium than in normal endometrium [168]. M-MDSCs, alongside inflammatory cytokines and exosome miRNA, appear to be involved in the progression of endometriosis [169]. Cysteine–Cysteine Chemokine Receptor 5 (CCR5) and its ligand, CCL5, could drive the progression of endometriosis by increasing the accumulation of MDSC [169]. On the other hand, MDSCs drive the process of endometriosis by enhancing angiogenesis [170].

Another critical issue in endometriosis is the role of immature dendritic cells in the lesions. Those cells are inefficient in antigen presentation and are inducers of tolerogenic responses [171]. The lack of mature dendritic cells in endometriosis is also related to the increase in Tregs, and as stated before, the effectiveness of the Tregs depends on the milieu. Li and coworkers [172] have postulated using dendritic cells for therapeutic use in endometriosis. The effectiveness of this proposal can likely be assessed soon.

Table 2. Innate immune proteins and cells in endometriosis.

Component	Characteristics	Ref
Complement pathway	Increased expression of the protein components of the pathway in human endometriosis.	[173]
	Increased levels of C1q, C1 inhibitor, mannose-binding lectin (MBL), C3c, C4, and the membrane attack complex (SC5b-9) in the peritoneal fluid of endometriosis patients. Increased expression of 1QA, C1QB, C1R, C1S, C2, C3, C4A/B, C5, C6, C7, C8A, CFB, CFH, and CFI in ectopic endometrium.	[174]
	C1q levels are correlated with vessel formation in endometriosis (human).	[175]
	The lectin pathway may not be involved in endometriosis in humans.	[176]
Defensins	There are no changes in defensin levels in women with endometriosis.	[177]
Neutrophils	Increased levels of human neutrophil peptides 1, 2, and 3 have been observed in the endometrial fluid of women with endometriosis.	[178]
	In endometriosis, neutrophil phagocytosis is impaired. Neutrophils support the survival of endometrial cells and help create a microenvironment conducive to the development and growth of lesions (mouse and human).	[179–181]
	Neutrophil depletion in mice reduces the formation of endometriotic lesions.	[181]
Macrophages	Elevated IL-8, C-C chemokine RANTES (CCL5), MCP-1, and MIF attracted more cells in advanced endometriosis lesions in humans and mice.	[182]
	There are different types of macrophages present in endometriomas (mouse model).	[183]
	High iron levels in the peritoneal fluid impair the phagocytic response and increase oxygen radical formation (human).	[173,179,184]
	Extracellular vesicles modulate macrophage response in endometriosis.	[185,186]
	The expression of CD36 in macrophages is inhibited by the high concentration of PGE2 in the endometrioma (human).	[187]
	An increased expression of CD200 correlates with reduced phagocytic activity and decreased CD36 expression in endometriosis (human).	[188]
	TLR4 and RAGE expression in peritoneal fluid macrophages inversely correlate with endometriosis severity (human).	[189]
	Macrophages play a vital role in both fibrosis and mesenchymal transdifferentiation (in humans and mice).	[190,191]
NK cells	There is a higher density of CD56 in uNK cells in patients with endometriosis undergoing IVF treatment.	[159–161]
	Uterine NK cell amounts are higher in patients with endometriosis.	[159,161,192]
	There is a decrease in tissue immature CD56 cells following the surgical removal of endometriomas (human).	[159,193]
	NK cell cytotoxic activity is significantly reduced in women with moderate to severe endometriosis (peripheral, peritoneal, and uNK).	[194,195]
	Granzyme B and perforin secretion were reduced in NK cells from endometriosis patients.	[195,196]
	The increase in soluble MICA/B levels in the peritoneal fluid of patients with endometriosis negatively affects the cytotoxic function of NK cells.	[196]
	Elevated levels of IL-6 and TGF-β1 in the peritoneal fluid of endometriosis patients are responsible for the impaired cytotoxic activity of NK cells.	[197,198]
	High IL-15 levels produced by ectopic endometrial stromal cells can inhibit NK cell function (human).	[199]
	IL-10 produced from co-cultures of macrophages can also inhibit NK cell cytotoxic response (mouse and human in vitro).	[200]
	NK cells from patients with endometriosis have a high density of NK inhibitory receptors and ligands. However, NK-activating receptors are also expressed at high levels.	[201–203]
Mast cells	High numbers of degranulated mast cells have been found in women with endometriotic lesions.	[204,205]
	Increased concentrations of stem cell factor in the peritoneal fluid of women with endometriosis are responsible for increased mast cell migration.	[162]
	Mast cells express estrogen receptors and are highly activated by the estrogens in the ectopic endometrium in patients with endometriosis.	[205]
	Mast cells are involved in pain in women with endometriosis.	[206]

Table 2. *Cont.*

Component	Characteristics	Ref
Dendritic cells	Increased immature cells (CD80lowCD1ahigh) and fewer mature cells (CD80highCD1alow) in the peritoneal fluid (mouse and human).	[207,208]
	The activity of enzyme 1-hydroxysteroid dehydrogenase type 1, which activates cortisol, impairs dendritic cell maturation in patients with endometriosis.	[209]
	CD1c expression on peripheral myeloid dendritic cells was higher during menstruation in patients with endometriosis.	[210]
	IL-10 produced by dendritic cells induces angiogenesis in patients with endometriosis	[211]

3.3. Adaptive Immune Response

Table 3 highlights the role of T and B lymphocytes in the adaptive response in endometriosis. Changes in CD8 populations are essential, while CD4 cell modifications can be categorized into early Th1 and late Th2 responses. Inflammatory lesions promote the production of anti-inflammatory cytokines to balance the inflammatory environment, revealing a complex local cytokine storm beyond just immune cell mediators.

In a recent review by Knez et al. [212], it becomes clear that different Tregs subpopulations, resting Tregs (rTregs; Foxp3loCD45RA+ T cells), suppressive Tregs (Foxp3hiCD45RA−), and non-suppressive Tregs (non-Tregs; Foxp3loCD45RA− T cells), should be considered when analyzing Tregs in endometriosis [212]. Tregs expressing CTLA-4 induce tolerogenic responses (reduced T cell activation and proliferation), while IL-17 and TGFβ are crucial for lesion formation and fibrosis, respectively. Tregs interact with T follicular cells, B cells, dendritic cells, and macrophages [212]. The suppressive response involves the induction of M2 macrophages and the production of IL-1, thereby decreasing the inflammatory milieu.

The role of B cells in endometriosis is less clear than that of T cells [213]. The generation of anti-endometrial autoantibodies [214] and the production of IL-17 and, in certain conditions, IL-35, illustrate the complex nature of cell interaction [11,213]. More research is required to understand the role of these cells in endometriosis and their probable link with autoimmune diseases.

Table 3. Adaptive immune cells in endometriosis.

Cell Type	Characteristics	Ref
T cells	In patients with endometriosis, circulating CD8+ cells and activated T cells increase, leading to higher secretion of proinflammatory cytokines and elevated autoantibody titers.	[214–216]
	CD8 cell apoptosis is elevated in endometriosis patients due to Fas-FasL interaction.	[151]
	Foxp3+CD39+CD73+ Treg cells are decreased in the blood of women with deep infiltrating endometriosis but increased in the peritoneum and endometriotic lesions.	[217,218]
	Elevated levels of estrogen and thymus-expressed chemokine (TECK/CCL25) lead to an increase in Tregs, which in turn reduces immune surveillance in endometriosis patients.	[219]
	Disruption of Th17/Treg balance leads to heightened inflammation in ectopic and eutopic endometria in women with endometriosis.	[220,221]

Table 3. *Cont.*

Cell Type	Characteristics	Ref
T cells	Peritoneal fluid from endometriosis patients promoted Treg cell generation and inhibited Th17 cell differentiation in CD4+ T cell cultures in vitro.	[221]
	Patients with endometriosis have higher amount of CD16+ CD8 T cells in their peripheral blood, and CD8 T cell cytotoxicity is increased in menstrual effluent.	[222]
	Patients with endometriosis show low amounts of perforin-CD8 T cells in peripheral blood.	[223]
	Potential T cell exhaustion indicated by PD-1 expression and increased PD-1L presence in tissues of endometriosis patients.	[224]
	The Th2 immune response (IL-4, IL-10) dominates later stages of endometriosis, whereas Th1 is present initially. CTLA-4 plays a role in chronic inflammation and endometriosis in humans and mice.	[178,225–227]
	Higher soluble circulating CTLA-4 levels in patients with endometriosis are associated with chronic inflammation.	[227]
	Estrogen plays a role in regulating the GATA3 transcription factor and Th2 differentiation in patients with endometriosis.	[228]
	The interleukin IL-4/IFN-γ, IL-10/IFN-γ, and IL-4/IL-2 ratios are higher in women with endometriosis, probably in the late stage.	[229]
B cells	Increased circulating levels of activated B cells in patients with endometriosis.	[230,231]
	Local B cells secrete high levels of IL-6 and IL-17, inducing local inflammation. They also produce anti-endometrial antibodies.	[231]
	The production of IL-35 by B cells is increased in patients with endometriosis.	[232]

4. Cytokines and Endometriosis

Cytokines play a critical role in generating endometriosis since the inflammatory milieu in endometriosis leads to poor quality of oocytes and infertility [6]. However, most of the focus of the published studies has referred to cytokines produced by immune cells, which does not represent the whole picture of events in endometriosis. The local tissue production of cytokines must be considered, as well as the role of adipokines, which may also have a dual role, regional and peripheral [22]. A clear example is the role of leptin in regulating the amount of stored energy by binding to specific neurons in the brain.

Alarmins are key inducers of cytokine release by activating DAMP receptors. HMGB1, a byproduct of cell death, enhances proinflammatory cytokine secretion, particularly under hypoxic conditions, making HIF-1α modulation crucial in endometriosis [233–236]. HMGB1 is also affected by mediators like prostaglandins [237], while the role of leukotrienes depends on LPS induction in the endometrium [237]. Early animal studies showed reduced endometrial inflammation with leukotriene receptor antagonists [237–240], but the results were inconclusive for human clinical trials.

Lipoxin A4 suppresses inflammation and activates autophagy, which helps reduce the proliferative effects of endometriosis [241–243]. Resolvins, as noted in research by Dimitrieva et al. [242] and Gu et al. [243], also contribute to the management of endometriosis by decreasing the inflammatory response through the signal transduction pathways induced upon receptor/ligand interaction [244]. Additionally, resolvins may offer a promising approach to alleviating the pain related to endometriosis [245].

Despite the enormous efforts in analyzing different types of biomarkers in endometriosis reviewed by Collie and coworkers [246], there is no clear consensus on most metabolites. The authors only reported 3-hydroxybutyrate, lactate, phosphatidic acids, succinate, pyru-

vate, tetradecenoyl carnitine, hypoxanthine, and xanthine as the most consistent biomarkers. Since these intermediate metabolites can be affected by different pathways, more research is required to determine the metabolic pathways involved. Hypoxia should be carefully analyzed as proposed by Wilson [247].

Ferroptosis represents a significant cellular event in endometriosis [248]. Iron within the endometrioma influences the generation of radical species in conjunction with immune cells that provoke proinflammatory and cytokine responses. As highlighted in tumor immunology [249], exploring ferroptosis, radical production, cellular senescence, cell death, and immune exhaustion in endometriosis is paramount. Further research is necessary to identify appropriate pharmacological targets.

Table 4 presents a comprehensive overview of the critical cytokines involved in endometriosis. Depending on the tissue environment, it categorizes these cytokines into proinflammatory, anti-inflammatory, and those with pro- or anti-inflammatory properties. Additionally, the table includes cytokines associated with angiogenesis, cell growth, chemokines, and inhibitory factors. While other mediators may play a role in the physiopathology of endometriosis, they have not yet been thoroughly studied. In addition, some critical issues must be considered: (1) there are differences in sample analysis, serum, peritoneal, or endometrial fluid, and endometrioma analysis; (2) in addition, some analyses were performed in patients with different stages of endometriosis. The table also includes whether the results are from the human, animal model, or in vitro, which is essential, considering possible differences that can be encountered.

Table 4. Cytokines involved in endometriosis.

Cytokine	Role in Endometriosis	Reference
Proinflammatory cytokines		
IL-1β	Increased levels in the follicular fluid of endometriosis patients.	[26,250,251]
IL-1 RA	Increased levels in the follicular fluid of endometriosis patients. It binds active IL-1β, reducing receptor binding and biological activity.	[252,253]
IL-2	Decreased levels in endometriotic lesions. Increase in soluble CD25 in peritoneal fluid.	[254–257]
	Increased levels were reported in patients with severe endometriosis.	[258]
IL-3	Increased levels were reported in endometriotic lesions.	[259–261]
IL-5	Increased levels were reported in the follicular fluid of endometriosis patients.	[260,261]
IL-6	Increased levels were reported in the follicular fluid of endometriosis patients. It is a proinflammatory cytokine.	[252,253,261]
IL-7	Higher in the eutopic as compared to the ectopic tissue of endometriosis patients.	[262]
	Associated with IL-15 in maintaining endometriosis.	[263]
IL-8	Increased levels were reported in the follicular fluid of endometriosis patients.	[264–266]
IL-12p40	Increased levels were reported in the follicular fluid of endometriosis patients.	[267,268]
IL-15	Higher levels were reported in the peritoneal fluid of women with endometriosis.	[263,269,270]

Table 4. *Cont.*

Cytokine	Role in Endometriosis	Reference
IL-15	Higher levels were reported in the peritoneal fluid of women with endometriosis.	[263,269,270]
IL-16	Increased levels were reported in the peritoneal fluid of patients with advanced stage endometriosis (III/IV).	[271,272]
IL-17	Elevated levels of IL-17 have been observed in patients during the early stages of the disease. IL-17 promotes the proliferation, invasion, and implantation of endometriotic cells. Additionally, increased IL-17 levels have been linked to higher levels of IL-8, VEGF, CSF-1, and GM-CSF.	[273–275]
IL-18	Increased levels have been reported in the peritoneal fluid of endometriosis patients. Affects endometrial receptivity.	[276]
IL-23	Increased levels are observed in the follicular fluid of endometriosis patients, stages III–IV > stages I–II. Involved in IL-17 production and inflammation.	[277]
IL-25	Increased levels were reported in the peritoneal fluid of patients with endometriosis.	[278]
IL-31	Increased levels were reported in the plasma of endometriosis patients	[279]
IL-32	Increased concentrations of IL-32 were reported in the peritoneal fluid of patients with endometriosis. An increase in IL-32 is correlated with elevated levels of IL-8 and CCL2 and enhanced cell proliferation.	[280,281]
IL-34	Increased serum levels in patients with endometriosis. Autocrine production promotes endometriosis.	[282]
IL-35	Enhanced levels are reported in ectopic endometrium. Suppresses immune response, increasing the growth of endometrial cells.	[283]
IL-36α, β, γ and Receptor	Increased levels are reported in the peritoneal fluid of endometriosis patients.	[284]
IFNγ	Decreased levels are reported in the peritoneal fluid of endometriosis patients. It induces macrophage activation (M1) and enhances the proinflammatory response.	[178,256,257]
TNFα	High levels of TNFα are found in patients with endometriosis, particularly at their highest in those with severe endometriosis.	[285,286]
CXCL chemokines	In women with endometriosis or polycystic ovary syndrome, the levels of CXCL1-8, 10, 12, 13, and 16 are increased, while CXCL9 and 14 are decreased.	[287]
FRACTAL-KINE	Decreased levels were reported in the peritoneal fluid of patients with endometriosis. Increased levels were reported in patients with endometriosis.	[288] [289]

Table 4. *Cont.*

Cytokine	Role in Endometriosis	Reference
MCP-1 (CCL2)	Increased follicular fluid levels in endometriosis correlate with severity and attract neutrophils, NK cells, and lymphocytes linked to RANTES and IL-8. Association with hepatocyte growth factor and insulin-like growth factor-1.	[290,291] [292]
MCP-2/3/4	Increased levels are reported in patients with endometriosis.	[286]
MIP-1α	A decrease in cytokine levels was reported in patients with endometriosis. Increased levels were reported.	[289]
MIP-1β	Increased levels were reported in patients with endometriosis.	[289]
eotaxin 2/3	Increased levels were reported in patients with endometriosis.	[289]
ENA-78	Increased levels were reported in patients with endometriosis.	[289]
RANTES (CCL5)	Increased levels were reported in patients with endometriosis.	[286,289]
MIF-1	Increased levels were reported in patients with endometriosis. The levels are associated with 17β-estradiol. MIF-1 is a proinflammatory cytokine.	[293–295]
CSF-1	Increased levels were reported in patients with severe endometriosis.	[296–298]
PDGF	Increased levels were reported in the peritoneal fluid of patients with endometriosis.	[298–300]
VEGF	Increased levels were reported in the peritoneal fluid of patients with endometriosis. Involved in increased vascularization.	[298–302]
bFGF	Increased levels were reported in the peritoneal fluid of patients with endometriosis.	[298–301,303]
Anti-inflammatory cytokines		
TGFβ	Patients with severe endometriosis exhibited increased levels of TGFβ, which play a role in the fibrosis observed in these individuals.	[77,304,305]
IL-10	Increased levels were found in the follicular fluid of patients with endometriosis, produced by various cells.	[266,306]
IL-19	A decrease in serum levels of IL-19 has been observed in patients with endometriosis.	[307]
IL-22	A decrease in serum levels was reported in patients with endometriosis. IL-22 is implicated in endometrial cell invasion in humans and mice and carcinoma cell proliferation.	[308] [309,310]
IL-37	Increased levels are reported in the peritoneal fluid of endometriosis patients. Involved in anti-inflammatory response in vitro and animal models.	[253,284,311]

Table 4. *Cont.*

Cytokine	Role in Endometriosis	Reference
IL-38	Increased levels are reported in the peritoneal fluid of endometriosis patients. Involved in anti-inflammatory response.	[284]
Mixed effects proinflammatory and antinflammatory		
IL-4	Increased levels in the follicular fluid of endometriosis patients.	[312–316]
IL-13	Differential expression in ectopic and eutopic endometrium in endometriosis patients. High levels of the cytokine have been associated with infertility.	[314,317]
IL-27	IL-2 + IL-27 are involved in the growth of human endometrial cells in vitro. Its role in endometriosis is still controversial.	[318]
IL-33	Increased serum levels were reported in the peritoneal fluid of patients with deep endometriosis, which could induce an anti-inflammatory response. It is involved in epithelial–mesenchymal transition.	[319,320] [321,322]
EGF	Increased levels were reported in the peritoneal fluid of endometriosis patients involved in endometrial invasion.	[298–301,303]
GM-CSF	Increased levels were reported in patients with severe endometriosis. It is controversial since it may have local anti-inflammatory effects. Autoantibodies against GM-CSF are present in the serum of patients with deep endometriosis.	[29,323,324] [325]

The table is divided into three parts: (1) proinflammatory cytokines, (2) anti-inflammatory cytokines, and (3) mixed effects. The separation facilitates the analysis based on the role of the cytokines. The cytokines with mixed effects refer to cytokines whose general description can be anti-inflammatory; however, their role in the lesion may differ.

Table 5 represents the list of adipokines that have been studied in endometriosis. However, it is essential to note that obesity is not prevalent in patients with endometriosis. Patients with endometriosis usually have a low BMI, and obesity increases its severity [298,303,326–328]. Various hypotheses have been proposed regarding the potential role of adipokines in endometriosis [326,328]. Even though there are disagreements about the relationship between obesity, BMI, and endometriosis, most researchers support the proposal of a dual effect of adipokines in the tissue and the central nervous system. The finding of adipokines in the lesion and their possible role in lesion growth and modulation of the immune response requires more research.

It is important to note that the precise mechanisms underlying the diverse cytokines involved in endometriosis remain unclear. A comprehensive understanding of the chronological progression of this condition is critical for developing novel treatment strategies aimed at reducing both the growth of lesions and associated pain.

Table 5. Adipokines involved in endometriosis.

Adipokine	Characteristics	References
Leptin	Elevated leptin levels have been observed in serum and peritoneal fluid in patients with endometriosis.	[327,329,330]
	Researchers found a positive association between leptin levels and endometriosis in the mouse model.	[21,331]
	Controversial results have been reported in humans.	[332]
	Elevated local leptin levels in endometriosis lesions are associated with increased transcription factor HIF-1α.	[333]
	Endometriosis may be related to dysfunctional adipose tissue, which affects metabolism, browning, body weight regulation, and pain pathways.	[21,334]
Adiponectin	Low circulating adiponectin levels in women are associated with endometriosis.	[335,336]
Resistin	Increased concentrations have been reported in women with endometriosis.	[337,338]
	Research suggests a potential correlation between resistin and IL-23 levels.	[277]
Retinol binding protein 4 (RTB4)	Increased plasma levels of RBP4 have been reported in patients with endometriosis.	[339]
	RTB4 may play a role in the infiltration of immune cells in human endometriosis.	[340]
Visfatin/NAMPT and resistin	The three adipokines may be secreted locally within the human endometrioma as part of an inflammatory response, regardless of the stage of endometriosis.	[341]
Ghrelin, GLP-1, visfatin, GLP-1.	A reduction in ghrelin, GLP-1, glucagon, and visfatin levels in the peritoneal fluid of women with endometriosis may contribute to lesion development by proinflammatory macrophages.	[341]

5. Mechanisms of Pain in Endometriosis

Endometriosis-associated pain stems from various mechanisms, including nociception, inflammation, and altered pain processing in the nervous system. It is frequently linked to psychological distress and fatigue. Additionally, angiogenesis leads to the growth of nerve fibers that contribute to this pain [341,342]. The size of the lesions appears to be related to pain intensity in patients with lesions on the intestinal wall [342–344]. However, there is no significant correlation between the graded severity of morphological characteristics and the intensity and character of pain symptoms [342–345]. It can be concluded that there is no consistent correlation between endometriosis and reported pain severity.

Two main descriptions of pain occur in endometriosis: (1) Nociceptive pain occurs due to physical damage to non-neural tissues, particularly from endometrial lesions and the surrounding structures, such as the pelvic lining. This type of pain can be classified as visceral, which relates to internal organs, or somatic, which pertains to muscles and skin [346]. (2) Nociplastic pain occurs when the nervous system becomes oversensitive, amplifying pain signals. Nociceptive stimuli can trigger it and persist even after the initial injury has healed. The effect is due to increased sensory nerve density and a reduced density of sympathetic nerve fibers in endometriotic lesions [347].

An imbalance in sensory and sympathetic nerve fiber density within lesions is associated with pain severity in women with endometriosis [346–348]. Compared to women without endometriosis, there is an increase in sensory nerve fibers and a decrease in sympathetic nerve fibers, which may contribute to pain [346–348]. In women diagnosed with endometriosis, there is a significant elevation in the density of nerve fibers within endometriotic lesions and the adjacent myometrium compared to normal peritoneal tissue. This heightened density, particularly of sensory nerve fibers, positively correlates with the severity of pain patients report [346–348]. The potential mechanisms contributing to the

severity of pain include (1) sensitization of nociceptors within the endometriotic microenvironment; (2) neurogenic inflammation accompanied by the release of proinflammatory neuromediators; and (3) central sensitization, which involves an amplification of central pain signal processing [342,343,346–348].

The interaction between macrophages and nerves constitutes a significant factor in pain associated with endometriosis [347–349]. Within this interaction, cytokines are linked to the phenomenon of inflammatory pain [346,347]. Moreover, various immune cells and cytokines can also play a role in the pain observed in lesions [348].

Endocannabinoids and phytocannabinoids possess anti-inflammatory, anti-nociceptive, and anti-proliferative properties that may aid in managing endometriosis, characterized by inflammation, increased vascularity, and pain [350–352]. While endometriotic lesions show varying levels of endocannabinoids, their exact role in disease progression and potential bystander effects remains unclear [350–352]. In vivo murine model studies indicate that synthetic cannabinoids and specific endocannabinoids, such as palmitoylethanolamide (PEA), possess anti-inflammatory properties and can inhibit the proliferation of endometriosis-like lesions [351]. However, the exact mechanism is still elusive.

According to Farooqi and colleagues [352], both the endocannabinoid system (ECS) and gut microbiota play significant roles in the pathophysiology of endometriosis. The ECS is essential for regulating inflammation and modulating pain perception, while gut microbiota significantly influences immune responses and hormonal equilibrium [352]. Worsening symptoms of endometriosis have been associated with an imbalance in the ECS and gut microbiota, linked to elevated levels of endocannabinoids resulting from alterations in CB1 receptor expression [352]. Furthermore, an increase in *Prevotella* and *Escherichia coli* prevalence within the gut microbiota correlates with exacerbated gastrointestinal and endometriosis symptoms [352]. These dysbioses are also associated with heightened circulating levels of proinflammatory cytokines, such as TNF-α and IL-6 [352]. Nevertheless, elevated endocannabinoids, particularly 2-AG, may confer protective effects on the gut by mitigating inflammation and enhancing gut permeability.

Increased levels of the neurotransmitters glutamate and glutamine were found in the anterior insula of endometriosis patients, enhancing connectivity to the prefrontal cortex (where pain-related memories are stored) [353,354]. Other areas of the brain are also affected. According to Eippert et al. [355], the periaqueductal gray, which is involved in pain-modulatory pathways, is enlarged in individuals with pain, and measurable changes are observed in the thalamus, insula, and putamen [342,353–355].

In endometrial lesions, macrophages and nerve fibers interact to promote pain [349,353–356]. Ectopic endometrial lesions secrete nerve fibers that produce CSF-1 and CCL2, which attract macrophages to the periphery of nerves and regulate their polarization toward the M2 phenotype [356]. On the other hand, macrophages, incubated with CSF-1 and estrogen, produce brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), which stimulate neurite growth from ganglia explants [356].

Endometriosis-related pain is classified as neuropathic or neuroinflammatory [357]. Ectopic endometriotic lesions promote inflammation and disrupt the transmission of inflammatory mediators, altering how nerve fibers process and transmit information [357,358]. Disorders that are characterized by sensory dysfunction, such as overactive bladder syndrome and irritable bowel syndrome, are commonly co-diagnosed with endometriosis [357,358]. These comorbidities suggest a more complex pathophysiology for pain in this condition that cannot be explained by endometrial lesions alone [342–344,353–358]. Chronic remodeling of the nervous system may occur in shared sensory neural pathways to induce a state of protracted peripheral and central sensitization and chronic pain in patients with endometriosis [357]. Microgliosis, astrogliosis, and enhanced substance P

neurokinin-1 receptor immunoreactivity have been observed within the spine in mice with endometriosis, suggesting the development of neuroinflammation and the sensitization of spinal circuitry in this condition [359]. Prostaglandin E2, TNFα, NGF, RANTES, IL-8, and IL-1β are elevated within the peritoneal fluid of endometriosis patients [360]. These mediators can all activate sensory nerve endings directly [12,357–360].

Neuroangiogenesis in ectopic endometriotic lesions explains the transmission of the pain. An increased density of miniature, unmyelinated nerve fibers (sensory afferents, sympathetic, and parasympathetic efferents) has been found in endometrial lesions [360,361]. The local production of VEGF and NGF by macrophages supports neuroangiogenesis [12,360–364]. On the other hand, the activation of sensory afferent nerves initiates the recruitment of mast cells and the subsequent release of proinflammatory cytokines (TNF-α, NGF, PGE2, IL-1β), which contributes to a chronic state of neurogenic inflammation [365]. Neurotrophic factors produced by macrophages, such as Netrin-1, insulin-like growth factor-1, and ten-eleven translocation 3 (TET3), play a role in the pain associated with endometriosis [365–367].

Recently, the role of IL-33 in macrophage/neuron-induced pain has been studied [368]. IL-33 enhanced the release of TNF-α and IL-1β, facilitating macrophage recruitment and neurogenesis in ectopic lesions [368]. IL-33 increased the expression of the transient receptor potential vanilloid 1 (TRPV1), which is responsible for the phenomenon [368]. In women with endometriosis and severe chronic pelvic pain, serum IL-16 levels were higher compared to women with mild pain [61].

Tregs may influence endometriosis pain by modulating macrophages to create a local tolerogenic response, which reduces proinflammatory cytokines, decreases cell migration, and mitigates estrogen's effects on endometriomas [213]. It has recently been found that the meningeal Treg (mTreg) inhibits nociception in female mice [369]. mTreg cells produced enkephalin, which acted on delta opioid receptors in MrgprD+ sensory neurons to reduce pain [369]. However, enkephalin was unnecessary for Treg cell-mediated immunosuppression, and the process depends on sex hormones [369]. One can envision that the understanding of pain in patients with endometriosis is just beginning.

6. Endometriosis and Autoimmunity

There is an association between endometriosis and autoimmune diseases. Women with endometriosis may have a higher risk of conditions such as systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, celiac disease, multiple sclerosis, and inflammatory bowel disease compared to those without endometriosis [13,370–372]. Endometriosis shares similarities with autoimmune diseases, featuring elevated cytokines, B cell activation, T and B cell function abnormalities, autoantibody formation, and decreased apoptosis [13]. Women with endometriosis have alterations in B cell activity and an increased incidence of autoantibodies [13]. These autoantibodies can be directed against various phospholipids, histones, and polynucleotides [13], and against the ovary, endometrium, nucleus, smooth muscle, cardiolipins, sperm, laminin, and lupus anticoagulant [13]. Antinuclear antibodies (ANAs) in pelvic endometriosis appear to be an immunological secondary effect and do not represent an aggravating factor in patients with pelvic endometriosis [373]. A correlation between the diameter of endometriomas and anti-thyroid peroxidase antibodies has been reported [374]. Patients with endometriosis exhibit elevated transferrin and alpha-2-HS glycoprotein levels in their serum and peritoneal fluid, which may contribute to observed autoimmunity to these proteins [375]. However, no recent reports of these autoantibodies (transferrin and alpha-2-HS glycoprotein) and their impact on the disease exist.

Dotan and coworkers [376] have addressed the issue of SARS-CoV-2 and molecular mimicry in endometriosis. Several other triggers of this process may be observed with viral

or bacterial infection and local or gut microbiota. This topic opens an interesting point to address from the pharmacological point of view, preventing autoimmunity.

IgG and complement deposits have been found in the eutopic endometrium in women with endometriosis, corresponding to a decrease in the total serum complement levels [175]. This may have been caused by the ectopic endometrium acting as a foreign trigger that induced an autoimmune response, resulting in infertility [175]. It is not yet clear whether the formation of autoantibodies in endometriosis is a natural response to chronic local tissue destruction or a pathological reaction leading to more generalized autoimmune dysfunction [175].

A singular report exists regarding the formation of autoantibodies to GM-CSF in individuals diagnosed with deep endometriosis [325]. Nonetheless, it is highly plausible that autoantibodies against additional cytokines are present in patients with endometriosis, considering the unique characteristics of this population. These autoantibodies could significantly impact the equilibrium of cytokines within the microenvironment and may contribute to the diminished immune responsiveness often observed in endometriosis. Further investigation into this subject is essential, as it may facilitate the classification of these patients while also providing new therapeutic targets and guidelines for treatment.

7. Immunological Therapies in Endometriosis

Figure 1 provides an overview of the cells and processes involved in endometriosis to understand the complexity of the endometrial lesion. Multiple factors generate autoimmunity based on cell death; however, the possible induction of malignancy, mainly ovarian carcinoma, is also represented.

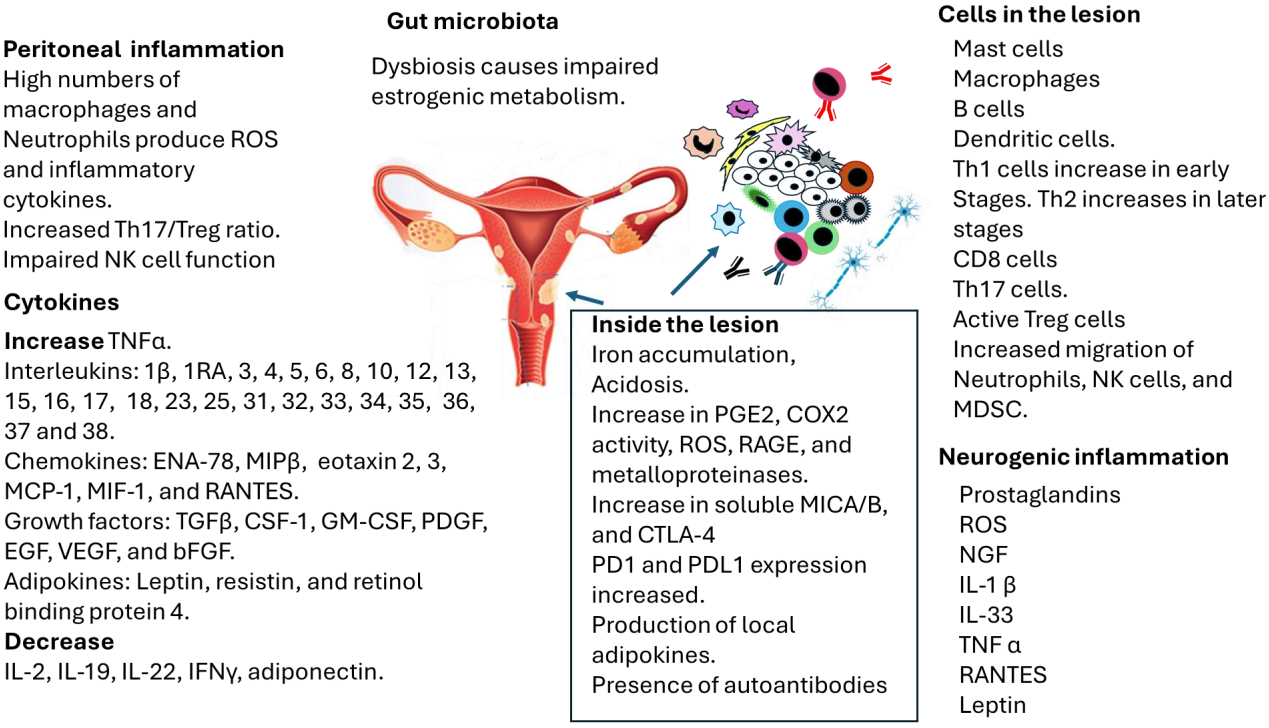

Figure 1. A general summary of endometriosis as discussed in this review.

Endometriosis is typically managed through various therapeutic options, including progestogens, combined oral contraceptives, gonadotropin-releasing hormone antagonists and agonists, androgens, aromatase inhibitors, selective progesterone receptor modulators, selective estrogen receptor modulators, nonsteroidal anti-inflammatory drugs, and/or surgical excision of endometriotic lesions [220,377]. However, many of these treatment

modalities are associated with adverse effects, particularly concerning the degree of hypoestrogenism, and there is a notable risk of recurrence following the cessation of therapy. Considering the significant inflammatory component of endometriosis, recent research has increasingly concentrated on utilizing anti-inflammatory and immunomodulatory therapies. Table 6 summarizes therapies for endometriosis with immunomodulatory and anti-inflammatory effects, ranging from common drug treatments to natural products. On the other hand, Table 7 is focused on cytokine inhibition or addition.

In a recent review, Zhang et al. [378] examined potential therapies targeting immune-associated factors in endometriosis. The objective is to improve the function of NK cells and macrophages. NK cells can be modulated by blocking inhibitory receptors, using cytokines such as IL-2 and IL-12, or through immune checkpoint therapy (anti-PD-1 or anti-PDL-1) [378]. Currently, this type of therapy has not been tested in patients with endometriosis [378]. Regarding macrophages, potential therapeutic targets include the suppression of the M2 phenotype or the activation of the M1 phenotype. These two approaches are lacking in the treatment of endometriosis. Another possible therapy option may be using C3 inhibitors or the blockade of C5a and C3a [378]. Anti-IL-33 antibody treatment of the endometriosis mouse model slightly, but not significantly, reduced peritoneal inflammation and reduced peritoneal cell concentration compared to the isotype control [379].

Combining immunophilin suppressors with steroid hormones, such as progesterone, may be a promising approach to treating chronic inflammation associated with endometriosis. Tacrolimus, cyclosporine, progesterone, and analogs can effectively suppress FKBP51, a common target of these agents [380].

Three different drugs that can block ribosome biogenesis, including inhibitors against mTOR/PI3K (GSK2126458) and RNA polymerase I (CX5461 and BMH21), were used in a mouse model with human endometriosis features [380]. The lesion numbers were reduced in treated mice compared to those treated with the vehicle [380].

Other treatment options include drugs with antiangiogenic effects, such as those targeting VEGF (anti-VEGF antibody) or inhibiting tyrosine kinase (Sorafenib, Sunitinib, Pazopanib) [19]. All the studies with these agents are in animal models. Another drug with antiangiogenic effects through VEGF receptor-2 is cabergoline (a dopamine agonist). In a clinical trial, this drug reduced endometrioma size more effectively than an LHRH agonist [381]. In another small trial, cabergoline decreased pain in patients with endometriosis [382].

Novel therapeutics have been proposed for the management of endometriosis. Iron chelators have demonstrated promising outcomes in animal models [383,384]. Other strategies aim to ameliorate hypoxic conditions. Sitagliptin has been shown to mitigate hypoxia-induced injury by inhibiting the overproduction of COX-2, PGE2, TNF-α, and IL-6, yielding successful results in animal studies [385,386]. The anti-hypoxic agent myo-inositol trispyrophosphate (IPP) enhances oxygen release from hemoglobin and has effectively inhibited the proliferation of endometrial cells in hypoxic conditions in preclinical models [387]. Research has examined the anti-cancer polypeptide vaccine RESAN, which has been shown to reduce lesion size in mouse models [388]. There are no human reports on the efficacy of this vaccine due to the absence of clinical trials. The use of extracellular vesicles to treat endometriosis presents a promising avenue, particularly for the delivery of miRNA [389]; nevertheless, this research domain necessitates further exploration and the establishment of consensus among the scientific community.

An interesting proposal has been published that involves modulating kisspeptin neurons, impacting the hypothalamic–pituitary axis and controlling LH and FSH, and consequently, endometrial growth [390]. Since the modulation of pain may involve sex hormones and the production of endorphins and sensory neurons [391], it would be

interesting to analyze the induction of endorphins as modulators of endometriosis growth in preclinical models. The topic is engaging, and many patients will benefit from therapy. Future research in this area is anticipated to focus on these patients.

Although pharmacological interventions targeting cytokines have not undergone analysis in clinical trials, epidemiological data concerning the efficacy of various inhibitors of TNFα and IL-1β concerning endometriosis and fertility must be examined. Such an examination may unveil novel pathways for both research and therapeutic intervention.

Table 6. Therapies for endometriosis with immunomodulatory and anti-inflammatory effects. Traditional drugs and natural products.

Drug	Effects	References
Glucocorticoids	Inhibit the inflammatory milieu in endometriosis. Prevent the self-renewal, migration, and differentiation of endometrial stem cells and endometriosis formation.	[392–394]
Statins	Statins reduce inflammation and inhibit the formation of new blood vessels, acting as anti-angiogenic agents in the murine model.	[395,396]
	In a pilot study, administering atorvastatin 10 mg daily for 7 days improved nitric oxide-mediated, endothelial-dependent cutaneous microvascular function in women with endometriosis.	[397]
Pentoxifylline	It reduces inflammation by regulating the immune response.	[398]
	There was an increased tendency for pregnancy after surgery in the group treated with pentoxifylline compared to the placebo.	[399]
	Patients who received pentoxifylline showed significantly improved visual analog scale scores after 3 months. There is insufficient evidence to recommend pentoxifylline for the treatment of subfertility and pain related to endometriosis.	[400–402]
Peroxisome proliferator receptor γ (PPARγ) activators	The compounds inhibit cell proliferation, induce apoptosis in endometriotic epithelial and stromal cells, reduce vascularization, and repress VEGF, IL-6, IL-8, and TNF-α gene expression.	[403]
	Ciglitazone decreased the size of ectopic endometriotic tissues in a rat model of endometriosis.	[404]
	In a baboon model of endometriosis, Rosiglitazone decreased the size of the endometriotic lesion. Pioglitazone improved embryo implantation rates in infertile women with endometriosis undergoing IVF by reducing serum RANTES.	[405]
	No clinical trial has been published.	[406]
Rapamycin (mTOR inhibitor)	Rapamycin treatment reduced the volume of lesions in a mouse model of endometriosis.	[407]
	In women with infertility due to endometriosis, rapamycin has improved rates of fertilization, implantation, clinical pregnancy, and live births. More clinical trials are needed to ascertain the possible benefit of rapamycin treatment.	[408]

Table 6. *Cont.*

Drug	Effects	References
Bentamapimod (c-Jun N-terminal kinase inhibitor)	In a mouse and rat model of endometriosis, bentamapimod led to a reduction in lesion size.	[409]
	In baboons with induced endometriosis, bentamapimod decreased the lesions' area and volume. No clinical trial has been published.	[410]
Ligustrazine (Tetramethylpyrazine)	A natural product has demonstrated a broad anti-inflammatory effect in preclinical trials. No clinical trial has been published.	[411]
Resveratrol	Several preclinical trials have published the anti-neoplastic, anti-inflammatory, anti-oxidative, anti-microbial, anti-atherogenic, and anti-angiogenic effects of resveratrol.	[412]
	Prevents the progression of experimental endometriosis in living organisms and reduces the invasiveness of endometrial stromal cells in laboratory tests.	[413]
	Resveratrol reduced MMP-2 and MMP-9 levels in the endometrium and blood of women with endometriosis.	[414]
	Treatment with resveratrol reduced TNF-α2 and VEGF expression in patients with endometriosis.	[415]
	There is not enough evidence to support the use of resveratrol in humans.	[416]
Astaxanthin (antioxidant)	Treatment with astaxanthin reduced serum levels of malondialdehyde, IL-1β, and TNF-α, decreasing IL-6 and TNF-α levels in follicular fluid in one triple-blind placebo-controlled clinical trial of patients undergoing assisted reproduction.	[417]
Curcumin	In ectopic endometrial stromal cells cultured in vitro, it suppresses the TNF-α-induced secretion of IL-6, IL-8, and MCP-1, and the mRNA expression of ICAM-1 and VCAM-1.	[418]
	In eutopic endometrial stromal cells of patients with endometriosis, in vitro treatment inhibits the secretion of IL-6, IL-8, G-CSF, MCP-1, and RANTES.	[419]
	In a small trial involving nano-micellar curcumin, inflammatory and oxidative patterns linked to IVF treatment in patients with endometriosis showed improvement.	[420]
	There is not enough evidence to support the use of curcumin in humans. Well-designed clinical trials are needed.	[421]
Quercetin	Experimental data on quercetin have demonstrated its antioxidant, anti-inflammatory, and anti-angiogenic properties.	[422]
	It decreased the volume of endometriosis lesions in a mouse model. No clinical trials have been published.	[423]

Table 6. *Cont.*

Drug	Effects	References
Epigallocatechin gallate (EGCG)	EGCG notably decreased the proliferation, migration, and invasion of endometrial and endometriotic stromal cells in vitro model of human endometriosis. In mouse models, it also reduced the growth of endometrial lesions. No clinical trials with the purified compound have been published, although trials utilizing green tea have shown some improvement.	[424,425]
N-palmitoyl ethanolamine plus trans-polydatin	It induces anti-inflammatory effects in women with endometriosis. It reduced pelvic pain in women after laparoscopy.	[426]
	A meta-analysis showed no conclusive evidence.	[427]
Cannabidiol	It reduced the diameter, volume, and area of lesions in rat models of endometriosis. It exhibited an anti-fibrotic effect, lowering IL-1β, TNF-α, and PGE2 levels in peritoneal fluids.	[428]
	It alleviated pelvic pain and related symptoms. Long-term use may be linked to cannabis use disorder, psychosis, and mood disturbances. No clinical trials have been published.	[429,430]
Fenretinide (synthetic retinoid)	Fenretinide reduces the levels of retinol fatty acid binding protein 4. It is used in cancer and cystic fibrosis, but there are no clinical trials in patients with endometriosis.	[431–434]
Vitamin D	The effects of vitamin D supplementation have produced controversial results that require further studies.	[435–437]

Table 7. Cytokine-related treatment for endometriosis.

Treatment	Effects	References
Antibody-based (anti-fibronectin F8) pharmacological delivery of interleukin 4 (F8-IL4)	In a mouse model of endometriosis, F8-IL4 reduced the number and volume of lesions while lowering the expression of genes related to cell adhesion, invasion, and neovascularization, such as integrin β1, MMP-3, MMP-9, and VEGF, without affecting inflammatory cytokines. No clinical studies have been performed in humans.	[438]
IL-12	IL-12 enhances cytokine production and increases NK cell activity. An intraperitoneal injection of IL-12 reduced lesion size in a mouse model by activating NK cells and inhibiting the development of endometriotic lesions. No studies have been performed in humans.	[439,440]
Interferon (IFN) I	In a rat model of endometriosis, the subcutaneous administration of IFN-α reduced the volume of endometriosis lesions.	[441]
	IFN-β1a inhibited the in vitro growth and movement of endometrial stromal cells obtained from patients.	[442]
	IFNα2b treatment increased the later recurrence of endometriosis in a small clinical trial.	[443]

Table 7. *Cont.*

Treatment	Effects	References
IL-37	Anti-inflammatory effects. In mouse models, IL-37 reduced the size and weight of endometriotic-like lesions and the expression of IL-1β, IL-6, IL-10, TNF-α, VEGF, and ICAM-1 in a murine model of endometriosis. No studies have been performed in humans.	[444,445]
Anti-TNF-α	In patients with endometriomas who were treated using assisted reproductive technology, etanercept was shown to increase the pregnancy rate and double the live birth rate. However, this result was not statistically significant. (p = 0.052).	[446]
	In a retrospective study, peri-implantation treatment with TNF-α inhibitor increased the implantation rate and clinical pregnancy rate significantly compared with non-treated controls; however, no changes in the pregnancy rate of live birth were observed. Cochrane reviews of humans with endometriosis did not find conclusive evidence.	[447]
	Epidemiological data on young women treated with anti-TNFα therapy and endometriosis incidence have not been published.	[448]
IL-1 antagonist (anakinra)	In a pilot study using anakinra, mild improvements were observed. A reduction in the inflammatory markers BDNF, IL-1RA, and IL-6 was reported.	[449]

8. Conclusions

Endometriosis is an inflammatory disorder characterized by elements of autoimmunity and a reduced state of immune surveillance. This condition is defined by the abnormal proliferation of functional endometrial glands and stroma located outside the uterine cavity, often resulting in significant pain and infertility. The pathogenesis of endometriosis is multifaceted, involving immunological, hormonal, and genetic factors. Cytokines, adipokines, and growth factors are integral components in this process. Furthermore, the ectopic endometrium may display functional properties that differ from the eutopic endometrium. A notable association has been established between endometriosis and ovarian cancer. Autoimmunity is frequently observed in patients diagnosed with endometriosis, and the generation of autoantibodies may be influenced by events occurring within the lesions. Increased iron accumulation, elevated formation of oxygen radicals, and infections (resulting from dysbiotic events within the microbiota) can enhance antigen secretion. Future investigations into molecular mimicry may elucidate the mechanisms underlying the generation of autoimmunity. While anti-inflammatory therapy presents a promising strategy for managing this condition, further clinical studies involving human subjects are necessary to validate its efficacy.

Further epidemiological studies are necessary to investigate the relationship between autoimmunity and endometriosis and to examine the use of immunomodulators among young women to assess the incidence of endometriosis. Additionally, the implementation of cytokine and anti-cytokine therapies in fertility clinics addressing issues such as implantation failure and recurrent miscarriages may yield valuable insights for longitudinal studies and facilitate the development of novel pharmacological treatments for endometriosis.

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References

1. Available online: https://www.who.int/news-room/fact-sheets/detail/endometriosis (accessed on 7 April 2025).
2. Tsamantioti, E.S.; Mahdy, H. Endometriosis. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2025. Available online: https://www.ncbi.nlm.nih.gov/books/NBK567777/ (accessed on 7 May 2025).
3. Smolarz, B.; Szyłło, K.; Romanowicz, H. Endometriosis: Epidemiology, classification, pathogenesis, treatment and genetics. *Int. J. Mol. Sci.* **2021**, *22*, 10554. [CrossRef] [PubMed]
4. Agarwal, S.K.; Chapron, C.; Giudice, L.C.; Laufer, M.R.; Leyland, N.; Missmer, S.A.; Singh, S.S.; Taylor, H.S. Clinical Diagnosis of Endometriosis: A Call to Action. *Am. J. Obstet. Gynecol.* **2019**, *220*, 354.e1–354.e12. [CrossRef] [PubMed]
5. Park, W.; Lim, W.; Kim, M.; Jang, H.; Park, S.J.; Song, G.; Park, S. Female reproductive disease, endometriosis: From inflammation to infertility. *Mol. Cells* **2025**, *48*, 100164. [CrossRef]
6. Simoens, S.; Dunselman, G.; Dirksen, C.; Hummelshoj, L.; Bokor, A.; Brandes, I.; Brodszky, V.; Canis, M.; Colombo, G.L.; DeLeire, T.; et al. The burden of endometriosis: Costs and quality of life of women with endometriosis and treated in referral centres. *Hum. Reprod.* **2012**, *27*, 1292–1299. [CrossRef]
7. Hadfield, R.; Mardon, H.; Barlow, D.; Kennedy, S. Delay in the diagnosis of endometriosis: A survey of women from the USA and the UK. *Hum. Reprod.* **1996**, *11*, 878–880. [CrossRef]
8. Swift, B.; Taneri, B.; Becker, C.M.; Basarir, H.; Naci, H.; Missmer, S.A.; Zondervan, K.T.; Rahmioglu, N. Prevalence, diagnostic delay and economic burden of endometriosis and its impact on quality of life: Results from an Eastern Mediterranean population. *Eur. J. Public Health* **2024**, *34*, 244–252. [CrossRef]
9. Taylor, H.S.; Kotlyar, A.M.; Flores, V.A. Endometriosis is a chronic systemic disease: Clinical challenges and novel innovations. *Lancet* **2021**, *397*, 839–852. [CrossRef]
10. Tariverdian, N.; Siedentopf, F.; Rücke, M.; Blois, S.M.; Klapp, B.F.; Kentenich, H.; Arck, P.C. Intraperitoneal immune cell status in infertile women with and without endometriosis. *J. Reprod. Immunol.* **2009**, *80*, 80–90. [CrossRef]
11. Amidifar, S.; Jafari, D.; Mansourabadi, A.H.; Sadaghian, S.; Esmaeilzadeh, A. Immunopathology of Endometriosis, Molecular Approaches. *Am. J. Reprod. Immunol.* **2025**, *93*, e70056. [CrossRef] [PubMed]
12. Bao, Q.; Zheng, Q.; Wang, S.; Tang, W.; Zhang, B. LncRNA HOTAIR regulates cell invasion and migration in endometriosis through miR-519b-3p/PRRG4 pathway. *Front. Oncol.* **2022**, *12*, 953055. [CrossRef]
13. Blanco, L.P.; Salmeri, N.; Temkin, S.M.; Shanmugam, V.K.; Stratton, P. Endometriosis and autoimmunity. *Autoimmun. Rev.* **2025**, *24*, 103752. [CrossRef] [PubMed]
14. Vercellini, P.; Viganò, P.; Somigliana, E.; Fedele, L. Endometriosis: Pathogenesis and treatment. *Nat. Rev. Endocrinol.* **2014**, *10*, 261–275. [CrossRef] [PubMed]
15. Gordts, S.; Koninckx, P.; Brosens, I. Pathogenesis of deep endometriosis. *Fertil. Steril.* **2017**, *108*, 872–885.e1. [CrossRef]
16. Guan, Y.; Chen, Y.; Lin, R.; Mo, T.; Li, S.; Cao, Y.; Yin, T.; Diao, L.; Li, Y. Endometriosis: A new perspective on epigenetics and oxidative stress. *J. Reprod. Immunol.* **2025**, *169*, 104462. [CrossRef]
17. Laganà, A.S.; Garzon, S.; Götte, M.; Viganò, P.; Franchi, M.; Ghezzi, F.; Martin, D.C. The Pathogenesis of Endometriosis: Molecular and Cell Biology Insights. *Int. J. Mol. Sci.* **2019**, *20*, 5615. [CrossRef]
18. Wang, Y.; Nicholes, K.; Shih, I.M. The Origin and Pathogenesis of Endometriosis. *Annu. Rev. Pathol.* **2020**, *15*, 71–95. [CrossRef]

19. Bo, C.; Wang, Y. Angiogenesis signaling in endometriosis: Molecules, diagnosis and treatment (Review). *Mol. Med. Rep.* **2024**, *29*, 43. [CrossRef]
20. Karimi-Zarchi, M.; Dehshiri-Zadeh, N.; Sekhavat, L.; Nosouhi, F. Correlation of CA-125 serum level and clinico-pathological characteristic of patients with endometriosis. *Int. J. Reprod. Biomed.* **2016**, *14*, 713–718. [CrossRef]
21. Neves, D.; Neto, A.C.; Salazar, M.; Fernandes, A.S.; Martinho, M.; Charrua, A.; Rodrigues, A.R.; Gouveia, A.M.; Almeida, H. A narrative review about the intricate crosstalk among endometrium, adipose tissue, and neurons in endometriosis. The multifaceted role of leptin. *Obes. Rev.* **2025**, *26*, e13879. [CrossRef]
22. Abulughod, N.; Valakas, S.; El-Assaad, F. Dietary and Nutritional Interventions for the Management of Endometriosis. *Nutrients* **2024**, *16*, 3988. [CrossRef]
23. Marquardt, R.M.; Kim, T.H.; Shin, J.H.; Jeong, J.W. Progesterone and Estrogen Signaling in the Endometrium: What Goes Wrong in Endometriosis? *Int. J. Mol. Sci.* **2019**, *20*, 3822. [CrossRef] [PubMed]
24. Lee, D.; Kim, S.K.; Lee, J.R.; Jee, B.C. Management of endometriosis-related infertility: Considerations and treatment options. *Clin. Exp. Reprod. Med.* **2020**, *47*, 1–11. [CrossRef] [PubMed]
25. García-Gómez, E.; Vázquez-Martínez, E.R.; Reyes-Mayoral, C.; Cruz-Orozco, O.P.; Camacho-Arroyo, I.; Cerbón, M. Regulation of Inflammation Pathways and Inflammasome by Sex Steroid Hormones in Endometriosis. *Front. Endocrinol.* **2020**, *10*, 935. [CrossRef]
26. Rolla, E. Endometriosis: Advances and controversies in classification, pathogenesis, diagnosis, and treatment. *F1000Research* **2019**, *8*, F1000-Faculty. [CrossRef]
27. Rocha, T.P.; Andres, M.P.; Carmona, F.; Baracat, E.C.; Abrão, M.S. Deep Endometriosis: The Involvement of Multiple Pelvic Compartments Is Associated with More Severe Pain Symptoms and Infertility. *Reprod. Sci.* **2023**, *30*, 1668–1675. [CrossRef]
28. Camboni, A.; Marbaix, E. Ectopic Endometrium: The Pathologist's Perspective. *Int. J. Mol. Sci.* **2021**, *22*, 10974. [CrossRef]
29. Istrate-Ofiţeru, A.M.; Berbecaru, E.I.; Zorilă, G.L.; Roşu, G.C.; Dîră, L.M.; Comănescu, C.M.; Drăguşin, R.C.; Ruican, D.; Nagy, R.D.; Iliescu, D.G.; et al. Specific Local Predictors That Reflect the Tropism of Endometriosis-A Multiple Immunohistochemistry Technique. *Int. J. Mol. Sci.* **2022**, *23*, 5614. [CrossRef]
30. Moraru, L.; Mitranovici, M.I.; Chiorean, D.M.; Moraru, R.; Caravia, L.; Tirón, A.T.; Cotoi, O.S. Adenomyosis and Its Possible Malignancy: A Review of the Literature. *Diagnostics* **2023**, *13*, 1883. [CrossRef]
31. Li, Q.; Chen, G.; Jiang, H.; Dai, H.; Li, D.; Zhu, K.; Zhang, K.; Shen, H.; Xu, H.; Li, S. ITGB3 promotes cisplatin resistance in osteosarcoma tumors. *Cancer Med.* **2023**, *12*, 8452–8463. [CrossRef]
32. Zhu, C.; Kong, Z.; Wang, B.; Cheng, W.; Wu, A.; Meng, X. ITGB3/CD61: A hub modulator and target in the tumor microenvironment. *Am. J. Transl. Res.* **2019**, *11*, 7195–7208.
33. Zhang, L.; Shao, W.; Li, M.; Liu, S. ITCH-Mediated Ubiquitylation of ITGB3 Promotes Cell Proliferation and Invasion of Ectopic Endometrial Stromal Cells in Ovarian Endometriosis. *Biomedicines* **2023**, *11*, 2506. [CrossRef] [PubMed]
34. Shigesi, N.; Kvaskoff, M.; Kirtley, S.; Feng, Q.; Fang, H.; Knight, J.C.; Missmer, S.A.; Rahmioglu, N.; Zondervan, K.T.; Becker, C.M. The association between endometriosis and autoimmune diseases: A systematic review and meta-analysis. *Hum. Reprod. Update* **2019**, *25*, 486–503. [CrossRef] [PubMed]
35. Zou, M.; Lin, M.; Hu, K.L.; Li, R. Cross-Tissue Regulatory Network Analyses Reveal Novel Susceptibility Genes and Potential Mechanisms for Endometriosis. *Biology* **2024**, *13*, 871. [CrossRef]
36. Wong, F.C.; Kim, C.E.; Garcia-Alonso, L.; Vento-Tormo, R. The human endometrium: Atlases, models, and prospects. *Curr. Opin. Genet. Dev.* **2025**, *92*, 102341. [CrossRef]
37. Sun, Y.; Liu, G. Endometriosis-associated Ovarian Clear Cell Carcinoma: A Special Entity? *J. Cancer* **2021**, *12*, 6773–6786. [CrossRef]
38. Giannini, A.; Massimello, F.; Caretto, M.; Cosimi, G.; Mannella, P.; Luisi, S.; Gadducci, A.; Simoncini, T. Factors in malignant transformation of ovarian endometriosis: A narrative review. *Gynecol. Endocrinol.* **2024**, *40*, 2409911. [CrossRef]
39. Murakami, K.; Kotani, Y.; Nakai, H.; Matsumura, N. Endometriosis-Associated Ovarian Cancer: The Origin and Targeted Therapy. *Cancers* **2020**, *12*, 1676. [CrossRef]
40. Capozzi, V.A.; Scarpelli, E.; dell'Omo, S.; Rolla, M.; Pezzani, A.; Morganelli, G.; Gaiano, M.; Ghi, T.; Berretta, R. Atypical Endometriosis: A Comprehensive Systematic Review of Pathological Patterns and Diagnostic Challenges. *Biomedicines* **2024**, *12*, 1209. [CrossRef]
41. Lei, L.; Xu, X.; Gong, C.; Lin, B.; Li, F. Integrated analysis of genome-wide gene expression and DNA methylation profiles reveals candidate genes in ovary endometriosis. *Front. Endocrinol.* **2023**, *14*, 1093683. [CrossRef]
42. Jung, J.; Kim, N.H.; Park, J.; Lim, D.; Kwon, M.; Gil, W.; Jung, S.; Go, M.; Kim, C.; Cheong, Y.H.; et al. Gremlin-2 is a novel tumor suppressor that negatively regulates ID1 in breast cancer. *Breast Cancer Res.* **2024**, *26*, 174. [CrossRef]
43. Zhai, M.; Yang, W.; Zou, C.; Du, S.; Wu, B.; Wang, C.; Lu, Y.; Zheng, Y. Predictive role of HPGD gene in carcinogenesis and immune environment monitoring in human cervical cancer. *Cancer Biomark. Sect. A Dis. Markers* **2024**, *41*, 18758592241296277. [CrossRef] [PubMed]

44. Xu, X.; Dai, X.; Huang, C.; Guan, X.; Zhang, C. 17beta-estradiol (E2) Regulates Malignancies and Stemness in Endometrial Carcinoma (EC) via Interacting with ESR1. *Reprod. Sci.* **2025**. [CrossRef] [PubMed]
45. Ma, R.; Zheng, Y.; Wang, J.; Xu, H.; Zhang, R.; Xie, Z.; Zhang, L.; Zhao, R. Identification of key genes associated with endometriosis and endometrial cancer by bioinformatics analysis. *Front. Oncol.* **2024**, *14*, 1387860. [CrossRef]
46. Anglesio, M.S.; Bashashati, A.; Wang, Y.K.; Senz, J.; Ha, G.; Yang, W.; Aniba, M.R.; Prentice, L.M.; Farahani, H.; Li Chang, H.; et al. Multifocal endometriotic lesions associated with cancer are clonal and carry a high mutation burden. *J. Pathol.* **2015**, *236*, 201–209. [CrossRef]
47. Wilbur, M.A.; Shih, I.M.; Segars, J.H.; Fader, A.N. Cancer Implications for Patients with Endometriosis. *Semin. Reprod. Med.* **2017**, *35*, 110–116. [CrossRef]
48. Lu, Y.; Cuellar-Partida, G.; Painter, J.N.; Nyholt, D.R.; Australian Ovarian Cancer Study; International Endogene Consortium (IEC). Shared genetics underlying epidemiological association between endometriosis and ovarian cancer. *Hum. Mol. Genet.* **2015**, *24*, 5955–5964. [CrossRef]
49. Parra-Herran, C.; Lerner-Ellis, J.; Xu, B.; Khalouei, S.; Bassiouny, D.; Cesari, M.; Ismiil, N.; Nofech-Mozes, S. Molecular-based classification algorithm for endometrial carcinoma categorizes ovarian endometrioid carcinoma into prognostically significant groups. *Mod. Pathol.* **2017**, *30*, 1748–1759. [CrossRef]
50. Chou, Y.C.; Chen, C.H.; Chen, M.J.; Chang, C.W.; Chen, P.H.; Yu, M.H.; Chen, Y.J.; Tsai, E.M.; Yang, P.S.; Lin, S.Y.; et al. Killer cell immunoglobulin-like receptors (KIR) and human leukocyte antigen-C (HLA-C) allorecognition patterns in women with endometriosis. *Sci. Rep.* **2020**, *10*, 4897. [CrossRef]
51. Marin, M.L.C.; Coelho, V.; Visentainer, J.E.L.; Alves, H.V.; Köhler, K.F.; Rached, M.R.; Abrão, M.S.; Kalil, J. Inhibitory KIR2DL2 Gene: Risk for Deep Endometriosis in Euro-descendants. *Reprod. Sci.* **2021**, *28*, 291–304. [CrossRef]
52. Kitawaki, J.; Xu, B.; Ishihara, H.; Fukui, M.; Hasegawa, G.; Nakamura, N.; Mizuno, S.; Ohta, M.; Obayashi, H.; Honjo, H. Association of killer cell immunoglobulin-like receptor genotypes with susceptibility to endometriosis. *Am. J. Reprod. Immunol.* **2007**, *58*, 481–486. [CrossRef]
53. Kula, H.; Balbal, B.; Timur, T.; Yalcın, P.; Yavuz, O.; Kızıldag, S.; Ulukus, E.C.; Posaci, C. NOD1, NOD2, PYDC1, and PYDC2 gene polymorphisms in ovarian endometriosis. *Front. Med.* **2025**, *11*, 1495002. [CrossRef] [PubMed]
54. Badie, A.; Saliminejad, K.; Salahshourifar, I.; Khorram Khorshid, H.R. Interleukin 1 alpha (IL1A) polymorphisms and risk of endometriosis in Iranian population: A case-control study. *Gynecol. Endocrinol.* **2020**, *36*, 135–138. [CrossRef] [PubMed]
55. Wang, X.Q.; Hu, M.; Chen, J.M.; Sun, W.; Zhu, M.B. Effects of gene polymorphism and serum levels of IL-2 and IL-6 on endometriosis. *Europ. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 4635–4641. [CrossRef]
56. Zhong, S.; Liang, Y.; Wu, Z.; Wei, L. Association between polymorphisms of cytokine genes and endometriosis: A comprehensive systematic review and meta-analysis. *J. Reprod. Immunol.* **2023**, *158*, 103969. [CrossRef]
57. Zhao, W.; Li, Y.; Zhao, J.; Kang, S. A functional promoter polymorphism in interleukin 12B gene is associated with an increased risk of ovarian endometriosis. *Gene* **2018**, *666*, 27–31. [CrossRef]
58. Zare, M.; Hesampour, F.; Poordast, T.; Valibeigi, M.; Enayatmehri, M.; Ahmadi, S.; Nasri, F.; Gharesi-Fard, B. Association between gene polymorphisms of IL-12, IL-12 receptor and IL-27 and organ involvement in Iranian endometriosis patients. *Inter. J. Immun.* **2023**, *50*, 24–33. [CrossRef]
59. Watrowski, R.; Schuster, E.; Van Gorp, T.; Hofstetter, G.; Fischer, M.B.; Mahner, S.; Polterauer, S.; Zeillinger, R.; Obermayr, E. Association of the Single Nucleotide Polymorphisms rs11556218, rs4778889, rs4072111, and rs1131445 of the Interleukin-16 Gene with Ovarian Cancer. *Int. J. Mol. Sci.* **2024**, *25*, 10272. [CrossRef]
60. Babah, O.A.; Ojewunmi, O.O.; Onwuamah, C.K.; Udenze, I.C.; Osuntoki, A.A.; Afolabi, B.B. Serum concentrations of IL-16 and its genetic polymorphism rs4778889 affect the susceptibility and severity of endometriosis in Nigerian women. *BMC Women's Health* **2023**, *23*, 253. [CrossRef]
61. Xie, Z.; Ding, X.; Wang, Y.; Zhang, M. The rs2275913 polymorphism of the interleukin-17A gene is associated with the risk of ovarian endometriosis. *J. Obstet. Gynaecol.* **2023**, *43*, 2199852. [CrossRef]
62. Balunathan, N.; Rani, G.U.; Perumal, V.; Kumarasamy, P. Single nucleotide polymorphisms of Interleukin -4, Interleukin-18, FCRL3 and sPLA2IIa genes and their association in pathogenesis of endometriosis. *Mol. Biol. Rep.* **2023**, *50*, 4239–4252. [CrossRef]
63. Mier-Cabrera, J.; Cruz-Orozco, O.; de la Jara-Díaz, J.; Galicia-Castillo, O.; Buenrostro-Jáuregui, M.; Parra-Carriedo, A.; Hernández-Guerrero, C. Polymorphisms of TNF-alpha (−308), IL-1beta (+3954) and IL1-Ra (VNTR) are associated to severe stage of endometriosis in Mexican women: A case control study. *BMC Women's Health* **2022**, *22*, 356. [CrossRef] [PubMed]
64. Chekini, Z.; Poursadoughian Yaran, A.; Ansari-Pour, N.; Shahhoseini, M.; Ramazanali, F.; Aflatoonian, R.; Afsharian, P. A novel gene-wide haplotype at the macrophage migration inhibitory factor (MIF) locus is associated with endometrioma. *Europ. J. Obst. Gynecol. Reprod. Biol.* **2020**, *247*, 6–9. [CrossRef] [PubMed]
65. Cardoso, J.V.; Machado, D.E.; da Silva, M.C.; de Mello, M.P.; Berardo, P.T.; Medeiros, R.; Perini, J.A. Influence of interleukin-8 polymorphism on endometriosis-related pelvic pain. *Hum. Immunol.* **2023**, *84*, 561–566. [CrossRef]

66. Le, K.N.; Benor, A.; Decherney, A. An update on epigenetic mechanisms in endometriosis. *Minerva Obstet. Gynecol.* **2024**. [CrossRef]
67. Bulun, S.E.; Yilmaz, B.D.; Sison, C.; Miyazaki, K.; Bernardi, L.; Liu, S.; Kohlmeier, A.; Yin, P.; Milad, M.; Wei, J. Endometriosis. *Endocr. Rev.* **2019**, *40*, 1048–1079. [CrossRef]
68. Raja, M.H.R.; Farooqui, N.; Zuberi, N.; Ashraf, M.; Azhar, A.; Baig, R.; Badar, B.; Rehman, R. Endometriosis, infertility and MicroRNA's: A review. *J. Gynecol. Obstet. Hum. Reprod.* **2021**, *50*, 102157. [CrossRef]
69. Hon, J.X.; Wahab, N.A.; Karim, A.K.A.; Mokhtar, N.M.; Mokhtar, M.H. MicroRNAs in Endometriosis: Insights into Inflammation and Progesterone Resistance. *Int. J. Mol. Sci.* **2023**, *24*, 15001. [CrossRef]
70. Azari, Z.D.; Aljubran, F.; Nothnick, W.B. Inflammatory MicroRNAs and the Pathophysiology of Endometriosis and Atherosclerosis: Common Pathways and Future Directions Towards Elucidating the Relationship. *Reprod. Sci.* **2022**, *29*, 2089–2104. [CrossRef]
71. Liao, Z.; Tang, S.; Jiang, P.; Geng, T.; Cope, D.I.; Dunn, T.N.; Guner, J.; Radilla, L.A.; Guan, X.; Monsivais, D. Impaired bone morphogenetic protein (BMP) signaling pathways disrupt decidualization in endometriosis. *Commun. Biol.* **2024**, *7*, 227. [CrossRef]
72. Abbaszadeh, M.; Karimi, M.; Rajaei, S. The landscape of non-coding RNAs in the immunopathogenesis of Endometriosis. *Front. Immunol.* **2023**, *14*, 1223828. [CrossRef]
73. González-Ramos, R.; Van Langendonckt, A.; Defrère, S.; Lousse, J.C.; Colette, S.; Devoto, L.; Donnez, J. Involvement of the nuclear factor-κB pathway in the pathogenesis of endometriosis. *Fertil. Steril.* **2010**, *94*, 1985–1994. [CrossRef] [PubMed]
74. Zdrojkowski, Ł.; Jasiński, T.; Ferreira-Dias, G.; Pawliński, B.; Domino, M. The Role of NF-κB in Endometrial Diseases in Humans and Animals: A Review. *Int. J. Mol. Sci.* **2023**, *24*, 2901. [CrossRef] [PubMed]
75. Vissers, G.; Giacomozzi, M.; Verdurmen, W.; Peek, R.; Nap, A. The role of fibrosis in endometriosis: A systematic review. *Hum. Reprod. Update* **2024**, *30*, 706–750. [CrossRef]
76. Anchan, M.M.; Kalthur, G.; Datta, R.; Majumdar, K.P.K.; Dutta, R. Unveiling the fibrotic puzzle of endometriosis: An overlooked concern calling for prompt action. *F1000Research* **2024**, *13*, 721. [CrossRef]
77. Almquist, L.D.; Likes, C.E.; Stone, B.; Brown, K.R.; Savaris, R.; Forstein, D.A.; Miller, P.B.; Lessey, B.A. Endometrial BCL6 testing for the prediction of in vitro fertilisation outcomes: A cohort study. *Fertil. Steril.* **2017**, *108*, 1063–1069. [CrossRef]
78. Saadat Varnosfaderani, A.; Kalantari, S.; Ramezanali, F.; Shahhoseini, M.; Amirchaghmaghi, E. Increased Gene Expression of LITAF, TNF-α and BCL6 in Endometrial Tissues of Women with Endometriosis: A Case-Control Study. *Cell J.* **2024**, *26*, 243–249. [CrossRef]
79. Wang, Z.; Guo, S.; Xie, Y.; Tong, Y.; Qi, W.; Wang, Z. Endometrial expression of ERRβ and ERRγ: Prognostic significance and clinical correlations in severe endometriosis. *Front. Endocrinol.* **2024**, *15*, 1489097. [CrossRef]
80. Cheng, C.W.; Licence, D.; Cook, E.; Luo, F.; Arends, M.J.; Smith, S.K.; Print, C.G.; Charnock-Jones, D.S. Activation of mutated K-ras in donor endometrial epithelium and stroma promotes lesion growth in an intact immunocompetent murine model of endometriosis. *J. Pathol.* **2011**, *224*, 261–269. [CrossRef]
81. Maeda, D.; Shih, I.-M. Pathogenesis and the role of ARID1A mutation in endometriosis-related ovarian neoplasms. *Adv. Anat. Pathol.* **2013**, *20*, 45–52. [CrossRef]
82. Steinbuch, S.C.; Lüß, A.M.; Eltrop, S.; Götte, M.; Kiesel, L. Endometriosis-Associated Ovarian Cancer: From Molecular Pathologies to Clinical Relevance. *Int. J. Mol. Sci.* **2024**, *25*, 4306. [CrossRef]
83. Pan, Y.; Pan, C.; Zhang, C. Unraveling the complexity of follicular fluid: Insights into its composition, function, and clinical implications. *J. Ovarian Res.* **2024**, *17*, 237. [CrossRef] [PubMed]
84. Wagner, M.; Hicks, C.; El-Omar, E.; Combes, V.; El-Assaad, F. The Critical Role of Host and Bacterial Extracellular Vesicles in Endometriosis. *Biomedicines* **2024**, *12*, 2585. [CrossRef] [PubMed]
85. Duval, C.; Wyse, B.A.; Tsang, B.K.; Librach, C.L. Extracellular vesicles and their content in the context of polycystic ovarian syndrome and endometriosis: A review. *J. Ovarian Res.* **2024**, *17*, 160. [CrossRef]
86. Nazri, H.M.; Imran, M.; Fischer, R.; Heilig, R.; Manek, S.; Dragovic, R.A.; Kessler, B.M.; Zondervan, K.T.; Tapmeier, T.T.; Becker, C.M. Characterization of exosomes in peritoneal fluid of endometriosis patients. *Fertil. Steril.* **2020**, *113*, 364–373.e2. [CrossRef]
87. Björk, E.; Israelsson, P.; Nagaev, I.; Nagaeva, O.; Lundin, E.; Ottander, U.; Mincheva-Nilsson, L. Endometriotic Tissue-derived Exosomes Downregulate NKG2D-mediated Cytotoxicity and Promote Apoptosis: Mechanisms for Survival of Ectopic Endometrial Tissue in Endometriosis. *J. Immunol.* **2024**, *213*, 567–576. [CrossRef]
88. Ding, D.; Liu, X.; Duan, J.; Guo, S.W. Platelets are an unindicted culprit in the development of endometriosis: Clinical and experimental evidence. *Hum. Reprod.* **2015**, *30*, 812–832. [CrossRef]
89. Bortot, B.; Di Florio, R.; Merighi, S.; Peacock, B.; Lees, R.; Valle, F.; Brucale, M.; Mangogna, A.; Di Lorenzo, G.; Romano, F.; et al. Platelets as key cells in endometriosis patients: Insights from small extracellular vesicles in peritoneal fluid and endometriotic lesions analysis. *FASEB J.* **2024**, *38*, e70267. [CrossRef]

90. Ding, S.; Lin, Q.; Zhu, T.; Li, T.; Zhu, L.; Wang, J.; Zhang, X. Is there a correlation between inflammatory markers and coagulation parameters in women with advanced ovarian endometriosis? *BMC Women's Health* **2019**, *19*, 169. [CrossRef]
91. Dantzler, M.D.; Miller, T.A.; Dougherty, M.W.; Quevedo, A. The Microbiome Landscape of Adenomyosis: A Systematic Review. *Reprod. Sci.* **2025**, *32*, 251–260. [CrossRef]
92. Guo, W.; Xu, Z.; Hu, S.; Shen, Y. Exploring Microbial Signatures in Endometrial Tissues with Endometriosis. *Int. Immunopharmacol.* **2025**, *148*, 114072. [CrossRef]
93. Qin, R.; Tian, G.; Liu, J.; Cao, L. The gut microbiota and endometriosis: From pathogenesis to diagnosis and treatment. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 1069557. [CrossRef] [PubMed]
94. Escorcia Mora, P.; Valbuena, D.; Diez-Juan, A. The Role of the Gut Microbiota in Female Reproductive and Gynecological Health: Insights into Endometrial Signaling Pathways. *Life* **2025**, *15*, 762. [CrossRef] [PubMed]
95. Hu, S.; Ding, Q.; Zhang, W.; Kang, M.; Ma, J.; Zhao, L. Gut microbial beta-glucuronidase: A vital regulator in female estrogen metabolism. *Gut Microbes* **2023**, *15*, 2236749. [CrossRef]
96. Baker, J.M.; Al-Nakkash, L.; Herbst-Kralovetz, M.M. Estrogen-gut microbiome axis: Physiological and clinical implications. *Maturitas* **2017**, *103*, 45–53. [CrossRef]
97. Chen, C.; Song, X.; Wei, W.; Zhong, H.; Dai, J.; Lan, Z.; Li, F.; Yu, X.; Feng, Q.; Wang, Z.; et al. The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. *Nat. Commun.* **2017**, *8*, 875. [CrossRef]
98. Wei, W.; Zhang, X.; Tang, H.; Zeng, L.; Wu, R. Microbiota composition and distribution along the female reproductive tract of women with endometriosis. *Ann. Clin. Microbiol. Antimicrob.* **2020**, *19*, 15. [CrossRef]
99. Ata, B.; Yildiz, S.; Turkgeldi, E.; Brocal, V.P.; Dinleyici, E.C.; Moya, A.; Urman, B. The Endobiota Study: Comparison of Vaginal, Cervical and Gut Microbiota Between Women with Stage 3/4 Endometriosis and Healthy Controls. *Sci. Rep.* **2019**, *9*, 2204. [CrossRef]
100. Huang, L.; Liu, B.; Liu, Z.; Feng, W.; Liu, M.; Wang, Y.; Peng, D.; Fu, X.; Zhu, H.; Cui, Z.; et al. Gut Microbiota Exceeds Cervical Microbiota for Early Diagnosis of Endometriosis. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 788836. [CrossRef]
101. Svensson, A.; Brunkwall, L.; Roth, B.; Orho-Melander, M.; Ohlsson, B. Associations Between Endometriosis and Gut Microbiota. *Reprod. Sci.* **2021**, *28*, 2367–2377. [CrossRef]
102. Shan, J.; Ni, Z.; Cheng, W.; Zhou, L.; Zhai, D.; Sun, S.; Yu, C. Gut microbiota imbalance and its correlations with hormone and inflammatory factors in patients with stage 3/4 endometriosis. *Arch. Gynecol. Obstet.* **2021**, *304*, 1363–1373. [CrossRef]
103. Ye, H.; Tian, Y.; Yu, X.; Li, L.; Hou, M. Association Between Pelvic Inflammatory Disease and Risk of Endometriosis: A Systematic Review and Meta-Analysis. *J. Women's Health* **2024**, *33*, 73–79. [CrossRef] [PubMed]
104. Garmendia, J.V.; De Sanctis, C.V.; Hajdúch, M.; De Sanctis, J.B. Microbiota and Recurrent Pregnancy Loss (RPL); More than a Simple Connection. *Microorganisms* **2024**, *12*, 1641. [CrossRef] [PubMed]
105. Sobstyl, A.; Chałupnik, A.; Mertowska, P.; Grywalska, E. How Do Microorganisms Influence the Development of Endometriosis? Participation of Genital, Intestinal and Oral Microbiota in Metabolic Regulation and Immunopathogenesis of Endometriosis. *Int. J. Mol. Sci.* **2023**, *24*, 10920. [CrossRef]
106. Leonardi, M.; Hicks, C.; El-Assaad, F.; El-Omar, E.; Condous, G. Endometriosis and the microbiome: A systematic review. *BJOG Int. J. Obstet. Gynaecol.* **2020**, *127*, 239–249. [CrossRef]
107. Jimenez, N.; Norton, T.; Diadala, G.; Bell, E.; Valenti, M.; Farland, L.V.; Mahnert, N.; Herbst-Kralovetz, M.M. Vaginal and rectal microbiome contribute to genital inflammation in chronic pelvic pain. *BMC Med.* **2024**, *22*, 283. [CrossRef]
108. Guo, C.; Zhang, C. Role of the gut microbiota in the pathogenesis of endometriosis: A review. *Front. Microbiol.* **2024**, *15*, 1363455. [CrossRef]
109. Brubaker, S.W.; Bonham, K.S.; Zanoni, I.; Kagan, J.C. Innate immune pattern recognition: A cell biological perspective. *Annu. Rev. Immunol.* **2015**, *33*, 257–290. [CrossRef]
110. Guo, B.; Chen, J.H.; Zhang, J.H.; Fang, Y.; Liu, X.J.; Zhang, J.; Zhu, H.Q.; Zhan, L. Pattern-recognition receptors in endometriosis: A narrative review. *Front. Immunol.* **2023**, *14*, 1161606. [CrossRef]
111. Zhang, Q.; Yang, D.; Han, X.; Ren, Y.; Fan, Y.; Zhang, C.; Sun, L.; Ye, T.; Wang, Q.; Ban, Y.; et al. Alarmins and their pivotal role in the pathogenesis of spontaneous abortion: Insights for therapeutic intervention. *Eur. J. Med. Res.* **2024**, *29*, 640. [CrossRef]
112. Chen, F.; Tang, H.; Cai, X.; Lin, J.; Kang, R.; Tang, D.; Liu, J. DAMPs in immunosenescence and cancer. *Semin. Cancer Biol.* **2024**, *106–107*, 123–142. [CrossRef]
113. Kobayashi, H.; Higashiura, Y.; Shigetomi, H.; Kajihara, H. Pathogenesis of endometriosis: The role of initial infection and subsequent sterile inflammation (Review). *Mol. Med. Rep.* **2014**, *9*, 9–15. [CrossRef] [PubMed]
114. Sobstyl, M.; Niedźwiedzka-Rystwej, P.; Grywalska, E.; Korona-Głowniak, I.; Sobstyl, A.; Bednarek, W.; Roliński, J. Toll-Like Receptor 2 Expression as a New Hallmark of Advanced Endometriosis. *Cells* **2020**, *9*, 1813. [CrossRef] [PubMed]
115. Noh, E.J.; Kim, D.J.; Lee, J.Y.; Park, J.H.; Kim, J.S.; Han, J.W.; Kim, B.C.; Kim, C.J.; Lee, S.K. Ureaplasma Urealyticum Infection Contributes to the Development of Pelvic Endometriosis Through Toll-Like Receptor 2. *Front. Immunol.* **2019**, *10*, 2373. [CrossRef]

116. de Azevedo, B.C.; Mansur, F.; Podgaec, S. systematic review of toll-like receptors in endometriosis. *Arch. Gynecol. Obstet.* **2021**, *304*, 309–316. [CrossRef]
117. Almasi, M.Z.; Hosseini, E.; Jafari, R.; Aflatoonian, K.; Aghajanpour, S.; Ramazanali, F.; Moini, A.; Shahhoseini, M.; Afsharian, P.; Aflatoonian, R. Evaluation of Toll-like receptor 3 (TLR3) signaling pathway genes and its genetic polymorphisms in ectopic and eutopic endometrium of women with endometriosis. *J. Gynecol. Obstet. Hum. Reprod.* **2021**, *50*, 102153. [CrossRef]
118. Allhorn, S.; Böing, C.; Koch, A.A.; Kimmig, R.; Gashaw, I. TLR3 and TLR4 expression in healthy and diseased human endometrium. *Reprod. Biol. Endocrinol.* **2008**, *6*, 40. [CrossRef]
119. Zheng, D.; Liwinski, T.; Elinav, E. Inflammasome activation and regulation: Toward a better understanding of complex mechanisms. *Cell Discov.* **2020**, *6*, 36. [CrossRef]
120. Al Mamun, A.; Geng, P.; Wang, S.; Shao, C. Role of Pyroptosis in Endometrial Cancer and Its Therapeutic Regulation. *J. Inflamm. Res.* **2024**, *17*, 7037–7056. [CrossRef]
121. Irandoost, E.; Najibi, S.; Talebbeigi, S.; Nassiri, S. Focus on the role of NLRP3 inflammasome in the pathology of endometriosis: A review on molecular mechanisms and possible medical applications. *Naunyn Schmiedeberg's Arch. Pharmacol.* **2023**, *396*, 621–631. [CrossRef]
122. Ahn, S.H.; Khalaj, K.; Young, S.L.; Lessey, B.A.; Koti, M.; Tayade, C. Immune-inflammation gene signatures in endometriosis patients. *Fertil. Steril.* **2016**, *106*, 1420–1431.e7. [CrossRef]
123. Fonseca, B.M.; Pinto, B.; Costa, L.; Felgueira, E.; Rebelo, I. Increased expression of NLRP3 inflammasome components in granulosa cells and follicular fluid interleukin(IL)-1beta and IL-18 levels in fresh IVF/ICSI cycles in women with endometriosis. *J. Assist. Reprod. Genet.* **2023**, *40*, 191–199. [CrossRef] [PubMed]
124. Murakami, M.; Osuka, S.; Muraoka, A.; Hayashi, S.; Bayasula; Kasahara, Y.; Sonehara, R.; Hariyama, Y.; Shinjo, K.; Tanaka, H.; et al. Effectiveness of NLRP3 Inhibitor as a Non-Hormonal Treatment for ovarian endometriosis. *Reprod. Biol. Endocrinol.* **2022**, *20*, 58. [CrossRef] [PubMed]
125. Liu, Y.; Jiang, Z.; Zhang, L.; Tian, W.; Lin, A.; Li, M. Blockage of the NLRP3 inflammasome by MCC950 inhibits migration and invasion in adenomyosis. *Reprod. Biomed. Online* **2024**, *49*, 104319. [CrossRef]
126. Zhang, M.; Shi, Z.; Peng, X.; Cai, D.; Peng, R.; Lin, Y.; Dai, L.; Li, J.; Chen, Y.; Xiao, J.; et al. NLRP3 inflammasome-mediated Pyroptosis induce Notch signal activation in endometriosis angiogenesis. *Mol. Cell. Endocrinol.* **2023**, *574*, 111952. [CrossRef]
127. Zhou, F.; Zhao, F.; Huang, Q.; Lin, X.; Zhang, S.; Dai, Y. NLRP3 activated macrophages promote endometrial stromal cells migration in endometriosis. *J. Reprod. Immunol.* **2022**, *152*, 103649. [CrossRef]
128. Bergqvist, A.; Bruse, C.; Carlberg, M.; Carlström, K. Interleukin 1beta, interleukin-6, and tumor necrosis factor-alpha in endometriotic tissue and in endometrium. *Fertil. Steril.* **2001**, *75*, 489–495. [CrossRef]
129. Xu, Y.; Liu, H.; Xiong, W.; Peng, Y.; Li, X.; Long, X.; Jin, J.; Liang, J.; Weng, R.; Liu, J.; et al. A novel mechanism regulating pyroptosis-induced fibrosis in endometriosis via lnc-MALAT1/miR-141-3p/NLRP3 pathway. *Biol. Reprod.* **2023**, *109*, 156–171. [CrossRef]
130. An, M.; Fu, X.; Meng, X.; Liu, H.; Ma, Y.; Li, Y.; Li, Q.; Chen, J. PI3K/AKT signaling pathway associates with pyroptosis and inflammation in patients with endometriosis. *J. Reprod. Immunol.* **2024**, *162*, 104213. [CrossRef]
131. Hang, Y.; Tan, L.; Chen, Q.; Liu, Q.; Jin, Y. E3 ubiquitin ligase TRIM24 deficiency promotes NLRP3/caspase-1/IL-1β-mediated pyroptosis in endometriosis. *Cell Biol. Int.* **2021**, *45*, 1561–1570. [CrossRef]
132. Han, S.J.; Jung, S.Y.; Wu, S.P.; Hawkins, S.M.; Park, M.J.; Kyo, S.; Lydon, J.P.; Tsai, S.Y.; Tsai, M.J.; DeMayo, F.J.; et al. Estrogen Receptor β Modulates Apoptosis Complexes and the Inflammasome to Drive the Pathogenesis of Endometriosis. *Cell* **2015**, *163*, 960–974. [CrossRef]
133. Choi, J.; Jo, M.; Lee, E.; Kim, S.E.; Lee, D.Y.; Choi, D. Inhibition of the NLRP3 inflammasome by progesterone is attenuated by abnormal autophagy induction in endometriotic cyst stromal cells: Implications for endometriosis. *Mol. Hum. Reprod.* **2022**, *28*, gaac007. [CrossRef]
134. Guo, B.; Zhu, H.; Xiao, C.; Zhang, J.; Liu, X.; Fang, Y.; Wei, B.; Zhang, J.; Cao, Y.; Zhan, L. NLRC5 exerts anti-endometriosis effects through inhibiting ERβ-mediated inflammatory response. *BMC Med.* **2024**, *22*, 351. [CrossRef] [PubMed]
135. Zhan, L.; Yao, S.; Sun, S.; Su, Q.; Li, J.; Wei, B. NLRC5 and autophagy combined as possible predictors in patients with endometriosis. *Fertil. Steril.* **2018**, *110*, 949–956. [CrossRef] [PubMed]
136. He, R.; Liu, X.; Zhang, J.; Wang, Z.; Wang, W.; Fu, L.; Fan, Y.; Sun, S.; Cao, Y.; Zhan, L.; et al. NLRC5 Inhibits Inflammation of Secretory Phase Ectopic Endometrial Stromal Cells by Up-Regulating Autophagy in Ovarian Endometriosis. *Front. Pharmacol.* **2020**, *11*, 1281. [CrossRef]
137. Yeo, S.G.; Won, Y.S.; Kim, S.H.; Park, D.C. Differences in C-type lectin receptors and their adaptor molecules in the peritoneal fluid of patients with endometriosis and gynecologic cancers. *Int. J. Med. Sci.* **2018**, *15*, 411–416. [CrossRef]
138. Izumi, G.; Koga, K.; Takamura, M.; Makabe, T.; Nagai, M.; Urata, Y.; Harada, M.; Hirata, T.; Hirota, Y.; Fujii, T.; et al. Mannose receptor is highly expressed by peritoneal dendritic cells in endometriosis. *Fertil. Steril.* **2017**, *107*, 167–173.e2. [CrossRef]

139. Wei, C.; Mei, J.; Tang, L.; Liu, Y.; Li, D.; Li, M.; Zhu, X. 1-Methyl-tryptophan attenuates regulatory T cells differentiation due to the inhibition of estrogen-IDO1-MRC2 axis in endometriosis. *Cell Death Dis.* **2016**, *7*, e2489. [CrossRef]
140. Sopasi, F.; Spyropoulou, I.; Kourti, M.; Vasileiadis, S.; Tripsianis, G.; Galazios, G.; Koutlaki, N. Oxidative stress and female infertility: The role of follicular fluid soluble receptor of advanced glycation end-products (sRAGE) in women with endometriosis. *Hum. Fertil.* **2023**, *26*, 1400–1407. [CrossRef]
141. Ajona, D.; Cragg, M.S.; Pio, R. The complement system in clinical oncology: Applications, limitations and challenges. *Semin. Immunol.* **2024**, *77*, 101921. [CrossRef]
142. Mastellos, D.C.; Hajishengallis, G.; Lambris, J.D. A guide to complement biology, pathology and therapeutic opportunity. *Nat. Rev. Immunol.* **2024**, *24*, 118–141. [CrossRef]
143. Zeller, J.M.; Henig, I.; Radwanska, E.; Dmowski, W.P. Enhancement of human monocyte and peritoneal macrophage chemiluminescence activities in women with endometriosis. *Am. J. Reprod. Immunol. Microbiol.* **1987**, *13*, 78–82. [CrossRef] [PubMed]
144. Lousse, J.C.; Defrère, S.; Van Langendonckt, A.; Gras, J.; González-Ramos, R.; Colette, S.; Donnez, J. Iron storage is significantly increased in peritoneal macrophages of endometriosis patients and correlates with iron overload in peritoneal fluid. *Fertil. Steril.* **2009**, *91*, 1668–1675. [CrossRef] [PubMed]
145. Chen, S.; Liu, Y.; Zhong, Z.; Wei, C.; Liu, Y.; Zhu, X. Peritoneal immune microenvironment of endometriosis: Role and therapeutic perspectives. *Front. Immunol.* **2023**, *14*, 1134663. [CrossRef]
146. Lousse, J.C.; Van Langendonckt, A.; González-Ramos, R.; Defrère, S.; Renkin, E.; Donnez, J. Increased activation of nuclear factor-kappa B (NF-kappaB) in isolated peritoneal macrophages of patients with endometriosis. *Fertil. Steril.* **2008**, *90*, 217–220. [CrossRef]
147. Wu, M.H.; Sun, H.S.; Lin, C.C.; Hsiao, K.Y.; Chuang, P.C.; Pan, H.A.; Tsai, S.J. Distinct mechanisms regulate cyclooxygenase-1 and -2 in peritoneal macrophages of women with and without endometriosis. *Mol. Hum. Reprod.* **2002**, *8*, 1103–1110. [CrossRef]
148. Lai, Z.Z.; Yang, H.L.; Ha, S.Y.; Chang, K.K.; Mei, J.; Zhou, W.J.; Qiu, X.M.; Wang, X.Q.; Zhu, R.; Li, D.J.; et al. Cyclooxygenase-2 in Endometriosis. *Int. J. Biol. Sci.* **2019**, *15*, 2783–2797. [CrossRef]
149. Chan, R.W.S.; Lee, C.L.; Ng, E.H.Y.; Yeung, W.S.B. Co-culture with macrophages enhances the clonogenic and invasion activity of endometriotic stromal cells. *Cell Prolif.* **2017**, *50*, e12330. [CrossRef]
150. Harada, T.; Kaponis, A.; Iwabe, T.; Taniguchi, F.; Makrydimas, G.; Sofikitis, N.; Paschopoulos, M.; Paraskevaidis, E.; Terakawa, N. Apoptosis in human endometrium and endometriosis. *Hum. Reprod. Update* **2004**, *10*, 29–38. [CrossRef]
151. Huang, E.; Wang, X.; Chen, L. Regulated Cell Death in Endometriosis. *Biomolecules* **2024**, *14*, 142. [CrossRef]
152. Capobianco, A.; Rovere-Querini, P. Endometriosis, a disease of the macrophage. *Front. Immunol.* **2013**, *4*, 9. [CrossRef]
153. Vallvé-Juanico, J.; Santamaria, X.; Vo, K.C.; Houshdaran, S.; Giudice, L.C. Macrophages display proinflammatory phenotypes in the eutopic endometrium of women with endometriosis with relevance to an infectious etiology of the disease. *Fertil. Steril.* **2019**, *112*, 1118–1128. [CrossRef] [PubMed]
154. Hudson, Q.J.; Ashjaei, K.; Perricos, A.; Kuessel, L.; Husslein, H.; Wenzl, R.; Yotova, I. Endometriosis Patients Show an Increased M2 Response in the Peritoneal CD14+low/CD68+low Macrophage Subpopulation Coupled with an Increase in the T-helper 2 and T-regulatory Cells. *Reprod. Sci.* **2020**, *27*, 1920–1931. [CrossRef] [PubMed]
155. Henlon, Y.; Panir, K.; McIntyre, I.; Hogg, C.; Dhami, P.; Cuff, A.O.; Senior, A.; Moolchandani-Adwani, N.; Courtois, E.T.; Horne, A.W.; et al. Single-cell analysis identifies distinct macrophage phenotypes associated with prodisease and proresolving functions in the endometriotic niche. *Proc. Natl. Acad. Sci. USA* **2024**, *121*, e2405474121. [CrossRef]
156. Laganà, A.S.; Salmeri, F.M.; Ban Frangež, H.; Ghezzi, F.; Vrtačnik-Bokal, E.; Granese, R. Evaluation of M1 and M2 macrophages in ovarian endometriomas from women affected by endometriosis at different stages of the disease. *Gynecol. Endocrinol.* **2020**, *36*, 441–444. [CrossRef]
157. Duan, J.; Liu, X.; Wang, H.; Guo, S.W. The M2a macrophage subset may be critically involved in the fibrogenesis of endometriosis in mice. *Reprod. Biomed. Online* **2018**, *37*, 254–268. [CrossRef]
158. Viganò, P.; Ottolina, J.; Bartiromo, L.; Bonavina, G.; Schimberni, M.; Villanacci, R.; Candiani, M. Cellular Components Contributing to Fibrosis in Endometriosis: A Literature Review. *J. Minim. Invasive Gynecol.* **2020**, *27*, 287–295. [CrossRef]
159. Garmendia, J.V.; De Sanctis, J.B. A Brief Analysis of Tissue-Resident NK Cells in Pregnancy and Endometrial Diseases: The Importance of Pharmacologic Modulation. *Immuno* **2021**, *1*, 174–193. [CrossRef]
160. Giuliani, E.; Parkin, K.L.; Lessey, B.A.; Young, S.L.; Fazleabas, A.T. Characterisation of uterine NK cells in women with infertility or recurrent pregnancy loss and associated endometriosis. *Am. J. Reprod. Immunol.* **2014**, *72*, 262–269. [CrossRef]
161. Garmendia, J.V.; De Sanctis, C.V.; Hajdúch, M.; De Sanctis, J.B. Exploring the Immunological Aspects and Treatments of Recurrent Pregnancy Loss and Recurrent Implantation Failure. *Int. J. Mol. Sci.* **2025**, *26*, 1295. [CrossRef]
162. Makoui, M.H.; Fekri, S.; Makoui, R.H.; Ansari, N.; Esmaeilzadeh, A. The Role of Mast Cells in the Development and Advancement of Endometriosis. *Am. J. Reprod. Immunol.* **2025**, *93*, e70019. [CrossRef]
163. Suszczyk, D.; Skiba, W.; Jakubowicz-Gil, J.; Kotarski, J.; Wertel, I. The Role of Myeloid-Derived Suppressor Cells (MDSCs) in the Development and/or Progression of Endometriosis-State of the Art. *Cells* **2021**, *10*, 677. [CrossRef] [PubMed]

164. Zhang, T.; He, Y.; Man, G.C.W.; Ding, Y.; Wang, C.C.; Chung, J.P.W. Myeloid-derived suppressor cells: A new emerging player in endometriosis. *Int. Rev. Cell Mol. Biol.* **2023**, *375*, 191–220. [CrossRef] [PubMed]
165. Satake, E.; Koga, K.; Takamura, M.; Izumi, G.; Elsherbini, M.; Taguchi, A.; Makabe, T.; Takeuchi, A.; Harada, M.; Hirata, T.; et al. The roles of polymorphonuclear myeloid-derived suppressor cells in endometriosis. *J. Reprod. Immunol.* **2021**, *148*, 103371. [CrossRef]
166. Chen, H.; Qin, S.; Lei, A.; Li, X.; Gao, Q.; Dong, J.; Xiao, Q.; Zhou, J. Expansion of monocytic myeloid-derived suppressor cells in endometriosis patients: A pilot study. *Int. Immunopharmacol.* **2017**, *47*, 150–158. [CrossRef]
167. Sun, Y.; Shao, J.; Jiang, F.; Wang, Y.; Yan, Q.; Yu, N.; Zhang, J.; Zhang, J.; Li, M.; He, Y. CD33+ CD14+ CD11b+ HLA-DR- monocytic myeloid-derived suppressor cells recruited and activated by CCR9/CCL25 are crucial for the pathogenic progression of endometriosis. *Am. J. Reprod. Immunol.* **2019**, *81*, e13067. [CrossRef]
168. Chen, Y.; Wang, K.; Xu, Y.; Guo, P.; Hong, B.; Cao, Y.; Wei, Z.; Xue, R.; Wang, C.; Jiang, H. Alteration of Myeloid-Derived Suppressor Cells, Chronic Inflammatory Cytokines, and Exosomal miRNA Contribute to the Peritoneal Immune Disorder of Patients With Endometriosis. *Reprod. Sci.* **2019**, *26*, 1130–1138. [CrossRef]
169. Guo, P.; Bi, K.; Lu, Z.; Wang, K.; Xu, Y.; Wu, H.; Cao, Y.; Jiang, H. CCR5/CCR5 ligand-induced myeloid-derived suppressor cells are related to the progression of endometriosis. *Reprod. Biomed. Online* **2019**, *39*, 704–711. [CrossRef]
170. Zhang, T.; Zhou, J.; Man, G.C.W.; Leung, K.T.; Liang, B.; Xiao, B.; Ma, X.; Huang, S.; Huang, H.; Hegde, V.L.; et al. MDSCs drive the process of endometriosis by enhancing angiogenesis and are a new potential therapeutic target. *Eur. J. Immunol.* **2018**, *48*, 1059–1073. [CrossRef]
171. Bosteels, V.; Janssens, S. Striking a balance: New perspectives on homeostatic dendritic cell maturation. *Nat. Rev. Immunol.* **2025**, *25*, 125–140. [CrossRef]
172. Li, W.; Lin, A.; Qi, L.; Lv, X.; Yan, S.; Xue, J.; Mu, N. Immunotherapy: A promising novel endometriosis therapy. *Front. Immunol.* **2023**, *14*, 1128301. [CrossRef]
173. Rahal, D.; Andrade, F.; Nisihara, R. Insights into the role of complement system in the pathophysiology of endometriosis. *Immunol. Lett.* **2021**, *231*, 43–48. [CrossRef] [PubMed]
174. Agostinis, C.; Balduit, A.; Mangogna, A.; Zito, G.; Romano, F.; Ricci, G.; Kishore, U.; Bulla, R. Immunological Basis of the Endometriosis: The Complement System as a Potential Therapeutic Target. *Front. Immunol.* **2021**, *11*, 599117. [CrossRef] [PubMed]
175. Agostinis, C.; Toffoli, M.; Zito, G.; Balduit, A.; Pegoraro, S.; Spazzapan, M.; Pascolo, L.; Romano, F.; Di Lorenzo, G.; Mangogna, A.; et al. Proangiogenic properties of complement protein C1q can contribute to endometriosis. *Front. Immunol.* **2024**, *15*, 1405597. [CrossRef]
176. Suryawanshi, S.; Huang, X.; Elishaev, E.; Budiu, R.A.; Zhang, L.; Kim, S.; Donnellan, N.; Mantia-Smaldone, G.; Ma, T.; Tseng, G.; et al. Complement pathway is frequently altered in endometriosis and endometriosis-associated ovarian cancer. *Clin. Cancer Res.* **2014**, *20*, 6163–6174. [CrossRef]
177. Abramiuk, M.; Grywalska, E.; Małkowska, P.; Sierawska, O.; Hrynkiewicz, R.; Niedźwiedzka-Rystwej, P. The Role of the Immune System in the Development of Endometriosis. *Cells* **2022**, *11*, 2028. [CrossRef]
178. Milewski, Ł.; Dziunycz, P.; Barcz, E.; Radomski, D.; Roszkowski, P.I.; Korczak-Kowalska, G.; Kamiński, P.; Malejczyk, J. Increased levels of human neutrophil peptides 1, 2, and 3 in peritoneal fluid of patients with endometriosis: Association with neutrophils, T cells and IL-8. *J. Reprod. Immunol.* **2011**, *91*, 64–70. [CrossRef]
179. Lukács, L.; Kovács, A.R.; Pál, L.; Szűcs, S.; Kövér, Á.; Lampé, R. Phagocyte function of peripheral neutrophil granulocytes and monocytes in endometriosis before and after surgery. *J. Gynecol. Obstet. Hum. Reprod.* **2021**, *50*, 101796. [CrossRef]
180. Wilson, T.R.; Kasper, S.; Burns, K.A. An emerging role for neutrophils in the pathogenesis of endometriosis. *npj Women's Health* **2025**, *3*, 9. [CrossRef]
181. Takamura, M.; Koga, K.; Izumi, G.; Urata, Y.; Nagai, M.; Hasegawa, A.; Harada, M.; Hirata, T.; Hirota, Y.; Wada-Hiraike, O.; et al. Neutrophil depletion reduces endometriotic lesion formation in mice. *Am. J. Reprod. Immunol.* **2016**, *76*, 193–198. [CrossRef]
182. Hogg, C.; Horne, A.W.; Greaves, E. Endometriosis-associated macrophages: Origin, phenotype, and function. *Front. Endocrinol.* **2020**, *11*, 7. [CrossRef] [PubMed]
183. Hogg, C.; Panir, K.; Dhami, P.; Rosser, M.; Mack, M.; Soong, D.; Pollard, J.W.; Jenkins, S.J.; Horne, A.W.; Greaves, E. Macrophages inhibit and enhance endometriosis depending on their origin. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2013776118. [CrossRef] [PubMed]
184. Liu, Y.Y.; Liu, Y.K.; Hu, W.T.; Tang, L.L.; Sheng, Y.R.; Wei, C.Y.; Li, M.Q.; Zhu, X.Y. Elevated heme impairs macrophage phagocytosis in endometriosis. *Reproduction* **2019**, *158*, 257–266. [CrossRef]
185. Gao, X.; Gao, H.; Shao, W.; Wang, J.; Li, M.; Liu, S. The Extracellular Vesicle-Macrophage Regulatory Axis: A Novel Pathogenesis for Endometriosis. *Biomolecules* **2023**, *13*, 1376. [CrossRef] [PubMed]
186. Martínez-Zamora, M.A.; Armengol-Badia, O.; Quintas-Marquès, L.; Carmona, F.; Closa, D. Macrophage Phenotype Induced by Circulating Small Extracellular Vesicles from Women with Endometriosis. *Biomolecules* **2024**, *14*, 737. [CrossRef]

187. Chuang, P.C.; Lin, Y.J.; Wu, M.H.; Wing, L.Y.; Shoji, Y.; Tsai, S.J. Inhibition of CD36-dependent phagocytosis by prostaglandin E2 contributes to the development of endometriosis. *Am. J. Pathol.* **2010**, *176*, 850–860. [CrossRef]
188. Weng, L.C.; Hou, S.H.; Lei, S.T.; Peng, H.Y.; Li, M.Q.; Zhao, D. Estrogen-regulated CD200 inhibits macrophage phagocytosis in endometriosis. *J. Reprod. Immunol.* **2020**, *138*, 103090. [CrossRef]
189. Shiraishi, T.; Ikeda, M.; Watanabe, T.; Negishi, Y.; Ichikawa, G.; Kaseki, H.; Akira, S.; Morita, R.; Suzuki, S. Downregulation of pattern recognition receptors on macrophages involved in aggravation of endometriosis. *Am. J. Reprod. Immunol.* **2024**, *91*, e13812. [CrossRef]
190. Symons, L.K.; Miller, J.E.; Kay, V.R.; Marks, R.M.; Liblik, K.; Koti, M.; Tayade, C. The Immunopathophysiology of Endometriosis. *Trends Mol. Med.* **2018**, *24*, 748–762. [CrossRef]
191. Li, X.; Liu, Y.; Tang, Y.; Xia, Z. Transformation of macrophages into myofibroblasts in fibrosis-related diseases: Emerging biological concepts and potential mechanism. *Front. Immunol.* **2024**, *15*, 1474688. [CrossRef]
192. Tuckerman, E.; Mariee, N.; Prakash, A.; Li, T.C.; Laird, S. Uterine natural killer cells in peri-implantation endometrium from women with repeated implantation failure after IVF. *J. Reprod. Immunol.* **2010**, *87*, 60–66. [CrossRef]
193. Kikuchi, Y.; Ishikawa, N.; Hirata, J.; Imaizumi, E.; Sasa, H.; Nagata, I. Changes of peripheral blood lymphocyte subsets before and after operation of patients with endometriosis. *Acta Obstet. Gynecol. Scand.* **1993**, *72*, 157–161. [CrossRef] [PubMed]
194. Azeze, G.G.; Wu, L.; Alemu, B.K.; Wang, C.C.; Zhang, T. Changes in the number and activity of natural killer cells and its clinical association with endometriosis: Systematic review and meta-analysis. *F&S Rev.* **2024**, *5*, 100072. [CrossRef]
195. Jeung, I.; Cheon, K.; Kim, M.R. Decreased Cytotoxicity of Peripheral and Peritoneal Natural Killer Cell in Endometriosis. *Biomed. Res. Int.* **2016**, *2016*, 2916070. [CrossRef]
196. González-Foruria, I.; Santulli, P.; Chouzenoux, S.; Carmona, F.; Batteux, F.; Chapron, C. Soluble ligands for the NKG2D receptor are released during endometriosis and correlate with disease severity. *PLoS ONE* **2015**, *10*, e0119961. [CrossRef]
197. Kang, Y.J.; Jeung, I.C.; Park, A.; Park, Y.J.; Jung, H.; Kim, T.D.; Lee, H.G.; Choi, I.; Yoon, S.R. An increased level of IL-6 suppresses NK cell activity in peritoneal fluid of patients with endometriosis via regulation of SHP-2 expression. *Hum. Reprod.* **2014**, *29*, 2176–2189. [CrossRef]
198. Guo, S.W.; Du, Y.; Liu, X. Platelet-derived TGF-β1 mediates the down-modulation of NKG2D expression and may be responsible for impaired natural killer (NK) cytotoxicity in women with endometriosis. *Hum. Reprod.* **2016**, *31*, 1462–1474. [CrossRef]
199. Yu, J.J.; Sun, H.T.; Zhang, Z.F.; Shi, R.X.; Liu, L.B.; Shang, W.Q.; Wei, C.Y.; Chang, K.K.; Shao, J.; Wang, M.Y.; et al. IL15 promotes growth and invasion of endometrial stromal cells and inhibits killing activity of NK cells in endometriosis. *Reproduction* **2016**, *152*, 151–160. [CrossRef]
200. Yang, H.L.; Zhou, W.J.; Chang, K.K.; Mei, J.; Huang, L.Q.; Wang, M.Y.; Meng, Y.; Ha, S.Y.; Li, D.J.; Li, M.Q. The crosstalk between endometrial stromal cells and macrophages impairs cytotoxicity of NK cells in endometriosis by secreting IL-10 and TGF-β. *Reproduction* **2017**, *154*, 815–825. [CrossRef]
201. Reis, J.L.; Rosa, N.N.; Ângelo-Dias, M.; Martins, C.; Borrego, L.M.; Lima, J. Natural Killer Cell Receptors and Endometriosis: A Systematic Review. *Int. J. Mol. Sci.* **2022**, *24*, 331. [CrossRef]
202. Saeki, S.; Fukui, A.; Mai, C.; Takeyama, R.; Yamaya, A.; Shibahara, H. Co-expression of activating and inhibitory receptors on peritoneal fluid NK cells in women with endometriosis. *J. Reprod. Immunol.* **2023**, *155*, 103765. [CrossRef]
203. Sugamata, M.; Ihara, T.; Uchiide, I. Increase of activated mast cells in human endometriosis. *Am. J. Reprod. Immunol.* **2005**, *53*, 120–125. [CrossRef] [PubMed]
204. Kirchhoff, D.; Kaulfuss, S.; Fuhrmann, U.; Maurer, M.; Zollner, T.M. Mast cells in endometriosis: Guilty or innocent bystanders? *Expert Opin. Ther. Targets* **2012**, *16*, 237–241. [CrossRef] [PubMed]
205. McCallion, A.; Nasirzadeh, Y.; Lingegowda, H.; Miller, J.E.; Khalaj, K.; Ahn, S.; Monsanto, S.P.; Bidarimath, M.; Sisnett, D.J.; Craig, A.W.; et al. Estrogen mediates inflammatory role of mast cells in endometriosis pathophysiology. *Front. Immunol.* **2022**, *13*, 961599. [CrossRef]
206. Xu, X.; Wang, J.; Guo, X.; Chen, Y.; Ding, S.; Zou, G.; Zhu, L.; Li, T.; Zhang, X. GPR30-mediated non-classic estrogen pathway in mast cells participates in endometriosis pain via the production of FGF2. *Front. Immunol.* **2023**, *14*, 1106771. [CrossRef]
207. Schulke, L.; Berbic, M.; Manconi, F.; Tokushige, N.; Markham, R.; Fraser, I.S. Dendritic cell populations in the eutopic and ectopic endometrium of women with endometriosis. *Hum. Reprod.* **2009**, *24*, 1695–1703. [CrossRef]
208. Qiaomei, Z.; Ping, W.; Yanjing, Z.; Jinhua, W.; Shaozhan, C.; Lihong, C. Features of peritoneal dendritic cells in the development of endometriosis. *Reprod. Biol. Endocrinol.* **2023**, *21*, 4. [CrossRef]
209. Yang, X.; Jiang, L.; Xu, Y. HSD11B1 overexpression in dendritic cells and stromal cells relates to endometriosis by inhibiting dendritic cell proliferation and maturation. *Gynecol. Endocrinol.* **2024**, *40*, 2411607. [CrossRef]
210. Maridas, D.E.; Hey-Cunningham, A.J.; Ng, C.H.M.; Markham, R.; Fraser, I.S.; Berbic, M. Peripheral and endometrial dendritic cell populations during the normal cycle and in the presence of endometriosis. *J. Endometr. Pelvic Pain Disord.* **2014**, *6*, 67–119. [CrossRef]

211. Suen, J.L.; Chang, Y.; Shiu, Y.S.; Hsu, C.Y.; Sharma, P.; Chiu, C.C.; Chen, Y.J.; Hour, T.C.; Tsai, E.M. IL-10 from plasmacytoid dendritic cells promotes angiogenesis in the early stage of endometriosis. *J. Pathol.* **2019**, *249*, 485–497. [CrossRef]
212. Knez, J.; Kovačič, B.; Goropevšek, A. The role of regulatory T-cells in the development of endometriosis. *Hum. Reprod.* **2024**, *39*, 1367–1380. [CrossRef]
213. Riccio, L.G.C.; Baracat, E.C.; Chapron, C.; Batteux, F.; Abrão, M.S. The role of the B lymphocytes in endometriosis: A systematic review. *J. Reprod. Immunol.* **2017**, *123*, 29–34. [CrossRef] [PubMed]
214. Kisovar, A.; Becker, C.M.; Granne, I.; Southcombe, J.H. The role of CD8+ T cells in endometriosis: A systematic review. *Front. Immunol.* **2023**, *14*, 1225639. [CrossRef] [PubMed]
215. Chopyak, V.V.; Koval, H.D.; Havrylyuk, A.M.; Lishchuk-Yakymovych, K.A.; Potomkina, H.A.; Kurpisz, M.K. Immunopathogenesis of endometriosis—A novel look at an old problem. *Cent. Eur. J. Immunol.* **2022**, *47*, 109–116. [CrossRef]
216. Hanada, T.; Tsuji, S.; Nakayama, M.; Wakinoue, S.; Kasahara, K.; Kimura, F.; Mori, T.; Ogasawara, K.; Murakami, T. Suppressive regulatory T cells and latent transforming growth factor-β-expressing macrophages are altered in the peritoneal fluid of patients with endometriosis. *Reprod. Biol. Endocrinol.* **2018**, *16*, 9. [CrossRef]
217. Riccio, L.G.C.; Andres, M.P.; Dehó, I.Z.; Fontanari, G.O.; Abrão, M.S. Foxp3+CD39+CD73+ regulatory T-cells are decreased in the peripheral blood of women with deep infiltrating endometriosis. *Clinics* **2024**, *79*, 100390. [CrossRef]
218. Li, M.Q.; Wang, Y.; Chang, K.K.; Meng, Y.H.; Liu, L.B.; Mei, J.; Wang, Y.; Wang, X.Q.; Jin, L.P.; Li, D.J. CD4+Foxp3+ regulatory T cell differentiation mediated by endometrial stromal cell-derived TECK promotes the growth and invasion of endometriotic lesions. *Cell Death Dis.* **2014**, *5*, e1436. [CrossRef]
219. Sisnett, D.J.; Zutautas, K.B.; Miller, J.E.; Lingegowda, H.; Ahn, S.H.; McCallion, A.; Bougie, O.; Lessey, B.A.; Tayade, C. The Dysregulated IL-23/TH17 Axis in Endometriosis Pathophysiology. *J. Immunol.* **2024**, *212*, 1428–1441. [CrossRef]
220. Shi, J.; Xu, Q.; Yu, S.; Zhang, T. Perturbations of the endometrial immune microenvironment in endometriosis and adenomyosis: Their impact on reproduction and pregnancy. *Semin. Immunopathol.* **2025**, *47*, 16. [CrossRef]
221. Olkowska-Truchanowicz, J.; Białoszewska, A.; Zwierzchowska, A.; Sztokfisz-Ignasiak, A.; Janiuk, I.; Dąbrowski, F.; Korczak-Kowalska, G.; Barcz, E.; Bocian, K.; Malejczyk, J. Peritoneal Fluid from Patients with Ovarian Endometriosis Displays Immunosuppressive Potential and Stimulates Th2 Response. *Int. J. Mol. Sci.* **2021**, *22*, 8134. [CrossRef]
222. Reis, J.L.; Rosa, N.N.; Martins, C.; Ângelo-Dias, M.; Borrego, L.M.; Lima, J. The Role of NK and T Cells in Endometriosis. *Int. J. Mol. Sci.* **2024**, *25*, 10141. [CrossRef]
223. Schmitz, T.; Hoffmann, V.; Olliges, E.; Bobinger, A.; Popovici, R.; Nößner, E.; Meissner, K. Reduced frequency of perforin-positive CD8+ T cells in menstrual effluent of endometriosis patients. *J. Reprod. Immunol.* **2021**, *148*, 103424. [CrossRef] [PubMed]
224. Hosseinzadeh, R.; Moini, A.; Hosseini, R.; Fatehnejad, M.; Yekaninejad, M.S.; Javidan, M.; Changaei, M.; Feizisani, F.; Rajaei, S. A higher number of exhausted local PD1+, but not TIM3+, NK cells in advanced endometriosis. *Heliyon* **2023**, *10*, e23294. [CrossRef] [PubMed]
225. Abramiuk, M.; Bębnowska, D.; Hrynkiewicz, R.; Polak, P.N.G.; Kotarski, J.; Roliński, J.; Grywalska, E. CLTA-4 Expression is Associated with the Maintenance of Chronic Inflammation in Endometriosis and Infertility. *Cells* **2021**, *10*, 487. [CrossRef]
226. Podgaec, S.; Abrao, M.S.; Días, J.A., Jr.; Rizzo, L.V.; de Oliveira, R.M.; Baracat, E.C. Endometriosis: An inflammatory disease with a Th2 immune response component. *Hum. Reprod.* **2007**, *22*, 1373–1379. [CrossRef]
227. Santoso, B.; Sa'adi, A.; Dwiningsih, S.R.; Tunjungseto, A.; Widyanugraha, M.Y.A.; Mufid, A.F.; Rahmawati, N.Y.; Ahsan, F. Soluble immune checkpoints CTLA-4, HLA-G, PD-1, and PD-L1 are associated with endometriosis-related infertility. *Am. J. Reprod. Immunol.* **2020**, *84*, e13296. [CrossRef]
228. Chen, P.; Wang, D.B.; Liang, Y.M. Evaluation of estrogen in endometriosis patients: Regulation of GATA-3 in endometrial cells and effects on Th2 cytokines. *J. Obstet. Gynaecol. Res.* **2016**, *42*, 669–677. [CrossRef]
229. Lin, K.R.; Li, P.X.; Zhu, X.H.; Mao, X.F.; Peng, J.L.; Chen, X.P.; SiTu, C.Y.; Zhang, L.F.; Luo, W.; Han, Y.B.; et al. Peripheral immune characteristics and subset disorder in reproductive females with endometriosis. *Front. Immunol.* **2024**, *15*, 1431175. [CrossRef]
230. Delbandi, A.A.; Mahmoudi, M.; Shervin, A.; Farhangnia, P.; Mohammadi, T.; Zarnani, A.H. Increased circulating T helper 17 (TH17) cells and endometrial tissue IL-17-producing cells in patients with endometriosis compared with non-endometriotic subjects. *Reprod. Biol.* **2025**, *25*, 101019, Advance online publication. [CrossRef]
231. Kitaya, K. B Cell Lineage in the Human Endometrium: Physiological and Pathological Implications. *Cells* **2025**, *14*, 648. [CrossRef]
232. Slawek, A.; Lorek, D.; Kedzierska, A.E.; Kubik, P.; Pajak, J.; Chrobak, A.; Chelmonska-Soyta, A. Peripheral blood subpopulations of Bregs producing IL-35 in women with endometriosis. *Am. J. Reprod. Immunol.* **2023**, *89*, e13675. [CrossRef]
233. Ren, Y.; Zhu, D.; Han, X.; Zhang, Q.; Chen, B.; Zhou, P.; Wei, Z.; Zhang, Z.; Cao, Y.; Zou, H. HMGB1: A double-edged sword and therapeutic target in the female reproductive system. *Front. Immunol.* **2023**, *14*, 1238785. [CrossRef] [PubMed]
234. Huang, J.; Chen, X.; Liu, J. High mobility group box 1 promotes endometriosis under hypoxia by regulating inflammation and autophagy in vitro and in vivo. *Int. Immunopharmacol.* **2024**, *127*, 111397. [CrossRef] [PubMed]
235. Dai, W.; Guo, R.; Na, X.; Jiang, S.; Liang, J.; Guo, C.; Fang, Y.; Na, Z.; Li, D. Hypoxia and the endometrium: An indispensable role for HIF-1α as therapeutic strategies. *Redox Biol.* **2024**, *73*, 103205. [CrossRef]

236. Huang, Y.; Li, R.; Hu, R.; Yao, J.; Yang, Y. PEG2-Induced Pyroptosis Regulates the Expression of HMGB1 and Promotes hEM15A Migration in Endometriosis. *Int. J. Mol. Sci.* **2022**, *23*, 11707. [CrossRef]
237. Jana, B.; Andronowska, A.; Całka, J.; Mówińska, A. Biosynthetic pathway for leukotrienes is stimulated by lipopolysaccharide and cytokines in pig endometrial stromal cells. *Sci. Rep.* **2025**, *15*, 2806. [CrossRef]
238. Ihara, T.; Uchiide, I.; Sugamata, M. Light and electron microscopic evaluation of antileukotriene therapy for experimental rat endometriosis. *Fertil. Steril.* **2004**, *81* (Suppl. S1), 819–823. [CrossRef]
239. Kiykac Altinbas, S.; Tapisiz, O.L.; Cavkaytar, S.; Simsek, G.; Oguztuzun, S.; Goktolga, U. Is montelukast effective in regression of endometrial implants in an experimentally induced endometriosis model in rats? *Europ. J. Obstet. Gynecol. Reprod. Biol.* **2015**, *184*, 7–12. [CrossRef]
240. Wu, R.; Zhou, W.; Chen, S.; Shi, Y.; Su, L.; Zhu, M.; Chen, Q.; Chen, Q. Lipoxin A4 suppresses the development of endometriosis in an ALX receptor-dependent manner via the p38 MAPK pathway. *Br. J. Pharmacol.* **2014**, *171*, 4927–4940. [CrossRef]
241. Huang, Z.X.; He, X.R.; Ding, X.Y.; Chen, J.H.; Lei, Y.H.; Bai, J.B.; Lin, D.C.; Hong, Y.H.; Lan, J.F.; Chen, Q.H. Lipoxin A4 depresses inflammation and promotes autophagy via AhR/mTOR/AKT pathway to suppress endometriosis. *Am. J. Reprod. Immunol.* **2023**, *89*, e13659. [CrossRef]
242. Dmitrieva, N.; Suess, G.; Shirley, R. Resolvins RvD1 and 17(R)-RvD1 alleviate signs of inflammation in a rat model of endometriosis. *Fertil. Steril.* **2014**, *102*, 1191–1196. [CrossRef]
243. Gu, Z.; Lamont, G.J.; Lamont, R.J.; Uriarte, S.M.; Wang, H.; Scott, D.A. Resolvin D1, resolvin D2 and maresin 1 activate the GSK3β anti-inflammatory axis in TLR4-engaged human monocytes. *Innate Immun.* **2016**, *622*, 186–195. [CrossRef] [PubMed]
244. de Fáveri, C.; Fermino, P.M.P.; Piovezan, A.P.; Volpato, L.K. The Inflammatory Role of Pro-Resolving Mediators in Endometriosis: An Integrative Review. *Int. J. Mol. Sci.* **2021**, *22*, 4370. [CrossRef] [PubMed]
245. Chávez-Castillo, M.; Ortega, Á.; Cudris-Torres, L.; Duran, P.; Rojas, M.; Manzano, A.; Garrido, B.; Salazar, J.; Silva, A.; Rojas-Gomez, D.M.; et al. Specialized Pro-Resolving Lipid Mediators: The Future of Chronic Pain Therapy? *Int. J. Mol. Sci.* **2021**, *22*, 10370. [CrossRef]
246. Collie, B.; Troisi, J.; Lombardi, M.; Symes, S.; Richards, S. The Current Applications of Metabolomics in Understanding Endometriosis: A Systematic Review. *Metabolites* **2025**, *15*, 50. [CrossRef]
247. Wilson, R.B. Hypoxia, cytokines and stromal recruitment: Parallels between pathophysiology of encapsulating peritoneal sclerosis, endometriosis and peritoneal metastasis. *Pleura Peritoneum* **2018**, *3*, 20180103. [CrossRef]
248. Ni, C.; Li, D. Ferroptosis and oxidative stress in endometriosis: A systematic review of the literature. *Medicine* **2024**, *103*, e37421. [CrossRef]
249. Zhu, W.; Liu, X.; Yang, L.; He, Q.; Huang, D.; Tan, X. Ferroptosis and tumor immunity: In perspective of the major cell components in the tumor microenvironment. *Eur. J. Pharmacol.* **2023**, *961*, 176124. [CrossRef]
250. Kondera-Anasz, Z.; Sikora, J.; Mielczarek-Palacz, A.; Jońca, M. Concentrations of interleukin (IL)-1alpha, IL-1 soluble receptor type II (IL-1 sRII) and IL-1 receptor antagonist (IL-1 Ra) in the peritoneal fluid and serum of infertile women with endometriosis. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2005**, *123*, 198–203. [CrossRef]
251. Sikora, J.; Ferrero, S.; Mielczarek-Palacz, A.; Kondera-Anasz, Z. The Delicate Balance between the Good and the Bad IL-1 Proinflammatory Effects in Endometriosis. *Curr. Med. Chem.* **2018**, *25*, 2105–2121. [CrossRef]
252. Malvezzi, H.; Hernandes, C.; Piccinato, C.A.; Podgaec, S. Interleukin in endometriosis-associated infertility-pelvic pain: Systematic review and meta-analysis. *Reproduction* **2019**, *158*, 1–12. [CrossRef]
253. Werdel, R.; Mabie, A.; Evans, T.L.; Coté, R.D.; Schlundt, A.; Doehrman, P.; Dilsaver, D.; Coté, J.J. Serum Levels of Interleukins in Endometriosis Patients: A Systematic Review and Meta-analysis. *J. Minim. Invasive Gynecol.* **2024**, *31*, 387–396.e11. [CrossRef] [PubMed]
254. Koumantakis, E.; Matalliotakis, I.; Neonaki, M.; Froudarakis, G.; Georgoulias, V. Soluble serum interleukin-2 receptor, interleukin-6 and interleukin-1a in patients with endometriosis and in controls. *Arch. Gynecol. Obstet.* **1994**, *255*, 107–112. [CrossRef] [PubMed]
255. Khan, K.N.; Guo, S.W.; Ogawa, K.; Fujishita, A.; Mori, T. The role of innate and adaptive immunity in endometriosis. *J. Reprod. Immunol.* **2024**, *163*, 104242. [CrossRef]
256. Xia, T.; Zeng, K.; Peng, Q.; Wu, X.; Lei, X. Clinical significance of serum Th1/Th2 cytokines in patients with endometriosis. *Women Health* **2023**, *63*, 73–82. [CrossRef]
257. Voltolini Velho, R.; Halben, N.; Chekerov, R.; Keye, J.; Plendl, J.; Sehouli, J.; Mechsner, S. Functional changes of immune cells: Signal of immune tolerance of the ectopic lesions in endometriosis? *Reprod. Biomed. Online* **2021**, *43*, 319–328. [CrossRef]
258. Mao, X.D.; Hu, C.Y.; Zhu, M.C.; Ou, H.L.; Qian, Y.L. Immunological microenvironment alterations in follicles of women with proven severe endometriosis undergoing in vitro fertilization. *Mol. Biol. Rep.* **2019**, *46*, 4675–4684. [CrossRef]
259. Oală, I.E.; Mitranovici, M.I.; Chiorean, D.M.; Irimia, T.; Crișan, A.I.; Melinte, I.M.; Cotruș, T.; Tudorache, V.; Moraru, L.; Moraru, R.; et al. Endometriosis and the Role of Pro-Inflammatory and Anti-Inflammatory Cytokines in Pathophysiology: A Narrative Review of the Literature. *Diagnostics* **2024**, *14*, 312. [CrossRef]

260. Ghodsi, M.; Hojati, V.; Attaranzadeh, A.; Saifi, B. Evaluation of IL-3, IL-5, and IL-6 concentration in the follicular fluid of women with endometriosis: A cross-sectional study. *Int. J. Reprod. Biomed.* **2022**, *20*, 213–220. [CrossRef]
261. Pellicer, A.; Albert, C.; Mercader, A.; Bonilla-Musoles, F.; Remohí, J.; Simón, C. The follicular and endocrine environment in women with endometriosis: Local and systemic cytokine production. *Fertil. Steril.* **1998**, *70*, 425–431. [CrossRef]
262. Monsanto, S.P.; Edwards, A.K.; Zhou, J.; Nagarkatti, P.; Nagarkatti, M.; Young, S.L.; Lessey, B.A.; Tayade, C. Surgical removal of endometriotic lesions alters local and systemic proinflammatory cytokines in endometriosis patients. *Fertil. Steril.* **2016**, *105*, 968–977.e5. [CrossRef]
263. Bellelis, P.; Frediani Barbeiro, D.; Gueuvoghlanian-Silva, B.Y.; Kalil, J.; Abrão, M.S.; Podgaec, S. Interleukin-15 and Interleukin-7 are the Major Cytokines to Maintain Endometriosis. *Gynecol. Obstet. Investig.* **2019**, *84*, 435–444. [CrossRef] [PubMed]
264. Akoum, A.; Lawson, C.; McColl, S.; Villeneuve, M. Ectopic endometrial cells express high concentrations of interleukin (IL)-8 in vivo regardless of the menstrual cycle phase and respond to oestradiol by up-regulating IL-1-induced IL-8 expression in vitro. *Mol. Hum. Reprod.* **2001**, *7*, 859–866. [CrossRef] [PubMed]
265. Sikora, J.; Smycz-Kubańska, M.; Mielczarek-Palacz, A.; Kondera-Anasz, Z. Abnormal peritoneal regulation of chemokine activation-The role of IL-8 in pathogenesis of endometriosis. *Am. J. Reprod. Immunol.* **2017**, *77*, e12622. [CrossRef] [PubMed]
266. Punnonen, J.; Teisala, K.; Ranta, H.; Bennett, B.; Punnonen, R. Increased levels of interleukin-6 and interleukin-10 in the peritoneal fluid of patients with endometriosis. *Am. J. Obstet. Gynecol.* **1996**, *174*, 1522–1526. [CrossRef]
267. Mazzeo, D.; Viganó, P.; Di Blasio, A.M.; Sinigaglia, F.; Vignali, M.; Panina-Bordignon, P. Interleukin-12 and its free p40 subunit regulate immune recognition of endometrial cells: Potential role in endometriosis. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 911–916. [CrossRef]
268. Rahmawati, N.Y.; Ahsan, F.; Santoso, B.; Mufid, A.F.; Sa'adi, A.; Dwiningsih, S.R.; Tunjungseto, A.; Widyanugraha, M.Y.A. IL-8 and IL-12p70 are associated with pelvic pain among infertile women with endometriosis. *Pain Med.* **2023**, *24*, 1262–1269. [CrossRef] [PubMed]
269. Chegini, N.; Roberts, M.; Ripps, B. Differential expression of interleukins (IL)-13 and IL-15 in ectopic and eutopic endometrium of women with endometriosis and normal fertile women. *Am. J. Reprod. Immunol.* **2003**, *49*, 75–83. [CrossRef]
270. Bailey, A.P.; Hill, A.S.; Beste, M.T.; Cook, C.D.; Sarda, V.; Laufer, M.R.; Isaacson, K.B.; Griffith, L.G.; Missmer, S.A. Comparison of cytokines in the peritoneal fluid and conditioned medium of adolescents and adults with and without endometriosis. *Am. J. Reprod. Immunol.* **2021**, *85*, e13347. [CrossRef]
271. Koga, K.; Osuga, Y.; Yoshino, O.; Hirota, Y.; Yano, T.; Tsutsumi, O.; Taketani, Y. Elevated interleukin-16 levels in the peritoneal fluid of women with endometriosis may be a mechanism for inflammatory reactions associated with endometriosis. *Fertil. Steril.* **2005**, *83*, 878–882. [CrossRef]
272. Zhang, J.; Zhao, W.; Zhou, Y.; Xi, S.; Xu, X.; Du, X.; Zheng, X.; Hu, W.; Sun, R.; Tian, Z.; et al. Pyroptotic T cell-derived active IL-16 has a driving function in ovarian endometriosis development. *Cell Rep. Med.* **2024**, *5*, 101476. [CrossRef]
273. Zhang, X.; Xu, H.; Lin, J.; Qian, Y.; Deng, L. Peritoneal fluid concentrations of interleukin-17 correlate with the severity of endometriosis and infertility of this disorder. *BJOG Int. J. Obstet. Gynaecol.* **2005**, *112*, 1153–1155. [CrossRef] [PubMed]
274. Ahn, S.H.; Edwards, A.K.; Singhm, S.S.; Young, S.L.; Lessey, B.A.; Tayade, C. IL-17A Contributes to the Pathogenesis of Endometriosis by Triggering Proinflammatory Cytokines and Angiogenic Growth Factors. *J. Immunol.* **2015**, *195*, 2591–2600. [CrossRef] [PubMed]
275. Shi, J.L.; Zheng, Z.M.; Chen, M.; Shen, H.H.; Li, M.Q.; Shao, J. IL-17: An important pathogenic factor in endometriosis. *Int. J. Med. Sci.* **2022**, *19*, 769–778. [CrossRef]
276. Arici, A.; Matalliotakis, I.; Goumenou, A.; Koumantakis, G.; Vassiliadis, S.; Mahutte, N.G. Altered expression of interleukin-18 in the peritoneal fluid of women with endometriosis. *Fertil. Steril.* **2003**, *80*, 889–894. [CrossRef]
277. Zhang, Q.F.; Chen, G.Y.; Liu, Y.; Huang, H.J.; Song, Y.F. Relationship between resistin and IL-23 levels in follicular fluid in infertile patients with endometriosis undergoing IVF-ET. *Adv. Clin. Exp. Med.* **2017**, *26*, 1431–1435. [CrossRef]
278. Bungum, H.F.; Nygaard, U.; Vestergaard, C.; Martensen, P.M.; Knudsen, U.B. Increased IL-25 levels in the peritoneal fluid of patients with endometriosis. *J. Reprod. Immunol.* **2016**, *114*, 6–9. [CrossRef]
279. O, D.; Waelkens, E.; Vanhie, A.; Peterse, D.; Fassbender, A.; D'Hooghe, T. The Use of Antibody Arrays in the Discovery of New Plasma Biomarkers for Endometriosis. *Reprod. Sci.* **2020**, *27*, 751–762. [CrossRef]
280. Lee, M.Y.; Kim, S.H.; Oh, Y.S.; Heo, S.H.; Kim, K.H.; Chae, H.D.; Kim, C.H.; Kang, B.M. Role of interleukin-32 in the pathogenesis of endometriosis: In vitro, human and transgenic mouse data. *Hum. Reprod.* **2018**, *33*, 807–816. [CrossRef]
281. Choi, Y.S.; Kim, S.; Oh, Y.S.; Cho, S.; Hoon Kim, S. Elevated serum interleukin-32 levels in patients with endometriosis: A cross-sectional study. *Am. J. Reprod. Immunol.* **2019**, *82*, e13149. [CrossRef]
282. Lin, K.; Ma, J.; Peng, Y.; Sun, M.; Xu, K.; Wu, R.; Lin, J. Autocrine Production of Interleukin-34 Promotes the Development of Endometriosis through CSF1R/JAK3/STAT6 signaling. *Sci. Rep.* **2019**, *9*, 16781. [CrossRef]
283. Zhang, C.; Peng, Z.; Ban, D.; Zhang, Y. Upregulation of Interleukin 35 in Patients With Endometriosis Stimulates Cell Proliferation. *Reprod. Sci.* **2018**, *25*, 443–451. [CrossRef] [PubMed]

284. Smycz-Kubanska, M.; Wendlocha, D.; Witek, A.; Mielczarek-Palacz, A. The role of selected cytokines from the interleukin-1 family in the peritoneal fluid of women with endometriosis. *Ginekol. Pol.* **2025**, *96*, 126–135. [CrossRef] [PubMed]
285. Xavier, P.; Belo, L.; Beires, J.; Rebelo, I.; Martinez-de-Oliveira, J.; Lunet, N.; Barros, H. Serum levels of VEGF and TNF-alpha and their association with C-reactive protein in patients with endometriosis. *Arch. Gynecol. Obst.* **2006**, *273*, 227–231. [CrossRef]
286. Iwabe, T.; Harada, T.; Terakawa, N. Role of cytokines in endometriosis-associated infertility. *Gynecol. Obst. Investig.* **2002**, *53* (Suppl. S1), 19–25. [CrossRef]
287. Ullah, A.; Wang, M.J.; Wang, Y.X.; Shen, B. CXC chemokines influence immune surveillance in immunological disorders: Polycystic ovary syndrome and endometriosis. *Biochim. Biophys. Acta Mol. Basis Dis.* **2023**, *1869*, 166704. [CrossRef]
288. Shimoya, K.; Zhang, Q.; Temma-Asano, K.; Hayashi, S.; Kimura, T.; Murata, Y. Fractalkine in the peritoneal fluid of women with endometriosis. *Int. J. Gynaecol. Obst.* **2005**, *91*, 36–41. [CrossRef]
289. Smycz-Kubańska, M.; Kondera-Anasz, Z.; Sikora, J.; Wendlocha, D.; Królewska-Daszczyńska, P.; Englisz, A.; Janusz, A.; Janusz, J.; Mielczarek-Palacz, A. The Role of Selected Chemokines in the Peritoneal Fluid of Women with Endometriosis—Participation in the Pathogenesis of the Disease. *Processes* **2021**, *9*, 2229. [CrossRef]
290. Arici, A.; Oral, E.; Attar, E.; Tazuke, S.I.; Olive, D.L. Monocyte chemotactic protein-1 concentration in peritoneal fluid of women with endometriosis and its modulation of expression in mesothelial cells. *Fertil. Steril.* **1997**, *67*, 1065–1072. [CrossRef]
291. Nirgianakis, K.; McKinnon, B.; Ma, L.; Imboden, S.; Bersinger, N.; Mueller, M.D. Peritoneal fluid biomarkers in patients with endometriosis: A cross-sectional study. *Horm. Mol. Biol. Clin. Investig.* **2020**, *42*, 113–122. [CrossRef]
292. Heidari, S.; Kolahdouz-Mohammadi, R.; Khodaverdi, S.; Tajik, N.; Delbandi, A.A. Expression levels of MCP-1, HGF, and IGF-1 in endometriotic patients compared with non-endometriotic controls. *BMC Women's Health* **2021**, *21*, 422. [CrossRef]
293. Han, M.T.; Cheng, W.; Zhu, R.; Wu, H.H.; Ding, J.; Zhao, N.N.; Li, H.; Wang, F.X. The cytokine profiles in follicular fluid and reproductive outcomes in women with endometriosis. *Am. J. Reprod. Immunol.* **2023**, *89*, e13633. [CrossRef] [PubMed]
294. Zhang, X.; Mu, L. Association between macrophage migration inhibitory factor in the endometrium and estrogen in endometriosis. *Exp. Ther. Med.* **2015**, *10*, 787–791. [CrossRef] [PubMed]
295. Elbaradie, S.M.Y.; Bakry, M.S.; Bosilah, A.H. Serum macrophage migration inhibition factor for diagnosing endometriosis and its severity: Case-control study. *BMC Women's Health* **2020**, *20*, 189. [CrossRef]
296. Fukaya, T.; Sugawara, J.; Yoshida, H.; Yajima, A. The role of macrophage colony stimulating factor in the peritoneal fluid in infertile patients with endometriosis. *Tohoku J. Exp. Med.* **1994**, *172*, 221–226. [CrossRef]
297. Budrys, N.M.; Nair, H.B.; Liu, Y.G.; Kirma, N.B.; Binkley, P.A.; Kumar, S.; Schenken, R.S.; Tekmal, R.R. Increased expression of macrophage colony-stimulating factor and its receptor in patients with endometriosis. *Fertil. Steril.* **2012**, *97*, 1129–1135.e1. [CrossRef]
298. Shi, J.; Tan, X.; Feng, G.; Zhuo, Y.; Jiang, Z.; Banda, S.; Wang, L.; Zheng, W.; Chen, L.; Yu, D.; et al. Research advances in drug therapy of endometriosis. *Front. Pharmacol.* **2023**, *14*, 1199010. [CrossRef]
299. Nisolle, M.; Casanas-Roux, F.; Anaf, V.; Mine, J.M.; Donnez, J. Morphometric study of the stromal vascularisation in peritoneal endometriosis. *Fertil. Steril.* **1993**, *59*, 681–684. [CrossRef]
300. McLaren, J.; Prentice, A.; Charnock-Jones, D.S.; Millican, S.A.; Müller, K.H.; Sharkey, A.M.; Smith, S.K. Vascular endothelial growth factor is produced by peritoneal fluid macrophages in endometriosis and is regulated by ovarian steroids. *J. Clin. Investig.* **1996**, *98*, 482–489. [CrossRef]
301. Lee, S.R.; Kim, S.H.; Lee, Y.J.; Hong, S.H.; Chae, H.D.; Kim, C.H.; Kang, B.M.; Choi, Y.M. Expression of epidermal growth factor, fibroblast growth factor-2, and platelet-derived growth factor-A in the eutopic endometrium of women with endometriosis. *J. Obstet. Gynaecol. Res.* **2007**, *33*, 242–247. [CrossRef] [PubMed]
302. Smolarz, B.; Szaflik, T.; Romanowicz, H.; Bryś, M.; Forma, E.; Szyłło, K. Analysis of VEGF, IGF1/2 and the Long Noncoding RNA (lncRNA) H19 Expression in Polish Women with Endometriosis. *Int. J. Mol. Sci.* **2024**, *25*, 5271. [CrossRef]
303. Pantelis, A.; Machairiotis, N.; Lapatsanis, D.P. The Formidable yet Unresolved Interplay between Endometriosis and Obesity. *Sci. World J.* **2021**, *2021*, 6653677. [CrossRef] [PubMed]
304. Oosterlynck, D.J.; Meuleman, C.; Waer, M.; Koninckx, P.R. Transforming growth factor-beta activity is increased in peritoneal fluid from women with endometriosis. *Obstet. Gynecol.* **1994**, *83*, 287–292. [PubMed]
305. Abdoli, M.; Hoseini, S.M.; Sandoghsaz, R.S.; Javaheri, A.; Montazeri, F.; Moshtaghioun, S.M. Endometriotic lesions and their recurrence: A Study on the mediators of immunoregulatory (TGF-β/miR-20a) and stemness (NANOG/miR-145). *J. Reprod. Immunol.* **2024**, *166*, 104336. [CrossRef]
306. Suen, J.L.; Chang, Y.; Chiu, P.R.; Hsieh, T.H.; His, E.; Chen, Y.C.; Chen, Y.F.; Tsai, E.M. Serum level of IL-10 is increased in patients with endometriosis, and IL-10 promotes the growth of lesions in a murine model. *Am. J. Pathol.* **2014**, *184*, 464–471. [CrossRef]
307. Santulli, P.; Borghese, B.; Chouzenoux, S.; Streuli, I.; Borderie, D.; de Ziegler, D.; Weill, B.; Chapron, C.; Batteux, F. Interleukin-19 and interleukin-22 serum levels are decreased in patients with ovarian endometrioma. *Fertil. Steril.* **2013**, *99*, 219–226.e2. [CrossRef]

308. Guo, Y.; Chen, Y.; Liu, L.B.; Chang, K.K.; Li, H.; Li, M.Q.; Shao, J. IL-22 in the endometriotic milieu promotes the proliferation of endometrial stromal cells via stimulating the secretion of CCL2 and IL-8. *Int. J. Clin. Exp. Pathol.* **2013**, *6*, 2011–2020.
309. Liu, S.; Zhao, R.; Zang, Y.; Huang, P.; Zhang, Q.; Fan, X.; Bai, J.; Zheng, X.; Zhao, S.; Kuai, D.; et al. Interleukin-22 promotes endometrial carcinoma cell proliferation and cycle progression via ERK1/2 and p38 activation. *Mol. Cell. Biochem.* **2025**, *480*, 3147–3160. [CrossRef]
310. Wang, Q.; Wang, L.; Shao, J.; Wang, Y.; Jin, L.P.; Li, D.J.; Li, M.Q. IL-22 enhances the invasiveness of endometrial stromal cells of adenomyosis in an autocrine manner. *Int. J. Clin. Exp. Pathol.* **2014**, *7*, 5762–5771.
311. Jiang, J.; Jiang, Z.; Xue, M. Serum and peritoneal fluid levels of interleukin-6 and interleukin-37 as biomarkers for endometriosis. *Gynecol. Endocrinol.* **2019**, *35*, 571–575. [CrossRef]
312. Hsu, C.C.; Yang, B.C.; Wu, M.H.; Huang, K.E. Enhanced interleukin-4 expression in patients with endometriosis. *Fertil. Steril.* **1997**, *67*, 1059–1064. [CrossRef]
313. OuYang, Z.; Hirota, Y.; Osuga, Y.; Hamasaki, K.; Hasegawa, A.; Tajima, T.; Hirata, T.; Koga, K.; Yoshino, O.; Harada, M.; et al. Interleukin-4 stimulates proliferation of endometriotic stromal cells. *Am. J. Pathol.* **2008**, *173*, 463–469. [CrossRef] [PubMed]
314. Krygere, L.; Jukna, P.; Jariene, K.; Drejeriene, E. Diagnostic Potential of Cytokine Biomarkers in En dometriosis: Challenges and Insights. *Biomedicines* **2024**, *12*, 2867. [CrossRef] [PubMed]
315. Wang, F.; Wang, H.; Jin, D.; Zhang, Y. Serum miR-17, IL-4, and IL-6 levels for diagnosis of endometriosis. *Medicine* **2018**, *97*, e10853. [CrossRef]
316. Sadat Sandoghsaz, R.; Montazeri, F.; Shafienia, H.; Mehdi Kalantar, S.; Javaheri, A.; Samadi, M. Expression of miR-21 &IL-4 in endometriosis. *Hum. Immunol.* **2024**, *85*, 110746. [CrossRef]
317. Wang, X.M.; Ma, Z.Y.; Song, N. Inflammatory cytokines IL-6, IL-10, IL-13, TNF-α and peritoneal fluid flora were associated with infertility in patients with endometriosis. *Eur. Rev. Med. Pharmacol. Sci.* **2018**, *22*, 2513–2518. [CrossRef]
318. Qiu, X.M.; Lai, Z.Z.; Ha, S.Y.; Yang, H.L.; Liu, L.B.; Wang, Y.; Shi, J.W.; Ruan, L.Y.; Ye, J.F.; Wu, J.N.; et al. IL-2 and IL-27 synergistically promote growth and invasion of endometriotic stromal cells by maintaining the balance of IFN-γ and IL-10 in endometriosis. *Reproduction* **2020**, *159*, 251–260. [CrossRef]
319. Miller, J.E.; Monsanto, S.P.; Ahn, S.H.; Khalaj, K.; Fazleabas, A.T.; Young, S.L.; Lessey, B.A.; Koti, M.; Tayade, C. Interleukin-33 modulates inflammation in endometriosis. *Sci. Rep.* **2017**, *7*, 17903. [CrossRef]
320. Miller, J.E.; Lingegowda, H.; Symons, L.K.; Bougie, O.; Young, S.L.; Lessey, B.A.; Koti, M.; Tayade, C. IL-33 activates group 2 innate lymphoid cell expansion and modulates endometriosis. *JCI Insight* **2021**, *6*, e149699. [CrossRef] [PubMed]
321. Ruan, J.; Tian, Q.; Li, S.; Zhou, X.; Sun, Q.; Wang, Y.; Xiao, Y.; Li, M.; Chang, K.; Yi, X. The IL-33-ST2 axis plays a vital role in endometriosis via promoting epithelial-mesenchymal transition by phosphorylating β-catenin. *Cell Commun. Signal.* **2024**, *22*, 318. [CrossRef]
322. Xiao, F.; Liu, X.; Guo, S.W. Interleukin-33 Derived from Endometriotic Lesions Promotes Fibrogenesis through Inducing the Production of Profibrotic Cytokines by Regulatory T Cells. *Biomedicines* **2022**, *10*, 2893. [CrossRef]
323. Sharpe-Timms, K.L.; Bruno, P.L.; Penney, L.L.; Bickel, J.T. Immunohistochemical localization of granulocyte-macrophage colony-stimulating factor in matched endometriosis and endometrial tissues. *Am. J. Obstet. Gynecol.* **1994**, *171*, 740–745. [CrossRef] [PubMed]
324. Propst, A.M.; Quade, B.J.; Nowak, R.A.; Stewart, E.A. Granulocyte macrophage colony-stimulating factor in adenomyosis and autologous endometrium. *J. Soc. Gynecol. Investig.* **2002**, *9*, 93–97. [CrossRef] [PubMed]
325. Toullec, L.; Batteux, F.; Santulli, P.; Chouzenoux, S.; Jeljeli, M.; Belmondo, T.; Hue, S.; Chapron, C. High Levels of Anti-GM-CSF Antibodies in Deep Infiltrating Endometriosis. *Reprod. Sci.* **2020**, *27*, 211–217. [CrossRef] [PubMed]
326. Zhao, Y.Q.; Ren, Y.F.; Li, B.B.; Wei, C.; Yu, B. The mysterious association between adiponectin and endometriosis. *Front. Pharmacol.* **2024**, *15*, 1396616. [CrossRef]
327. Matarese, G.; Alviggi, C.; Sanna, V.; Howard, J.K.; Lord, G.M.; Carravetta, C.; Fontana, S.; Lechler, R.I.; Bloom, S.R.; De Placido, G. Increased leptin levels in serum and peritoneal fluid of patients with pelvic endometriosis. *J. Clin. Endocrinol. Metab.* **2000**, *85*, 2483–2487. [CrossRef]
328. Hong, J.; Yi, K.W. What is the link between endometriosis and adiposity? *Obstet. Gynecol. Sci.* **2022**, *65*, 227–233. [CrossRef]
329. Tian, Z.; Wang, Y.; Zhao, Y.; Chang, X.H.; Zhu, H.L. Serum and peritoneal fluid leptin levels in endometriosis: A systematic review and meta-analysis. *Gynecol. Endocrinol.* **2021**, *37*, 689–693. [CrossRef]
330. Wójtowicz, M.; Zdun, D.; Owczarek, A.J.; Skrzypulec-Plinta, V.; Olszanecka-Glinianowicz, M. Evaluation of adipokines concentrations in plasma, peritoneal, and endometrioma fluids in women operated on for ovarian endometriosis. *Front. Endocrinol.* **2023**, *14*, 1218980. [CrossRef]
331. Kim, T.H.; Bae, N.; Kim, T.; Hsu, A.L.; Hunter, M.I.; Shin, J.H.; Jeong, J.W. Leptin Stimulates Endometriosis Development in Mouse Models. *Biomedicines* **2022**, *10*, 2160. [CrossRef]

332. Kalaitzopoulos, D.R.; Lempesis, I.G.; Samartzis, N.; Kolovos, G.; Dedes, I.; Daniilidis, A.; Nirgianakis, K.; Leeners, B.; Goulis, D.G.; Samartzis, E.P. Leptin concentrations in endometriosis: A systematic review and meta-analysis. *J. Reprod. Immunol.* **2021**, *146*, 103338. [CrossRef]
333. Wu, M.H.; Chen, K.F.; Lin, S.C.; Lgu, C.W.; Tsai, S.J. Aberrant expression of leptin in human endometriotic stromal cells is induced by elevated levels of hypoxia inducible factor-1alpha. *Am. J. Pathol.* **2007**, *170*, 590–598. [CrossRef] [PubMed]
334. Zyguła, A.; Sankiewicz, A.; Sakowicz, A.; Dobrzyńska, E.; Dakowicz, A.; Mańka, G.; Kiecka, M.; Spaczynski, R.; Piekarski, P.; Banaszewska, B.; et al. Is the leptin/BMI ratio a reliable biomarker for endometriosis? *Front. Endocrinol.* **2024**, *15*, 1359182. [CrossRef] [PubMed]
335. Takemura, Y.; Osuga, Y.; Harada, M.; Hirata, T.; Koga, K.; Morimoto, C.; Hirota, Y.; Yoshino, O.; Yano, T.; Taketani, Y. Serum adiponectin concentrations are decreased in women with endometriosis. *Hum. Reprod.* **2005**, *20*, 3510–3513. [CrossRef]
336. Zhao, Z.; Wu, Y.; Zhang, H.; Wang, X.; Tian, X.; Wang, Y.; Qiu, Z.; Zou, L.; Tang, Z.; Huang, M. Association of leptin and adiponectin levels with endometriosis: A systematic review and meta-analysis. *Gynecol. Endocrinol.* **2021**, *37*, 591–599. [CrossRef]
337. Yi, K.W.; Shin, J.H.; Park, H.T.; Kim, T.; Kim, S.H.; Hur, J.Y. Resistin concentration is increased in the peritoneal fluid of women with endometriosis. *Am. J. Reprod. Immunol.* **2010**, *64*, 318–323. [CrossRef]
338. Oh, Y.K.; Ha, Y.R.; Yi, K.W.; Park, H.T.; Shin, J.H.; Kim, T.; Hur, J.Y. Increased expression of resistin in ectopic endometrial tissue of women with endometriosis. *Am. J. Reprod. Immunol.* **2017**, *78*, e12726. [CrossRef]
339. Lee, J.C.; Kim, S.H.; Oh, Y.S.; Kim, J.H.; Lee, S.R.; Chae, H.D. Increased Expression of Retinol-Binding Protein 4 in Ovarian Endometrioma and Its Possible Role in the Pathogenesis of Endometriosis. *Int. J. Mol. Sci.* **2021**, *22*, 5827. [CrossRef]
340. Lv, S.J.; Sun, J.N.; Gan, L.; Sun, J. Identification of molecular subtypes and immune infiltration in endometriosis: A novel bioinformatics analysis and In vitro validation. *Front. Immunol.* **2023**, *14*, 1130738. [CrossRef]
341. Krasnyi, A.M.; Sadekova, A.A.; Smolnova, T.Y.; Chursin, V.V.; Buralkina, N.A.; Chuprynin, V.D.; Yarotskaya, E.; Pavlovich, S.V.; Sukhikh, G.T. The Levels of Ghrelin, Glucagon, Visfatin and Glp-1 Are Decreased in the Peritoneal Fluid of Women with Endometriosis along with the Increased Expression of the CD10 Protease by the Macrophages. *Int. J. Mol. Sci.* **2022**, *23*, 10361. [CrossRef]
342. Morotti, M.; Vincent, K.; Becker, C.M. Mechanisms of pain in endometriosis. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2017**, *209*, 8–13. [CrossRef]
343. Zheng, P.; Zhang, W.; Leng, J.; Lang, J. Research on central sensitisation of endometriosis-associated pain: A systematic review of the literature. *J. Pain Res.* **2019**, *12*, 1447–1456. [CrossRef] [PubMed]
344. Monnin, N.; Fattet, A.J.; Koscinski, I. Endometriosis: Update of Pathophysiology, (Epi) Genetic and Environmental Involvement. *Biomedicines* **2023**, *11*, 978. [CrossRef] [PubMed]
345. Liu, S.J.; Lv, W. A laparoscopic surgery for deep infiltrating endometriosis and the review of literature. *Clin. Exp. Obstet. Gynecol.* **2016**, *43*, 616–618. [CrossRef]
346. Gentles, A.; Goodwin, E.; Bedaiwy, Y.; Marshall, N.; Yong, P.J. Nociplastic Pain in Endometriosis: A Scoping Review. *J. Clin. Med.* **2024**, *13*, 7521. [CrossRef]
347. Godin, S.K.; Wagner, J.; Huang, P.; Bree, D. The role of peripheral nerve signaling in endometriosis. *FASEB BioAdvances* **2021**, *3*, 802–813. [CrossRef]
348. Astruc, A.; Roux, L.; Robin, F.; Sall, N.R.; Dion, L.; Lavoué, V.; Legendre, G.; Leveque, J.; Bessede, T.; Bertrand, M.; et al. Advanced Insights into Human Uterine Innervation: Implications for Endometriosis and Pelvic Pain. *J. Clin. Med.* **2024**, *13*, 1433. [CrossRef]
349. Fattori, V.; Zaninelli, T.H.; Rasquel-Oliveira, F.S.; Heintz, O.K.; Jain, A.; Sun, L.; Seshan, M.L.; Peterse, D.; Lindholm, A.E.; Anchan, R.M.; et al. Nociceptor-to-macrophage communication through CGRP/RAMP1 signaling drives endometriosis-associated pain and lesion growth in mice. *Sci. Transl. Med.* **2024**, *16*, eadk8230. [CrossRef]
350. Lingegowda, H.; Williams, B.J.; Spiess, K.G.; Sisnett, D.J.; Lomax, A.E.; Koti, M.; Tayadeet, C. Role of the endocannabinoid system in the pathophysiology of endometriosis and therapeutic implications. *J. Cannabis Res.* **2022**, *4*, 54. [CrossRef]
351. Clayton, P.; Subah, S.; Venkatesh, R.; Hill, M.; Bogoda, N. Palmitoylethanolamide: A Potential Alternative to Cannabidiol. *J. Diet. Supp.* **2023**, *20*, 505–530. [CrossRef]
352. Farooqi, T.; Bhuyan, D.J.; Low, M.; Sinclair, J.; Leonardi, M.; Armour, M. Cannabis and Endometriosis: The Roles of the Gut Microbiota and the Endocannabinoid System. *J. Clin. Med.* **2023**, *12*, 7071. [CrossRef]
353. Vercellini, P.; Fedele, L.; Aimi, G.; Pietropaolo, G.; Consonni, D.; Crosignani, P.G. Association between endometriosis stage, lesion type, patient characteristics and severity of pelvic pain symptoms: A multivariate analysis of over 1000 patients. *Hum. Reprod.* **2007**, *22*, 266–271. [CrossRef] [PubMed]
354. As-Sanie, S.; Kim, J.; Schmidt-Wilcke, T.; Sundgren, P.C.; Clauw, D.J.; Napadow, V.; Harris, R.E. Functional Connectivity is Associated With Altered Brain Chemistry in Women with Endometriosis-Associated Chronic Pelvic Pain. *J. Pain* **2016**, *17*, 1–13. [CrossRef] [PubMed]
355. Eippert, F.; Tracey, I.; Chen, A.; De, E.; Argoff, C. Pain and the PAG: Learning from painful mistakes. *Nat. Neurosci.* **2014**, *17*, 1438–1439. [CrossRef]

356. Tran, L.V.; Tokushige, N.; Berbic, M.; Markham, R.; Fraser, I.S. Macrophages and nerve fibres in peritoneal endometriosis. *Hum. Reprod.* **2009**, *24*, 835–841. [CrossRef]
357. Wei, Y.; Liang, Y.; Lin, H.; Dai, Y.; Yao, S. Autonomic nervous system and inflammation interaction in endometriosis-associated pain. *J. Neuroinflamm.* **2020**, *17*, 80. [CrossRef]
358. Wu, J.; Xie, H.; Yao, S.; Liang, Y. Macrophage and nerve interaction in endometriosis. *J. Neuroinflamm.* **2017**, *14*, 53. [CrossRef]
359. Castro, J.; Maddern, J.; Erickson, A.; Harrington, A.M.; Brierley, S.M. Peripheral and central neuroplasticity in a mouse model of endometriosis. *J. Neurochem.* **2024**, *168*, 3777–3800. [CrossRef]
360. Machairiotis, N.; Vasilakaki, S.; Thomakos, N. Inflammatory Mediators and Pain in Endometriosis: A Systematic Review. *Biomedicines* **2021**, *9*, 54. [CrossRef]
361. Maddern, J.; Grundy, L.; Castro, J.; Brierley, S.M. Pain in Endometriosis. *Front. Cell. Neurosci.* **2020**, *14*, 590823. [CrossRef]
362. Greaves, E.; Temp, J.; Esnal-Zufiurre, A.; Mechsner, S.; Horne, A.W.; Saunders, P.T. Estradiol is a critical mediator of macrophage-nerve cross talk in peritoneal endometriosis. *Am. J. Pathol.* **2015**, *185*, 2286–2297. [CrossRef]
363. Falcone, T.; Flyckt, R. Clinical Management of Endometriosis. *Obstet. Gynecol.* **2018**, *131*, 557–571. [CrossRef] [PubMed]
364. Bajaj, P.; Bajaj, P.; Madsen, H.; Arendt-Nielsen, L. Endometriosis is associated with central sensitization: A psychophysical controlled study. *J. Pain* **2003**, *4*, 372–380. [CrossRef] [PubMed]
365. Ding, S.; Guo, X.; Zhu, L.; Wang, J.; Li, T.; Yu, Q.; Zhang, X. Macrophage-derived netrin-1 contributes to endometriosis-associated pain. *Ann. Transl. Med.* **2021**, *9*, 29. [CrossRef]
366. Forster, R.; Sarginson, A.; Velichkova, A.; Hogg, C.; Dorning, A.; Horne, A.W.; Saunders, P.T.K.; Greaves, E. Macrophage-derived insulin-like growth factor-1 is a key neurotrophic and nerve-sensitizing factor in pain associated with endometriosis. *FASEB J.* **2019**, *33*, 11210–11222. [CrossRef]
367. Hosseinirad, H.; Rahman, M.S.; Jeong, J.W. Targeting TET3 in macrophages provides a concept strategy for the treatment of endometriosis. *J. Clin. Investig.* **2024**, *134*, e185421. [CrossRef]
368. Li, J.; Wu, Z.; Li, N.; Wang, J.; Huang, M.; Zhu, L.; Wan, G.; Zhang, Z. Exploring macrophage and nerve interaction in endometriosis-associated pain: The inductive role of IL-33. *Inflamm. Res.* **2025**, *74*, 42. [CrossRef]
369. Midavaine, É.; Moraes, B.C.; Benitez, J.; Rodriguez, S.R.; Braz, J.M.; Kochhar, N.P.; Eckalbar, W.L.; Tian, L.; Domingos, A.I.; Pintar, J.E.; et al. Meningeal regulatory T cells inhibit nociception in female mice. *Science* **2025**, *388*, 96–104. [CrossRef]
370. Nielsen, N.M.; Jørgensen, K.T.; Pedersen, B.V.; Rostgaard, K.; Frisch, M. The co-occurrence of endometriosis with multiple sclerosis, systemic lupus erythematosus and Sjogren syndrome. *Hum. Reprod.* **2011**, *26*, 1555–1559. [CrossRef]
371. Matalliotaki, C.; Matalliotakis, M.; Zervou, M.I.; Trivli, A.; Matalliotakis, I.; Mavromatidis, G.; Spandidos, D.A.; Albertsen, H.M.; Chettier, R.; Ward, K.; et al. Co-existence of endometriosis with 13 non-gynecological co-morbidities: Mutation analysis by whole exome sequencing. *Mol. Med. Rep.* **2018**, *18*, 5053–5057. [CrossRef]
372. Hamouda, R.K.; Arzoun, H.; Sahib, I.; Escudero Mendez, L.; Srinivasan, M.; Shoukrie, S.I.; Dhanoa, R.K.; Selvaraj, R.; Malla, J.; Selvamani, T.Y.; et al. The Comorbidity of Endometriosis and Systemic Lupus Erythematosus: A Systematic Review. *Cureus* **2023**, *15*, e42362. [CrossRef]
373. Días, J.A., Jr.; de Oliveira, R.M.; Abrao, M.S. Antinuclear antibodies and endometriosis. *Int. J. Gynaecol. Obstet.* **2006**, *93*, 262–263. [CrossRef] [PubMed]
374. Kirkegaard, S.; Uldall Torp, N.M.; Andersen, S.; Andersen, S.L. Endometriosis, polycystic ovary syndrome, and the thyroid: A review. *Endocr. Connect.* **2024**, *13*, e230431. [CrossRef] [PubMed]
375. Mathur, S.P.; Holt, V.L.; Lee, J.H.; Jiang, H.; Rust, P.F. Levels of antibodies to transferrin and alpha 2-HS glycoprotein in women with and without endometriosis. *Am. J. Reprod. Immunol.* **1998**, *40*, 69–73. [CrossRef] [PubMed]
376. Dotan, A.; Kanduc, D.; Muller, S.; Makatsariya, A.; Shoenfeld, Y. Molecular mimicry between SARS-CoV-2 and the female reproductive system. *Am. J. Reprod. Immunol.* **2021**, *86*, e13494. [CrossRef]
377. Garvey, M. Endometriosis: Future Biological Perspectives for Diagnosis and Treatment. *Int. J. Mol. Sci.* **2024**, *25*, 12242. [CrossRef]
378. Zhang, W.; Li, K.; Jian, A.; Zhang, G.; Zhang, X. Prospects for potential therapy targeting immune associated factors in endometriosis (Review). *Mol. Med. Rep.* **2025**, *31*, 57. [CrossRef]
379. Kato, T.; Yasuda, K.; Matsushita, K.; Ishii, K.J.; Hirota, S.; Yoshimoto, T.; Shibahara, H. Interleukin-1/-33 Signaling Pathways as Therapeutic Targets for Endometriosis. *Front. Immunol.* **2019**, *10*, 2021. [CrossRef]
380. Fedotcheva, T.A.; Fedotcheva, N.I.; Shimanovsky, N.L. Progesterone as an Anti-Inflammatory Drug and Immunomodulator: New Aspects in Hormonal Regulation of the Inflammation. *Biomolecules* **2022**, *12*, 1299. [CrossRef]
381. Chang, C.Y.; Chiang, A.J.; Yan, M.J.; Lai, M.T.; Su, Y.Y.; Huang, H.Y.; Chang, C.Y.; Li, Y.H.; Li, P.F.; Chen, C.M.; et al. Ribosome biogenesis serves as a therapeutic target for treating endometriosis and the associated complications. *Biomedicines* **2022**, *10*, 185. [CrossRef]
382. Hamid, A.M.; Madkour, W.A.; Moawad, A.; Elzaher, M.A.; Roberts, M.P. Does cabergoline help in decreasing endometrioma size compared to LHRH agonist? A prospective randomized study. *Arch. Gynecol. Obstet.* **2014**, *290*, 677–682. [CrossRef]

383. DiVasta, A.D.; Stamoulis, C.; Gallagher, J.S.; Laufer, M.R.; Anchan, R.; Hornstein, M.D. Nonhormonal therapy for endometriosis: A randomized, placebo-controlled, pilot study of cabergoline versus norethindrone acetate. *F&S Rep.* **2021**, *2*, 454–461. [CrossRef]
384. Wyatt, J.; Fernando, S.M.; Powell, S.G.; Hill, C.J.; Arshad, I.; Probert, C.; Ahmed, S.; Hapangama, D.K. The role of iron in the pathogenesis of endometriosis: A systematic review. *Hum. Reprod. Open* **2023**, *2023*, hoad033. [CrossRef] [PubMed]
385. Tewary, S.; Lucas, E.S.; Fujihara, R.; Kimani, P.K.; Polanco, A.; Brighton, P.J.; Muter, J.; Fishwick, K.J.; Da Costa, M.J.M.D.; Ewington, L.J.; et al. Impact of sitagliptin on endometrial mesenchymal stem-like progenitor cells: A randomised, double-blind placebo-controlled feasibility trial. *eBioMedicine* **2020**, *51*, 102597. [CrossRef] [PubMed]
386. Li, Y.; Lv, X.; Jiang, M.; Jin, Z. Sitagliptin ameliorates hypoxia-induced damages in endometrial stromal cells: An implication in endometriosis. *Bioengineered* **2022**, *13*, 800–809. [CrossRef]
387. Grzymajlo, K.; El Hafny-Rahbi, B.; Kieda, C. Tumour suppressor PTEN activity is differentially inducible by myo-inositol phosphates. *J. Cell. Mol. Med.* **2023**, *27*, 879–890. [CrossRef]
388. Dera-Szymanowska, A.; Chmaj-Wierzchowska, K.; Horst, N.; Stryjakowska, K.; Wirlstein, P.; Andrusiewicz, M.; Florek, E.; Beltrano, J.; Szymanowski, K.; Wolun-Cholewa, M. Immunomodulation inhibits the development of endometriosis in rats. *J. Physiol. Pharmacol.* **2020**, *71*, 145–153. [CrossRef]
389. Chu, X.; Hou, M.; Li, Y.; Zhang, Q.; Wang, S.; Ma, J. Extracellular vesicles in endometriosis: Role and potential. *Front. Endocrinol.* **2024**, *15*, 1365327. [CrossRef]
390. Meczekalski, B.; Nowicka, A.; Bochynska, S.; Szczesnowicz, A.; Bala, G.; Szeliga, A. Kisspeptin and Endometriosis-Is There a Link? *J. Clin. Med.* **2024**, *13*, 7683. [CrossRef]
391. Chen, Y.; Li, T. Unveiling the Mechanisms of Pain in Endometriosis: Comprehensive Analysis of Inflammatory Sensitization and Therapeutic Potential. *Int. J. Mol. Sci.* **2025**, *26*, 1770. [CrossRef]
392. Genovese, T.; Siracusa, R.; D'Amico, R.; Cordaro, M.; Peritore, A.F.; Gugliandolo, E.; Crupi, R.; Trovato Salinaro, A.; Raffone, E.; Impellizzeri, D.; et al. Regulation of Inflammatory and Proliferative Pathways by Fotemustine and Dexamethasone in Endometriosis. *Int. J. Mol. Sci.* **2021**, *22*, 5998. [CrossRef]
393. Maksym, R.B.; Hoffmann-Młodzianowska, M.; Skibińska, M.; Rabijewski, M.; Mackiewicz, A.; Kieda, C. Immunology and Immunotherapy of Endometriosis. *J. Clin. Med.* **2021**, *10*, 5879. [CrossRef] [PubMed]
394. Park, S.R.; Kim, S.K.; Kim, S.R.; Kim, D.; Kim, K.W.; Hong, I.S.; Lee, H.Y. Noncanonical functions of glucocorticoids: A novel role for glucocorticoids in performing multiple beneficial functions in endometrial stem cells. *Cell Death Dis.* **2021**, *12*, 612. [CrossRef] [PubMed]
395. Jiao, X.F.; Li, H.; Zeng, L.; Yang, H.; Hu, Y.; Qu, Y.; Chen, W.; Sun, Y.; Zhang, W.; Zeng, X.; et al. Use of statins and risks of ovarian, uterine, and cervical diseases: A cohort study in the UK Biobank. *Eur. J. Clin. Pharmacol.* **2024**, *80*, 855–867. [CrossRef] [PubMed]
396. Qin, X.; Wang, Q.; Xu, D.; Sun, Y.; Xu, W.; Wang, B.; Yang, Z.; Hao, L. Atorvastatin exerts dual effects of lesion regression and ovarian protection in the prevention and treatment of endometriosis. *Eur. J. Pharmacol.* **2024**, *964*, 176261. [CrossRef]
397. Dillon, G.A.; Stanhewicz, A.E.; Serviente, C.; Flores, V.A.; Stachenfeld, N.; Alexander, L.M. Seven days of statin treatment improves nitric-oxide mediated endothelial-dependent cutaneous microvascular function in women with endometriosis. *Microvasc. Res.* **2022**, *144*, 104421. [CrossRef]
398. Perelló, M.; González-Foruria, I.; Castillo, P.; Martínez-Florensa, M.; Lozano, F.; Balasch, J.; Carmona, F. Oral Administration of Pentoxifylline Reduces Endometriosis-Like Lesions in a Nude Mouse Model. *Reprod. Sci.* **2017**, *24*, 911–918. [CrossRef]
399. Creus, M.; Fábregues, F.; Carmona, F.; del Pino, M.; Manau, D.; Balasch, J. Combined laparoscopic surgery and pentoxifylline therapy for treatment of endometriosis-associated infertility: A preliminary trial. *Hum. Reprod.* **2008**, *23*, 1910–1916. [CrossRef]
400. Kamencic, H.; Thiel, J.A. Pentoxifylline after conservative surgery for endometriosis: A randomized, controlled trial. *J. Minim. Invasive Gynecol.* **2008**, *15*, 62–66. [CrossRef]
401. Alborzi, S.; Ghotbi, S.; Parsanezhad, M.E.; Dehbashi, S.; Alborzi, S.; Alborzi, M. Pentoxifylline therapy after laparoscopic surgery for different stages of endometriosis: A prospective, double-blind, randomized, placebo-controlled study. *J. Minim. Invasive Gynecol.* **2007**, *14*, 54–58. [CrossRef]
402. Grammatis, A.L.; Georgiou, E.X.; Becker, C.M. Pentoxifylline for the treatment of endometriosis-associated pain and infertility. *Cochrane Database Syst. Rev.* **2021**, *8*, CD007677. [CrossRef]
403. Clemenza, S.; Sorbi, F.; Noci, I.; Capezzuoli, T.; Turrini, I.; Carriero, C.; Buffi, N.; Fambrini, M.; Petraglia, F. From pathogenesis to clinical practice: Emerging medical treatments for endometriosis. *Best Pract. Res. Clin. Obstet. Gynaecol.* **2018**, *51*, 92–101. [CrossRef] [PubMed]
404. Lebovic, D.I.; Kir, M.; Casey, C.L. Peroxisome proliferator-activated receptor-gamma induces regression of endometrial explants in a rat model of endometriosis. *Fertil. Steril.* **2004**, *82* (Suppl. S3), 1008–1013. [CrossRef] [PubMed]
405. Lebovic, D.I.; Mwenda, J.M.; Chai, D.C.; Mueller, M.D.; Santi, A.; Fisseha, S.; D'Hooghe, T. PPAR-gamma receptor ligand induces regression of endometrial explants in baboons: A prospective, randomized, placebo- and drug-controlled study. *Fertil. Steril.* **2007**, *88* (Suppl. S4), 1108–1119. [CrossRef]

406. Kim, C.H.; Lee, Y.J.; Kim, J.B.; Lee, K.H.; Kwon, S.K.; Ahn, J.W.; Kim, S.H.; Chae, H.D.; Kang, B.M. Effect of Pioglitazone on Production of Regulated upon Activation Normal T-cell Expressed and Secreted (RANTES) and IVF Outcomes in Infertile Women with Endometriosis. *Dev. Reprod.* **2013**, *17*, 207–213. [CrossRef]
407. Ren, X.U.; Wang, Y.; Xu, G.; Dai, L. Effect of rapamycin on endometriosis in mice. *Exp. Therap. Med.* **2016**, *12*, 101–106. [CrossRef]
408. Fan, J.; Chen, C.; Zhong, Y. A cohort study on IVF outcomes in infertile endometriosis patients: The effects of rapamycin treatment. *Reprod. Biomed. Online* **2024**, *48*, 103319. [CrossRef]
409. Palmer, S.S.; Altan, M.; Denis, D.; Tos, E.G.; Gotteland, J.P.; Osteen, K.G.; Bruner-Tran, K.L.; Nataraja, S.G. Bentamapimod (JNK Inhibitor AS602801) Induces Regression of Endometriotic Lesions in Animal Models. *Reprod. Sci.* **2016**, *23*, 11–23. [CrossRef]
410. Hussein, M.; Chai, D.C.; Kyama, C.M.; Mwenda, J.M.; Palmer, S.S.; Gotteland, J.P.; D'Hooghe, T.M. c-Jun NH2-terminal kinase inhibitor bentamapimod reduces induced endometriosis in baboons: An assessor-blind placebo-controlled randomized study. *Fertil. Steril.* **2016**, *105*, 815–824.e5. [CrossRef]
411. Feng, Y.; Dong, H.; Zheng, L. Ligustrazine inhibits inflammatory response of human endometrial stromal cells through the STAT3/IGF2BP1/RELA axis. *Pharm. Biol.* **2023**, *61*, 666–673. [CrossRef]
412. Jiang, T.; Chen, Y.; Gu, X.; Miao, M.; Hu, D.; Zhou, H.; Chen, J.; Teichmann, A.T.; Yang, Y. Review of the Potential Therapeutic Effects and Molecular Mechanisms of Resveratrol on Endometriosis. *Int. J. Women's Health* **2023**, *15*, 741–763. [CrossRef]
413. Bruner-Tran, K.L.; Osteen, K.G.; Taylor, H.S.; Sokalska, A.; Haines, K.; Duleba, A.J. Resveratrol inhibits development of experimental endometriosis in vivo and reduces endometrial stromal cell invasiveness in vitro. *Biol. Reprod.* **2011**, *84*, 106–112. [CrossRef] [PubMed]
414. Kodarahmian, M.; Amidi, F.; Moini, A.; Kashani, L.; Shabani Nashtaei, M.; Pazhohan, A.; Bahramrezai, M.; Berenjian, S.; Sobhani, A. The modulating effects of Resveratrol on the expression of MMP-2 and MMP-9 in endometriosis women: A randomized exploratory trial. *Gynecol. Endocrinol.* **2019**, *35*, 719–726. [CrossRef]
415. Khodarahmian, M.; Amidi, F.; Moini, A.; Kashani, L.; Salahi, E.; Danaii-Mehrabad, S.; Nashtaei, M.S.; Mojtahedi, M.F.; Esfandyari, S.; Sobhani, A. A randomized exploratory trial to assess the effects of resveratrol on VEGF and TNF-α 2 expression in endometriosis women. *J. Reprod. Immunol.* **2021**, *143*, 103248. [CrossRef] [PubMed]
416. Podgrajsek, R.; Ban Frangez, H.; Stimpfel, M. Molecular Mechanism of Resveratrol and Its Therapeutic Potential on Female Infertility. *Int. J. Mol. Sci.* **2024**, *25*, 3613. [CrossRef] [PubMed]
417. Rostami, S.; Alyasin, A.; Saedi, M.; Nekoonam, S.; Khodarahmian, M.; Moeini, A.; Amidi, F. Astaxanthin ameliorates inflammation, oxidative stress, and reproductive outcomes in endometriosis patients undergoing assisted reproduction: A randomized, triple-blind placebo-controlled clinical trial. *Front. Endocrinol.* **2023**, *14*, 1144323. [CrossRef]
418. Kamal, D.A.M.; Salamt, N.; Yusuf, A.N.M.; Kashim, M.I.A.M.; Mokhtar, M.H. Potential Health Benefits of Curcumin on Female Reproductive Disorders: A Review. *Nutrients* **2021**, *13*, 3126. [CrossRef]
419. Chowdhury, I.; Banerjee, S.; Driss, A.; Xu, W.; Mehrabi, S.; Nezhat, C.; Sidell, N.; Taylor, R.N.; Thompson, W.E. Curcumin attenuates proangiogenic and proinflammatory factors in human eutopic endometrial stromal cells through the NF-κB signaling pathway. *J. Cell. Physiol.* **2019**, *234*, 6298–6312. [CrossRef]
420. Jannatifar, R.; Asa, E.; Cheraghi, E.; Verdi, A. Nanomicelle curcumin improves oxidative stress, inflammatory markers, and assisted reproductive techniques outcomes in endometriosis cases: A randomized clinical trial. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2025**. [CrossRef]
421. Hipólito-Reis, M.; Neto, A.C.; Neves, D. Impact of curcumin, quercetin, or resveratrol on the pathophysiology of endometriosis: A systematic review. *Phytother. Res.* **2022**, *36*, 2416–2433. [CrossRef]
422. Jian, X.; Shi, C.; Luo, W.; Zhou, L.; Jiang, L.; Liu, K. Therapeutic effects and molecular mechanisms of quercetin in gynecological disorders. *Biomed. Pharmacother.* **2024**, *173*, 116418. [CrossRef]
423. Park, S.; Lim, W.; Bazer, F.W.; Whang, K.Y.; Song, G. Quercetin inhibits proliferation of endometriosis regulating cyclin D1 and its target microRNAs in vitro and in vivo. *J. Nutr. Biochem.* **2019**, *63*, 87–100. [CrossRef] [PubMed]
424. Włodarczyk, M.; Ciebiera, M.; Nowicka, G.; Łoziński, T.; Ali, M.; Al-Hendy, A. Epigallocatechin Gallate for the Treatment of Benign and Malignant Gynecological Diseases-Focus on Epigenetic Mechanisms. *Nutrients* **2024**, *16*, 559. [CrossRef] [PubMed]
425. Hung, S.W.; Liang, B.; Gao, Y.; Zhang, R.; Tan, Z.; Zhang, T.; Chung, P.W.J.; Chan, T.H.; Wang, C.C. An In-Silico, In-Vitro and In-Vivo Combined Approach to Identify NMNATs as Potential Protein Targets of ProEGCG for Treatment of Endometriosis. *Front. Pharmacol.* **2021**, *12*, 714790. [CrossRef]
426. Stochino Loi, E.; Pontis, A.; Cofelice, V.; Pirarba, S.; Fais, M.F.; Daniilidis, A.; Melis, I.; Paoletti, A.M.; Angioni, S. Effect of ultramicronized-palmitoylethanolamide and co-micronized palmitoylethanolamide/polydatin on chronic pelvic pain and quality of life in endometriosis patients: An open-label pilot study. *Int. J. Women's Health* **2019**, *11*, 443–449. [CrossRef]
427. Indraccolo, U.; Indraccolo, S.R.; Mignini, F. Micronized palmitoylethanolamide/trans-polydatin treatment of endometriosis-related pain: A meta-analysis. *Ann. Ist. Super. Sanita* **2017**, *53*, 125–134. [CrossRef]

428. Genovese, T.; Cordaro, M.; Siracusa, R.; Impellizzeri, D.; Caudullo, S.; Raffone, E.; Macrí, F.; Interdonato, L.; Gugliandolo, E.; Interlandi, C.; et al. Molecular and Biochemical Mechanism of Cannabidiol in the Management of the Inflammatory and Oxidative Processes Associated with Endometriosis. *Int. J. Mol. Sci.* **2022**, *23*, 5427. [CrossRef]
429. Sinclair, J.; Collett, L.; Abbott, J.; Pate, D.W.; Sarris, J.; Armour, M. Effects of cannabis ingestion on endometriosis-associated pelvic pain and related symptoms. *PLoS ONE* **2021**, *16*, e0258940. [CrossRef]
430. Mistry, M.; Simpson, P.; Morris, E.; Fritz, A.K.; Karavadra, B.; Lennox, C.; Prosser-Snelling, E. Cannabidiol for the Management of Endometriosis and Chronic Pelvic Pain. *J. Minim. Invasive Gynecol.* **2022**, *29*, 169–176. [CrossRef]
431. Dimitrov, N.V.; Meyer, C.J.; Perloff, M.; Ruppenthal, M.M.; Phillipich, M.J.; Gilliland, D.; Malone, W.; Minn, F.L. Alteration of retinol-binding-protein concentrations by the synthetic retinoid fenretinide in healthy human subjects. *Am. J. Clin. Nutr.* **1990**, *51*, 1082–1087. [CrossRef]
432. Pavone, M.E.; Malpani, S.S.; Dyson, M.; Kim, J.J.; Bulun, S.E. Fenretinide: A Potential Treatment for Endometriosis. *Reprod. Sci.* **2016**, *23*, 1139–1147. [CrossRef]
433. Garić, D.; Dumut, D.C.; Shah, J.; De Sanctis, J.B.; Radzioch, D. The role of essential fatty acids in cystic fibrosis and normalizing effect of fenretinide. *Cell. Mol. Life Sci.* **2020**, *77*, 4255–4267. [CrossRef] [PubMed]
434. Aristarco, V.; Serrano, D.; Maisonneuve, P.; Guerrieri-Gonzaga, A.; Lazzeroni, M.; Feroce, I.; Macis, D.; Cavadini, E.; Albertazzi, E.; Jemos, C.; et al. Fenretinide in Young Women at Genetic or Familial Risk of Breast Cancer: A Placebo-Controlled Biomarker Trial. *Cancer Prev. Res.* **2024**, *17*, 255–263. [CrossRef] [PubMed]
435. Yarmolinskaya, M.; Denisova, A.; Tkachenko, N.; Ivashenko, T.; Bespalova, O.; Tolibova, G.; Tral, T. Vitamin D significance in pathogenesis of endometriosis. *Gynecol. Endocrinol.* **2021**, *37* (Suppl. S1), 40–43. [CrossRef] [PubMed]
436. Kalaitzopoulos, D.R.; Samartzis, N.; Daniilidis, A.; Leeners, B.; Makieva, S.; Nirgianakis, K.; Dedes, I.; Metzler, J.M.; Imesch, P.; Lempesis, I.G. Effects of vitamin D supplementation in endometriosis: A systematic review. *Reprod. Biol. Endocrinol.* **2022**, *20*, 176. [CrossRef]
437. Xie, B.; Liao, M.; Huang, Y.; Hang, F.; Ma, N.; Hu, Q.; Wang, J.; Jin, Y.; Qin, A. Association between vitamin D and endometriosis among American women: National Health and Nutrition Examination Survey. *PLoS ONE* **2024**, *19*, e0296190. [CrossRef]
438. Quattrone, F.; Sanchez, A.M.; Pannese, M.; Hemmerle, T.; Viganò, P.; Candiani, M.; Petraglia, F.; Neri, D.; Panina-Bordignon, P. The Targeted Delivery of Interleukin 4 Inhibits Development of Endometriotic Lesions in a Mouse Model. *Reprod. Sci.* **2015**, *22*, 1143–1152. [CrossRef]
439. Somigliana, E.; Viganò, P.; Rossi, G.; Carinelli, S.; Vignali, M.; Panina-Bordignon, P. Endometrial ability to implant in ectopic sites can be prevented by interleukin-12 in a murine model of endometriosis. *Hum. Reprod.* **1999**, *14*, 2944–2950. [CrossRef]
440. Itoh, H.; Sashihara, T.; Hosono, A.; Kaminogawa, S.; Uchida, M. Interleukin-12 inhibits development of ectopic endometriotic tissues in peritoneal cavity via activation of NK cells in a murine endometriosis model. *Cytotechnology* **2011**, *63*, 133–141. [CrossRef]
441. Altintas, D.; Kokcu, A.; Tosun, M.; Cetinkaya, M.B.; Kandemir, B. Efficacy of recombinant human interferon alpha-2b on experimental endometriosis. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2008**, *139*, 95–99. [CrossRef]
442. Dicitore, A.; Castiglioni, S.; Saronni, D.; Gentilini, D.; Borghi, M.O.; Stabile, S.; Vignali, M.; Di Blasio, A.M.; Persani, L.; Vitale, G. Effects of human recombinant type I IFNs (IFN-α2b and IFN-β1a) on growth and migration of primary endometrial stromal cells from women with deeply infiltrating endometriosis: A preliminary study. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2018**, *230*, 192–198. [CrossRef]
443. Acién, P.; Quereda, F.; Campos, A.; Gomez-Torres, M.J.; Velasco, I.; Gutierrez, M. Use of intraperitoneal interferon alpha-2b therapy after conservative surgery for endometriosis and postoperative medical treatment with depot gonadotropin-releasing hormone analog: A randomized clinical trial. *Fertil. Steril.* **2002**, *78*, 705–711. [CrossRef] [PubMed]
444. He, Y.; Xiong, T.; Guo, F.; Du, Z.; Fan, Y.; Sun, H.; Feng, Z.; Zhang, G. Interleukin-37b inhibits the growth of murine endometriosis-like lesions by regulating proliferation, invasion, angiogenesis and inflammation. *Mol. Hum. Reprod.* **2020**, *26*, 240–255. [CrossRef] [PubMed]
445. Li, L.; Liao, Z.; Ye, M.; Jiang, J. Recombinant human IL-37 inhibited endometriosis development in a mouse model through increasing Th1/Th2 ratio by inducing the maturation of dendritic cells. *Reprod. Biol. Endocrinol.* **2021**, *19*, 128. [CrossRef]
446. Önalan, G.; Tohma, Y.A.; Zeyneloğlu, H.B. Effect of Etanercept on the Success of Assisted Reproductive Technology in Patients with Endometrioma. *Gynecol. Obstet. Investig.* **2018**, *83*, 358–364. [CrossRef]
447. Liu, M.; Li, Y.; Yuan, Y.; Jiang, M.; Yin, P.; Yang, D. Peri-implantation treatment with TNF-α inhibitor for endometriosis and/or adenomyosis women undergoing frozen-thawed embryo transfer: A retrospective cohort study. *J. Reprod. Immunol.* **2025**, *167*, 104415. [CrossRef]

448. Lu, D.; Song, H.; Shi, G. Anti-TNF-α treatment for pelvic pain associated with endometriosis. *Cochrane Database Syst. Rev.* **2013**, *2013*, CD008088. [CrossRef]
449. Sullender, R.T.; Agarwal, R.K.; Jacobs, M.B.; Wessels, J.M.; Foster, W.G.; Agarwal, S.K. Pilot Study of IL-1 Antagonist Anakinra for Treatment of Endometriosis. *Int. J. Women's Health* **2024**, *16*, 1583–1593. [CrossRef]