




Endometriosis and cardiovascular disease

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Received 15 October 2021; revised 13 November 2021; editorial decision 4 January 2022; online publish-ahead-of-print 2 February 2022

Handling Editor: Magnus Bäck

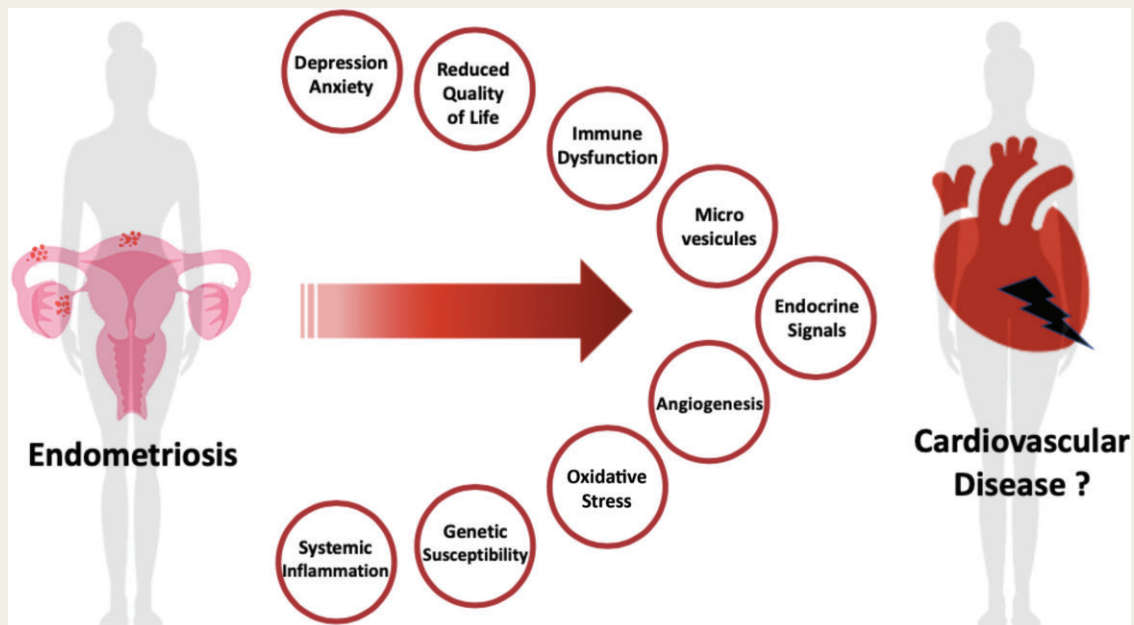
Endometriosis is a chronic gynaecological disease affecting 1 in 10 reproductive-age women. It is defined as the presence of endometrium-like tissue outside the uterus. Beyond this placid anatomical definition, endometriosis is a complex, hormonal, inflammatory, and systemic condition that poses significant familial, psychological, and economic burden. The interaction between the cardiovascular system and endometriosis has become a field of interest as the underlying mutual mechanisms become better understood. On the basis of accumulating fundamental and clinical evidence, it is likely that there exists a close relationship between endometriosis and the cardiovascular system. Therefore, investigating the endometriosis—cardiovascular interaction is highly clinically significant. In this review, we highlight our current understanding of the pathophysiology of endometriosis with systemic hormonal, pro-inflammatory, pro-angiogenic, immunologic, and genetic processes beyond the peritoneal microenvironment. Additionally, we provide current clinical evidence about how endometriosis interacts with cardiovascular risk factors and cardiovascular disease (CVD). To date, only small associations between endometriosis and CVD have been reported in observational studies, inherently limited by the potential influence of unmeasured confounding. Cardiovascular disease in women with endometriosis remains understudied, under-recognized, and underdiagnosed. More detailed study of the cardiovascular-endometriosis interaction is needed to fully understand its clinical relevance, underlying pathophysiology, possible means of early diagnosis and prevention.

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Graphical Abstract



Keywords

Endometriosis • Cardiovascular disease • Heart disease • Women

Introduction

Endometriosis is a chronic gynaecological disease estimated to affect 10% of reproductive-age women.¹ Recent insights have linked endometriosis to several pathological mechanisms ranging from systemic inflammation, pro-atherogenic lipid profile, and enhanced oxidative stress to endothelial dysfunction.² Considered as a systemic disease, the pathogenesis of endometriosis and the impact of the disease remain poorly understood. Robust knowledge is restricted to data from women surgically diagnosed with endometriosis limiting the development of multidisciplinary approaches to ameliorate the substantial cumulative burden of this condition.

A focused update consensus document on gynaecological and obstetric conditions that impact cardiovascular risk in women was released in March 2021.³ The scarcity of a strong dataset limited the ability to provide clear evidence regarding the pathophysiology, pathogenesis, and prognosis of endometriosis in cardiovascular disease (CVD). Here, we review relevant evidence regarding the relationship between endometriosis and CVD.

The purpose of this review article is to further our understanding of the shared mechanisms underlying endometriosis and atherosclerotic CVD, by contextualizing biological pathways common to both diseases, addressing the association between cardiovascular risk factors and endometriosis, and finally, highlighting key clinical evidence that link endometriosis with adverse cardiovascular events.

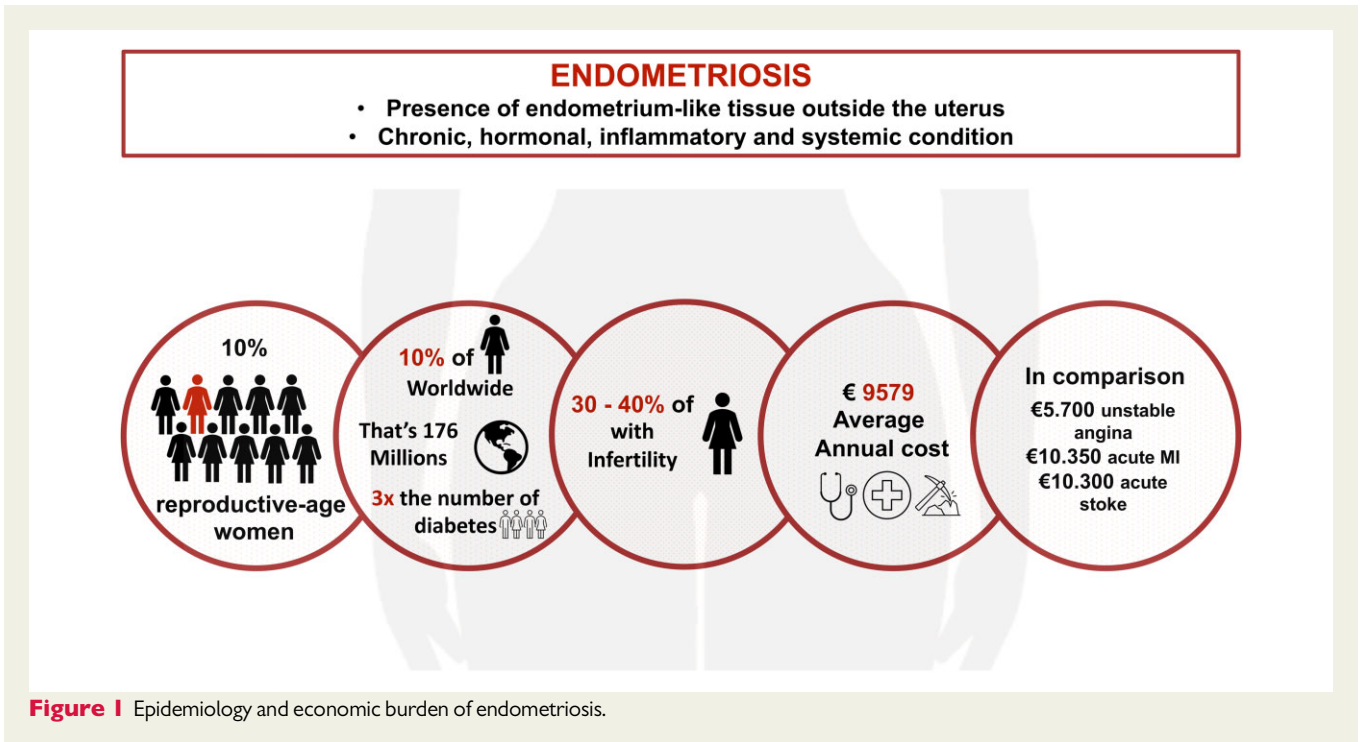
Endometriosis: overview

Endometriosis: epidemiology, symptoms, diagnosis, and treatment

Endometriosis is estimated to affect 10% of reproductive-age women. The true prevalence of endometriosis remains unknown since historically, diagnoses have only been made using laparoscopy and more recently multimodal imaging techniques. Misdiagnosis remains common, and diagnosis is often largely delayed by years. Currently, the prevalence ranges from 2% to 11% among asymptomatic women, 5% to 50% among infertile women, and 5% to 21% among women with pelvic pain.^{1,4,5}

The most common signs and symptoms of endometriosis include chronic pelvic pain, dyspareunia, dysmenorrhoea, and infertility, although asymptomatic cases can arise.⁶ Subsequently, decreased quality of life, fatigue, depression, high analgesic consumption, and reduced work productivity may occur. Endometriosis poses a major economic burden, similar to diabetes, with an estimated annual cost per patient of €9579⁷ (Figure 1). The condition presents with four phenotypes: superficial peritoneal lesions, ovarian endometriomas, deep infiltrating endometriosis, and extragenital areas including such as peripheral nerves as well as rectal, diaphragmatic, and pleural locations.^{6,8,9}

Because endometriosis manifests in a wide spectrum of severity, from asymptomatic cases to severe conditions, diagnosis is challenging and often delayed. Classical symptoms such as chronic pelvic pain,



dysmenorrhoea, and dyspareunia are non-specific and can overlap with other conditions involving the urinary or digestive tract. Key features of endometriosis can be identified during patient interviews through a family history of endometriosis, including a cyclic nature of pelvic pain, poor or no response to analgesics, severe primary dysmenorrhoea during adolescence and infertility.⁶ Although a normal physical examination does not rule out endometriosis, pelvic and rectal examination may detect infiltration and palpable sensitive areas involving the pelvic cavity (vagina, rectovaginal septum, uterosacral ligaments, and pouch of Douglas). The low diagnostic performance of physical examinations may improve during menstruation^{10,11} but a key step in diagnosis now involves non-invasive imaging techniques with transvaginal ultrasound^{12,13} and magnetic resonance imaging.^{14,15} Diagnosis of endometriosis should be based on patient interviews, examination and imaging, and surgery should be restricted to diagnostic uncertainty and persistent symptoms despite an optimal medical therapy.⁶ Currently available therapeutic approaches include medical treatment with non-hormonal (non-steroidal anti-inflammatory drugs) and hormonal treatments (combined oral contraceptives, progestins, and gonadotropin-releasing hormone analogues), surgery (conservative and definitive), and assisted reproductive technologies in patients with endometriosis-related infertility.

The pathobiology of endometriosis

The pathobiology of endometriosis is complex, and synergistic biological pathways are required to facilitate the establishment and persistence of endometriotic debris within the peritoneal cavity and ectopic regions. Endometriotic debris is characterized by epithelial, stromal, endothelial, glandular, and immune cell components with

altered immunoinflammatory profiles compared with normal endometrium.^{16,17} A pro-inflammatory, pro-angiogenic, and aberrant immune-endocrine environment is required to facilitate the growth and survival of endometriotic lesions (Figure 2).

Immune cells are predominantly implicated in endometriosis pathogenesis, including neutrophils, macrophages, monocytes, and regulatory T cells. Intense neutrophil and macrophages infiltration has been observed in eutopic endometrium and the peritoneal fluid.¹⁸ At sites of inflammation, macrophages and mast cells drive neutrophil recruitment through the release of chemokines. A localized and systemic inflammatory response is observed in endometriosis, with elevated cytokine levels (IL-6, IL-8, IL-17, IL-33, TNF- α , etc.) in both the peritoneal fluid and plasma. Impaired T cell, B cell, mast cell, dendritic cell, and natural killer cell function influences disease establishment and progression.¹⁹ Collectively, this promotes aberrant local and systemic chronic inflammation. Angiogenesis is supported by damage-associated molecular patterns, such as high-mobility group box 1, IL-33 and other cytokines, and high VEGF expression. Local synthesis of oestradiol from endometriotic lesions combined with enhanced oestrogen receptor (OR) expression in endometriotic tissues contributes to disease progression. Enhanced OR expression has been associated with enhanced inflammatory activity through cytokine release, anti-apoptotic signalling, angiogenesis, and subsequent lesion growth.^{20,21} Endothelial cell damage, endothelial dysfunction, increased oxidative stress,²² and increased levels of microvesicles²³ have been reported both at the site of endometriosis and in peripheral blood.

Most processes and biomarkers discussed in the pathobiology of endometriosis demonstrate compelling associations with atherosclerosis and CVD development in general. Future research is

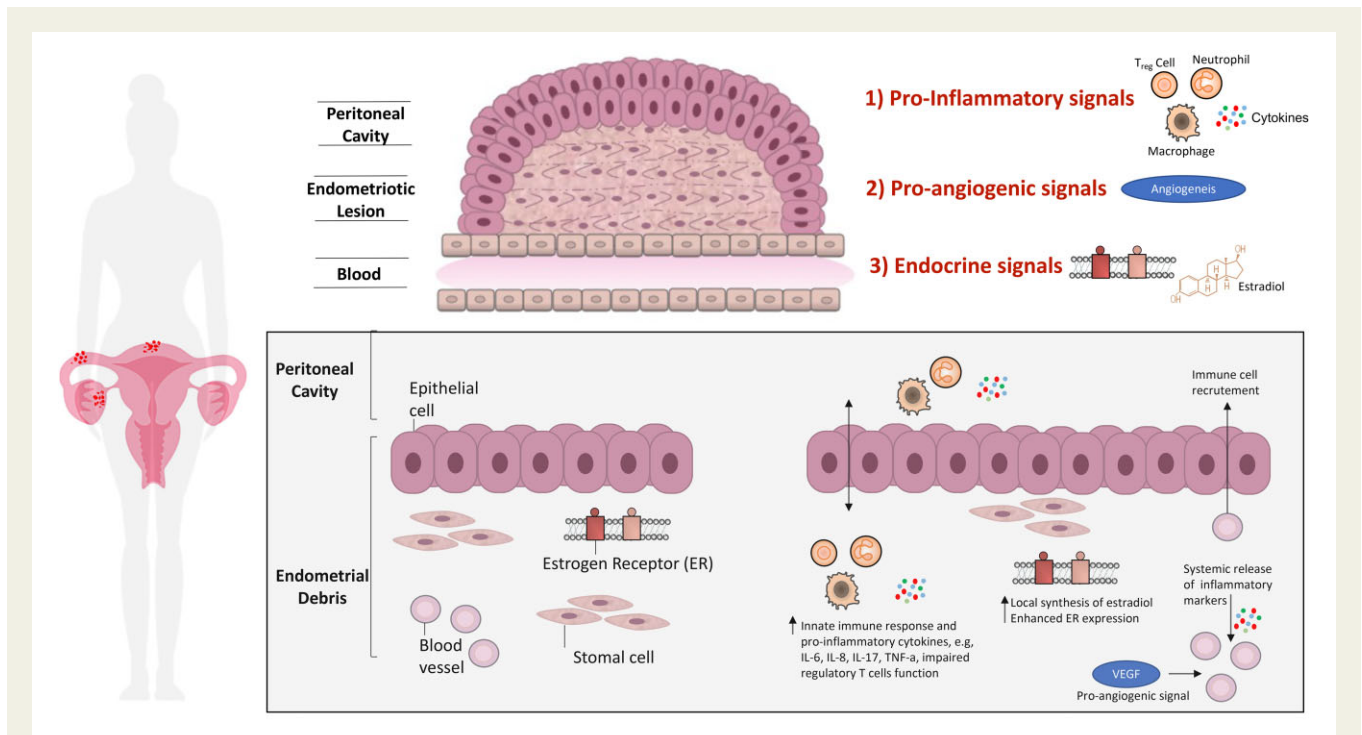


Figure 2 Molecular pathways underpinning endometriosis. Endometriotic lesions are characterized by a unique environment. The interplay between pro-inflammatory signals, pro-angiogenic signals, and a unique endocrine signature contribute to the pathogenesis of endometriosis. This schematic representation of the endometriotic lesion identifies three distinct molecular pathways that facilitate lesion growth in endometriosis. (1) Pro-inflammatory signals: increased neutrophil infiltration in the peritoneal fluid; increased macrophage populations in the peritoneal fluid and eutopic endometrium; elevated cytokine levels (IL-6, IL-8, IL-17, IL-33, TNF- α , etc.) in both the peritoneal fluid and plasma; at sites of inflammation, macrophages and mast cells drive neutrophil recruitment through the release of chemokines; impair regulatory T cells function. (2) Pro-angiogenic signals: Damage-associated molecular patterns: high-mobility group box 1, elevated IL-33 level, etc.; vascular endothelial growth factor. (3) Endocrine signals: local synthesis of oestradiol by endometriotic lesions; enhanced oestrogen receptor expression. ILs, interleukins; OR, oestrogen receptor; Treg cells, regulatory T cells; VEGF, vascular endothelial growth factor.

necessary to clarify the mechanistic roles of these intercellular communication mediators in endometriosis relative to facilitating the development of other comorbid conditions (Figure 3).

Endometriosis and atherosclerosis

Endometriosis and atherosclerosis: shared pathophysiological mechanisms

The most widely accepted pathophysiological hypothesis for endometriosis is based on retrograde menstruation, which occurs in most patients.²⁴ Menstrual blood containing endometrial cells flows back through the fallopian tubes and into the pelvic cavity, where the cells implant, develop, continue to thicken, and bleed over the course of each menstrual cycle. Alternative theories involving endometrial stem cells, stem cells from bone marrow, lymphovascular emboli of endometrial cells, and coelomic metaplasia have been proposed to explain the unusual locations of endometriosis.

Endometriosis and atherosclerosis are traditionally viewed as distinct entities, with endometriosis typically affecting young reproductive-age women, while atherosclerosis is an aging-related

process. Recent insights have unveiled cellular and molecular overlaps between the two conditions. Chronic inflammation, enhanced oxidative stress, endothelial dysfunction, and cellular proliferation are the hallmarks of both atherosclerosis and endometriosis.^{24–28} The full spectrum of the pathogenesis and pathophysiology of endometriosis has been extensively detailed elsewhere,^{2,24,29} and it is now widely acknowledged that endometriosis is a multifactorial condition involving hormonal, pro-inflammatory, pro-angiogenic, immunologic, and genetic processes. Briefly, the hormone-dependent process and proliferation of endometrial fragments require oestradiol provided by systemic hormones and favoured by disrupted hormonal signalling pathways.^{30,31} Significant macrophage recruitment combined with intense activation of cytokines and pro-angiogenic factors facilitates neovascularization and ectopic lesion growth^{32,33} in an enhanced local and systemic pro-inflammatory environment.^{34,35} Building on this biological overlap between atherosclerosis and endometriosis, recent research has provided evidence supporting an association between atherosclerotic CVD and endometriosis. Increased arterial stiffness³⁶ and impaired flow-mediated dilation,^{37,38} a surrogate marker of endothelial dysfunction potentially reversible after surgical treatment,³⁹ were associated with endometriosis.

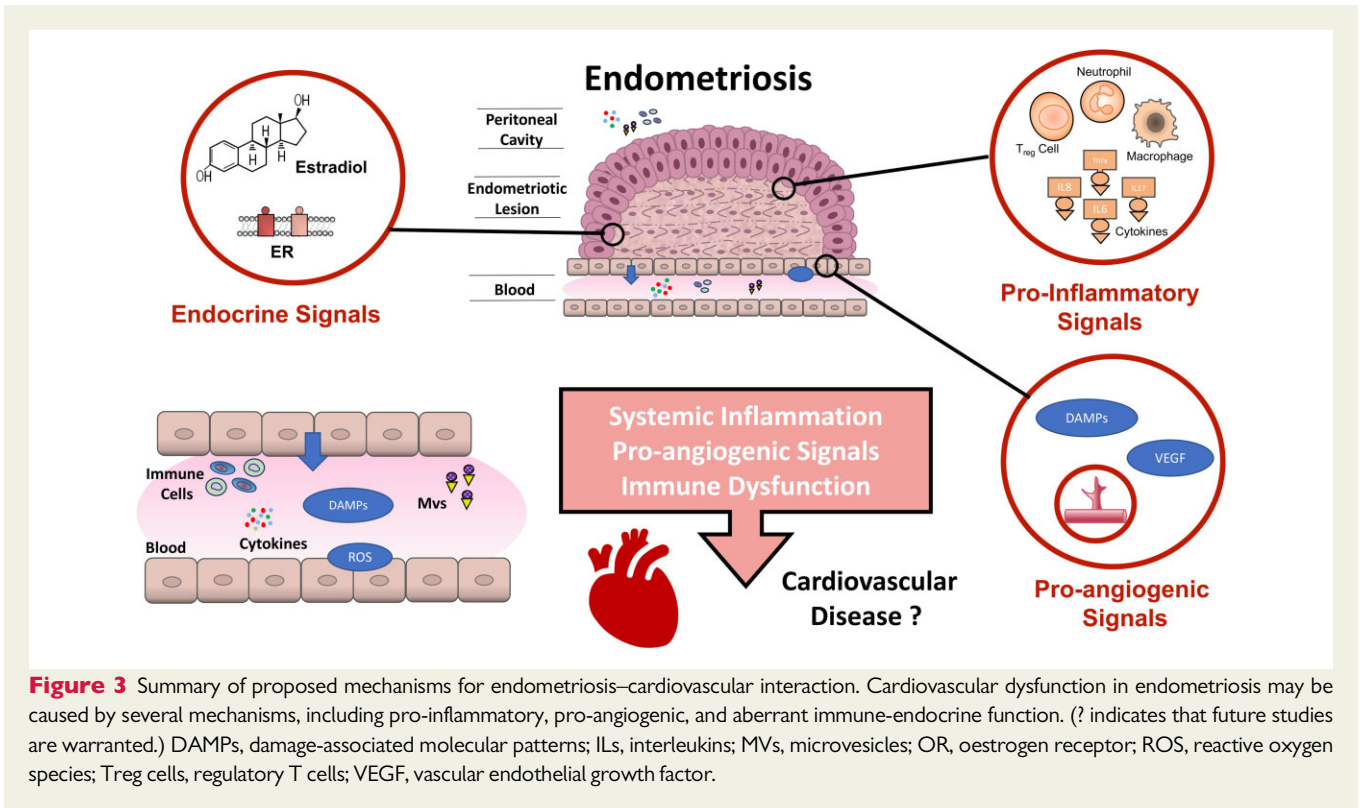


Figure 3 Summary of proposed mechanisms for endometriosis–cardiovascular interaction. Cardiovascular dysfunction in endometriosis may be caused by several mechanisms, including pro-inflammatory, pro-angiogenic, and aberrant immune-endocrine function. (? indicates that future studies are warranted.) DAMPs, damage-associated molecular patterns; ILs, interleukins; MVs, microvesicles; OR, oestrogen receptor; ROS, reactive oxygen species; Treg cells, regulatory T cells; VEGF, vascular endothelial growth factor.

Shared genetic susceptibility to endometriosis and atherosclerosis

Recent advances have identified variants at *CDKN2BAS* on chromosome 9p21 as a susceptibility locus for endometriosis⁴⁰ and atherosclerotic phenotypes, such as intracranial aneurysm, abdominal aortic aneurysm, peripheral vascular disease, diabetes, and stroke.⁴¹ Similarly, locus 7q22 has been associated with endometriosis and CVD.⁴² *CDKN2B-AS* transcript levels are known to correlate with the severity of atherosclerosis,⁴³ and a recently published genome-wide association study (GWAS) identified that rs10965235 single-nucleotide polymorphism (SNP) in the *CDKN2B-AS* gene is associated with endometriosis.⁴⁴ Advances in GWASs and the application of SNPs in the identification of increased genetic susceptibility to CVD in women with endometriosis may be of particular interest in tomorrow's research.

Endometriosis and cardiovascular risk factors

Cardiovascular risk factors are being increasingly recognized as having a significant association with endometriosis.

Hypertension

Pioneer work by Mu *et al.*⁴⁵ found a strong association between endometriosis and hypertension. In a prospective cohort of 116 430 nurses between 25 and 42 years of age followed for 20 years, 4244

women were diagnosed with laparoscopically confirmed endometriosis. After adjusting for cofounders, the relative risk (RR) for the development of hypertension was 1.14 [95% confidence interval (CI), 1.09–1.18] among women with endometriosis (Table 1). Conversely, the RR of developing laparoscopically confirmed endometriosis was 1.29 (95% CI 1.18–1.41) among hypertensive women. Several hypotheses for such associations have been proposed, starting with the inflammatory process surrounding endometriosis known for decades as a key component in the pathogenesis of hypertension.⁷¹ Overall, 30% of the reported association between endometriosis and hypertension was accounted for by treatment effects, namely hysterectomy/oophorectomy and earlier age of surgery. A decline in the production of sex hormones either in postmenopausal women or after ovariectomy is known to significantly increase the risk of hypertensive disorders.^{72,73} Non-steroidal anti-inflammatory drugs aimed to reduce pelvic pain are known to increase blood pressure and may be an important co-founder. Okoth *et al.*⁴⁷ found an adjusted odds ratio (aOR) of 1.12 (95% CI 1.07–1.17) for hypertension among 56 090 women with endometriosis compared with 223 669 matched controls. Finally, endometriosis is an independent and significant risk factor for the occurrence of gestational hypertension-pre-eclampsia.^{46,48–50}

Dyslipidaemia

Observational studies have suggested a strong association between endometriosis and an enhanced atherogenic lipid profile. The most convincing evidence was provided by Mu *et al.*⁴⁵ in Nurses' Health Study II (NHSII; *n* = 116 430), with a 25% increased risk (95% CI

Table 1 Summary of observed associations between endometriosis and cardiovascular risk factors

Author(s)	Study name	Location	Population	Design	Method of data collection	Ascertainment period (year)	Findings
Hypertension and gestational hypertension-pre-eclampsia							
Mu et al. ⁴⁵	NHSII (Nurses' Health Study II)	USA	116 430 female nurses aged 25–42. 4244 women with laparoscopically confirmed endometriosis and 91 554 control women	Prospective cohort study	Self-completed questionnaire	1989–2009	Hypertension (RR 1.14, 95% CI 1.09–1.18)
Nagai et al. ⁴⁶	JNHS (Japan Nurses' Health Study)	Japan	49 927 female nurses aged 41.2 ± 7.9. Estimated age at peak incidence: 36 years of age and cumulative incidence at 50 years of age: 7.4%	Prospective cohort study	Self-completed questionnaire	2001–07	Hypertension (OR 1.26, 95% CI 1.07–1.47)
Okoth et al. ⁴⁷		UK	Women aged between 16 and 50. 56 090 women with endometriosis and 223 669 matched control women	Population-based cohort study	Electronic health records	1995–2018	Hypertension (aHR 1.12, 95% CI 1.07–1.17)
Pan et al. ⁴⁸		Taiwan	6300 women with endometriosis and 10 312 matched control women	Population-based cohort study	Electronic health records	1998–2012	Gestational hypertension and/or pre-eclampsia (aOR 2.27, 95% CI 1.76–2.93)
Lalani et al. ⁴⁹			33 studies; 280 488 patients	Meta-analysis of observational studies		1990–2017	Pre-eclampsia (OR 1.18, 95% CI 1.01–1.39); Gestational hypertension and/or pre-eclampsia (OR 1.24, 95% CI 1.05–1.39)
Dyslipidaemia							
Farland et al. ⁵⁰	NHSII (Nurses' Health Study II)	USA	116 430 female nurses aged 25 to 42. 4244 women with laparoscopically confirmed endometriosis and 91 554 control women. 196 722 reported pregnancies	Prospective cohort study	Self-completed questionnaire	1989–2009	Gestational hypertension and/or pre-eclampsia (RR 1.30, 95% CI 1.16–1.45)
Mu et al. ⁴⁵	NHSII (Nurses' Health Study II)	USA	116 430 female nurses aged 25 to 42. 4244 women with laparoscopically confirmed endometriosis and 91 554 control women	Prospective cohort study	Self-completed questionnaire	1989–2009	Hypercholesterolaemia (RR 1.25, 95% CI 1.21–1.30)
Nagai et al. ⁴⁶	JNHS (Japan Nurses' Health Study)	Japan	49 927 female nurses aged 41.2 ± 7.9. Estimated age at peak incidence: 36 years of age and cumulative incidence at 50 years of age: 7.4%	Prospective cohort study	Self-completed questionnaire	2001–07	Hypercholesterolaemia (OR 1.30, 95% CI 1.15–1.47)
Tani et al. ³⁶		Japan	28 women with laparoscopically confirmed endometriosis. 21 control women	Case-control study	Laboratory data	August 2010 to May 2013	Lower HDL-C ($P < 0.01$). No difference in TG; LDL-C
Santoro et al. ³⁸		Italy	37 women with laparoscopically confirmed endometriosis. 31 control women	Cross-sectional study	Laboratory data	July 2010 to June 2011	Higher HDL-C ($P = 0.045$). No difference in TG; LDL-C

Continued

Table 1 Continued

Author(s)	Study name	Location	Population	Design	Method of data collection	Ascertainment period (year)	Findings
Melo <i>et al.</i> ⁵¹		Brazil	40 women with laparoscopically confirmed endometriosis. 80 control women	Cross-sectional study	Laboratory data		Higher LDL-C ($P < 0.001$); higher TG ($P = 0.02$); higher HDL-C ($P = 0.008$)
Crook <i>et al.</i> ⁵²		UK	29 women with laparoscopically confirmed endometriosis. 29 controls	Case-control study	Laboratory data		Higher TG level ($P < 0.02$) and LP(a) level ($P < 0.01$). No difference in LDL-C; HDL-C
Hopeman <i>et al.</i> ⁵³		USA	24 women with endometriosis. 181 infertile controls with <i>in vitro</i> fertilization	Cross-sectional study	Laboratory data		Lower eicosapentaenoic acid ($P = 0.009$)
Kinugasa <i>et al.</i> ³⁷		Japan	41 women with laparoscopically confirmed endometriosis. 28 control women	Cross-sectional study	Laboratory data	April 2009 to March 2010	Higher asymmetric dimethylarginine (ADMA) level ($P = 0.04$). No difference in TG; HDL-C; LDL-C
Pretta <i>et al.</i> ⁵⁴		Italy	66 women with laparoscopically confirmed endometriosis. 66 matched control women	Case-control study	Laboratory data		No difference in TG; HDL-C; LDL-C
Verit <i>et al.</i> ⁵⁵		Turkey	47 women with laparoscopically confirmed endometriosis. 40 matched control women	Case-control study	Laboratory data	November 2006 to May 2007	Higher TG; LDL-C ($P < 0.0001$); lower HDL-C ($P < 0.0001$)
Obesity Ferrero <i>et al.</i> ⁵⁶		Italy	366 women with laparoscopically confirmed endometriosis. 248 control women	Prospective cohort study	Electronic health records	August 2000 to February 2004	Lower BMI (21.17 ± 2.86 vs. 22.33 ± 3.68 ; $P < 0.001$). No difference in BMI according to endometriosis stages and severity
Holdsworth-Carson <i>et al.</i> ⁵⁷		Australia	357 women with laparoscopically confirmed endometriosis. 152 control women	Retrospective case-control study	Electronic health records	May 2012 to March 2016	Lower BMI (25.0 ± 0.3 vs. 27.2 ± 0.5 ; $P < 0.001$). Inverse relationship between BMI and frequency of endometriosis ($P < 0.001$)
Shah <i>et al.</i> ⁵⁸	NHSII (Nurses' Health Study II)	USA	5504 incident cases of endometriosis during 1 299 349 woman-years (incidence rate = 385 per 100 000 woman-years)	Prospective cohort study	Self-completed questionnaire	September 1989 to June 2011	BMI at age 18 and current BMI: each significantly inversely associated with endometriosis ($P < 0.0001$)

Continued

Table 1 Continued

Author(s)	Study name	Location	Population	Design	Method of data collection	Ascertainment period (year)	Findings
Missmer et al. ⁵⁹	NHSII (Nurses' Health Study II)	USA	1721 women with laparoscopically confirmed endometriosis	Prospective cohort study	Self-completed questionnaire	September 1989 to June 1999	Inverse relation with BMI at age 18 years (for BMI of >30 vs. 19–20.4 kg/m ² : RR 0.8, 95% CI 0.6–1.1; P = 0.004)
Hediger et al. ⁶⁰		USA	32 women with laparoscopically confirmed endometriosis. 52 control women	Prospective cohort study	Self-completed questionnaire	April 1999 to January 2000	Lower BMI (23.7 ± 3.8 vs. 26.9 ± 6.2, 95% CI P = 0.006). For every unit increase in BMI, 12–14% decrease in the likelihood of being diagnosed with endometriosis
Lafay Pillet et al. ⁶¹		France	238 women with laparoscopically confirmed endometriosis. 238 matched control women	Case-control study		February 2005 to October 2008	Lower BMI (21.70 ± 3.7 vs. 23.29 ± 4, 95% CI P < 0.001)
Farland et al. ⁶²	E3N (Teachers Health Study)	France	98 995 female teachers. 2416 women with laparoscopically confirmed endometriosis and 61 208 control women.	Prospective cohort study	Self-completed questionnaire		Odds of endometriosis were lower among women with a large vs. lean body size at 8 years (P = 0.003), at menarche (P < 0.0001) and at ages 20–25 years (P < 0.0001)
Liu et al. ⁶³			11 studies; 9298 women with endometriosis	Meta-analysis of observational studies			33% reduction in the risk of endometriosis for each 5 kg/m ² increase in BMI (RR = 0.67, 95% CI 0.53–0.84); with statistically significant heterogeneity across the studies (P < 0.001, I ² = 86.9%)
Tang et al. ⁶⁴		China	709 women with laparoscopically confirmed endometriosis. 807 matched control women	Retrospective case-control study		January 2018 to August 2019	No difference in BMI (21.1 vs. 20.9, 95% CI P = 0.223). OR 1.979% (95% CI 1.15–3.52, P = 0.0185) for

Continued

Table 1 Continued

Author(s)	Study name	Location	Population	Design	Method of data collection	Ascertainment period (year)	Findings
Tobacco smoking Cramer <i>et al.</i> ⁶⁵		USA	317 women with laparoscopically confirmed endometriosis. 4023 control women	Prospective cohort study		January 1981 to June 1983	endometriosis in obese (BMI > 27.50) Decreased risk for endometriosis among smokers who began before age 17 years and \geq one pack a day
Calhaz-Jorge <i>et al.</i> ⁶⁶		Portugal	488 women with laparoscopically confirmed endometriosis. 591 control women	Prospective cohort study		1993–2000	Decreased risk for endometriosis: 1–10 cigarettes/day (OR 0.57, 95% CI 0.39–0.79); 11–20 cigarettes/day (OR 0.52, 95% CI 0.34–0.79); > 20 cigarettes/day (OR 0.56, 95% CI 0.32–0.99)
Bravi <i>et al.</i> ⁶⁷			38 studies. 13 129 women diagnosed with endometriosis	Meta-analysis of observational studies		Publications up to September 2014	No evidence for an association between tobacco smoking and the risk of endometriosis. Non-smokers RR 0.96 (95% CI 0.86–1.08); Former smokers RR 0.95 (95% CI 0.81–1.11); Current smokers RR 0.92 (95% CI 0.82–1.04); Moderate smokers RR 0.87 (95% CI 0.70–1.07) and heavy smokers RR 0.93 (95% CI 0.69–1.26)
Air pollution exposure Mahalingaiah <i>et al.</i> ⁶⁸	NHSII (Nurses' Health Study II)	USA	2486 women with laparoscopically confirmed endometriosis, over 710 230 person-years of follow-up		Geographic information system software	1993–2007	No association between endometriosis risk and distance to road or exposure to particulate matter
Diabetes and gestational diabetes Farland <i>et al.</i> ⁶⁹	NHSII (Nurses' Health Study II)	USA		Prospective cohort study	Self-completed questionnaire	1989 to June 2017	No association between endometriosis and risk of

Continued

Table 1 Continued

Author(s)	Study name	Location	Population	Design	Method of data collection	Ascertainment period (year)	Findings
Pérez-López et al. ⁷⁰			112 037 female nurses. 5242 women with laparoscopically confirmed endometriosis and 106 795 control women	Meta-analysis of observational studies		Publications up to April 2017	type 2 diabetes in multivariable confounder-adjusted models (HR 1.06; 95% CI 0.98–1.13) or models accounting for potential mediating factors (HR 0.94; 95% CI 0.87–1.00) No significant effect on gestational diabetes risk (OR = 1.14; 95% CI 0.86–1.51; $P = 0.35$, $I^2 = 56%$, Egger's test $P = 0.45$)

aHR, adjusted hazard ratio; BMI, body mass index; HDL-C, high-density lipoprotein (HDL) cholesterol; LDL-C, low-density lipoprotein (LDL) cholesterol; Lp(a), lipoprotein(a); OR, odds ratio; RR, relative risk; TG, triglycerides.

1.21–1.30) to develop hypercholesterolaemia in endometriosis and a 22% increased risk (95% CI 1.15–1.31) of developing laparoscopically confirmed endometriosis in women with hypercholesterolaemia. The Japan Nurses' Health Study, a cross-sectional survey of 49 927 women (2001–07), confirmed a 30% increased odds of hypercholesterolaemia (95% CI 1.15–1.47) in women with endometriosis although there was no adjustment for confounding factors.⁴⁶

Focusing on the lipid profile, in a cross-sectional study of 120 women, 40 of whom had laparoscopically proven endometriosis, Melo *et al.*⁵¹ reported higher levels of total cholesterol, LDL-cholesterol, triglycerides, and HDL-cholesterol. The altered lipid profile in endometriosis has been further investigated by several reports and yielded inconsistent results. Tan *et al.*⁷⁴ effectively addressed these varying results in a recent analysis of nine studies^{24,30,37,51–55,75} investigating the RRs of dyslipidaemia among women with endometriosis. Overall, these studies were limited by a small number of patients, differences in both parameters measured, and timing of measurements; therefore, these results should be interpreted with caution.

A preclinical study demonstrated altered serum lipid profiles in mice with endometriosis.⁷⁶ Later reports confirmed that dysregulated phospholipid and sphingolipid metabolism plays a key role in endometriosis pathogenesis.^{77–80} Sphingolipids serve as biologically active components of cell membranes and are involved in many processes, such as proliferation, maturation, and apoptosis. Lee *et al.*⁷⁸ provided evidence of altered sphingolipid metabolism flux in the serum, peritoneal fluid, and endometrial tissue of women with endometriosis. They observed up-regulation of specific sphingolipid enzymes (sphingomyelin synthase 1, sphingomyelinase 3, and glucosylceramide synthase) in endometriotic debris, with corresponding increased glucosylceramide, decreased sphingomyelin levels, and decreased apoptosis in the endometrium. Ceramides act as second messengers in activating the apoptotic cascade and precursors for many other sphingolipids. Elevated ceramide levels were evidenced in the peritoneal fluid of infertile endometriotic women, triggering reactive oxygen species formation, and leading to oocytotoxicity.⁸¹ Similarly, several investigations have suggested a pivotal role for sphingolipids in the pathogenesis of myocardial infarction, hypertension, stroke, and diabetes.⁸² This set of evidence suggests that sphingolipids may function as mediators of interorgan and intercellular communication. Future studies are warranted to investigate the role of sphingolipids in endometriosis and investigate whether endometriosis-induced sphingolipids promote a systemic pro-inflammatory and pro-oxidant cascade, which then leads to dysfunction of other organs including those associated with the cardiovascular system.

Obesity

An inverse relationship between endometriosis and body mass index (BMI) is commonly acknowledged,^{56–63} although some studies of limited impact have reported otherwise.^{64,83} Reduction in the adipose stem cell population,⁸⁴ an anorexigenic effect through altered hepatic gene expression,⁸⁵ and promotion of lipid dysfunction and fat loss⁷⁶ are key mechanisms thought to be involved in the clinically low BMI phenotype observed in women with endometriosis.

Smoking, air pollution exposure, and diabetes

While tobacco smoking is an established risk factor for ischaemic heart disease, its relationship with endometriosis is puzzling. Indeed, intense variation and conflicting data regarding the association between smoking and endometriosis have been reported. Several studies have suggested that smoking may be associated with a decreased risk of endometriosis,^{65,66,86} but recently published data dismissed any link between endometriosis and tobacco smoking habits.⁶⁷ Similarly, the association between endometriosis and pollution exposures remains speculative.^{87,88} Only one study from NHSII showed no increased risk for endometriosis with regards to air pollution exposure.⁶⁸

Despite the potential overlap in the molecular pathways between endometriosis and diabetes, namely type 1, there is no robust evidence for an association between diabetes and endometriosis to date.⁸⁹ Indeed, no association between laparoscopically confirmed endometriosis and risk of type 2 diabetes risk in a multivariable analysis could be evidenced in the NHSII.⁶⁹ The risk of gestational diabetes mellitus among women with endometriosis remains controversial with discordant data across studies and meta-analyses.^{49,50,70}

Endometriosis and cardiovascular disease

Endometriosis and ischaemic burden (coronary artery disease and stroke)

The first hint suggesting a possible association between ischaemic heart disease and inflammation of the upper genital tract came with evidence that women with pelvic inflammatory disease are more likely to have myocardial infarction and stroke than the general population.^{90,91} A limited number of studies suggested an association between endometriosis, coronary artery disease (CAD), and stroke.^{47,53,92–94} Only two large population-based cohort studies have shown an association between ischaemic heart disease and endometriosis (Table 2). Okoth *et al.*⁴⁷ conducted a retrospective study of 279 759 women (1995–2018) and found an aOR of 1.24 (95% CI 1.13–1.37) for a composite endpoint of ischaemic heart disease, heart failure (HF), and cerebrovascular disease if endometriosis was present. In addition, endometriosis was associated with a 1.40-fold (95% CI 1.22–1.61) increased risk for ischaemic heart disease and 1.19-fold (95% CI 1.04–1.36) increased risk for cerebrovascular disease. Similarly, NHSII included 116 430 US women (1989–2009) and found a 52% greater risk for myocardial infarction (RR 1.52; 95% CI 1.17–1.98) in laparoscopically confirmed endometriosis.⁹² Laparoscopically confirmed endometriosis was independently associated with a 1.62-fold (95% CI 1.39–1.89) increased risk of the composite of myocardial infarction, angiographically confirmed angina, and revascularization either by coronary artery bypass graft surgery or by percutaneous coronary intervention. It is worth noting that co-occurring endometriosis among women with myocardial infarction did not translate into worse in-hospital outcomes.⁹⁴

The association of endometriosis with the prevalence and incidence of CVD appears likely from the aforementioned studies, but

Table 2 Description of large-scale studies on observed associations between endometriosis and cardiovascular disease

Author(s)	Study name	Location	Population	Design	Method of data collection	Ascertainment period (year)	Findings
Okoth <i>et al.</i> ⁴⁷		UK	Women aged between 16 and 50. 56 090 women with endometriosis and 223 669 matched control women	Population-based cohort study	Electronic health records	1995–2018	Endometriosis composite outcome: IHD, HF, cerebrovascular disease (aHR, 1.24; 95% CI 1.13–1.37) IHD (aHR 1.40; 95% CI 1.22–1.61); cerebrovascular disease (aHR, 1.19; 95% CI 1.04–1.36); arrhythmia (aHR, 1.26; 95% CI 1.11–1.43)
Mu <i>et al.</i> ⁹²	NHSII (Nurses' Health Study II)	USA	116 430 female nurses aged 25–42. 4244 women with laparoscopically confirmed endometriosis and 91 554 control women	Prospective cohort study	Self-completed questionnaire	1989–2009	Myocardial infarction (RR, 1.52, 95% CI 1.17–1.98); angiographically confirmed angina (RR 1.91, 95% CI 1.59–2.29); CABG/coronary angioplasty procedure/stent (RR 1.35, 95% CI 1.08–1.69)
Chiang <i>et al.</i> ⁹³		Taiwan	Women aged between 18 and 50. 17 543 women with endometriosis women and 70 172 matched control women	Retrospective population-based cohort	Electronic health records	1997–2013	Composite outcome: Myocardial infarction, HF, stroke (aHR 1.17, 95% CI 1.05–1.29)
Sugiura-Ogasawara <i>et al.</i> ⁹⁵	Japan Environment and Children's Study (JECS)	Japan	103 070 pregnancies	Prospective cohort study	Self-completed questionnaire	January 2011 to March 2014	Endometriosis: independent predictors for VTE (OR 2.70, 95% CI 1.21–6.00)

aHR, adjusted hazard ratio; CABG, coronary artery bypass graft; HF, heart failure; IHD, ischaemic heart disease; OR, odds ratio; RR, relative risk; VTE, venous thrombo-embolic events.

after considering the advances all these studies bring to the field, their limitations must also be considered. First, the populations studied were primarily Caucasian Europeans, limiting the generalizability of the evidence to other ethnicities. Despite efforts to harmonize these datasets, there are inevitable inconsistencies, including known and unknown factors, across these reports. For instance, the definitions of endometriosis (e.g. surgically confirmed, clinical suspicion, etc.) and CAD (e.g. acute myocardial infarction, coronary stenosis, etc.) varied widely across studies. This inhomogeneity among definition added uncertainty to the cardiovascular endpoints, particularly because the pathophysiology of acute myocardial infarction (plaque rupture and thrombosis) is not the same as the process of stable CAD. Furthermore, some observational cohorts inconsistently shared control groups.

Second, hysterectomy in women aged 50 years or younger has been associated with a significantly increased risk of ischaemic heart disease, with oophorectomy linked to an increased risk of both CAD and stroke.^{96,97} Similar risk was evidenced in the NHSII cohort,⁹² as 42% of the association between CAD and endometriosis was potentially explained by the greater frequency of hysterectomy/oophorectomy and earlier age at surgery following an endometriosis diagnosis. Accordingly, the adverse outcome portended by hysterectomy regardless of oophorectomy status was associated with the adverse risk factor profile of women who underwent hysterectomy.⁹⁸

Finally, the role of hormonal treatment strategies for endometriosis, including combined oral contraceptives, progestins, and gonadotrophin-releasing hormone (GnRH) analogues, has been highly questioned regarding a potentially enhanced lipid profile,⁹⁹ cardiovascular risk profile, and weight gain.^{100–102}

Endometriosis and venous thrombo-embolic events

Systemic inflammation is known to up-regulate procoagulant factors, increase platelet reactivity, and favour thrombo-embolic events.¹⁰³ As such, endometriosis was initially defined as a hormonal-dependent and inflammatory disease to perfectly link inflammation and thrombosis; however, the current picture differs substantially from this simplistic model. Basic research and evidence reporting an enhanced prothrombotic and inflammatory state in endometriosis did not translate into a clinically increased risk of venous thrombo-embolic events (VTE).

A review of the literature discloses several studies reporting an association between endometriosis and a procoagulant state. High tissue factor expression,¹⁰⁴ increased procoagulant microparticle levels,³⁹ and modest systemic changes of coagulation parameters¹⁰⁵ have been reported, but these variables did not translate into increased VTE rates. To date, no studies have shown that endometriosis is associated with an increased risk of VTE except during pregnancy. Only anecdotal case series reported episodes of VTE mainly favoured by extrinsic compression, pelvic mass, and immobilization.^{106–109} However, careful attention should be paid to pregnant women with endometriosis. In a nationwide Japanese birth cohort study of 103 070 pregnancies, the frequency of VTE was 7.5 per 10 000 women during the pregnancy and post-partum period. Endometriosis and recurrent pregnancy loss were identified as novel independent risk factors for VTE.⁹⁵

Regarding pregnancy, these results indicate that there is either no or a weak, direct interaction between VTE and endometriosis. Assisted reproductive techniques and, most notably, exogenous hormones are nonetheless key indirect contributors to the risk of venous thrombosis and ischaemic endpoints (Myocardial infarction, stroke, etc.) in endometriosis.^{110,111} Although successful fertility therapy was not associated with an increased risk of CVD later in life in the general population,¹¹¹ recent updated studies reported assisted reproductive techniques increased the risk of venous thrombosis in women with endometriosis.¹¹²

Endometriosis, arrhythmias, and heart failure

The literature is limited regarding HF and arrhythmias in endometriosis. Only one study conducted by Okoth *et al.*⁴⁷ examined the association between endometriosis and several cardiovascular outcomes including HF and arrhythmia, in a large UK retrospective matched cohort study. They found that endometriosis was associated with a higher risk of arrhythmia (adjusted HR 1.26; 95% CI 1.11–1.43; $P=0.001$). The noxious impact of chronic inflammation has been proposed by the authors to explain the association between endometriosis and arrhythmia. These results should be interpreted with caution, as no reference is made to the type of arrhythmia and several well-known cofactors associated with arrhythmia onset were omitted from the model (left ventricular ejection fraction, sleep disorders, treatment strategies in particular hormonal treatments, hysterectomy/oophorectomy status, dietary patterns, physical activity, inflammatory biological burden, etc.). Furthermore, cancer antigen-125, a well-established tumour biomarker related to ovarian cancer, has been associated with endometriosis¹¹³ and more recently with HF^{114,115} and new-onset atrial fibrillation (AF).^{116,117} To date, there is insufficient evidence to support a causal relationship between endometriosis or arrhythmias and HF.

Endometriosis and cardiovascular pharmacology

Several cardiovascular medications have been tested in animal models, with promising results on the establishment and maintenance of endometriotic lesions. However, their translation into human clinical trials has been very limited.

Statins, classically known for their roles in lowering cholesterol and anti-inflammatory properties, have been shown to play a role in endometriosis by modifying cell signalling in preclinical studies using human endometriotic stromal cell cultures. Statins therapy lead to increased apoptosis, decreased proliferation, and impaired cell adhesion and motility.^{118,119} Additionally, statins inhibited stromal cell invasion and reduced angiogenesis.^{120–122} Recent findings showed that platelets play important roles in the development of endometriosis in general and in fibrogenesis in particular.^{123,124} Antiplatelet treatment was demonstrated to impede the progressive epithelial-mesenchymal transition, fibroblast-to-myofibroblast transdifferentiation, and smooth muscle metaplasia, resulting in reduced lesion size of endometriotic lesions and fibrogenesis.¹²³ Low-dose aspirin, used in a preclinical setting, has lately been proposed for its ability to

down-regulate progesterone resistance and a target for endometriosis-related infertility.¹²⁵

Women with endometriosis tend to have higher levels of psychological stress, which is known to promote tumour growth and metastasis. B-Adrenergic receptor blockade in a mouse model of endometriosis completely abolished the promotional effect of chronic stress, through suppression of ADRB2 and CREB activation, thus suppressing angiogenesis and proliferation.¹²⁶ Additionally, perioperative use of propranolol in a mouse model of endometriosis significantly decelerated the growth of residual lesions that were intentionally left out during the primary surgery.¹²⁷ Similarly, telmisartan inhibited vascularization, immune cell content, and growth of murine endometriosis-like lesions.^{128,129}

Summary and authors' perspectives

Cardiovascular disease remains the leading cause of mortality among women, causing 1 in 3 deaths each year,¹³⁰ whereas endometriosis affects 1 in 10 reproductive-age women. This unequivocal epidemiological observation should be considered in the field of future cardiovascular research in women. Current clinical evidence is insufficient to implicate a strong association and potential role for endometriosis in CVD.

The literature is sparse regarding the association between CVD and endometriosis (*Graphical Abstract*). The epidemiologically observed associations between the two should be interpreted with caution for several reasons. Current evidence is limited by small sample sizes, observational designs, and the specific characteristics of the population from which the samples are derived (high-income countries, cohort study of hospital-based healthcare workers, primarily Caucasian Europeans, etc.). Only small associations between endometriosis and CVD have been reported in the literature, although inconsistently. Representation of participants with endometriosis in cardiovascular clinical trials and registries is challenging, as endometriosis remains under-recognized. Endometriosis is usually diagnosed in higher socioeconomic groups and likely related to inequities in access to health care. In addition to socioeconomic impact, multiple factors can be identified as barriers to inclusion of women with endometriosis in CV studies: misdiagnosis is common; as diagnosis remains challenging and largely delayed by years; unawareness about ongoing trials, combined cardiac and gynaecologic care, and monitoring in clinical trials, etc. The chronic and heterogeneous nature of endometriosis (e.g. disease stage and lesion type) and the confounding influence of hormonal, non-hormonal, and pain-related interventions further complicate the cause-and-effect relationship in CV endpoints.

Cardiovascular disease risk estimation remains challenging, especially in women with endometriosis. Further research is needed to better understand how endometriosis should be incorporated into risk prediction models alongside well-established risk factors. Indeed, the reduced quality of life and psychosocial risk factors such as depression and anxiety may overlap and help to explain the predisposition for CVD. In considering women with endometriosis, there is a need to better understand the potential associations with CVD and risk factors and to clarify the pathophysiology of the female heart at a broader level (*Graphical Abstract*).

Inclusivity is therefore mandatory, and specific registries, studies, and trials are urgently needed to address the underlying biological mechanisms potentially shared between CVD and endometriosis, clarify whether endometriosis can cause CVD; assess the prognosis of endometriosis in cardiovascular patients, and finally, advance potential innovative solutions and tailored management of CVD in women with endometriosis.

Multicentre case-controlled and cross-sectional studies may be of particular interest in women admitted to cardiology departments to ascertain the association between endometriosis and various CVDs (ischaemic cardiomyopathy, HF, AF, etc.) and risk factors. However, the benefits of such study designs are limited by the fact that (i) endometriosis is greatly underdiagnosed, (ii) there are asymptomatic cases, and (iii) the assessment of specific CVD phenotypes and risk factors distributions among endometriosis patients necessitates a large sample. Only international and/or national levels initiatives may have the power to address the prevalence, links, impact, and prognosis of endometriosis and CVD by analysing data from large-scale surveys. Strong evidence regarding the association between these two conditions obtained from large-scale cohorts or large population-based studies, may contribute to a change in the prevention, screening, early detection, and treatment of CV risk factors among women with endometriosis.

Lead author biography



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Conflict of interest: The authors declare that there is no conflict of interest regarding the publication of this article. O.M. received institutional research grants from Fondation Coeur et Vaisseaux, AstraZeneca and Boehringer Ingelheim. K.M. received a grant from Edwards Lifesciences (THV-F20-142). The manuscript has been read and approved for submission by all authors. The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Funding

This work was supported by Groupe pour l'Enseignement, la Prévention et la Recherche Cardiologique en Alsace (GERCA).

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