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Review

The interplay between endometriosis and obesity

Md Saidur Rahman [1,3], Yunjeong Park [2,3,5], Hossein Hosseinirad [1], Jung-Ho Shin [2,4,*], and Jae-Wook Jeong [1,4,*]

Endometriosis, characterized by uterine-like tissue growth outside the uterus, is a complex disorder with significant clinical implications. This review explores how body composition – both low body mass index (BMI) and obesity – modulates endometriosis progression through metabolic, hormonal, and immune-inflammatory pathways. Obesity-driven leptin signaling emerges as a pivotal link, promoting systemic inflammation, angiogenesis, and lesion persistence via Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathways. Shared molecular mechanisms between endometriosis and obesity highlight opportunities for precision medicine and targeted therapies. By addressing leptin-driven pathways and metabolic dysfunction, we introduce innovative strategies, offering novel insights into the improved management of this multifaceted condition.

Highlights

Body composition remarkably influences endometriosis, with both low body mass index (BMI) and obesity driving disease progression via distinct metabolic and inflammatory mechanisms.

Obesity-associated leptin signaling fuels systemic inflammation, angiogenesis, and ectopic lesion persistence in endometriosis, presenting novel therapeutic targets.

Shared molecular pathways between endometriosis and obesity provide a foundation for precision medicine approaches.

Emerging therapies targeting inflammation and metabolic dysfunction offer promising strategies for improved endometriosis management.

Decoding endometriosis: a brief insight into pathophysiology

Endometriosis is a complex disorder where tissue resembling the uterine lining grows outside the uterus, leading to chronic pain, inflammation, and infertility challenges. Despite being documented for over two millennia, its pathophysiology remains only partially understood, with no single hypothesis fully capturing its diverse manifestations. The primary theory, **retrograde menstruation** (see Glossary), suggests that menstrual fluid flows into the pelvic cavity, leading to **ectopic lesion** development on the peritoneal and intestinal mucosa, fallopian tubes, and ovaries [1]. Yet, this does not explain cases in distant locations (e.g., lungs, skin) or in individuals without a uterus, like those with **Mayer–Rokitansky–Küster–Hauser syndrome** [2]. Alternative hypotheses – including extrauterine stem cells, hematogenous spread, **coelomic metaplasia**, and **Müllerian remnants** – also offer only partial insights [3].

The development of endometriosis relies on **immune evasion**, cell adhesion, neurovascular remodeling, and **angiogenesis** to establish and sustain ectopic growth [4]. Impaired immune clearance contributes to endometriosis progression, with ectopic tissue inhibiting the cytotoxic activity of **natural killer (NK) cells** [5]. Additionally, peritoneal fluid and eutopic endometrial tissue in affected women also exhibit enhanced immunosuppressive properties, further compromising NK cell function compared with that in controls [5]. However, the mechanisms by which endometrial cells evade immune surveillance and survive in ectopic lesions remain elusive. Reduced NK cell function, possibly modulated by **cytokines** such as interleukin (IL)-6, IL-10, IL-12, IL-15, and transforming growth factor β (TGF-β), appears to support ectopic lesion survival [6]. Altered functions in macrophages, T cells, and B cells also suggest an immune dysfunction underlying endometriosis [7]. In addition, eutopic endometrium from women with endometriosis exhibits increased cellular proliferation and reduced apoptosis, especially during the late **secretory phase** and early **proliferative phase** of the menstrual cycle [8], likely due to elevated B cell lymphoma 2 (**Bcl-2 protein**) and decreased **BCL2-associated X (BAX) protein** expression [9]. This selective inhibition of apoptosis may involve genetic or local cytokine factors.

[1]Department of Obstetrics, Gynecology, and Women's Health, University of Missouri School of Medicine, Columbia, MO 65211, USA
[2]Department of Obstetrics and Gynecology, Guro Hospital, Korea University Medical Center, Seoul 02841, Republic of Korea
[3]These authors contributed equally to this work.
[4]These authors are joint senior authors of this work.
[5]Current Address: Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Seoul, 03722, Republic of Korea.

*Correspondence:
lateroman@gmail.com (J.-H. Shin) and
jeongjw@missouri.edu (J.-W. Jeong).

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Further survival of ectopic lesions requires adherence to target tissues and vascular support. Endometrial stromal cells readily adhere to the peritoneal mesothelial surface [10], facilitated by increased expression of adhesion molecules such as integrins and E-cadherin–catenin complexes in affected women [11]; once adhered, elevated **matrix metalloproteinases (MMPs)** and reduced MMP inhibitors in endometrial cells promoted invasion into mesothelial tissue [12]. After attachment and invasion, these cells rely on a new blood supply through angiogenesis to survive. Ectopic lesions have reduced apoptosis and enhanced angiogenic potential, driven by factors such as vascular endothelial growth factor-A (VEGF-A), Bcl-2, and Bcl-xL, which support their persistence and growth [13]. Thus, the role of adhesion molecules in ectopic tissue stability and the therapeutic potential of targeting these molecules warrants further exploration.

Beyond cellular adhesion and invasion, systemic, metabolic, and inflammatory factors also influence the endometriotic microenvironment. Growing evidence suggests that body composition – both low BMI and **obesity** – influences disease progression by modulating chronic inflammation, hormonal balance, and immune responses [14]. As research continues to uncover these complex interactions, integrating metabolic health into the broader understanding of endometriosis provides a more comprehensive view of its pathophysiology. As such, this review summarizes emerging epidemiological, molecular, and clinical findings, providing critical insights that may refine the diagnosis, management, and treatment of endometriosis.

What drives the development of endometriosis?

Endometriosis development results from a complex interplay of reproductive, environmental, lifestyle, and molecular factors. An overview of these factors, along with the associated hormonal and molecular changes, is given in Figure 1. Early menarche, severe cramps, and heavy menstrual flow have been linked to increased risk, whereas multiparity may reduce the prevalence [15]. Additionally, increased ovulation frequency has been correlated with the disease [16]. However, these associations remain inconsistent, highlighting the need for further studies with larger, more diverse samples, including asymptomatic cases, to clarify their significance.

Several environmental and lifestyle factors also impact endometriosis risk. While height, waist/hip ratio, and caffeine intake showed no link, age, race, body composition, and alcohol use were associated with increased risk [17]. Endometriosis affects an estimated 5–15% of individuals of reproductive age, with a lower occurrence in postmenopausal women (2–5%) [18]. Body composition plays a complex role, as both low BMI and obesity potentially influence disease risk through mechanisms explored in later sections. Conversely, smoking demonstrated an inverse association, potentially due to its anti-estrogenic effects, manipulation of prostaglandin production, and activation of cholinergic receptors [19]. Physical activity shows mixed associations, with one study [20] finding up to an 80% reduced risk of endometriosis with regular exercise, while another [21] observed a modest inverse association. It has been suggested that most of the earlier case–control studies may have been biased, as symptoms could reduce activity levels [21]. Despite this, regular exercise remains beneficial, and practices like Hatha yoga and muscle relaxation are suggested to reduce pain and stress in patients with endometriosis. Emerging evidence highlights the impact of **endocrine-disrupting chemicals (EDCs)** – such as bisphenol A (BPA), dioxins (TCDD), polychlorinated biphenyls (PCBs), and phthalates – on endometriosis risk, as these environmental pollutants disrupt the hormonal balance by mimicking or antagonizing endogenous estrogen and other steroid hormones [22]. Exposure to TCDD and PCBs is associated with an increased prevalence of endometriosis, potentially through their ability to promote inflammation and alter immune function [23]. Similarly, BPA, a common plasticizer, has been linked to epigenetic changes that may contribute to establishing and progressing endometriotic lesions [22]; epidemiological studies have shown a significant association between high BPA

Glossary

Angiogenesis: the development and formation of new blood vessels, a process supporting the growth of ectopic lesions.
BCL2-associated X (BAX) protein: a molecule that regulates cell survival and death, with imbalances contributing to lesion persistence in endometriosis.
Bcl-2 protein: a molecule that regulates cell survival and death, with imbalances contributing to lesion persistence in endometriosis.
Coelomic metaplasia: a theory suggesting that cells lining the abdominal cavity can transform into endometrium-like cells.
Cytokines: proteins that act as messengers in the immune system, with some promoting inflammation observed in endometriosis.
Ectopic lesions: abnormal growths of tissue resembling the uterine lining found in locations such as the ovaries, fallopian tubes, or peritoneum.
Endocrine-disrupting chemicals (EDCs): a diverse group of natural or synthetic compounds that interfere with the normal function of the endocrine system. EDCs can mimic, block, or alter the production, release, transport, metabolism, or elimination of natural hormones, leading to adverse developmental, reproductive, neurological, immune, or metabolic effects.
Epigenetics: the study of changes in gene activity that do not involve alterations to the DNA sequence; such changes play a role in endometriosis pathophysiology.
Immune evasion: the ability of cells, like those in endometriosis, to avoid detection and destruction by the immune system.
JAK–STAT pathway: a molecular signaling pathway involved in cell growth and immune responses, activated in endometriosis by several predisposing factors, including leptin.
Matrix metalloproteinases (MMPs): enzymes that degrade the extracellular matrix, allowing endometrial cells to invade surrounding tissues such as the ovaries, fallopian tubes, or peritoneum.
Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome: a rare condition where parts of the female reproductive tract fail to develop; it is sometimes linked to endometriosis.

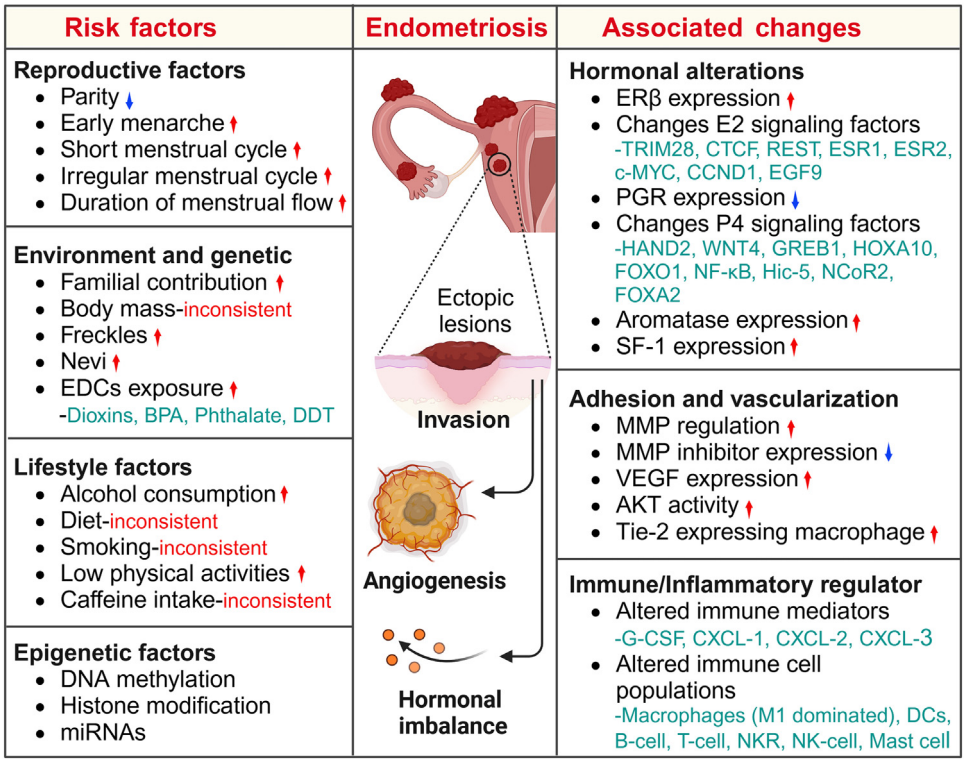

Figure 1. Factors contributing to the development and progression of endometriosis: the interplay between risk factors (left panel), pathological processes in endometriosis (middle panel), and endometriosis-associated molecular and cellular changes (right panel). Risk factors include reproductive, environmental, genetic, lifestyle, and epigenetic influences. Molecular and cellular changes driving endometriosis involve hormonal imbalances, for example, altered estrogen receptor β (ERβ) and progesterone receptor (PGR) expression, aromatase activity, immune dysfunction (e.g., macrophage polarization, chemokine production), and vascular remodeling. These processes drive ectopic lesion formation, invasion, angiogenesis, and chronic inflammation, culminating in the pathophysiology of endometriosis. Arrows indicate regulatory trends: ↑ (red) for upregulation, ↓ (blue) for downregulation, while findings labeled 'inconsistent' reflect inconclusive or variable associations. The green text highlights key genes or molecules involved in endometriosis-related hormonal and immune regulation. Abbreviations: AKT, protein kinase B; BPA, bisphenol A; CXCL, chemokine ligand; DC, dendritic cell; DDT, dichlorodiphenyltrichloroethane; E2, estradiol; EDCs, endocrine disrupting chemicals; EGF, epidermal growth factor; ESR, estrogen receptor; G-CSF, granulocyte colony-stimulating factor; miRNAs, microRNAs; MMP, matrix metalloproteinase; NK, natural killer cell; P4, progesterone; SF-1, steroidogenic factor-1; TRIM28, tripartite motif-containing 28; VEGF, vascular endothelial growth factor. Figure created with BioRender.

Müllerian remnants: residual embryonic structures that may persist and develop into endometrial-like tissue.
Natural killer (NK) cells: immune cells that help eliminate abnormal or infected cells, often found to be less active in individuals with endometriosis.
Non-steroidal anti-inflammatory drugs (NSAIDs): a class of drugs that reduce inflammation, pain, and fever by inhibiting cyclooxygenase enzymes; NSAIDs are commonly used to manage endometriosis-related pain, but they do not alter disease progression.
Obesity: a condition characterized by an excessive amount of body fat, often associated with a high BMI that influences metabolic and hormonal processes that may exacerbate inflammation and disease progression, including endometriosis.
Proliferative phase: the phase of the menstrual cycle when the uterine lining thickens, preparing for potential implantation.
Retrograde menstruation: a proposed mechanism where menstrual blood flows backward into the pelvic cavity, potentially leading to endometriosis.
Revised American Society for Reproductive Medicine (rASRM) score: a staging system that classifies endometriosis severity (stages I–IV) based on the size, location, and extent of lesions and adhesions. Stage I has small superficial implants, while stage IV includes large endometriomas and extensive adhesions.
Secretory phase: the progesterone-dominant phase following ovulation, characterized by endometrial gland secretion, stromal edema, and tissue remodeling to support embryo implantation.

exposure and increased odds of endometriosis [24]. At the molecular level, both BPA and phthalates disrupt estrogen signaling and inflammatory pathways, which are critical in the pathogenesis of endometriosis [24]. Given that endometriosis is an estrogen-dependent disease, the role of EDCs in disrupting hormonal signaling and promoting aberrant inflammatory responses requires further investigation. Sun exposure and skin sensitivity are additional factors, individuals with endometriosis reporting higher photosensitivity and sun avoidance [25]. Similarly, another study linked endometriosis risk to skin sensitivity, freckles, and naevi, suggesting a genetic links between endometriosis and pigmentation traits, also warranting further investigation [26]. Familial and genetic factors further contribute to endometriosis risk, as seen in both humans and Rhesus monkeys [27]. The risk is estimated to be seven times higher for mothers and sisters of affected individuals [28], while daughters face a two-fold increased risk [29]. Genome-wide association studies have identified polygenic risk factors, with multiple single-nucleotide polymorphisms contributing modest effects [27]. It is important to note that the increased

hereditary risk of endometriosis likely arises from a variety of genetic variations, each with modest individual effects.

While genetic factors play a complex role, recent research underscores the growing importance of **epigenetics** in endometriosis. Epigenetic enzymes, including DNA methyltransferases and histone deacetylases, impact molecular changes in the eutopic endometrium and ectopic lesions, especially in sex steroid signaling pathways [30]. MicroRNAs (miRNAs) are also increasingly recognized for their regulatory roles in these changes [30]. Since epigenetic changes are heritable yet reversible, understanding these mechanisms could provide promising therapeutic strategies for the treatment of endometriosis.

Obesity, BMI, and endometriosis: understanding the link

Insights from human epidemiological studies and preclinical animal research

There is still no cure for endometriosis, making it essential to understand its risk factors to guide informed decisions based on evidence rather than assumptions. While obesity is a well-known health risk, an exceptionally low BMI may also indicate underlying health concerns, including an increased susceptibility to endometriosis. But how does body composition shape the narrative of endometriosis? The relationship is far from straightforward. Research reveals intriguing patterns: a low BMI appears to be linked to a higher risk of endometriosis, while obesity correlates with a lower incidence but more advanced disease stages. Adding to the complexity, some studies find no clear connection between BMI and endometriosis at all. Although BMI is widely used, alternative anthropometric measures such as waist-to-hip ratio and body adiposity content may provide further insights into the relationship between obesity and endometriosis [31]. However, current studies remain limited, underscoring the need for further research into these parameters. Table 1 comprehensively summarizes human and preclinical animal studies, highlighting the complex relationship between obesity, BMI, and endometriosis.

Earlier studies reported an inverse relationship between BMI and endometriosis [32], with very low BMI (<18.5) linked to a higher risk of deep infiltrating endometriosis [33]. However, many of these studies rely on self-reported diagnoses, introducing potential bias [34], and the lack of ideal control groups also complicates the interpretation. Chronic pain associated with endometriosis may suppress appetite, while gastrointestinal side effects of **non-steroidal anti-inflammatory drugs (NSAIDs)**, a common therapy, could reduce food tolerance and contribute to weight loss [35]. These observations suggest that the BMI–endometriosis relationship is more complex than a simple inverse association, inquiring a re-evaluation of whether low BMI is causal or consequential.

Conversely, population-based studies from Australia, Sweden, Israel, and China have reported fewer endometriosis cases in individuals with low BMI than those with normal or high BMI (Table 1). Some studies found no correlation, while others suggest that obesity correlates with a lower incidence of endometriosis (Table 1). This is debated since endometriosis is an estrogen-dependent condition, and excess body fat elevates estrogen levels, potentially fueling the inflammatory processes involved in its progression [36]. By contrast, it was hypothesized that elevated estrogen in obesity might disrupt ovulation, shortening menstrual cycles and reducing endometriosis risk; however, no statistical link between BMI and cycle length was found [37]. A possible mechanism linking obesity, dysfunctional adipose tissue, and endometriosis is presented in Figure 2.

Hospital-based studies further complicate the picture. In the Korean population, low BMI was associated with increased endometriosis-related pain [38], suggesting that women with obesity may experience fewer symptoms and undergo fewer surgical procedures, reducing laparoscopic

Table 1. Integrated insights from human and preclinical studies on endometriosis and body composition

Country/model	Study design/model	Sample size (case, control)	Key findings	Relevance	Refs
Poland	Case–control	40, 30	No significant BMI differences between cases and controls	Highlights lack of BMI distinction in some cases	[57]
Russia	Case–control	90, 44	No significant BMI differences between groups	Reinforces BMI variability in endometriosis patients	[73]
Spain	Case–control	179, 65	BMI comparisons show no major differences across groups	Suggests that other factors may influence outcomes	[74]
Italy	Cross-sectional	194, 58	Controls had higher BMI than endometriosis cases	Indicates lower BMI trends in endometriosis patients	[75]
Australia	Cross-sectional	380, 6606	BMI ≥30 significantly increases endometriosis risk	Links high BMI to increased disease risk	[76]
India	Cross-sectional	30, 30	Obesity (BMI ≥30) and WHR ≥0.85 associated with increased risk	Highlights obesity as a risk factor for endometriosis	[77]
Australia	Cross-sectional	223, 11175	BMI extremes (BMI <18.5 or ≥30) associated with varying endometriosis risks	Demonstrates BMI's role in disease risk variation	[78]
Indonesia	Case–control	63, 63	Higher WHR and BMI ≤25 associated with increased endometriosis risk	Emphasizes WHR and BMI's influence	[79]
Iran	Cross-sectional	65, 43	Controls had higher BMI than cases	Suggests leaner profiles in endometriosis patients	[80]
Finland	Cross-sectional	348, 3487	BMI differences significant with age progression; no differences in adolescence	Links BMI changes to life stages in endometriosis	[81]
Mice with induced lesions	Immunocompetent wild-type mice	NA	High-fat diet increases lesion numbers and inflammation without weight gain	Shows that diet-induced inflammation exacerbates progression	[44]
C57BL/6 mice	Preclinical model	NA	Liver metabolism dysregulation leads to reduced body weight and fat in endometriosis	Links hepatic changes to BMI and disease progression	[45]
Mice with lesion genotypes	Preclinical model	NA	Genotype and high-fat diet influence inflammation and oxidative stress in lesions	Demonstrates genetic and dietary interactions	[82]
Obese mice	Preclinical model	NA	Obesity delays endometrial repair and alters inflammatory markers	Links obesity to impaired endometrial function	[48]
Obese mice and human cells	Preclinical model	NA	Obesity impairs implantation and decidualization, disrupting autophagy	Connects obesity to reproductive challenges in endometriosis	[83]

Abbreviations: NA, not applicable; WHR, waist-to-hip ratio.

diagnoses. Women with obesity often exhibit higher **revised American Society for Reproductive Medicine (rASRM) scores** and increased postoperative recurrence rates [39]. The evidence further supports the link between body composition and endometriosis severity, showing that severe ureteral endometriosis is more common in women with lower BMI [40]. While obesity is often linked to advanced disease stages, lower BMI may also contribute to increased risk of specific subtypes of endometriosis, such as deep infiltrating endometriosis with ureteral compression. These findings emphasize the complexity of the obesity–endometriosis relationship and the need for a nuanced understanding of how body composition influences disease progression.

Diagnostic delays further affect the overall outcomes of the disease. In an analysis of surgically diagnosed patients, categorized by BMI and time to diagnosis, patients with obesity faced the longest delays, averaging 18.4 months, compared with 9.0 months for overweight and 3.8 months for normal/underweight patients [41]. This highlights a potential link between increasing BMI and longer diagnostic times, possibly reflecting more severe disease. Supporting this, patients with a BMI >30 kg/m^2 often have more severe forms of the disease [42], potentially due to hesitancy to undergo surgery or less detectable lesions on ultrasound. Moreover, women with

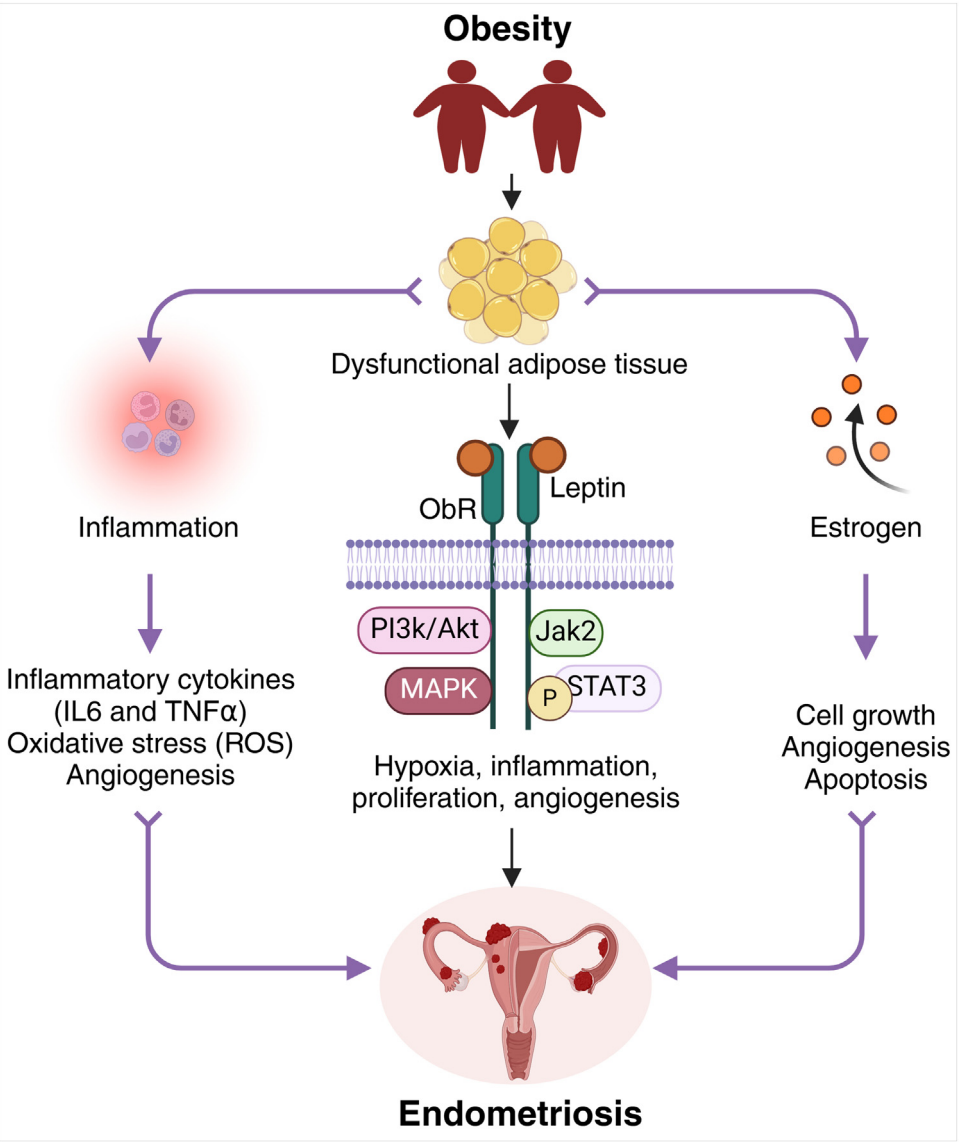

Figure 2. Role of obesity in the pathogenesis of endometriosis. Dysfunctional adipose tissue in obese individuals produces leptin, which binds to its receptor (ObR) and activates signaling pathways such as phosphoinositide 3-kinase–protein kinase B (PI3K–Akt), mitogen-activated protein kinase (MAPK), Janus kinase 2 (Jak2), and signal transducer and activator of transcription 3 (STAT3). These pathways contribute to hypoxia, inflammation, and angiogenesis, promoting the development of endometriosis. Additionally, increased estrogen production from adipose tissue stimulates cell growth, angiogenesis, and apoptosis. Chronic inflammation driven by adipose-tissue-derived inflammatory cytokines [e.g., interleukin 6 (IL6) and tumor necrosis factor α (TNFα)], oxidative stress (reactive oxygen species, ROS), and angiogenesis further exacerbates the condition, establishing a feedback loop that perpetuates endometriosis. Other abbreviation: P, phosphorylation. Figure created with BioRender.

obesity are more frequently diagnosed with superficial peritoneal endometriosis, while underweight women were more likely to have deep infiltrating endometriosis [43]. Endometriosis is linked to a hyperestrogenic state, with adipose tissue playing a critical role in estrogen production. Although lower BMI is often linked to endometriosis, obesity is not protective and may exacerbate symptoms through adipose tissue dysfunction, inflammation, and altered immune responses.

Animal models offer a controlled environment to investigate how obesity and dietary factors drive endometriosis progression, providing valuable insights that enhance and broaden our understanding of this complex relationship. In mice, a high-fat diet worsens endometriosis by increasing lesion numbers and inflammation, independently of weight gain [44]. Moreover, endometriosis has been linked to liver metabolic dysregulation, contributing to reduced body weight and fat, similar to patterns observed in affected women [45]. Furthermore, endometriosis-related miRNAs disrupt adipocyte metabolism, reducing fat storage and contributing to disease progression [46]. Obesity-induced metabolic changes, such as altered adipocyte function and inflammation, exacerbate endometriosis by initiating a proinflammatory environment that accelerates lesion development [47].

Obesity can further disrupt key physiological processes, impairing endometrial repair by reducing cell proliferation and promoting inflammation [48]. It also affects decidualization in both mice and human endometrial cells, linking high BMI to poor reproductive outcomes [14]. Collectively, these findings underscore the complex interplay between diet, obesity, and disease mechanisms in endometriosis. Although low BMI is common in women with endometriosis due to disease-driven metabolic changes, higher BMI exacerbates outcomes by promoting inflammation and impairing reproductive health. This highlights the need for further research into how metabolic dysfunction influences endometriosis progression and severity.

Linking endometriosis to body composition through transcriptomics and proteomics

Identifying transcriptomic and proteomic overlaps between endometriosis and obesity is key to understanding molecular interactions that worsen disease severity. Shared pathways and biomarkers – such as inflammation, immune response, and metabolic dysregulation – offer insights for early detection and therapeutic intervention. Proinflammatory cytokines such as IL-6 and TNF-α, elevated in obesity, are also found in the ectopic microenvironment, while oxidative stress links adipose tissue dysfunction in obesity to ectopic endometrial tissue in endometriosis [49]. However, genes involved in lipid metabolism, insulin resistance, and adipogenesis are dysregulated in both diseases, further highlighting a metabolic connection [50]. Proteomic studies have identified upregulated proteins involved in extracellular matrix remodeling and angiogenesis, key processes in both conditions [51]. These findings suggest that obesity may worsen endometriosis via shared inflammatory and metabolic pathways. Moreover, genetic loci (e.g., 7p15.2, KIFAP3, WNT4) have been linked to both endometriosis and obesity-related fat distribution, emphasizing fat distribution as a key factor influencing both conditions [52]. Although limited, emerging research highlights the potential of targeting shared pathways to mitigate the reciprocal impact of obesity and endometriosis, facilitating the development of personalized treatments.

Leptin signaling in obesity and endometriosis: insights across human and preclinical animal models

Leptin, a cytokine secreted by adipose tissue, regulates energy balance by suppressing hunger, and it reflects body fat mass under stable weight conditions [53]. Beyond energy regulation, leptin influences immune, inflammatory, and angiogenic responses, potentially contributing to the pathophysiology of endometriosis [54], though the mechanisms remain unclear. Table 2 highlights evidence from human studies linking obesity-driven leptin signaling to endometriosis progression. It is important to note that while elevated leptin levels were frequently observed in patients with endometriosis, results varied, and BMI differences were generally minor. Common limitations included small sample sizes and inconsistent inclusion of healthy controls, emphasizing the need for standardized, large-scale studies.

Comparing women with endometriosis with controls, elevated leptin levels were reported in the peritoneal and follicular fluids of those with endometriosis, though no significant differences were

Table 2. Comparison of leptin levels, BMI, and age between endometriosis and control groups across studies

Study location	Study type	Quantification method (leptin)	Sample analyzed	Sample size (case, control)	Confirmatory diagnosis-endometriosis	Leptin (ng/ml), case, control	BMI (case, control)	Age (case, control)	Conclusions	Study limitation	Refs
Poland	Cross-sectional	SPRI	Plasma	40, 30	Laparoscopy	15.5 ± 5.1, 15.5 ± 6.4 (P = 0.97)	22.23 ± 4.20, 21.58 ± 5.38	31.60 ± 5.33, 30.87 ± 7.06	No significant difference	Small sample size	[57]
			PF	38, 29		13.6 ± 5.3, 13.5 ± 6.2 (P = 0.97)					
Iraq	Cross-sectional	ELISA	Serum	30, 30	Laproscopy	289.7 ± 65.01, 222.6 ± 40.4 (pg/ml), (P = 0.0001)	NA	32.3 ± 4.4, 29.0 ± 6.6	Serum leptin levels are elevated in women with endometriosis	Small sample size	[84]
Czech Republic	Case–control	ELISA	FF	7, 72	Oocyte retrieval (infertility treatment)	Median 802, 1228 pg/ml		Median 26	Lower leptin levels in infertility cases	Small sample size	[85]
Brazil	Case–control	ELISA	Serum	15, 5	Laparoscopy or laparotomy	19.25 ± 1.84 (rASRM4), 14.7 ± 2.63, P <0.0001	22.51 ± 1.6, 24.37 ± 0.81	32.87 ± 1.16, 33.10 ± 2.32	Serum leptin levels are elevated in women with endometriosis	Small sample size	[86]
			PF			7.71 ± 0.59, 6.68 ± 0.43, P = 0.18			No significant difference		
Turkey	Case–control	ELISA	Serum	60 rASRM 1–4: 7,11,16,26, respectively, 20	Laparoscopy or laparotomy	4.3 (IQR 5.1), 5.2 (IQR 11.2)	24.3 ± 3.8, 24.21 ± 2.9, 22.3 ± 4.6, 24.2 ± 4.9, 24.8 ± 5.1 (rASRM 1,2,3,4,control)	28.2 ± 3.2, 29.6 ± 4.0, 31.8 ± 9.1, 34.8 ± 6.4, 34.2 ± 6.8 (rASRM 1,2,3,4,control)	No significant difference	Small sample size	[87]
India	Cross-sectional	ELISA	PF	19, 31	Laparoscopy	11.65 ± 9.40, 6.67 ± 6.18, P = 0.040	24.06 ± 3.1, 23.19 ± 2.38	28.6 ± 5.1, 29.9 ± 4.2	PF leptin levels were elevated in women with endometriosis	Small sample size, Lack of healthy controls	[88]
Korea	Case–control	IHC	Ovarian tissue	44, 42	Laparoscopy	100%, 59.5%, P <0.001		35.2 ± 6.2, 35.2 ± 6.6	Positive expression rates of leptin were significantly higher in endometriosis	Small sample size	[89]

USA	Case–control	ELISA	Plasma	350, 694	Laparoscopy (questionnaire)	17.5 (IQR 10.5–33.0), 16.6 (IQR 9.7–30.7), $P = 0.24$		41.7 ± 4.6, 42.1 ± 4.5	No significant difference	Inability to differentiate the time of endometriosis 'diagnosis' from the time of disease 'onset'	[90]
China	Case–control	ELISA	PF	28 (endometriosis infertility), 23 (fallopian infertility), 24 (myoma infertility)	Laparoscopy	4.3 ± 5.4, 3.1 ± 2.8, 1.95 ± 1.39	20.25 ± 2.60, 22.14 ± 3.81, 20.46 ± 1.84	28.95 ± 3.95, 28.55 ± 3.20, 31.63 ± 5.44	No significant difference	Small sample size	[91]
Egypt	Case–control	ELISA	PF	24, 14 (unexplained infertility)	Laparoscopy	23.15 ± 6.73, 11.29 ± 3.49, $P < 0.001$	23.21 ± 1.19, 23.53 ± 1.27	27.12 ± 4.25, 26.78 ± 5.38	PF leptin levels are elevated in women with endometriosis	Small sample size	[92]
			Serum	24, 14 (unexplained infertility)		11.06 ± 3.91, 10.39 ± 4.59, $P = 0.636$			No significant difference		
Italy	Case–control	ELISA	PF	27 (superficial 11, deep 16), 10 (idiopathic infertility)	Laparoscopy	29.2 ± 1.71, 23.4 ± 1.1, 19.4 ± 1.44, $P < 0.01$	22.9 ± 1.5, 21.9 ± 1.6	29.5 ± 4.6, 29.7 ± 4.4	PF leptin levels are elevated in women with endometriosis	Small sample size	[93]
USA	Case–control	ELISA	Serum	63, 78	Laparoscopy	Significantly higher in the endometriosis group ($P = 0.024$)		34 (18–48), 33 (23-48)	Serum leptin levels are elevated in women with endometriosis	Different racial distribution between case and control, Selection bias	[94]
Switzerland	Case–control	ELISA	FF	47, 279	Oocyte retrieval	11.38 (2.01–56.73), 14.15 (1.23–66.95), $P = 0.1655$	22.8 ± 3.7, 23.9 ± 3.8	33.0 ± 3.7, 33.2 ± 4.1	No significant difference		[95]
Greece	Case–control	ELISA	PF	60 rASRM1/2 36 rASRM3/4 14, 18	Laparoscopy	34.9 ± 7.9[b], 38.36 ± 6.1[a], 26.36 ± 4.8[a], 17.9 ± 4.1[b], $P^b < 0.001$, $P^a < 0.001$ (case, rASRM1/2, rASRM3/4, control)		32.54 ± 5.93, 31.2 ± 6.69	PF leptin levels are elevated in women with endometriosis	Small sample size	[96]
Germany	Case–control	RIA	Serum	42, rASRM1/2 20, rASRM3/4 22, 25	Laparoscopy	12.5 ± 8.4, 11.8 ± 7.7, 12.5 ± 9.4	21.5 ± 2.6, 22.6 ± 4.9	32.5 [23–46], 33 [17–40]	No significant difference	Small sample size	[97]

Abbreviations: ELISA, enzyme-linked immunosorbent assay; IHC, immunohistochemistry; IQR, interquartile range; PF, peritoneal fluid; rASRM, revised American society for reproductive medicine; SPRI, solid phase reversible immobilization.

[a]Leptin levels between the proliferative and secretory phases in the control group: $P < 0.001$.

[b]Leptin levels between the proliferative and secretory phases in women with endometriosis: $P < 0.001$.

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observed in serum or plasma leptin levels [55]. Further analysis of peritoneal fluid samples revealed no variation in leptin concentrations between stages 1–2 and 3–4 of endometriosis, suggesting that leptin acts locally regardless of disease severity [55]. A sub-analysis of 14 studies adjusting for BMI showed significantly higher leptin levels in endometriosis patients, with an increased leptin/BMI ratio in peritoneal fluid [56], while other studies reported no overall difference [57]. Notably, a lower leptin/BMI ratio was observed in patients with primary infertility, though this was limited by a small sample size [57]. These findings highlight the complex role of leptin in endometriosis, emphasizing its localized activity in the peritoneal environment and its potential links to BMI and infertility.

The leptin/BMI ratio, a measure of leptin efficiency relative to body fat, is useful for identifying leptin resistance. Elevated leptin levels may indicate increased inflammatory responses or metabolic stress, while leptin resistance may stem from downregulated leptin receptor (Ob-R) genes in endometriosis [58]. Despite its potential clinical value, the limited research has produced inconsistent findings, emphasizing the need for further studies to understand the role of the leptin/BMI ratio in disease progression and therapeutic applications.

Leptin signals through its receptor, Ob-R, primarily via the **JAK–STAT pathway**. Upon binding, JAK2 activates STAT3, which regulates genes involved in inflammation, cell proliferation, and angiogenesis [59]. In endometriosis, excessive STAT3 activation may drive abnormal endometrial cell proliferation and invasion [59,60]. Additionally, leptin-induced VEGF expression and PI3K–Akt pathway activation contribute to angiogenesis and disease progression, while inflammatory responses in adipose tissue and immune cell activation exacerbate the condition [61]. Additionally, the shift in macrophage polarization from an anti-inflammatory to a proinflammatory phenotype, along with increased adipocytokines such as TNF-α and IL-6 and systemic metabolic dysfunction, further contributes to disease progression [62]. A proposed model illustrating the Ob-R, its downstream signaling pathways, and their association with endometriosis is shown in Figure 2.

Animal models also highlight the role of leptin in endometriosis and obesity. Leptin and its receptor are essential for disease progression, with obesity exacerbating endometriosis by increasing leptin levels [63]. Leptin produced by ectopic endometrial tissue contributes to chronic pain in an estrogen-dependent manner, underscoring the interplay between reproductive hormones, leptin's inflammatory effects, and the increased severity of endometriosis in individuals with obesity [64]. Moreover, leptin receptor overexpression in ectopic tissues drives cell proliferation via the JAK2–STAT3 and extracellular signal-regulated kinase (ERK) pathways [65]. Additionally, disrupting leptin signaling reduced lesion formation, angiogenesis, and inflammation in murine models, underscoring leptin's role in lesion development and maintenance [66].

In conclusion, evidence from human and preclinical studies proposes leptin as a key mediator linking obesity and endometriosis. Leptin contributes to lesion formation, maintenance, pain, and inflammation, highlighting obesity as a significant risk factor for disease progression. Therefore, targeting leptin pathways, such as JAK2–STAT3 and ERK, may offer promising therapeutic opportunities to mitigate the impact of obesity on endometriosis and enable personalized treatment based on metabolic profiles.

Therapeutic approaches targeting obesity-driven inflammation and metabolic dysregulation to improve endometriosis outcomes

Exploring obesity as a modifiable factor presents a compelling strategy to improve endometriosis management and outcomes. Therapeutic interventions such as lifestyle changes, bariatric surgery, and pharmacotherapy can alleviate endometriosis symptoms by reducing systemic inflammation, correcting metabolic imbalances, and regulating hormonal profiles. Structured diet and

exercise programs not only promote weight loss but also lower inflammation and improve insulin sensitivity, both critical in endometriosis pathophysiology [67]. These interventions can also alleviate chronic pain and enhance overall wellbeing.

Bariatric surgery, often recommended for severe obesity, has demonstrated significant weight loss, reduced estrogen levels, and improved inflammatory markers [68]. These metabolic shifts may help reduce lesion progression and pain severity in endometriosis [68], though further clinical research is warranted to establish direct benefits. Similarly, pharmacological therapies such as glucagon-like peptide-1 receptor agonists aid in weight management, modulate metabolic health, and decrease adipose-driven inflammation and leptin levels, key contributors to endometriosis progression [69].

Targeting JAK2–STAT3 and ERK signaling is a promising therapeutic strategy for endometriosis and obesity-related inflammation [70]. Obesity-driven leptin overexpression activates these pathways, promoting chronic inflammation, angiogenesis, and lesion growth. JAK2–STAT3 inhibition with tofacitinib reduces lesion size and adhesion formation by suppressing STAT3 phosphorylation, hypoxia-inducible factor 1α (HIF-1α), and VEGF, key regulators of vascularization and lesion progression [60]. Given that obesity-induced adipose tissue dysfunction fosters a proinflammatory state and elevated estrogen production [62], controlling obesity-related inflammatory pathways may help mitigate lesion development and disease severity.

Additionally, nanoceria, a non-steroidal anti-inflammatory nano-drug, mitigates oxidative stress and inflammation while shifting macrophages from a proinflammatory to an anti-inflammatory phenotype, thereby regulating immune-driven disease progression [59]. Since obesity amplifies STAT3 activation, chronic inflammation, and macrophage dysregulation, therapies such as nanoceria and JAK2–STAT3 inhibitors could counteract obesity-driven inflammation and reduce lesion burden in individuals with endometriosis (Figure 2).

Further, WP1066, another JAK2–STAT3 inhibitor, has been demonstrated to suppress endometrial stromal cell proliferation and invasion by inhibiting hypoxia-induced angiogenesis [71]. Similarly, ERK pathway inhibitors (PD98059 and U0126) effectively reduce endometriotic cell proliferation, presenting an additional viable approach for controlling disease progression [72]. Given the overlapping inflammatory pathways in obesity and endometriosis, these targeted interventions hold the potential for modulating systemic inflammation and improving patient outcomes. However, further clinical validation is required to confirm their long-term efficacy and safety.

Future research should elucidate the molecular connections between obesity, immune modulation, and endometriosis pathogenesis. Special emphasis should be placed on leptin signaling, adipokines, and macrophage-driven inflammation as potential therapeutic targets. Investigating the direct impact of these interventions on lesion size, pain, and fertility will be essential for optimizing personalized treatment strategies. Integrating obesity management into comprehensive endometriosis care may provide a multifaceted approach to improving patient outcomes.

Concluding remarks and future perspectives

Endometriosis is a complex disease influenced by immune dysfunction, metabolic alterations, and chronic inflammation. While research has advanced our understanding, significant gaps remain in uncovering the immune evasion mechanisms of ectopic lesions, the role of adipose tissue dysfunction, and the metabolic interplay between obesity and disease progression (see Outstanding questions).

Outstanding questions

What drives immune evasion in ectopic endometrial lesions?

How do metabolic changes in obesity exacerbate endometriosis?

Can leptin signaling pathways be effectively targeted?

How does body composition, beyond BMI, influence endometriosis progression?

What is the long-term impact of obesity-targeted interventions on endometriosis outcomes?

How can diagnostic delays and cultural variations in disease perception be addressed?

How does adipose tissue dysfunction and systemic metabolic changes exacerbate endometriosis?

Body composition significantly impacts disease severity, with both low BMI and obesity contributing through distinct mechanisms. Obesity-driven metabolic dysfunction intensifies systemic inflammation, while leptin signaling promotes angiogenesis, lesion survival, and chronic pain. Therefore, investigating how adipose-tissue-derived cytokines and oxidative stress sustain lesion persistence is essential for identifying new metabolic and immunomodulatory targets. Additionally, the long-term effects of obesity-targeted interventions on endometriosis outcomes remain unclear and warrant further investigation. Future research should explore how ectopic lesions escape immune clearance, with a focus on cytokine networks, immune cell dysfunction, and genetic factors that drive chronic inflammation. Investigating leptin-mediated JAK–STAT and ERK pathways could provide new opportunities for endometriosis therapy. Large-scale, population-based studies are also needed to better define the relationships among BMI, lifestyle factors, and disease risk, particularly in understanding diagnostic delays and cultural differences in disease perception.

Indeed, a multidisciplinary approach integrating molecular research, metabolic profiling, and personalized medicine is essential for advancing new treatment strategies. Expanding knowledge of the complex interactions between metabolism, immunity, and endometriosis will enable more precise and effective therapeutic interventions. Ultimately, combining scientific research, clinical innovation, and holistic care is critical for improving patient outcomes and enhancing the quality of life for those affected by endometriosis.

Author contributions

M.S.R., J.H.S., and J.W.G. conceptualized the manuscript. M.S.R., Y.P., and H.H. drafted the initial version of the manuscript. M.S.R. and J.W.G. prepared the figures and visual materials. M.S.R., Y.P., J.W.G., and J.H.S. critically reviewed and edited the manuscript. All authors have reviewed and approved the final version for submission.

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Declaration of interests

The authors declare no competing interests.

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