International Journal of Biological and Pharmaceutical Sciences Archive

ISSN: 0799-6616 (Online)

Journal homepage: https://ijbpsa.com/

(REVIEW ARTICLE)

Endometriosis as an underrecognized risk factor for heart failure: Mechanistic insights from inflammation, estrogen dysregulation, and cardiometabolic overlap

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International Journal of Biological and Pharmaceutical Sciences Archive, 2026, 11(02), 009-022

Publication history: Received on 24 February 2026; revised on 16 April 2026; accepted on 18 April 2026

Article DOI: https://doi.org/10.53771/ijbpsa.2026.11.2.0036

Abstract

Endometriosis is often treated as a localised gynaecological issue, but a growing body of evidence shows it has broader systemic effects including an increase in the risk of heart failure. The condition affects roughly 10% of women of reproductive age and is linked through large cohort studies and meta-analyses to elevated rates of ischaemic heart disease (IHD), stroke and arrhythmias (adjusted hazard ratios typically 1.1 to 1.5), with heart failure emerging as a signal in several nationwide registries. The connection appears to arise from three overlapping mechanisms; Persistent low-grade inflammation releases pro-inflammatory cytokines (notably IL-6, TNF-α, and IL-1β) into the circulation which promotes endothelial dysfunction and oxidative stress, Oestrogen dysregulation which plays a paradoxical role: locally, excessive production in endometriotic lesions sustains inflammation while systemic hormonal imbalance can undermine vascular protection and contribute to pro-thrombotic or arrhythmogenic effects. Concurrent cardiometabolic disturbances such as insulin resistance, atherogenic dyslipidaemia, central adiposity and elevated cardiometabolic index further strain the myocardium and predisposes one to diastolic dysfunction particularly in the heart failure with preserved ejection fraction phenotype that disproportionately affects women. Clinically, this means endometriosis should no longer be managed in isolation. Routine cardiovascular risk assessment such as blood pressure, lipid profile, glucose tolerance and possibly selected inflammatory markers should become standard in follow-up especially for younger patients or those with long disease duration or have had prior surgery. Closer collaboration between gynaecologists and cardiologists together with prospective studies that track true heart failure incidence and evaluate targeted interventions (anti-inflammatory strategies, optimised hormonal regimens, lifestyle modification) could substantially reduce preventable cardiac morbidity in this population.

Keywords: Endometriosis; Heart Failure; Inflammation; Estrogens; Risk Factors; Cardiovascular Diseases; Insulin Resistance; Metabolic Syndrome

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1. Introduction

1.1. Overview

Endometriosis is a chronic, estrogen-dependent gynecological disorder characterized by the presence of endometrial-like tissue outside the uterus, leading to debilitating symptoms such as pelvic pain, dysmenorrhea, dyspareunia and infertility. It affects millions of women worldwide and imposes a significant burden on quality of life. Healthcare systems also play a part due to diagnostic delays and limited curative options. Emerging evidence suggests systemic implications beyond reproductive health, including potential links to cardiovascular disease (CVD) through mechanisms like chronic inflammation and hormonal dysregulation. This review focuses on endometriosis as an underrecognized risk factor for heart failure (HF). In this study, epidemiological data and mechanistic insights from inflammation, estrogen dysregulation, and cardiometabolic overlap are synthesized in order to advocate for greater awareness and targeted cardiovascular screening in affected women.

1.2. Epidemiology and Burden of Endometriosis

Endometriosis predominantly affects women of reproductive age with global prevalence estimates varying based on diagnostic methods and population studied [1]. In general population or health system data, prevalence ranges from approximately 1 to 10% while higher rates (up to 30 to 50%) are reported in women with infertility or chronic pelvic pain [2,3]. For instance, population-based studies indicate a prevalence of around 6 to 10% among women of reproductive age though administrative or insurance data often report lower figures (around 1 to 2%) due to underdiagnosis [1,4]. Diagnostic challenges, including reliance on laparoscopy for confirmation and average delays of 7 -to 10 years from symptom onset contribute to this variability and underestimate the true burden [1,5].

The chronic nature of endometriosis manifests as recurrent pelvic pain, infertility in around 30% to 50% of cases and reduced quality of life, often requiring long-term management with hormonal therapies, surgery or pain control [1,3]. These factors impose substantial economic and psychosocial costs, with affected women experiencing higher rates of absenteeism, healthcare utilization as well as comorbid conditions [3]. Early menarche, short menstrual cycles and nulliparity are established risk factors while parity and higher body mass index appear protective in some cohorts [1].

Despite advances in awareness, endometriosis remains underrecognized as a systemic disease, with limited longitudinal data on long-term extrapelvic effects. This gap highlights the need to explore its associations with other chronic conditions including cardiovascular implications.

1.3. Overview of Cardiovascular Disease in Women and Heart Failure Epidemiology

Cardiovascular disease remains the leading cause of mortality in women globally, yet sex-specific differences in presentation, risk factors, and outcomes are often underappreciated [6]. Women tend to develop CVD later than men but experience higher morbidity from conditions like heart failure with preserved ejection fraction (HFpEF), which predominates in postmenopausal women and is linked to inflammation and metabolic factors [7,8]. Traditional risk factors (hypertension, diabetes, dyslipidemia) interact with female-specific elements such as hormonal transitions, pregnancy complications, and autoimmune/inflammatory conditions [6].

Heart failure affects millions worldwide, with increasing incidence in women due to aging populations and rising cardiometabolic comorbidities. HFpEF in particular shows a female predominance (women comprise approximately 55% of HFpEF cases) and is associated with chronic low-grade inflammation, endothelial dysfunction and estrogen fluctuations pathways that overlap with endometriosis [7,8]. Sex hormones play a protective role in premenopausal women, but dysregulation can contribute to vascular stiffness and cardiac remodeling [7].

The underrecognition of non-traditional risk factors in women, including chronic inflammatory gynecological disorders may delay prevention strategies. Emerging data suggest that conditions like endometriosis could amplify CVD susceptibility through shared mechanisms.

1.4. Rationale for Linking Endometriosis to Cardiovascular Disease and Heart Failure

Endometriosis involves systemic chronic inflammation, oxidative stress and estrogen/progesterone imbalances, which parallel pathways in CVD pathogenesis, including endothelial dysfunction and atherosclerosis [9]. Large cohort studies have demonstrated modest but significant associations between endometriosis and increased risks of ischemic heart disease, stroke, arrhythmias and composite CVD events, with adjusted hazard ratios typically in the 1.1 to 1.5 range [10,11]. While HF-specific links are emerging and sometimes modest or inconsistent across meta-analyses, recent

nationwide data indicate a small elevated risk (adjusted HR ~1.11 for HF) especially in long-term follow-up [12]. These associations may be amplified by confounders like early hysterectomy/oophorectomy in endometriosis patients which accelerates estrogen decline and CVD risk. The underrecognition of endometriosis as a CVD/HF contributor stems from its primary gynecological framing, despite mechanistic relationship with inflammatory and hormonal drivers of cardiac remodeling [9].

This review synthesizes these connections, emphasizing mechanistic insights to position endometriosis as an underrecognized HF risk factor warranting multidisciplinary attention.

2. Epidemiological Evidence Linking Endometriosis to Heart Failure and Cardiovascular Outcomes

2.1. Overview

The epidemiological landscape of endometriosis in relation to cardiovascular outcomes has expanded substantially in recent years, driven by large cohort studies and meta-analyses of population-based data. While initial observations focused on broader cardiovascular disease (CVD) associations, attention has increasingly turned to specific endpoints, including heart failure (HF), ischemic heart disease (IHD), stroke, arrhythmias, and composite major adverse cardiovascular events (MACE). This section reviews key evidence from cohort studies and systematic reviews/meta-analyses, highlighting modest but consistent risk elevations for several CVD outcomes, with particular emphasis on HF associations that remain modest and sometimes heterogeneous. Subgroup considerations, such as surgical history (hysterectomy/oophorectomy), are also addressed to contextualize potential confounders.

2.2. Key Cohort Studies and Nationwide Registries

Large population-based cohorts have provided robust evidence for an association between endometriosis and increased CVD risk. In a nationwide Danish registry study involving over 60,000 women with endometriosis matched to controls, the adjusted hazard ratio (HR) for the composite endpoint of acute myocardial infarction and ischemic stroke was 1.15 (95% CI 1.11 to 1.20) over long-term follow-up (median 16 years) [13]. This study also reported elevated risks for arrhythmias (adjusted HR 1.21; 95% CI 1.17 to 1.25) and heart failure (adjusted HR 1.11; 95% CI 1.05 to 1.18), though absolute risk differences remained small [13].

Similar patterns emerge from other registries. A Canadian population-based analysis of over 166,000 women with endometriosis found an increased risk of hospital admission for CVD (adjusted HR 1.14; 95% CI 1.10 to 1.19), including secondary CVD events (adjusted HR 1.26; 95% CI 1.23 to 1.30), with specific elevations in congestive heart failure among secondary outcomes [14]. Earlier prospective cohorts such as the Nurses' Health Study II, demonstrated higher relative risks for myocardial infarction (RR 1.52; 95% CI 1.17 to 1.98) and composite coronary heart disease endpoints (RR 1.62; 95% CI 1.39 to 1.89) in laparoscopically confirmed cases, independent of traditional confounders [15]. These findings underscore a consistent, albeit modest, signal across diverse populations.

2.3. Meta-Analyses of Cardiovascular Risk

Systematic reviews and meta-analyses have synthesized these cohort data to quantify pooled risks. A recent meta-analysis of seven studies (totaling ~1.4 million participants) reported significantly elevated risks for cerebrovascular disease (HR 1.19; 95% CI 1.13 to 1.24), ischemic heart disease (HR 1.35; 95% CI 1.32 to 1.39), MACE (HR 1.15; 95% CI 1.13 to 1.19) and arrhythmias (HR 1.21; 95% CI 1.17 to 1.25) in women with endometriosis [16]. Notably, no significant association was observed for heart failure (HR 0.96; 95% CI 0.66 to 1.37) or all-cause mortality in this analysis, highlighting heterogeneity and limited power for HF-specific endpoints [16].

Earlier meta-analyses align with these observations. A 2023 review of six cohorts found endometriosis linked to increased ischemic heart disease (HR 1.50; 95% CI 1.37 to 1.65) and cerebrovascular disease (HR 1.17; 95% CI 1.07 to 1.29), with low heterogeneity [17]. Another analysis confirmed elevated pooled odds for ischemic heart disease (OR 1.36; 95% CI 1.32 to 1.40), stroke (OR 1.18; 95% CI 1.13–1.22), and composite CVD (OR 1.16; 95% CI 1.12–1.20), though HF data were sparse [18]. These syntheses indicate modest risk elevations predominantly for atherosclerotic and cerebrovascular outcomes, with HF associations less robust and warranting further investigation.

To provide a concise comparison of the main findings across study types, Table 1 summarizes the key epidemiological evidence presented in this section, including pooled risk estimates and heart failure-specific results where available.

Table 1 Overview of Epidemiological Evidence on Endometriosis and Cardiovascular Risk

Type of Evidence	Key Studies / Sources	Main Cardiovascular Outcomes Studied	Risk Estimates (Adjusted)	Heart Failure (HF) Specific Finding	Overall Strength / Notes	References
Nationwide Registries & Large Cohorts	Danish nationwide registry	Composite AMI + stroke, arrhythmias, HF	Composite AMI/stroke: HR 1.15 (1.11–1.20) Arrhythmias: HR 1.21 (1.17–1.25)	HR 1.11 (1.05–1.18) – modest increase	Long follow-up (median 16 years); absolute risks small; strong for arrhythmias	[12], [13]
	Canadian population-based cohort	CVD hospital admission, secondary CVD events, congestive HF	CVD admission: HR 1.14 (1.10–1.19) Secondary CVD: HR 1.26 (1.23–1.30)	Elevated in secondary outcomes (HR not specified)	Large sample (>166,000); HF mentioned but not primary endpoint	[14]
	Nurses' Health Study II (prospective cohort)	Myocardial infarction, composite coronary heart disease	MI: RR 1.52 (1.17–1.98) Composite CHD: RR 1.62 (1.39–1.89)	Not specifically reported	Laparoscopically confirmed cases; independent of traditional risk factors	[11], [15]
Meta-Analyses & Systematic Reviews	Recent meta-analysis (7 studies, ~1.4 million)	Cerebrovascular disease, IHD, MACE, arrhythmias, HF	Cerebrovascular: HR 1.19 (1.13–1.24) IHD: HR 1.35 (1.32–1.39) MACE: HR 1.15 (1.13–1.19) Arrhythmias: HR 1.21 (1.17–1.25)	HF: HR 0.96 (0.66–1.37) – not significant	Strongest signals for IHD, stroke, arrhythmias; HF association weak / underpowered	[9], [16]
	2023 review (6 cohorts)	Ischemic heart disease, cerebrovascular disease	IHD: HR 1.50 (1.37–1.65) Cerebrovascular: HR 1.17 (1.07–1.29)	Not specifically reported	Low heterogeneity; consistent with atherosclerotic focus	[10]
	Other pooled analyses	IHD, stroke, composite CVD	IHD: OR 1.36 (1.32–1.40) Stroke: OR 1.18 (1.13–1.22) Composite CVD: OR 1.16 (1.12–1.20)	HF data sparse	Confirms modest elevations; limited HF-specific power	[18]
Subgroup & Confounding Factors	Hysterectomy / oophorectomy	Amplifies risk via premature estrogen decline	Higher CHD risk in surgical subgroups: HR 1.51 (1.34–1.71)	Contributes to overall CVD increase	Common in endometriosis; partial attenuation when adjusted; major confounder	[15], [16], [19]
	Age & follow-up duration	Stronger risks in younger women or longer follow-up	Not quantified separately	Longer follow-up strengthens HF signal	Risks appear to increase over time	[13], [15]

	Mendelian randomization studies	Limited causality for some endpoints	No strong causal link to coronary heart disease	Not specifically reported	Suggests residual confounding; causality not fully established	[20]

Where: AMI - Acute Myocardial Infarction; IHD - Ischemic Heart Disease; CHD - Coronary Heart Disease; HR - Hazard Ratio; CI - Confidence Interval; OR - Odds Ratio; CVD - Cardiovascular Disease; RR - Relative Risk (or Risk Ratio); HF - Heart Failure; MACE - Major Adverse Cardiovascular Events

2.4. Subgroup Analyses and Confounding Factors

Subgroup and sensitivity analyses reveal important modifiers. Hysterectomy and/or oophorectomy, common in endometriosis management, amplify CVD risks through premature estrogen decline. In one cohort, adjustment for these procedures partially attenuated associations, with higher CHD risk in surgical subgroups (HR 1.51; 95% CI 1.34 to 1.71) [15]. Meta-analyses note that treatment-related factors (e.g., early oophorectomy) may confound estimates, as many studies lack full adjustment [16,19].

Age at diagnosis and follow-up duration also influence findings; risks appear stronger in younger women or longer-term cohorts [13,15]. Conflicting results from Mendelian randomization studies suggest limited causality for some endpoints (e.g., no strong link to coronary heart disease), underscoring potential residual confounding [20]. Overall, while epidemiological evidence supports endometriosis as a contributor to CVD burden, HF-specific data remain modest and inconsistent, emphasizing the need for targeted prospective studies.

3. Chronic Inflammation as a Core Mechanism

3.1. Overview

Chronic inflammation constitutes a central pathophysiological feature of endometriosis, extending beyond local peritoneal involvement to contribute to systemic effects that may predispose affected women to cardiovascular complications, including heart failure. This section examines the inflammatory milieu in endometriosis, focusing on key pro-inflammatory mediators, their spillover from peritoneal sources into circulation, associated biomarkers of systemic activation, and the pathways through which sustained inflammation promotes endothelial injury, atherosclerosis, and adverse cardiac remodeling. Evidence from biomarker studies and mechanistic reviews illustrates how these processes parallel those in established inflammatory conditions linked to increased heart failure risk, underscoring inflammation as a plausible bridge between endometriosis and cardiac vulnerability.

3.2. Pathophysiology of Systemic Inflammation in Endometriosis

Endometriosis is characterized by a pro-inflammatory peritoneal microenvironment, with ectopic endometrial tissue eliciting recruitment and activation of immune cells that release elevated levels of pro-inflammatory cytokines [21]. Key mediators include interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) which are consistently higher in peritoneal fluid of affected women compared to controls which contribute to local tissue remodeling and pain [22]. These cytokines produced by macrophages, endometriotic stromal cells and mesothelial cells promote a self-sustaining inflammatory cycle through autocrine and paracrine signaling.

Systemic spillover occurs as peritoneal cytokines and inflammatory mediators enter the circulation, leading to low-grade chronic inflammation detectable in serum [23]. Studies demonstrate elevated circulating IL-6, TNF-α, and IL-1β in women with endometriosis, particularly in advanced stages, correlating with disease severity and symptom burden [24]. This transition from localized to systemic inflammation is facilitated by increased vascular permeability in endometriotic lesions and peritoneal mesothelial activation, allowing diffusion of soluble factors into the bloodstream [25]. Consequently, affected women exhibit persistent immune activation that may extend beyond gynecological confines.

3.3. Inflammation-Driven Endothelial Dysfunction and Atherosclerosis

Chronic inflammation in endometriosis induces endothelial dysfunction, a critical early step in atherogenesis, through cytokine-mediated impairment of nitric oxide bioavailability and increased oxidative stress [21,26]. Pro-inflammatory mediators such as IL-6 and TNF-α promote expression of adhesion molecules on endothelial cells, facilitating leukocyte recruitment and plaque initiation [23]. Non-invasive assessments reveal reduced reactive hyperemia index (indicating

endothelial impairment) and elevated advanced glycation end-products in skin (reflecting arterial stiffness) among women with endometriosis compared to controls [24].

These vascular changes align with accelerated atherosclerosis progression, as systemic inflammation fosters lipid oxidation, foam cell formation, and plaque instability [22]. Observational data link endometriosis-associated inflammation to higher prevalence of subclinical atherosclerotic markers, including increased intima-media thickness and coronary artery calcification in some cohorts [27]. The interplay between persistent cytokine elevation and endothelial injury thus provides a mechanistic basis for the modest but reproducible cardiovascular risk elevations observed epidemiologically.

The interconnected mechanisms underlying the endometriosis-cardiovascular disease link are illustrated in Figure 1 which is a schematic diagram highlighting inflammation, oxidative stress and endothelial pathways

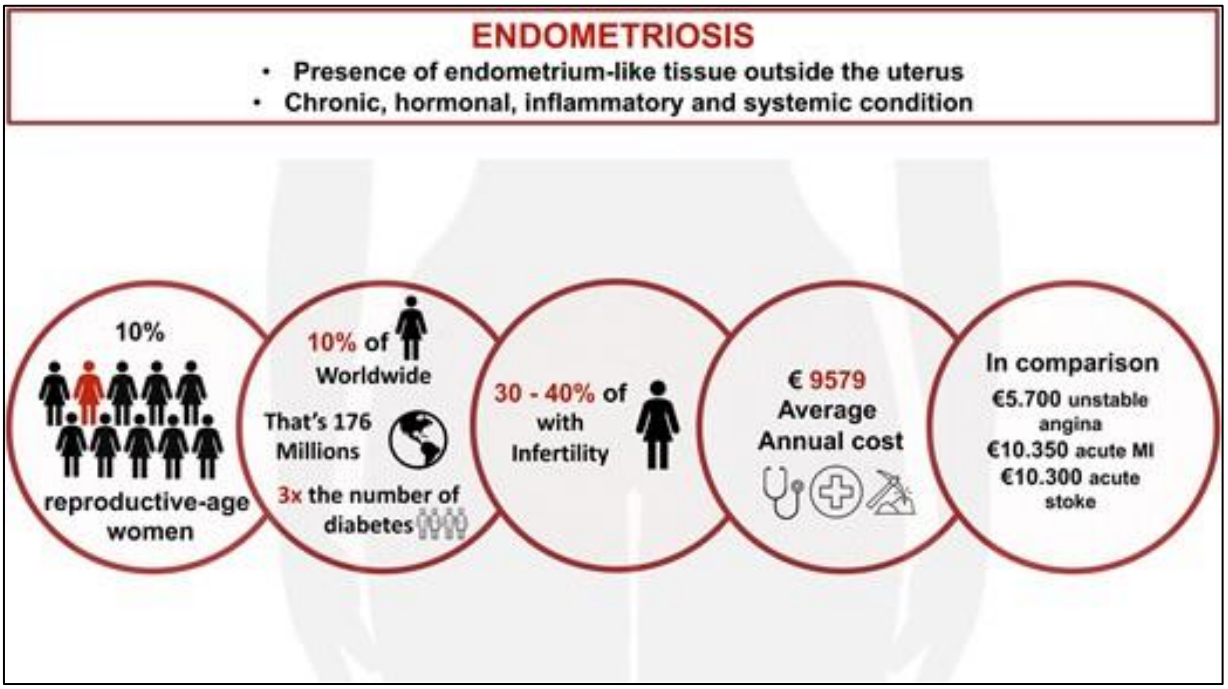

Figure 1 Schematic Diagram of Pathophysiological Links Between Endometriosis and CVD [53]

3.4. Links to Cardiac Remodeling and Heart Failure Pathways

Sustained systemic inflammation contributes to cardiac remodeling through cytokine effects on cardiomyocytes and fibroblasts thereby promoting fibrosis, hypertrophy and diastolic dysfunction which are hallmarks of heart failure with preserved ejection fraction (HFpEF) which predominates in women [28]. Elevated IL-6 and TNF-α activate signaling pathways (e.g., NF-κB, JAK/STAT) that drive myocardial inflammation and extracellular matrix deposition, impairing ventricular compliance [29]. Biomarker studies in endometriosis cohorts show increased C-reactive protein (CRP) and oxidative stress markers, which correlate with endothelial dysfunction and predict adverse cardiac outcomes in broader inflammatory contexts [30].

Parallels exist with other chronic inflammatory disorders, such as rheumatoid arthritis and inflammatory bowel disease, where similar cytokine profiles (IL-6, TNF-α) confer elevated heart failure risk via myocardial inflammation and remodeling [31]. In endometriosis, the chronicity of inflammation may amplify these effects, particularly in the presence of comorbidities or surgical interventions that exacerbate systemic burden [32]. While direct cardiac involvement remains understudied, these overlapping pathways position inflammation as a plausible contributor to heart failure susceptibility in endometriosis.

4. Estrogen Dysregulation and Its Cardiovascular Implications

4.1. Overview

Estrogen plays a pivotal yet complex role in endometriosis, where local overproduction and systemic dysregulation contribute to disease persistence and potentially broader health sequelae. This section explores the hormonal landscape of endometriosis, emphasizing excessive local estrogen synthesis in ectopic lesions, progesterone resistance and the dualistic cardiovascular effects of estrogen which is protective under physiological conditions but potentially detrimental when dysregulated or suppressed. Evidence from clinical and mechanistic studies highlights how these alterations influence vascular tone, lipid metabolism, and cardiac electrophysiology, alongside the cardiovascular consequences of therapeutic interventions that modulate estrogen levels.

4.2. Estrogen Excess and Progesterone Resistance in Endometriotic Lesions

Endometriotic lesions exhibit autonomous estrogen production through upregulated aromatase expression, leading to elevated local estradiol concentrations that sustain tissue proliferation and inflammation independent of ovarian cycling [34]. This intracrine estrogen synthesis, coupled with reduced inactivation pathways, creates a hyperestrogenic milieu within implants, perpetuating the disease process [35]. Progesterone resistance further exacerbates this imbalance, as endometriotic tissue demonstrates diminished responsiveness to progesterone's antiproliferative and anti-inflammatory actions, often due to altered receptor isoforms or signaling defects [34,36].

These hormonal perturbations extend systemically in some patients, with evidence of altered circulating estrogen metabolites and impaired luteal phase progesterone support [35]. The resulting imbalance favors pro-inflammatory cytokine release and oxidative stress, which may indirectly influence distant tissues, including the vasculature [37]. Such dysregulation underscores why endometriosis manifests as a hormone-dependent disorder with potential extrapelvic ramifications.

4.3. Dual Role of Estrogen in Cardiovascular Protection and Dysregulation

Estrogen exerts well-documented protective effects on the cardiovascular system under physiological conditions, including promotion of vasodilation via endothelial nitric oxide synthase activation, inhibition of smooth muscle proliferation, and favorable modulation of lipid profiles [35]. In premenopausal women, these actions contribute to lower atherosclerosis risk compared to age-matched men [38]. However, in endometriosis, chronic local estrogen excess and associated inflammation may override these benefits, potentially promoting endothelial dysfunction through heightened oxidative stress and pro-thrombotic tendencies [34].

Dysregulated estrogen signaling such as altered receptor expression or metabolite profiles can shift toward adverse vascular effects, including increased arterial stiffness and impaired flow-mediated dilation observed in some endometriosis cohorts [35]. These changes parallel mechanisms in other hyperestrogenic states where excess estrogen contributes to inflammation-driven vascular injury [37]. The net cardiovascular impact thus depends on the balance between protective systemic effects and localized pathological overdrive.

Table 2 contrasts the physiological protective effects of estrogen with its actions in endometriosis and the resulting cardiovascular consequences.

Table 2 Comparison of Estrogen Dysregulation Pathways and Cardiovascular Implications in Endometriosis

Context	Estrogen Level / Action	Vascular Effect	Lipid Profile Effect	Cardiac Effect	Clinical Implication in Endometriosis	Reference
Physiological (premenopausal)	Normal circulating levels	Vasodilation (eNOS activation), anti-atherogenic	Favorable (↑HDL, ↓LDL)	Protective against remodeling	Normal protection lost in some patients	[35], [38]

Local in endometriotic lesions	Excessive intracrine production (aromatase ↑)	Pro-inflammatory, oxidative stress	Not directly affected	Indirect via inflammation	Sustains local disease and systemic spillover	[34], [35]
Systemic dysregulation	Erratic / altered metabolites	Endothelial dysfunction, ↑ stiffness	Potentially atherogenic	Arrhythmogenic potential	Paradoxical loss of protection	[34], [43]
Post-GnRH agonist / surgical menopause	Suppression (hypoestrogenic)	Loss of vasodilation, ↑ stiffness	Dyslipidemia (↑LDL, ↓HDL)	Increased cardiac strain	Amplifies CVD risk	[33], [36]

Where: eNOS - Endothelial Nitric Oxide Synthase; LDL - Low-Density Lipoprotein; GnRH - Gonadotropin-Releasing Hormone;'↑' – Increase; HDL - High-Density Lipoprotein; '↓' – decrease; HFpEF - Heart Failure with Preserved Ejection Fraction

The effects of estrogen in endometriosis is protective under normal conditions but potentially detrimental when dysregulated, this is depicted in Figure 2 which is a schematic overview of mechanisms linking endometriosis to cardiovascular disease

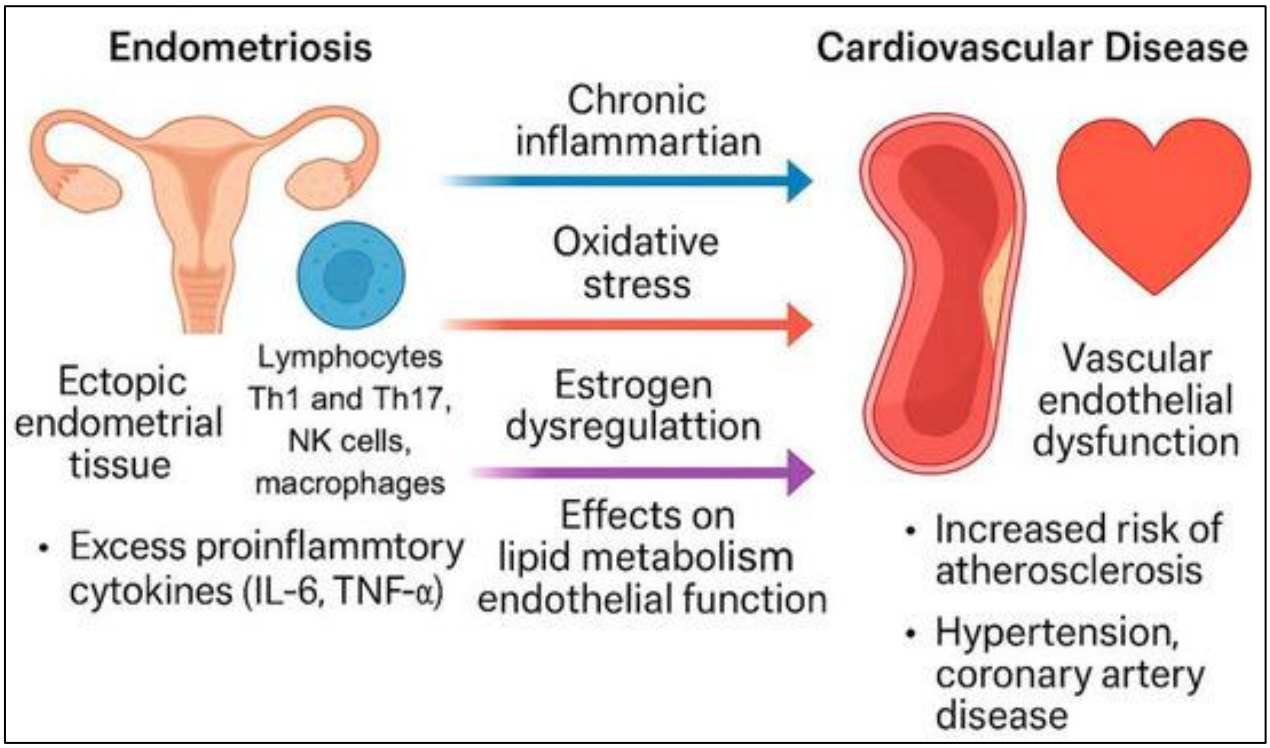

Figure 2 Mechanisms linking endometriosis with cardiovascular disease [23].

4.4. Effects of Treatments Altering Estrogen Levels and Cardiovascular Risk

Therapeutic suppression of estrogen via gonadotropin-releasing hormone (GnRH) agonists or antagonists induces a hypoestrogenic state to regress lesions, but this comes with metabolic and cardiovascular trade-offs [36]. GnRH therapies suppress ovarian estrogen production, leading to adverse changes such as dyslipidemia, insulin resistance, and increased arterial stiffness, which elevate risks for atherosclerosis and ischemic events in prolonged use [39]. Observational data indicate heightened cardiovascular vulnerability in patients receiving long-term GnRH analogues, particularly through estrogen withdrawal effects on endothelial function and lipid metabolism [37].

Add-back hormone regimens (low-dose estrogen/progestin) aim to mitigate hypoestrogenic sequelae like bone loss and vasomotor symptoms, yet their impact on cardiovascular risk remains incompletely defined [33]. Surgical interventions, such as oophorectomy, accelerate estrogen decline and associate with amplified CVD risk in endometriosis patients

[34]. These findings emphasize the need for individualized hormonal management that weighs gynecological benefits against potential long-term vascular consequences.

5. Cardiometabolic Overlap: Metabolic Syndrome, Insulin Resistance, and Dyslipidemia

5.1. Overview

Cardiometabolic disturbances represent an important intersection between endometriosis and cardiovascular vulnerability, with shared pathways involving chronic inflammation, hormonal imbalance, and metabolic dysregulation potentially contributing to insulin resistance, dyslipidemia, central adiposity, and components of metabolic syndrome. This section reviews epidemiological associations between endometriosis and metabolic syndrome or its elements, mechanistic links through inflammation-driven insulin resistance and lipid alterations, and implications for heart failure—particularly the preserved ejection fraction phenotype prevalent in women—where metabolic stress amplifies diastolic dysfunction and cardiac strain.

5.2. Association with Metabolic Syndrome Components

Women with endometriosis exhibit a higher prevalence of metabolic syndrome compared to unaffected controls, as evidenced by population-based and cross-sectional studies. In one large cohort, the adjusted odds ratio for metabolic syndrome was 1.99 (95% CI 1.20 to 3.30), driven primarily by increased central obesity (high waist circumference) and low HDL-cholesterol [40]. Similar findings from NHANES-derived analyses report adjusted odds of metabolic syndrome ranging from 1.55 (95% CI 1.01 to 2.35) to higher in specific subgroups, though associations may attenuate after accounting for surgical history such as hysterectomy [41].

Dyslipidemia emerges consistently, with endometriosis linked to atherogenic profiles including elevated triglycerides and reduced HDL [42]. Cross-sectional data indicate endometriosis patients have higher odds of low HDL (adjusted OR 2.07; 95% CI 1.02 to 4.20) and central adiposity, independent of age and lifestyle factors [40]. These components cluster to form metabolic syndrome in a subset of patients, potentially exacerbating systemic inflammation and cardiovascular risk beyond gynecological manifestations.

5.3. Insulin Resistance Mechanisms: Inflammation and Estrogen Interplay

Insulin resistance in endometriosis arises from chronic low-grade inflammation, where elevated cytokines (e.g., IL-6, TNF-α) impair insulin signaling in adipose and muscle tissue, promoting glucose intolerance and hyperinsulinemia [42]. Estrogen dysregulation amplifies this process: local excess in lesions sustains inflammatory cycles, while systemic fluctuations may contribute to adipose tissue dysfunction and oxidative stress, further driving resistance [43]. Mechanistic studies highlight how inflammation disrupts glucose uptake and lipid handling, creating a feedback loop with progesterone resistance that favors metabolic derangements.

Cross-sectional evidence supports these pathways, with endometriosis cohorts showing altered insulin sensitivity markers correlated with disease severity [41]. Such resistance aligns with broader cardiometabolic phenotypes, where persistent metabolic stress fosters endothelial dysfunction and vascular stiffness—precursors to cardiac strain.

5.4. Links to Heart Failure and Cardiometabolic Indices

The cardiometabolic index (CMI), integrating triglycerides-to-HDL ratio and waist-to-height ratio, serves as a surrogate for metabolic dysfunction and visceral adiposity. Recent NHANES analyses demonstrate positive associations between higher CMI and endometriosis prevalence, with fully adjusted odds ratios of 1.21 to 1.78 for the highest vs. lowest quartiles, and linear increases beyond CMI thresholds (~0.67) yielding ~20% risk elevation per unit increment [37,38]. These findings suggest CMI as a potential screening tool for metabolic burden in endometriosis.

In the context of heart failure, particularly HFpEF, cardiometabolic overlap predisposes women through inflammation, insulin resistance, and dyslipidemia-driven myocardial remodeling and diastolic impairment [44]. Endometriosis-related metabolic changes may contribute to this phenotype by amplifying systemic stress, though direct longitudinal data remain limited. Addressing these overlaps through lifestyle or targeted interventions could mitigate progression to cardiac complications.

Table 3 summarizes the cardiometabolic abnormalities most frequently reported in women with endometriosis and their proposed mechanistic contributions to heart failure development.

Table 3 Cardiometabolic Features in Endometriosis and Their Link to Heart Failure Risk

Cardiometabolic Feature	Prevalence / Association in Endometriosis	Key Supporting Data	Proposed Mechanism Linking to HF	Strength of Evidence	Reference
Metabolic syndrome	Higher prevalence (OR 1.55–1.99)	Adjusted OR 1.99 (1.20–3.30)	Inflammation + insulin resistance → myocardial strain	Moderate	[40], [41]
Insulin resistance	Increased markers	Correlated with disease severity	Lipotoxicity + inflammation → diastolic dysfunction	Moderate	[42], [43]
Dyslipidemia (low HDL, high TG)	Higher odds of low HDL (OR 2.07)	Consistent across cohorts	Atherogenic profile → endothelial/myocardial stress	Strong	[40], [42]
Central adiposity / elevated CMI	Positive association with CMI	Adjusted OR 1.21–1.78 (highest vs lowest quartile)	Visceral fat → systemic inflammation → HFpEF	Emerging	[37], [38], [39]
HFpEF predisposition	Indirect via metabolic/inflammatory overlap	Parallels in women with MetS	Diastolic dysfunction from metabolic stress	Indirect / plausible	[44]

Where: CMI — Cardiometabolic Index; OR — Odds Ratio;HDL — High-Density Lipoprotein; TG — Triglycerides; HF — Heart Failure; MetS — Metabolic Syndrome; HFpEF — Heart Failure with Preserved Ejection Fraction;'→' – which leads to…

6. Integrated Mechanisms and Emerging Hypotheses

6.1. Overview

The pathways linking endometriosis to heart failure risk converge through intertwined processes of chronic inflammation, estrogen dysregulation and cardiometabolic alterations creating potential feedback loops that amplify systemic effects. This section integrates evidence from preceding discussions, examining how these elements interact to promote endothelial injury, metabolic stress, and cardiac remodeling. It also addresses emerging hypotheses on direct myocardial involvement and persistent gaps in HF-specific mechanistic data with implications for future biomarker development and risk stratification.

6.2. Synthesis of Inflammation, Estrogen Dysregulation and Cardiometabolic Factors

Chronic inflammation in endometriosis, marked by elevated IL-6, TNF-α and IL-1β intersects with estrogen overproduction in ectopic lesions to sustain a pro-inflammatory state that extends systemically [45]. Local estrogen excess drives cytokine release and oxidative stress, while systemic fluctuations may enhance vascular inflammation and impair endothelial function, forming a self-reinforcing cycle [45,50]. This interplay parallels cardiometabolic disturbances, where inflammation-induced insulin resistance and dyslipidemia (e.g., low HDL, high triglycerides) further exacerbate oxidative damage and atherogenesis [46,47].

Cardiometabolic index elevations in endometriosis cohorts reflect this overlap, with higher CMI associating with increased disease odds through visceral adiposity and lipid dysregulation that amplify inflammatory signaling [46]. Estrogen's dual role which are protective via nitric oxide pathways under normal conditions but pro-inflammatory when dysregulated contributes to arterial stiffness and plaque instability, particularly when compounded by metabolic factors [45,48]. These integrated mechanisms suggest a vicious cycle whereby inflammation sustains estrogen imbalance, metabolic stress perpetuates cytokine production, and the resulting endothelial/myocardial strain heightens HF vulnerability.

6.3. Potential Direct Cardiac Involvement and Vicious Cycles

Emerging evidence points to direct effects on cardiac tissue, as sustained cytokines and oxidative stress from endometriosis may promote myocardial inflammation, fibrosis, and diastolic dysfunction characteristic of HFpEF

[49,51]. Estrogen signaling alterations could influence cardiomyocyte function and extracellular matrix remodeling, while metabolic overload from insulin resistance adds lipotoxic stress to the myocardium [52]. Animal models and limited human data support these pathways, though causality remains inferred from parallels in other inflammatory conditions [50].

Such vicious cycles where inflammation drives estrogen dysregulation which in turn worsens metabolic profiles and endothelial injury may explain amplified risks in subgroups with surgical estrogen depletion or prolonged disease duration [48]. However, heterogeneity in observational data underscores that these interactions are likely modulated by genetic, lifestyle, and treatment factors.

6.4. Gaps and Future Directions

Despite converging evidence, HF-specific longitudinal studies are scarce, with most data derived from broader CVD endpoints or cross-sectional associations [49]. Direct mechanistic investigations, including cardiac imaging in endometriosis cohorts or targeted animal models of lesion-induced inflammation, are needed to clarify myocardial involvement [45]. Biomarker panels integrating CRP, IL-6, estrogen metabolites, and CMI could aid risk stratification, potentially identifying high-risk patients for early intervention [46,47].

Prospective cohorts with serial assessments of inflammatory, hormonal and metabolic markers would strengthen causal inference and guide multidisciplinary management. Targeted therapies addressing shared pathways such as anti-inflammatory agents or optimized hormonal modulation represent promising avenues to mitigate progression to cardiac complications.

7. Conclusion

Endometriosis which is long viewed primarily as a gynecological condition increasingly emerges as a contributor to systemic health risks, including modest but clinically meaningful elevations in cardiovascular disease burden and in particular heart failure susceptibility. The mechanistic threads such as chronic low-grade inflammation with cytokine spillover, estrogen dysregulation favoring pro-inflammatory and vascular effects and cardiometabolic overlap manifesting as insulin resistance, dyslipidemia and metabolic syndrome components interweave to create pathways that promote endothelial dysfunction, atherosclerosis, myocardial remodeling and diastolic impairment especially in the context of heart failure with preserved ejection fraction. These shared processes, often amplified by surgical interventions or prolonged disease duration explain why affected women may face heightened long-term cardiac vulnerability despite the generally modest hazard ratios reported in epidemiological syntheses.

Recognizing endometriosis as an underrecognized risk factor for heart failure carries important clinical implications. Routine cardiovascular risk assessment encompassing blood pressure, lipid profiles, glucose tolerance, inflammatory markers and cardiometabolic indices should be considered in women with confirmed or suspected endometriosis particularly those with advanced disease, early surgical menopause or additional traditional risk factors. Multidisciplinary collaboration between gynecologists, cardiologists and endocrinologists would facilitate timely identification and mitigation of modifiable elements, potentially through lifestyle optimization, judicious hormonal management or targeted anti-inflammatory strategies.

Substantial gaps persist, especially in prospective longitudinal data tracking heart failure incidence, direct myocardial effects and intervention efficacy. Addressing these through dedicated cohorts, advanced imaging and mechanistic studies remains essential to refine risk stratification and inform preventive approaches. Ultimately, broadening the clinical lens on endometriosis beyond pelvic symptoms may improve long-term outcomes for millions of women worldwide.

Compliance with ethical standards

Acknowledgements

The authors recognize the hard work of all the scholars and colleagues who together wrote and refined this review paper. The team carried out this work with their intellectual and academic efforts, without any aid or funding from outside sources like individuals, institutions, or organizations.

Disclosure of conflict of interest

The authors confirm they have no financial interests or personal connections that might have affected the research shared in this paper.

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