

Table SI. Role of inflammatory cytokines and immune cells in AM formation and fertility.

A, Pro-inflammatory cytokines				
Molecular marker	Expression in AM	Mechanisms promoting AM formation	Role in fertility	(Refs.)
IL-6	Upregulated	1. Activates the TLR4/NF- κ B, IL-6/JAK2/STAT3, PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways; 2. Promotes proliferation and invasion; 3. Correlates with the severity of dysmenorrhea.	1. Persistent activation of the JAK/STAT3 pathway impairs endometrial receptivity and affects embryo implantation; 2. Causes immune and vascular dysfunction at the placental/decidual interface; 3. Targeted therapy (such as tocilizumab) may improve pregnancy outcomes.	(1-4)
CXCL8	Upregulated	1. Activates the CXCL8/CXCR1 axis and FAK/PI3K/AKT signaling pathway; 2. Enhances the adhesion and invasive capacity of stromal cells; 3. Loss of cyclical expression patterns leads to disordered repair of the eutopic endometrium and aberrant angiogenesis.	1. Reduced cervical mucus fertilization environment; 2. Correlated with oocyte maturation and embryo quality; 3. Interferes with blastocyst implantation via CXCR1.	(5-8)
IL1B	Upregulated	1. Activates the TLR/MyD88 pathway; 2. Upregulates IL-6, CXCL8, COX-2 and VEGF through the canonical NF- κ B pathway.	1. Disrupts Th17/Treg balance; 2. IL-1Ra/IL-1 β predicts adverse pregnancy; 3. Impairs E2/P-mediated ER; 4. Inhibits sperm-zona pellucida binding.	(9-13)
COX-2	Upregulated	1. Promotes proliferation, angiogenesis and immune suppression; 2. Activates PGE2/CYP19A1 (estrogen-inflammation loop); 3. Serves as a biomarker for dysmenorrhea in patients with AM.	1. Impairs telocyte function; 2. Disrupts the gamete transport/implantation microenvironment.	(14-17)
IL-15	Upregulated	1. Drives endometriosis-associated inflammation.	1. Induces abnormal uNK proliferation and maturation; 2. Exacerbates lesion inflammation; 3. Causes decidualization defects.	(18,19)
IL22	Upregulated	1. Enhances the invasiveness of stromal cells; 2. Upregulates the expression of pro-angiogenic factors such as VEGF, IL-6 and IL-8.	Serum levels are inversely correlated with the IVF embryo implantation rate.	(20-22)
NF- κ B	Upregulated	1. A central hub of inflammatory responses regulates multiple pro-inflammatory mediators (such as IL-6, IL-8, TNF- α and COX-2);	1. Alters Th17/Treg cell ratio, affecting trophoblast invasion and angiogenesis in the placenta; 2. Downregulates PR-B expression;	(23-26)

		2. Modulates inflammation, proliferation, angiogenesis and tissue remodeling.	3. Alters LIF expression.	
B, Anti-inflammatory cytokines				
Molecular marker	Expression in AM	Mechanisms promoting AM formation	Role in fertility	(Refs.)
IL10	Upregulated	1. Induces HLA-G; 2. Downregulates classical class I and class II antigens; 3. Suppresses pro-inflammatory cytokines; 4. Evades immune surveillance.	1. Regulates the STAT3/HOXA10 signaling pathway, affecting ER; 2. Reduces the levels of uNK cells at the maternal-placental interface, supporting normal pregnancy.	(27-29)
IL-33	Downregulated	Inhibits NF- κ B transcriptional activity. Its function in the endometrium is not yet clear.	1. IL-33/ST2 pathway regulates the expression of HOXA10; 2. Affects the decidualization process.	(30)
C, Immune cell-derived cytokines				
Molecular marker	Expression in AM	Mechanisms promoting AM formation	Role in fertility	(Refs.)
TGF- β	Upregulated	1. Activates Smad2/3 phosphorylation; 2. Induces EMT, FMT and SMM, 3. Promotes collagen synthesis in the ECM; 4. Inhibits MMPs, leading to ECM metabolic imbalance.	1. Anti-TGF- β 1 therapy can improve fibrosis progression and pregnancy outcomes; 2. TGF- β 1 may serve as a potential target for improving endometrial receptivity.	(31-33)
IL11	Downregulated	1. Key implantation regulator; 2. Together with its receptor, it is downregulated in AM.	1. Involved in aberrant gp130 signaling; 2. Reduced expression leads to defective decidualization.	(34,35)
LIF	Downregulated	1. IL-6 cytokine family member; 2. Regulates decidualization and endometrial receptivity.	Mediates blastocyst development, decidualization and trophoblast differentiation	(36)
D, Immunocytes				
Molecular marker	Expression in AM	Mechanisms promoting AM formation	Role in fertility	(Refs.)
Macrophages	M1 are downregulated and M2 are upregulated	1. Imbalance in M1/M2 macrophage phenotypes; 2. M2 secretes IL-10, TGF- β and other factors; 3. Promote angiogenesis and proliferation of ectopic lesions; 4. CCL2/CCR2 axis, miR-301a-3p and EV-LGMNP1 drive M2 polarization.	1. Disrupt maternal-fetal interface in pro-inflammatory microenvironments; 2. Impair LIF production; 3. Affect endometrial receptivity.	(17,37-40)

NK cells	Upregulated	1. Increases uNK cells count; 2. Reduces expression of KIRs.	1. Linked to recurrent miscarriage/implantation failure; 2. Mediates spiral artery/placental development.	(41-43)
Mast cells	Upregulated	1. Releases TGF- β 1 and FGF; 2. Promotes disease progression.	No clear reports are available.	(44)
T cells	Upregulated	Elevated T cell subsets (CD3 ⁺ T cells and CD4 ⁺ and CD8 ⁺ T cells) in eutopic endometrium.	1. Imbalance in the Th17/Treg ratio weakens the maternal-fetal immune tolerance; 2. Increases implantation immune rejection risk.	(45)

AM, adenomyosis; TLR4, Toll-like receptor 4; NF- κ B, nuclear factor κ -B; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; AKT, protein kinase B; mTOR, mammalian target of rapamycin; RAS, rat sarcoma virus; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase kinase; ERK, extracellular regulated protein kinases; E2, estradiol; CXCL8, interleukin-8; CXCR1, C-X-C chemokine receptor type 1; FAK, focal adhesion kinase; VEGF, vascular endothelial growth factor; IL, interleukin; MyD88, myeloid differentiation primary response 88; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; CYP19A1, cytochrome P450 family 19 subfamily A member 1; uNK, Uterine natural killer cells; IVF, *in vitro* fertilization; HLA-G, human leukocyte antigen-G; ST2, suppression of tumorigenicity 2; HOXA10, homeobox A10; ER, endometrial receptivity; TGF- β , transforming growth factor- β ; EMT, epithelial-mesenchymal transition; FMT, fibroblast-myofibroblast transition; SMM, smooth muscle metaplasia; ECM, extracellular matrix; MMPs, matrix metalloproteinases; gp130, glycoprotein 130; LIF, leukemia inhibitory factor; CCL2, C-C motif chemokine ligand 2; CCR2, C-C chemokine receptor type 2; EV-LGMNP1, extracellular vesicle-derived long non-coding RNA gastric cancer metastasis-associated lncRNA 1; KIRs, killer cell immunoglobulin-like receptors; FGF, fibroblast growth factor; Th17, T helper 17 cells; Treg, regulatory T cells.

Table SII. Summary of drugs for the treatment of female infertility associated with adenomyosis based on inflammatory cytokines.

A, Non-steroidal anti-inflammatory drugs				
Medication	Experimental model/study design	Key drug targets	Function	(Refs.)
Celecoxib	<i>In vitro</i> (ESCs) and clinical trial.	COX-2, NF- κ B and IL1B/IL-6/TNF	1. Downregulates IL1B, IL-6, TNF and NF- κ B expression; 2. Inhibits COX-2 and PGE2; 3. Improves inflammation-related pregnancy failure.	(46,47)
B, Hormonotherapy				
Medication	Experimental model/study design	Key drug targets	Function	(Refs.)
GnRH-a	Clinical trial, mice, <i>in vitro</i> and ESCs.	GnRH receptor, IL1B/MCP-1/VEGF and HOXA10/HOXA11	1. Decreases IL1B, MCP-1 and VEGF; 2. Increases HOXA10, HOXA11, integrin β 3 and LIF, improving the level of embryo implantation.	(48-51)
GnRH-A	Clinical trial.	Pituitary GnRH receptor and pro-inflammatory cytokines	1. Blocks pituitary GnRH receptors (no “flare-up effect”); 2. Rapid ovarian function recovery; 3. Downregulates pro-inflammatory cytokines	(50,52)
Dienogest	<i>In vitro</i> , ESCs and clinical trial.	HPO axis, IL-1 β /IL-6/IL-8/TNF- α and NK cells	1. Inhibits HPO axis (E2: 30-50 pg/ml); 2. Suppresses immunity, inflammation and angiogenesis; 3. Regulates key inflammatory cytokine expression (such as IL-1 β , IL-6, IL-8, IL-10, IL-18, MCP-1 and TNF- α); 3. Increases NK cells (promote immune tolerance)	(53,54)
C, Immunomodulators - interleukin-targeted therapies				
Medication	Experimental model/study design	Key drug targets	Function	(Refs.)
Tocilizumab	<i>In vitro</i> and ESCs.	IL-6 receptor and JAK2/STAT3	1. Inhibits exosome-induced cell proliferation and migration and induces G1/S cell cycle arrest; 2. Suppresses the IL-6/JAK2/STAT3 signaling pathway.	(55)
AMY109	<i>In vivo</i> and monkey model.	IL-8/MCP-1 and neutrophil chemokine receptors	1. Inhibits neutrophil recruitment; 2. Decreases IL-8 and MCP-1; 3. No impairment to ovarian function.	(56,57)
Metformin	<i>In vivo</i> (mice) and clinical trial.	IL-6/IL-8, VEGF/MMP9 and LIF/HOXA10	1. Reduces uterine volume and AM incidence; 2. Downregulates pro-inflammatory cytokines (IL-6 and IL-8) and angiogenic factors (VEGF and MMP9); 3. Upregulates LIF and HOXA10, enhances endometrial receptivity and supports successful pregnancy outcomes.	(58,59)
Anakinra	Clinical trial.	IL-1 receptor	1. Reduces VAS pain scores;	(60)

			2. No effect on ovulation/menstrual regularity.	
LXA4	<i>In vivo</i> (mice).	IL1B/IL-6, COX-2, VEGF/HIF1A and TGF-β	1. Downregulates proinflammatory cytokines IL1B and IL-6, COX-2 and PGE; 2. Decreases VEGF and HIF1A; 3. Regulates the TGF-β subtypes, decreases lesion size and improves fertility	(61,62)
D, Immunomodulators - NF-κB Inhibitors				
Medication	Experimental model/study design	Key drug targets	Function	(Refs.)
Disulfiram	<i>In vivo</i> (rats)	NF-κB (nuclear translocation) and VEGF-A/MMP2	1. Decreases total antioxidant status, TNF-α and IL-1β; 2. Inhibits NF-κB; 3. Downregulates VEGF-A and MMP2 expression; 4. Reduces postoperative inflammatory adhesions.	(63,64)
Melatonin	<i>In vivo</i> (mouse)	ROS, TNF/IL1B, NF-κB and VEGF	1. Inhibits ROS, TNF and IL1B (suppress NF-κB); 2. Increases the expression of VEGF; 3. Alleviates uterine oxidative damage.	(65,66)
E, Immunomodulators - TNF-α inhibitors				
Medication	Experimental model/study design	Key drug targets	Function	(Refs.)
Etanercept	<i>In vivo</i> (baboon) and <i>in vitro</i> (rat).	TNF-α and VEGF/IL-6	1. Downregulates VEGF, IL-6 and TNF; 2. Reduces lesion volume; 3. Improves pregnancy outcomes.	(67-69)
Pentoxifylline	<i>In vivo</i> (rat) and <i>in vivo</i> (human).	IL1B and TNF	1. Downregulates IL1B, TNF and other inflammatory cytokines; 2. Alleviates postoperative pain; 3. Improves pregnancy outcomes.	(70,71)
F, Development of new technologies - specialized targeting materials				
Medication	Experimental model/study design	Key drug targets	Function	(Refs.)
Intralipid	<i>In vitro</i> (NK cells).	NK cell activity (immunoreceptors)	1. Suppresses NK cell activity (anti-inflammatory and immunosuppressive effects); 2. Increases live birth rates; 3. Improves adverse pregnancy outcomes.	(72-74)
Nanoparticles	<i>In vivo</i> and human	IL-4 plasmid (macrophages), ROS and oocyte protective proteins	1. Targeted delivery of IL-4 (reverse M2 polarization); 2. Eliminates ROS to inhibit angiogenesis and protect oocytes.	(75-78)

MicroRNA	<i>In vitro</i> and ESCs.	NF- κ B (miR-182), IKK β (miR-199a) and IL-8	1. miR-182 inhibits proliferation, migration, invasion and EMT (suppress NF- κ B); 2. miR-199a targets IKK β (inhibits NF- κ B/IL-8).	(23,79-83)
G, Traditional Chinese Medicine				
Medication	Experimental model/study design	Key drug targets	Function	(Refs.)
Paeoniflorin sodium	<i>In vitro</i> and ESCs	PGE2 and PGF2 α (prostaglandin synthases)	1. Reduces PGE2 and PGF2 α ; 2. Alleviates lesion inflammation.	(84)
Resveratrol	<i>In vivo</i> (mice) and <i>in vivo</i> (human).	COX-2 and aromatase (CYP19A1)	1. Inhibits myometrial infiltration and pain (no hormonal homeostasis); 2. Downregulates COX-2 and aromatase expression.	(85)
Oleuropein	<i>In vivo</i> (mice).	ER β , NLRP3 inflammasome, TNF α /NF- κ B and IL-6/JAK/STAT3	1. Inhibits ER β /NLRP3 (suppresses IL-1 β); 2. Regulates multiple signaling pathways, including TNF α /NF- κ B, ROS and IL-6/JAK/STAT3; 3. Repairs decidualization defects.	(86,87)
Quercetin	<i>In vitro</i> and ESCs.	Fascin/ezrin and MMP-2/MMP-9 (invasion proteins)	1. Inhibits ectopic ESC migration and invasion (dose-dependent); 2. Downregulates invasion-related proteins such as fascin, ezrin and MMP-2/MMP-9.	(88)
Tanshinone IIA sulfonate	<i>In vivo</i> (rats),	TGF- β 1/Smad3/NF- κ B;	Sodium tanshinone IIA sulfonate inhibits platelet aggregation and suppresses the TGF- β 1/Smad3 and NF- κ B signaling pathways, thus attenuating fibrosis.	(89)
Rhein	<i>In vivo</i> (mice)	NF- κ B/Wnt/ β -catenin	Rhein reduces IL-1 β -induced NF- κ B expression and inhibits Wnt/ β -catenin; exerts anti-inflammatory/fibrotic effect.	(50)
Berberine	<i>In vitro</i> and EESC.	IL-6/IL-8 and ESC proliferation	Berberine reduces invasiveness, downregulates IL-6 and IL-8 and promotes ESCs apoptosis.	(90)

COX-2, cyclooxygenase-2; CYP19A1, cytochrome P450 family 19 subfamily A member 1; E2, estradiol; EMT, epithelial-mesenchymal transition; EESC, ectopic endometrial stromal cells; ESCs, endometrial stromal cells; Er β , estrogen receptor β ; GnRH-a, gonadotropin-releasing hormone agonist; GnRH-A, gonadotropin-releasing hormone antagonist; HIF1A, hypoxia-inducible factor 1 α ; HPO, hypothalamic-pituitary-ovarian; HOXA10, homeobox A10; HOXA11, homeobox A11; IKK β , I κ B kinase β ; IL, interleukin; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; LIF, leukemia inhibitory factor; MCP-1, monocyte chemoattractant protein-1; MMP, Matrix Metalloproteinase; miR, microRNA; NK cells, natural killer cells; NLRP3, nod-like receptor family pyrin domain containing 3; PGE2, prostaglandin E2; PGF2 α , prostaglandin F2 α ; ROS, reactive oxygen species; TGF- β , transforming growth factor- β ; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

References

1. Zhihong N, Yun F, Pinggui Z, Sulian Z and Zhang A: Cytokine profiling in the eutopic endometrium of adenomyosis during the implantation window after ovarian stimulation. *Reprod Sci* 23: 124-133, 2016.
2. Incognito GG, Di Guardo F, Gulino FA, Genovese F, Benvenuto D, Lello C and Palumbo M: Interleukin-6 as a useful predictor of endometriosis-associated infertility: A systematic review. *Int J Fertil Steril* 17: 226-230, 2023.
3. Wei LH, Kuo ML, Chen CA, Chou CH, Lai KB, Lee CN and Hsieh CY: Interleukin-6 promotes cervical tumor growth by VEGF-dependent angiogenesis via a STAT3 pathway. *Oncogene* 22: 1517-1527, 2003.
4. Guo J, Chen L, Luo N, Li C, Chen R, Qu X, Liu M, Kang L and Cheng Z: LPS/TLR4-mediated stromal cells acquire an invasive phenotype and are implicated in the pathogenesis of adenomyosis. *Sci Rep* 6: 21416, 2016.
5. Liu XN and Cheng ZP: Expression of high-mobility group box-1 in eutopic/ectopic endometrium and correlations with inflammation-related factors in adenomyosis. *Gynecol Endocrinol* 39: 2269265, 2023.
6. Ulukus EC, Ulukus M, Seval Y, Zheng W and Arici A: Expression of interleukin-8 and monocyte chemoattractant protein-1 in adenomyosis. *Hum Reprod* 20: 2958-2963, 2005.
7. Zheng D, Duan H, Wang S, Xu Q, Gan L, Li J and Dong Q: FAK regulates epithelial-mesenchymal transition in adenomyosis. *Mol Med Rep* 18: 5461-5472, 2018.
8. Kataranovski M, Radojčić L, Prokić V and Vojvodić D: Presence of interleukin-8 and the IL-1 receptor antagonist in the cervical mucus of fertile and infertile women. *Vojnosanit Pregl* 61: 359-364, 2004.
9. De Nardo D: Toll-like receptors: Activation, signalling and transcriptional modulation. *Cytokine* 74: 181-189, 2015.
10. Dinarello CA: Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol* 27: 519-550, 2009.
11. Equils O, Kellogg C, McGregor J, Gravett M, Neal-Perry G and Gabay C: The role of the IL-1 system in pregnancy and the use of IL-1 system markers to identify women at risk for pregnancy complications†. *Biol Reprod* 103: 684-694, 2020.
12. Wang H, Shi G, Li M, Fan H, Ma H and Sheng L: Correlation of IL-1 and HB-EGF with endometrial receptivity. *Exp Ther Med* 16: 5130-5136, 2018.
13. Faber BM, Chegini N, Mahony MC and Coddington CC III: Macrophage secretory products and sperm zona pellucida binding. *Obstet Gynecol* 98: 668-673, 2001.
14. Li C, Chen R, Jiang C, Chen L and Cheng Z: Correlation of LOX-5 and COX-2 expression with inflammatory pathology and clinical features of adenomyosis. *Mol Med Rep* 19: 727-733, 2019.
15. Zhang J, Shi L, Duan J, Li M and Li C: Proteomic detection of COX-2 pathway-related factors in patients with adenomyosis. *PeerJ* 12: e16784, 2024.

16. Yang XJ, Yang J, Liu Z, Yang G and Shen ZJ: Telocytes damage in endometriosis-affected rat oviduct and potential impact on fertility. *J Cell Mol Med* 19: 452-462, 2015.
17. Mechsner S, Grum B, Gericke C, Loddenkemper C, Dudenhausen JW and Ebert AD: Possible roles of oxytocin receptor and vasopressin-1 α receptor in the pathomechanism of dysperistalsis and dysmenorrhea in patients with adenomyosis uteri. *Fertil Steril* 94: 2541-2546, 2010.
18. Godbole G and Modi D: Regulation of decidualization, interleukin-11 and interleukin-15 by homeobox A 10 in endometrial stromal cells. *J Reprod Immunol* 85: 130-139, 2010.
19. Chegini N, Roberts M and 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* 49: 75-83, 2003.
20. Wang Q, Wang L, Shao J, Wang Y, Jin LP, Li DJ and Li MQ: L-22 enhances the invasiveness of endometrial stromal cells of adenomyosis in an autocrine manner. *Int J Clin Exp Pathol* 7: 5762-5771, 2014.
21. Heidari Z, Moudi B, Sheibak N, Asemi-Rad A, Keikha N, Mahmoudzadeh-Sagheb H and Ghasemi M: Interleukin 22 expression during the implantation window in the endometrium of women with unexplained recurrent pregnancy loss and unexplained infertility compared to healthy parturient individuals. *J Interferon Cytokine Res* 41: 461-468, 2021.
22. Shang WQ, Yu JJ, Zhu L, Zhou WJ, Chang KK, Wang Q and Li MQ: Blocking IL-22, a potential treatment strategy for adenomyosis by inhibiting crosstalk between vascular endothelial and endometrial stromal cells. *Am J Transl Res* 7: 1782-1797, 2015.
23. Wu M and Zhang Y: MiR-182 inhibits proliferation, migration, invasion and inflammation of endometrial stromal cells through deactivation of NF- κ B signaling pathway in endometriosis. *Mol Cell Biochem* 476: 1575-1588, 2021.
24. Xu L, Yu Y, Sang R, Ge B, Wang M, Zhou H and Zhang X: Inonotus obliquus polysaccharide protects against adverse pregnancy caused by *Toxoplasma gondii* infection through regulating Th17/Treg balance via TLR4/NF- κ B pathway. *Int J Biol Macromol* 146: 832-840, 2020.
25. Nakamura H, Kimura T, Ogita K, Nakamura T, Takemura M, Shimoya K, Koyama S, Tsujie T, Koyama M and Murata Y: NF-kappaB activation at implantation window of the mouse uterus. *Am J Reprod Immunol* 51: 16-21, 2004.
26. Balkwill FR, Capasso M and Hagemann T: The tumor microenvironment at a glance. *J Cell Sci* 125: 5591-5596, 2012.
27. Thellin O, Coumans B, Zorzi W, Igout A and Heinen E: Tolerance to the foeto-placental 'graft': Ten ways to support a child for nine months. *Curr Opin Immunol* 12: 731-737, 2000.
28. Wang J, Huang C, Jiang R, Du Y, Zhou J, Jiang Y, Yan Q, Xing J, Hou X, Zhou J, *et al*: Decreased endometrial IL-10 impairs endometrial receptivity by downregulating HOXA10 expression in women with adenomyosis. *Biomed Res Int* 2018: 2549789, 2018.

29. Sowmya S, Sri Manjari K, Ramaiah A, Sunitha T, Nallari P, Jyothy A and Venkateshwari A: Interleukin 10 gene promoter polymorphisms in women with early-onset pre-eclampsia. *Clin Exp Immunol* 178: 334-341, 2014.
30. He B, Teng XM, Hao F, Zhao M, Chen ZQ, Li KM and Yan Q: Decreased intracellular IL-33 impairs endometrial receptivity in women with adenomyosis. *Front Endocrinol (Lausanne)* 13: 928024, 2022.
31. Zhang H, Li C, Li W, Xin W and Qin T: Research advances in adenomyosis-related signaling pathways and promising targets. *Biomolecules* 14: 1402, 2024.
32. Kay N, Huang CY, Shiu LY, Yu YC, Chang Y, Schatz F, Suen JL, Tsai EM and Huang SJ: TGF- β 1 neutralization improves pregnancy outcomes by restoring endometrial receptivity in mice with adenomyosis. *Reprod Sci* 28: 877-887, 2021.
33. Wang T, Yuan J, Zhang J, Tian R, Ji W, Zhou Y, Yang Y, Song W, Zhang F and Niu R: Anxa2 binds to STAT3 and promotes epithelial to mesenchymal transition in breast cancer cells. *Oncotarget* 6: 30975-30992, 2015.
34. Gellersen B and Brosens JJ: Cyclic decidualization of the human endometrium in reproductive health and failure. *Endocr Rev* 35: 851-905, 2014.
35. Kuivasaari P, Hippeläinen M, Anttila M and Heinonen S: Effect of endometriosis on IVF/ICSI outcome: Stage III/IV endometriosis worsens cumulative pregnancy and live-born rates. *Hum Reprod* 20: 3130-3135, 2005.
36. Salleh N and Giribabu N: Leukemia inhibitory factor: Roles in embryo implantation and in nonhormonal contraception. *ScientificWorldJournal* 2014: 201514, 2014.
37. Itoh F, Komohara Y, Takaishi K, Honda R, Tashiro H, Kyo S, Katabuchi H and Takeya M: Possible involvement of signal transducer and activator of transcription-3 in cell-cell interactions of peritoneal macrophages and endometrial stromal cells in human endometriosis. *Fertil Steril* 99: 1705-1713, 2013.
38. Huang Y, Zhu L, Li H, Ye J, Lin N, Chen M, Pan D and Chen Z: Endometriosis derived exosomal miR-301a-3p mediates macrophage polarization via regulating PTEN-PI3K axis. *Biomed Pharmacother* 147: 112680, 2022.
39. Sun SG, Guo JJ, Qu XY, Tang XY, Lin YY, Hua KQ and Qiu JJ: The extracellular vesicular pseudogene LGMNP1 induces M2-like macrophage polarization by upregulating LGMN and serves as a novel promising predictive biomarker for ovarian endometriosis recurrence. *Hum Reprod* 37: 447-465, 2022.
40. Zhang D, Yu Y, Duan T and Zhou Q: The role of macrophages in reproductive-related diseases. *Heliyon* 8: e11686, 2022.
41. Díaz-Hernández I, Alecsandru D, García-Velasco JA and Domínguez F: Uterine natural killer cells: From foe to friend in reproduction. *Hum Reprod Update* 27: 720-746, 2021.
42. Shi J, Xu Q, Yu S and Zhang T: Perturbations of the endometrial immune microenvironment in endometriosis and adenomyosis: Their impact on reproduction and pregnancy. *Semin Immunopathol* 47: 16, 2025.

43. Mei J, Zhou WJ, Zhu XY, Lu H, Wu K, Yang HL, Fu Q, Wei CY, Chang KK, Jin LP, *et al*: Suppression of autophagy and HCK signaling promotes PTGS2^{high} FCGR3⁺ NK cell differentiation triggered by ectopic endometrial stromal cells. *Autophagy* 14: 1376-1397, 2018.
44. Niu W, Zhang Y, Liu H, Liang N, Xu L, Li Y, Yao W, Shi W and Liu Z: Single-cell profiling uncovers the roles of endometrial fibrosis and microenvironmental changes in adenomyosis. *J Inflamm Res* 16: 1949-1965, 2023.
45. Hoe E, Anderson J, Nathanielsz J, Toh ZQ, Marimla R, Balloch A and Licciardi PV: The contrasting roles of Th17 immunity in human health and disease. *Microbiol Immunol* 61: 49-56, 2017.
46. Olivares C, Bilotas M, Buquet R, Borghi M, Sueldo C, Tesone M and Meresman G: Effects of a selective cyclooxygenase-2 inhibitor on endometrial epithelial cells from patients with endometriosis. *Hum Reprod* 23: 2701-2708, 2008.
47. Nyachieo A, Siristatidis CS and Vaidakis D: Nonsteroidal anti-inflammatory drugs for assisted reproductive technology. *Cochrane Database Syst Rev* 10: CD007618, 2019.
48. Zippel AL, Kyvelidou C, Frank M, Gapp E, Reiser E, Braun AS, Feil K, Schuchter S, Rockenschaub P, Toth B and Seeber B: The impact of GnRH agonists on endometrial immune cells in patients with adenomyosis: A prospective cohort study. *BMC Med* 23: 338, 2025.
49. Khan KN, Kitajima M, Hiraki K, Fujishita A, Sekine I, Ishimaru T and Masuzaki H: Changes in tissue inflammation, angiogenesis and apoptosis in endometriosis, adenomyosis and uterine myoma after GnRH agonist therapy. *Hum Reprod* 25: 642-653, 2010.
50. Guo S, Li Z, Yan L, Sun Y and Feng Y: GnRH agonist improves pregnancy outcome in mice with induced adenomyosis by restoring endometrial receptivity. *Drug Des Devel Ther* 12: 1621-1631, 2018.
51. Wang PH, Liu WM, Fuh JL, Cheng MH and Chao HT: Comparison of surgery alone and combined surgical-medical treatment in the management of symptomatic uterine adenomyoma. *Fertil Steril* 92: 876-885, 2009.
52. Barretta M, Vignali M, La Marca A and Grandi G: The oral GnRH antagonists, a new class of drugs in gynecology: From pharmacokinetics to possible clinical applications. *Expert Opin Drug Metab Toxicol*: 1-13, 2024 (Epub ahead of print).
53. Horie S, Harada T, Mitsunari M, Taniguchi F, Iwabe T and Terakawa N: Progesterone and progestational compounds attenuate tumor necrosis factor alpha-induced interleukin-8 production via nuclear factor kappa B inactivation in endometriotic stromal cells. *Fertil Steril* 83: 1530-1535, 2005.
54. Prathoomthong S, Tingthanatikul Y, Lertvikool S, Rodratn N, Waiyaput W, Dittharot K, Sroyraya M and Sophonsritsuk A: The effects of dienogest on macrophage and natural killer cells in adenomyosis: A randomized controlled study. *Int J Fertil Steril* 11: 279-286, 2018.
55. Jiang X and Chen X: Endometrial cell-derived exosomes facilitate the development of adenomyosis via the IL-6/JAK2/STAT3 pathway. *Exp Ther Med* 26: 526, 2023.

56. Yamamoto N, Kitano S, Koyama T, Ikeda M, Mizugaki H, Narikiyo T, Yamaguchi Y, Ishida T, Takubo R, Ogami C, *et al*: Phase I study of the safety and clinical activity of the interleukin-8 inhibitor AMY109 combined with atezolizumab in patients with advanced solid cancers. *J Immunother Cancer* 12: e009262, 2024.
57. Nishimoto-Kakiuchi A, Sato I, Nakano K, Ohmori H, Kayukawa Y, Tanimura H, Yamamoto S, Sakamoto Y, Nakamura G, Maeda A, *et al*: A long-acting anti-IL-8 antibody improves inflammation and fibrosis in endometriosis. *Sci Transl Med* 15: eabq5858, 2023.
58. Cheng J, Li C, Ying Y, Lv J, Qu X, McGowan E, Lin Y and Zhu X: Metformin alleviates endometriosis and potentiates endometrial receptivity via decreasing VEGF and MMP9 and increasing leukemia inhibitor factor and HOXA10. *Front Pharmacol* 13: 750208, 2022.
59. Hou Y, Qin Z, Fan K, Xu Y and Huang X: Combination therapeutic effects of high intensity focused ultrasound and Metformin for the treatment of adenomyosis. *Exp Ther Med* 15: 2104-2108, 2018.
60. Sullender RT, Agarwal RK, Jacobs MB, Wessels JM, Foster WG and Agarwal SK: Pilot study of IL-1 antagonist anakinra for treatment of endometriosis. *Int J Womens Health* 16: 1583-1593, 2024.
61. Xu Z, Zhao F, Lin F, Chen J and Huang Y: Lipoxin A4 inhibits the development of endometriosis in mice: The role of anti-inflammation and anti-angiogenesis. *Am J Reprod Immunol* 67: 491-497, 2012.
62. Kumar R, Clerc AC, Gori I, Russell R, Pellegrini C, Govender L, Wyss JC, Golshayan D and Canny GO: Lipoxin A4 prevents the progression of de novo and established endometriosis in a mouse model by attenuating prostaglandin E2 production and estrogen signaling. *PLoS One* 9: e89742, 2014.
63. Celik O, Ersahin A, Acet M, Celik N, Baykus Y, Deniz R, Ozerol E and Ozerol I: Disulfiram, as a candidate NF- κ B and proteasome inhibitor, prevents endometriotic implant growing in a rat model of endometriosis. *Eur Rev Med Pharmacol Sci* 20: 4380-4389, 2016.
64. Akdaş Reis Y, Tapisiz OL, Göktolga Ü, Şimşek G, Erten Ö, Kiykaç Altınbaş Ş and Erkaya S: The effect of disulfiram in the prevention of postoperative adhesion formation in an experimental rat uterine horn model. *Reprod Sci* 28: 2650-2660, 2021.
65. Guan X, Liu D, Zhou H, Dai C, Wang T, Fang Y, Jia Y and Li K: Melatonin improves pregnancy outcomes in adenomyosis mice by restoring endometrial receptivity via NF-kappaB/apoptosis signaling. *Ann Transl Med* 10: 1317, 2022.
66. Chuffa LGDA, Lupi LA, Cuciello MS, Silveira HS, Reiter RJ and Seiva FRF: Melatonin promotes uterine and placental health: Potential molecular mechanisms. *Int J Mol Sci* 21: 300, 2019.
67. Barrier BF, Bates GW, Leland MM, Leach DA, Robinson RD and Propst AM: Efficacy of anti-tumor necrosis factor therapy in the treatment of spontaneous endometriosis in baboons. *Fertil Steril* 81 (Suppl 1): S775-S779, 2004.
68. Zulfikaroglu E, Kilic S, Islimye M, Aydin M, Zergeroğlu S and Batioglu S: Efficacy of anti-tumor necrosis factor therapy on endometriosis in an experimental rat model. *Arch Gynecol Obstet* 283: 799-804, 2011.

69. Önalın G, Tohma YA and Zeynelođlu HB: Effect of etanercept on the success of assisted reproductive technology in patients with endometrioma. *Gynecol Obstet Inves* 83: 358-364, 2018.
70. Etemadi S, Abtahi Froushani SM, Hashemi Asl SM and Mahmoudian A: Combined atorvastatin and pentoxifylline in ameliorating inflammation induced by complete Freund's adjuvant. *Inflammopharmacology* 30: 935-944, 2022.
71. Creus M, Fábregues F, Carmona F, del Pino M, Manau D and Balasch J: Combined laparoscopic surgery and pentoxifylline therapy for treatment of endometriosis-associated infertility: A preliminary trial. *Hum Reprod* 23: 1910-1916, 2008.
72. Roussev RG, Ng SC and Coulam CB: Natural killer cell functional activity suppression by intravenous immunoglobulin, intralipid and soluble human leukocyte antigen-G. *Am J Reprod Immunol* 57: 262-269, 2007.
73. Coulam CB: Intralipid treatment for women with reproductive failures. *Am J Reprod Immunol* 85: e13290, 2021.
74. Etrusco A, Barra F, Chiantera V, Ferrero S, Bogliolo S, Evangelisti G, Oral E, Pastore M, Izzotti A, Venezia R, *et al*: Current medical therapy for adenomyosis: From bench to bedside. *Drugs* 83: 1595-1611, 2023.
75. Wang H, Gan Z, Wang Y, Hu D, Zhang L, Ye F and Duan P: A noninvasive menstrual blood-based diagnostic platform for endometriosis using digital droplet enzyme-linked immunosorbent assay and single-cell RNA sequencing. *Research (Wash D C)* 8: 0652, 2025.
76. Moses AS, Taratula OR, Lee H, Luo F, Grenz T, Korzun T, Lorenz AS, Sabei FY, Bracha S, Alani AWG, *et al*: Nanoparticle-based platform for activatable fluorescence imaging and photothermal ablation of endometriosis. *Small* 16: e1906936, 2020.
77. Wu N, Han Z, Lv W, Huang Y, Zhu J, Deng J and Xue Q: Reprogramming peritoneal macrophages with outer membrane vesicle-coated PLGA nanoparticles for endometriosis prevention. *Biomaterials* 319: 123198, 2025.
78. Yuxue J, Ran S, Minghui F and Minjia S: Applications of nanomaterials in endometriosis treatment. *Front Bioeng Biotechnol* 11: 1184155, 2023.
79. Zhu Y, Zheng B, Zhang Y, Li M, Jiang Y, Zhou J, Zhang Y, Kang N, Wu M, Yan Y, *et al*: Ectopic endometrial stromal cell-derived extracellular vesicles encapsulating microRNA-25-3p induce endometrial collagen I deposition impairing decidualization in endometriosis. *Mol Hum Reprod* 30: gaae042, 2024.
80. Mari-Alexandre J, Barceló-Molina M, Belmonte-López E, García-Oms J, Estellés A, Braza-Boils A and Gilabert-Estellés J: Micro-RNA profile and proteins in peritoneal fluid from women with endometriosis: Their relationship with sterility. *Fertil Steril* 109: 675-684.e2, 2018.
81. Dai L, Gu L and Di W: MiR-199a attenuates endometrial stromal cell invasiveness through suppression of the IKK β /NF- κ B pathway and reduced interleukin-8 expression. *Mol Hum Reprod* 18: 136-145, 2012.
82. Abdulmonem WA, Ahsan M, Mallick AK, Mohamed AH, Waggiallah HA, Shafie A, Alzahrani HS, Ashour AA, Rab SO, Mirdad MT and Ali HTO: The role of exosomal miRNAs in female infertility: Therapeutic potential and mechanisms of action. *Stem Cell Rev Rep* 21: 1141-1159, 2025.

83. Juárez-Barber E, Segura-Benítez M, Carbajo-García MC, Bas-Rivas A, Faus A, Vidal C, Giles J, Labarta E, Pellicer A, Cervelló I and Ferrero H: Extracellular vesicles secreted by adenomyosis endometrial organoids contain miRNAs involved in embryo implantation and pregnancy. *Reprod Biomed Online* 46: 470-481, 2023.
84. Guan YG, Liao JB, Li KY, Li YC, Song Y, Ling J and Su ZR: Potential mechanisms of an antiadenomyosis chinese herbal formula shaoyao-gancao decoction in primary cell culture model. *Evid Based Complement Alternat Med* 2014: 982913, 2014.
85. Maia H Jr, Haddad C, Pinheiro N and Casoy J: Advantages of the association of resveratrol with oral contraceptives for management of endometriosis-related pain. *Int J Womens Health* 4: 543-549, 2012.
86. Han SJ, Jung SY, Wu SP, Hawkins SM, Park MJ, Kyo S, Qin J, Lydon JP, Tsai SY, Tsai MJ, *et al*: Estrogen receptor β modulates apoptosis complexes and the inflammasome to drive the pathogenesis of endometriosis. *Cell* 163: 960-974, 2015.
87. Park Y, Cho YJ, Sung N, Park MJ, Guan X, Gibbons WE, O'Malley BW and Han SJ: Oleuropein suppresses endometriosis progression and improves the fertility of mice with endometriosis. *J Biomed Sci* 29: 100, 2022.
88. Xu W, Song Y, Li K, Zhang B and Zhu X: Quercetin inhibits adenomyosis by attenuating cell proliferation, migration and invasion of ectopic endometrial stromal cells. *Drug Des Devel Ther* 14: 3815-3826, 2020.
89. Jiang X, Chen Y, Zhu H, Wang B, Qu P, Chen R and Sun X: Sodium tanshinone IIA sulfonate ameliorates bladder fibrosis in a rat model of partial bladder outlet obstruction by inhibiting the TGF- β /Smad pathway activation. *PLoS One* 10: e129655, 2015.
90. Liu L, Chen L, Jiang C, Guo J, Xie Y, Kang L and Cheng Z: Berberine inhibits the LPS-induced proliferation and inflammatory response of stromal cells of adenomyosis tissues mediated by the LPS/TLR4 signaling pathway. *Exp Ther Med* 14: 6125-6130, 2017.