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REVIEW

Atherosclerotic cardiovascular disease in women with endometriosis: a systematic review of risk factors and prospects for early surveillance

BIOGRAPHY

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KEY MESSAGE

Currently available evidence suggests that women with endometriosis are at higher lifetime risk of developing atherosclerotic cardiovascular disease (ASCVD) than women without endometriosis. However, robust evidence is still severely lacking and future studies are needed to more definitively evaluate a possible causal association between ASCVD risk and endometriosis.

ABSTRACT

Endometriosis and atherosclerotic cardiovascular disease (ASCVD) share similar pathogenic mechanisms. Hence, this systematic review evaluates the association between endometriosis and lifetime ASCVD risk including co-prevalence with dyslipidaemia, atherosclerosis and non-invasive markers of endothelial dysfunction. The electronic databases Embase, PubMed, MEDLINE, Cochrane Register of Trials and ClinicalTrials.gov were systematically searched for relevant articles. Two prospective cohort studies demonstrated an increased lifetime ASCVD risk after controlling for demographic and lifestyle confounders in women with endometriosis, as measured by higher incidence of myocardial infarction (relative risk [RR] 1.52), angiography-confirmed angina (RR 1.91), or requiring coronary artery bypass graft surgery (RR 1.35). Among 10 studies that included 407 patients with surgically proven endometriosis and 557 controls, RR of developing hypercholesterolemia and hypertension were 1.25 and 1.14, respectively, while higher serum lipoprotein a and lower paraoxonase 1 levels were found in women with endometriosis that was negatively correlated with stage of disease ($r = -0.74$, $P < 0.0001$). Hence, currently available evidence suggests that women with endometriosis are at higher lifetime risk of developing ASCVD than women without endometriosis. However, robust causal evidence is still lacking and future studies are needed to determine whether women with endometriosis represent a high-risk population for lifelong ASCVD risk.

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KEYWORDS

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Endometriosis
Endothelial dysfunction

INTRODUCTION

Endometriosis is a poorly understood chronic medical condition that poses a diagnostic dilemma for physicians. Through a combination of genetic predisposition, hormone dysregulation and immunologic susceptibility, hormonally active endometrial tissue has the capacity to spread and subsist outside the uterine cavity in affected individuals (*Giudice and Kao, 2004*). Although epidemiological studies are lacking, it is estimated that endometriosis affects up to 10% of reproductive age women. Manifestations of endometriosis are varied in both extent and severity, but typically include some combination of pelvic, gastrointestinal and genitourinary symptoms, dyspareunia and infertility. Endometriosis is asymptomatic in one-third of cases, but it has been shown to significantly reduce quality of life in the majority of affected women (*de Ziegler et al., 2010*). Despite its wide prevalence and significant morbidity burden, few epidemiological studies have elucidated the pathophysiology and natural history of the disease.

Endometriosis has been implicated in multiple immune-mediated processes related to systemic inflammation, increased oxidative stress and an atherogenic lipid profile (*de Ziegler et al., 2010*; *Santanam et al., 2002*). Most likely through a combination of factors involving dysregulated hormone receptors and activation of inflammatory genes, the levels of markers for each of these processes have been shown to be elevated in peritoneal fluid and serum of women with endometriosis compared with controls (*Akoaum et al., 2008*; *Bedaiwy and Falcone, 2003*, *Bedaiwy et al., 2002*). Indeed, these markers of oxidative stress and reactive oxygen species have also been implicated in the disease processes of autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis that manifest with both rheumatological symptoms and severe systematic comorbidities (*Van Langendonckt et al., 2002*). Due to a similar process, it has been suggested that endometriosis could induce, or at least be associated with, similar adverse effects on other body systems. This could lead to long-term systemic comorbidities that may negatively affect the lifelong health of women (*Hughes et al., 2015*; *Sinaii et al., 2002*; *Taskin et al., 2019*). Given the widely accepted association between subclinical systemic inflammation and endometriosis (*Agic et al., 2006*; *Berkes et al., 2014*; *Jaeger-Lansky et al., 2018*; *Kobayashi et al., 2014*; *Yun et al., 2018*), there is emerging evidence that endometriosis may predispose these patients to a spectrum of disorders later in life, including multiple cancers, inflammatory bowel disease, endocrine disorders and atherosclerosis (*Hughes et al., 2015*).

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality for women globally. The population-adjusted risk of cardiovascular mortality is greater for women than men (20.9% versus 14.9%), despite numerous improvements in evidence-based treatments for established ASCVD and increased awareness of ASCVD risk factors (*McSweeney et al., 2016*; *Yusuf et al., 2004*). Traditional ASCVD risk factors include diabetes, hypertension, dyslipidaemia, smoking, obesity and physical inactivity (*Brown et al., 2018*; *McSweeney et al., 2016*; *Mosca et al., 2011*). However, ASCVD risk in women also encompasses numerous non-traditional ASCVD risk factors such as hypertensive disorders of pregnancy, a history of preterm labour, gestational diabetes, breast cancer treatment, autoimmune diseases and depression (*Agic et al., 2006*; *Giudice and Kao, 2004*). Furthermore, a potential influence of immunologic and sex-related disorders associated with chronic inflammation on lifetime ASCVD risk is a subject of ongoing research.

Recent epidemiological studies have reported a similar potential association between endometriosis and ASCVD, citing similar pathogenic mechanisms such as systemic chronic inflammation, increased oxidative stress, coronary microvascular dysfunction, endothelial dysfunction and atherogenic lipid profile (*Kinugasa et al., 2011*; *Melo et al., 2010*; *Pretta et al., 2007*; *Santoro et al., 2012*, *2014*). Moreover, *Shen et al. (2008)* demonstrated that chromosome 9p21 confers a higher risk for the development of acute myocardial infarction and endothelial dysfunction, while *Uno et al. (2010)* reported a similar association between endometriosis and several CDKN2CBAS genetic variants on chromosome 9p21. Ultimately, this association and plausible mechanistic similarities suggest that women with endometriosis may represent a high-risk population for the development of ASCVD and severe cardiovascular complications due to longstanding states of chronic inflammation and early onset progression of atherosclerosis (*Hughes et al., 2015*; *Santanam et al., 2002*).

Clear identification of a link between endometriosis and lifelong cardiovascular disease would necessitate a radical shift in public health management. Beyond treatments for infertility and chronic pelvic pain, it would signal the need for targeted prevention and early detection guidelines for chronic and life-threatening diseases for which women with endometriosis would be at greater risk. This systematic review considers the evidence for associations between endometriosis and cardiovascular disease, including markers of atherogenic dyslipidaemia, endothelial dysfunction and subclinical atherosclerosis; such associations would reflect an increased predisposition to cardiovascular disease as a clinical endpoint independent of other known ASCVD risk factors.

Sources

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (*Liberati et al., 2009*).

The electronic databases Embase, PubMed, MEDLINE, Cochrane Register of Trials and ClinicalTrials.gov were systematically searched from inception to May 2018. The following search terms were used: 'endometriosis', 'atherosclerosis', 'cardiovascular disease', 'lipids', 'endometrial dysfunction', 'dyslipidemia', 'oxidative stress' and 'chronic inflammation'. A summary of the search strategy performed through Embase and MEDLINE is included in Supplementary Table 1.

All original research articles, including cohort studies, randomized and non-randomized controlled trials published up to 1 May 2018 were analysed. Included studies reported cardiovascular disease outcomes among women with endometriosis as measured by either direct incidence of cardiovascular events, imaging assessment of subclinical disease, or assessment of markers of endothelial dysfunction and abnormal lipid profiling. Additional studies were extracted from

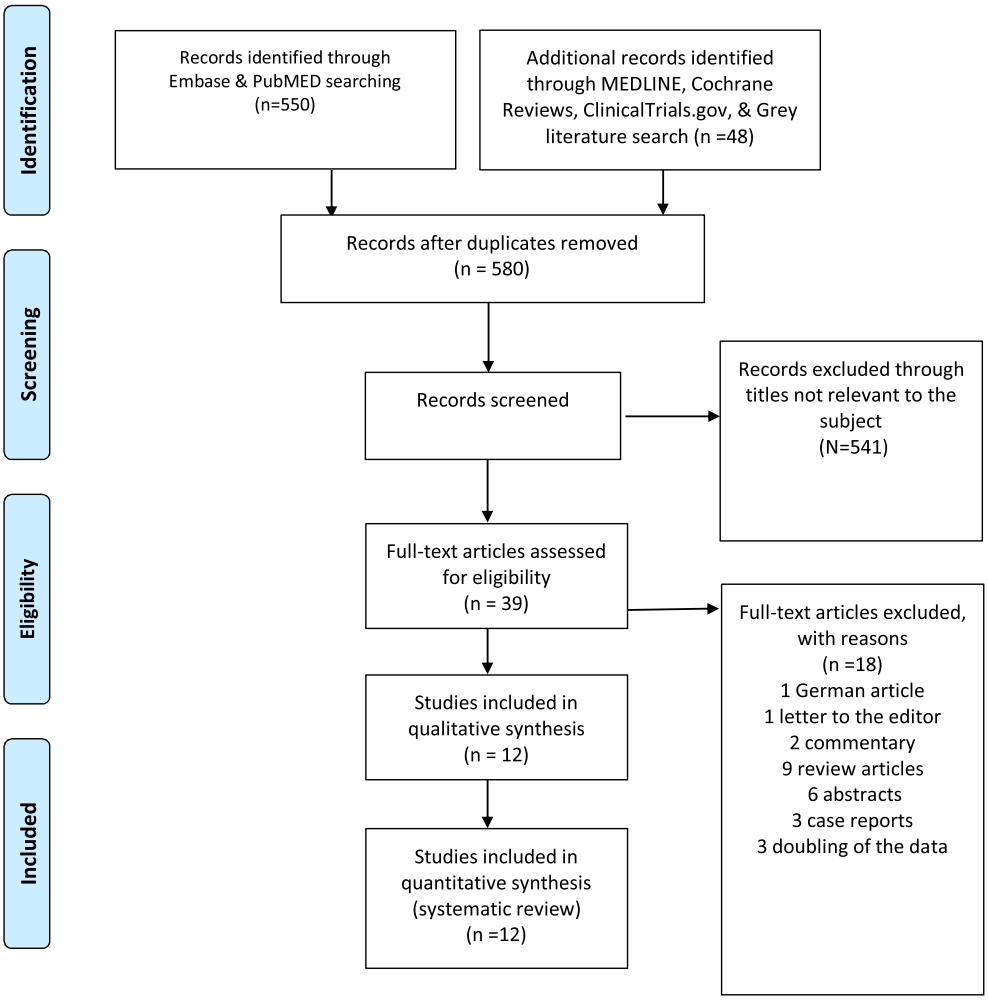

FIGURE 1 Flow chart of included studies and search strategy.

the references in the full-text articles. Only articles published in English were included; published abstracts from conferences were also considered.

Study selection

Studies were assigned to one of three groups: (i) epidemiological studies that assessed the relative risk of direct ASCVD outcomes among women with endometriosis; (ii) studies that investigated the association between endometriosis and serum markers of dyslipidaemia (serum paraoxonase 1 [PON-1], polyunsaturated fatty acids [PFA], eicosapentaenoic acid [EPA], total cholesterol, low-density lipoprotein cholesterol [LDL], high-density lipoprotein cholesterol [HDL], triglycerides, lipoprotein a [Lp(a)]); and (iii) studies pertaining to the prevalence of serum and instrumental markers as indirect measures of future ASCVD risk and subclinical atherosclerosis among women with endometriosis.

Pertinent serum markers included serum inflammatory markers (SIM), asymmetric dimethylarginine (ADMA), serum amyloid A (SAA), endothelial activation parameters (EAP), interleukin-6 (IL-6), TNF-alpha, vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), E-selectin, ristocetin cofactor and von Willebrand factor (vWF). Instrumental markers of subclinical atherosclerosis included carotid artery intima media thickness (ccIMT), distensibility coefficient, flow mediated dilation (FMD), brachial-ankle pulse wave velocity (baPWV) and uterine artery pulsatility/resistance index and diameter (UtA PI/RI/d).

The primary outcome measure was ASCVD risk, defined as dyslipidaemia, increase in SIM or increases in EAP. Secondary markers measured were the effects of surgical and/or medical therapy on endothelial function and ASCVD risk. Two authors (OT and MI) independently searched and reviewed the retrieved articles and results were compared. Any disagreement was resolved by discussion and included studies were evaluated according to the Newcastle–Ottawa Quality Assessment Scale (Supplementary Table 2) (*Wells et al., 2013*).

RESULTS

FIGURE 1 is a flow chart of the studies included. Unfortunately, no randomized controlled trials and only one comparative follow-up study were identified in the search. Most of the included articles were cross-sectional and case-controlled studies. An initial search of studies that described endometriosis and cardiovascular risk resulted in identification of 598 articles, reduced to 580 after removal of duplicates. After review of title and abstracts, 39 articles were deemed relevant to the topic and were subsequently reviewed in full.

TABLE 1 PROSPECTIVE COHORT STUDIES ON EPIDEMIOLOGY OF ENDOMETRIOSIS AND CARDIOVASCULAR MORBIDITY/ATHEROSCLEROSIS

Study	Method	Clinical endpoints	Diagnosis by	RR among women with endometriosis versus controls
Mu et al. (2016)[a]	Prospective cohort	Myocardial infarction Angiographically-confirmed angina Bypass graft surgery/coronary angioplasty procedure/stent	Surgery	1.52 (95% CI 1.17–1.98) 1.91 (95% CI 1.59–2.29) 1.35 (95% CI 1.08–1.69)
Mu et al (2017)[a]	Prospective cohort	Hypercholesterolemia Hypertension	Surgery	1.25 (95% CI 1.21–1.30) 1.14 (95% CI 1.09–1.18)

[a] Both studies used the same cohort.

ASCVD = cardiovascular disease; MI = myocardial infarction; RR = relative risk.

Among the full-text articles reviewed, 27 were excluded for various reasons (one German article, one letter to the editor, two commentaries, nine review articles, seven abstracts-only, three case reports, four doubling of the data). Ultimately, 12 studies were deemed eligible and included in qualitative synthesis: this included two prospective cohort studies (*Mu et al., 2016*, *2017*), four studies reporting lipid profile (*Crook et al., 1997*; *Hopeman et al., 2015*; *Melo et al., 2010*; *Verit et al., 2008*) and six studies (three cross-sectional, three case-control) that compared lipid profiles as well as other markers of endothelial dysfunction and atherosclerosis (*Kinugasa et al., 2011*; *Pretta et al., 2007*; *Santoro et al., 2012*, *2014*; *Tani et al., 2015*; *Waratani et al., 2017*).

ASCVD, hypertension and hypercholesterolemia in women with endometriosis

A summary of epidemiological data is provided in TABLE 1. First, an examination of the association between surgically confirmed endometriosis and subsequent ASCVD among 116,430 women demonstrated an increased risk of ASCVD compared with women without endometriosis (1.62; 95% confidence interval [CI]:1.39–1.89), independent of any demographic and lifestyle confounders (*Mu et al., 2016*). This association was higher among younger women and those who underwent a hysterectomy and/or oophorectomy. Secondly, among women with surgically confirmed endometriosis, the relative risks for developing hypercholesterolemia and hypertension were 1.25 (95% CI 1.21–1.30) and 1.14 (95% CI 1.09–1.18), respectively. In a second population-based study using the same cohort, women with hypercholesterolemia and hypertension had relative risks of also having laparoscopically confirmed endometriosis of 1.22 (95% CI 1.15–1.31) and 1.29 (95% CI 1.18–1.41), respectively (*Mu et al., 2017*).

Dyslipidaemia in women with endometriosis

The findings in nine studies (*Crook et al., 1997*; *Hopeman et al., 2015*; *Kinugasa et al., 2011*; *Melo et al., 2010*; *Pretta et al., 2007*; *Santoro et al., 2012, 2014*; *Tani et al., 2015*; *Verit et al., 2008*) investigating the relative risks of dyslipidaemia among women with endometriosis are summarized in TABLE 2 and FIGURE 2. A comparison of results demonstrates varying conclusions regarding the association of lipid levels among 334 women with and without endometriosis. For example, serum lipoprotein a [Lp(a)] levels were five-fold higher (15 mg/dl versus 3.1 mg/dl, $P < 0.05$) (*Crook et al., 1997*) and serum paraoxonase 1 (PON-1) activity was found to be significantly lower among women with endometriosis (106.5 ± 37.4 IU/l versus 183.7 ± 22.3 IU/l, $P < 0.05$) (*Verit et al., 2008*). Furthermore, a significant negative correlation was found between PON-1 activity and stage of the disease ($r = -0.74$, $P < 0.0001$) (*Verit et al., 2008*).

Among women with endometriosis, triglycerides, total cholesterol and LDL levels were increased compared with controls (all $P < 0.05$) (*Melo et al., 2010*; *Verit et al., 2008*) (TABLE 2, FIGURE 2). While serum HDL levels were decreased among women with endometriosis in certain studies (*Tani et al., 2015*; *Verit et al., 2008*), a cross-sectional study by *Melo et al. (2010)* found significantly higher HDL levels in women with endometriosis compared with the control group (HDL: 60.8 ± 19.0 mg/dl versus 53.5 ± 10.4 mg/dl, $P = 0.008$).

Hopeman et al. (2015) performed a cross-sectional study of serum polyunsaturated fatty acids (PUFA) and clinical data from 205 women undergoing IVF based on previous evidence, suggesting a decreased risk of endometriosis in women with high n-3 PUFA intake (*Covens et al., 1988*; *Gazvani et al., 2001*; *Herington et al., 2013*; *Netsu et al., 2008*; *Tomio et al., 2013*). They found that women with high serum EPA levels were 82% less likely to have endometriosis compared with women with low EPA levels (odds ratio 0.18, 95% CI 0.04–0.78).

Atherosclerosis and serum markers of ASCVD associated with endometriosis

A summary of the six studies (*Kinugasa et al., 2011*; *Pretta et al., 2007*; *Santoro et al., 2012*, *2014*; *Tani et al., 2015*; *Waratani et al., 2017*) that examined markers of subclinical atherosclerosis in women with and without surgically diagnosed endometriosis is provided in TABLES 3 and 4. Regarding instrumental markers of subclinical atherosclerosis, ccIMT measurements in two of the studies found no significant differences between women with surgically diagnosed endometriosis and those without (*Pretta et al., 2007*; *Santoro et al., 2012*). However, *Santoro et al. (2012)* demonstrated that women with endometriosis had significantly lower FMD than controls (mean difference −4.62, 95% CI −6.52 to 2.73; $P < 0.001$) with no linear association between FMD and the severity of endometriosis. A recent study by *Kinugasa et al. (2011)* similarly reported lower FMD in women with endometriosis compared with those without (8.39 ± 0.43% versus 10.79 ± 0.54%, $P = 0.001$). Furthermore, a case-control study using baPWV as an instrumental measure of endothelial dysfunction found significantly higher values in women with endometriosis (1187.5 ± 142.5 versus 1063.1 ± 12.3, $P < 0.05$), which reflects an increased ASCVD risk (*Tani et al., 2015*). A recent study also reported increased UtA RI on the ipsilateral side in patients with an endometrioma compared with those without (*Waratani et al., 2017*). In addition, the diameter of the ascending branch of the UtA was significantly

TABLE 2 STUDIES COMPARING ATHEROGENIC LIPID PROFILE AMONG SURGICALLY DIAGNOSED WOMEN WITH AND WITHOUT ENDOMETRIOSIS

Study	Method	Age (years)	Cases	Controls	Diagnosis	Pathology	Treatment	Parameters studied
Crook et al. (1997)	Cross-sectional	21–41	29	29	Laparoscopy	N/A	None	Lp(a)[a], apo a[a], apo b, TC, LDL, HDL, TG[a]
Pretta et al. (2007)	Case-controlled	35–44	66	66	Laparoscopy	Yes	Hormonal therapy	TC, LDL, HDL, TG
Verit et al. (2008)	Cross-sectional	18–35	47	40	Laparoscopy / laparotomy	Yes	None	Serum PON-1[a], TC[a], LDL[a], HDL[a], TG[a]
Kinugasa et al. (2011)	Cross-sectional	36–40	41	28	Laparoscopy	Yes	None	TC, LDL, HDL, TG
Melo et al. (2010)	Cross-sectional	18–40	40	80	Laparoscopy	Yes	None	TC[a], LDL[a], HDL[a], TG[a]
Santoro et al. (2012)	Cross-sectional	26–40	37	31	Laparoscopy / laparotomy	Yes	None	TC, LDL, HDL, TG
Santoro et al. (2014)	Cross-sectional	28–44	22	10	Laparoscopy / laparotomy	Yes	Surgical ablation	TC, LDL[a,b], HDL, TG
Hopeman et al. (2015)	Cross-sectional	27–38	24	181	Surgical	N/A	N/A, ART patients with ovarian stimulation	Serum PFA, EPA[a]
Tani et al. (2015)	Case-controlled	27–42	28	21	Laparoscopy / laparotomy	Yes	None	LDL, HDL[a], TG

[a] $P < 0.05$.

[b] Follow-up levels after surgical treatment in patients with endometriosis.

apo A/B = apolipoprotein a/b; ART = assisted reproductive technology; EPA = eicosapentaenoic acid; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein a; N/A = not available; PFA = polyunsaturated fatty acids; PON-1 = paraoxonase 1; TC = total cholesterol; TG = triglycerides.

greater on the side of the endometrioma than the contralateral side among women with endometriosis and ipsilateral side among normal controls (3.91 ± 0.15 mm versus 3.50 ± 0.23 mm versus 3.42 ± 0.15 mm, $P < 0.01$, respectively).

Most studies found no significant difference in serum markers of inflammation between women with and without endometriosis. However, *Kinugasa et al. (2011)* found elevated levels of ADMA (409.7 ± 10.1 pmol/l versus 383.0 ± 48.3 pmol/l, $P = 0.04$), high-sensitivity C-reactive protein (hs-CRP) (1053.3 ± 252.0 ng/ml versus 272.0 ± 83.3 ng/ml, $P = 0.02$), SAA (8.00 ± 1.53 *g/ml versus 3.82 ± 0.42 *g/ml, $P = 0.04$) and IL-6 (2.73 ± 0.75 pg/ml versus 1.05 ± 0.60 pg/ml, $P = 0.04$). In a study that compared changes in endometrial activation parameters (EAP) in women with endometriosis, significantly higher levels of VCAM (446 ± 52 ng/ml versus 389 ± 47 ng/ml, $P < 0.001$), ICAM (236 ± 32 ng/ml versus 168 ± 27 ng/ml, $P < 0.001$), E-selectin (50.7 ± 15.1 ng/ml versus 40.2 ± 17 ng/ml, $P < 0.001$), ristocetin cofactor (107.5 ± 26.2% versus 89.5 ± 16.2%, $P < 0.001$) and vWF (115.6% versus 97.5%, $P < 0.001$) were observed compared with controls (*Santoro et al., 2012*).

In the only follow-up study that investigated the effect of surgically treated endometriosis (STE) on markers of endothelial dysfunction and subclinical atherosclerosis in women with endometriosis, *Santoro et al. (2014)* found an overall improvement in FMD 2 years post-operatively. More specifically, FMD increased significantly with respect to baseline (average pre- to post-difference 5.07%, 95% CI 3.50–6.63; $P < 0.001$). However, no significant change in FMD was noted between the initial and 2-year follow-up values in the control group (average difference 1.56%, 95% CI −0.55 to 3.67). Similarly, follow-up FMD values were not significantly different (average difference 1.50%, 95% CI −1.24 to 4.23) and SIM were also similar between STE and control groups. As shown in FIGURE 3, EAP levels (VCAM-1, ICAM-1, vWF, ristocetin cofactor) were significantly higher in the STE group than in controls ($P < 0.05$), but this difference did not persist at 2-year follow-up. Finally, markers of inflammation and endothelial cell activation were similar between the STE and control groups at follow-up.

DISCUSSION

There are many ways to evaluate the association between endometriosis and cardiovascular disease. Large population-based studies provide the most direct evidence by assessing the relative incidence of various cardiovascular endpoints such as myocardial infarction, hypertension and hypercholesterolemia among women with laparoscopically-confirmed endometriosis compared with women without the disease. Because a diagnosis of endometriosis is typically made at a younger premenopausal age due to presenting symptoms such as pelvic pain and infertility, while cardiovascular disease typically manifests later in life, such studies provide sufficient temporal follow-up to observe the association directly. However, population-based studies require large databases, and these are rare and susceptible to bias due to their observational design. Hence, an alternative approach is to indirectly evaluate ASCVD risk by measuring subclinical or preclinical disease markers among women with endometriosis. In this way, a myriad of pathologic processes, such as increased local shear stress from hypertension, dysregulated plasma concentrations of LDL and HDL, and systematic inflammation and oxidative stress that promote vascular damage and atherosclerosis, have been implicated in the cardiovascular disease process. Several imaging and biochemical markers have also been used to evaluate cardiovascular disease risk based on these processes and can be used to evaluate the relative cardiovascular risk among endometriosis patients.

Two large prospective cohort studies demonstrate that women with endometriosis are at an increased risk of lifelong cardiovascular events including myocardial infarction (RR

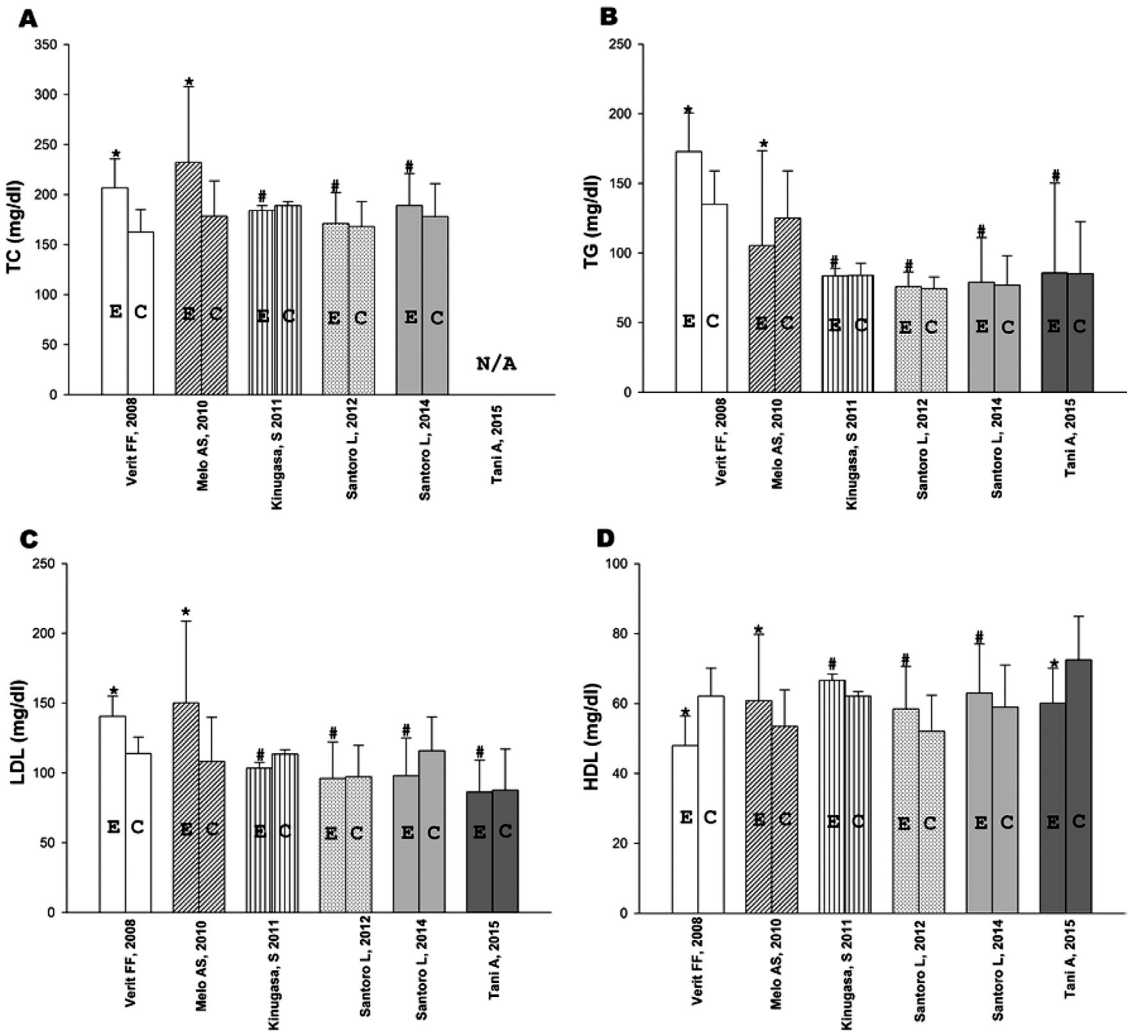

FIGURE 2 Serum levels of investigated lipids in women with and without endometriosis among the reviewed studies (C = control group; E = endometriosis group; HDL = high-density lipoprotein; LDL = low-density lipoprotein; N/A = not available; TC = total cholesterol; TG = triglycerides; *$P < 0.05$; #follow-up levels after surgical treatment in patients with endometriosis).

1.52) and angiographically confirmed angina (RR 1.91). These risks appear to be independent of specific demographic and lifestyle confounders and were most highly associated with women found to have endometriosis at a younger age. Furthermore, women with endometriosis are at increased relative risk of atherosclerosis requiring bypass, angioplasty or stenting procedure (RR 1.35) and hypertension (RR 1.14) (TABLE 1; *Mu et al., 2016*, *2017*), yet conflicting evidence was noted with respect to dyslipidaemia (FIGURE 2). A similar discrepancy was found among case-control and cross-sectional studies, as *Melo et al. (2010)* found higher levels of LDL and non-HDL cholesterol among women with endometriosis, irrespective of age and BMI, while two studies (*Pretta et al., 2007*; *Santoro et al., 2012*) found no difference in the lipid profiles of women with surgically confirmed endometriosis compared with controls (FIGURE 2, TABLE 2). However, it is important to note that women in these studies were on hormonal medication, which could ultimately have biased the results.

In order to facilitate interpretation of the indirect and preclinical markers discussed in the included studies, a review of the validity and clinical significance of each set of vascular (ccIMT, FMD, baPWV, UtA), atherogenic (Apo-E, PON-1), inflammatory (hs-CRP, CRP, IL-6, SAA, ICAM, VCAM) and thrombotic (vWF, ADMA, ristocetin cofactor, EPA) markers associated with ASCVD is summarized in Supplementary Tables 3 to 6.

Endothelial dysfunction has been shown to be one of the earliest stages in the atherosclerotic process, preceding structural vascular alterations. Endothelial dysfunction can be the result of a variety of processes, including systemic chronic inflammation, increased oxidative stress and an atherogenic lipid profile (*Gimbrone and Garcia-Cardena, 2016*; *Santoro et al., 2015*). *Santanam et al. (2002)* emphasized that various inflammatory factors, markers of oxidative stress and lipids have been shown to be elevated in the atherosclerotic lesions, peritoneal fluid and serum of women with endometriosis compared with controls. Moreover, it is clear that these changes may be associated with a systemic state of subclinical inflammation (*Agic et al., 2006*), which parallels a similar pathogenic mechanism in the development of atherosclerosis and may contribute to early onset or 'accelerated atherosclerosis' among women with endometriosis (*Hansson,*

TABLE 3 SUMMARY OF STUDIES ON ENDOTHELIAL DYSFUNCTION AND VASCULAR REACTIVITY AS NON-INVASIVE MARKERS OF SUBCLINICAL ATHEROSCLEROSIS AMONG SURGICALLY DIAGNOSED WOMEN WITH AND WITHOUT ENDOMETRIOSIS

Study	Study design	Cases	Controls	Variable	Outcome
Pretta et al. (2007)	Case-controlled	66	66	ccIMT, DC, SIM	No increased risk of subclinical atherosclerosis
Kinugasa et al. (2011)	Cross-sectional	41	28	FMD*, ADMA*, SAA*, IL-6*, hs-CRP*, lipids	Increased inflammation, endothelial dysfunction
Santoro et al. (2012)	Cross-sectional	37	31	ccIMT, FMD, VCAM-1*, ICAM-1*, E-selectin*, ristocetin cofactor*, vWF*	Higher risk of ASCVD, increased subclinical atherosclerosis
Santoro et al. (2014)	Cross-sectional	22	10	ccIMT, FMD, VCAM-1, ICAM-1, E-selectin, ristocetin cofactor, vWF	Regression of endothelial dysfunction with surgical ablation of endometriosis
Tani et al. (2015)	Case-controlled	28	21	baPWV*, SIM, endothelial function parameters	Increased arterial stiffness/inflammation denoting future atherosclerosis risk
Waratani et al. (2017)	Case-controlled	73	71	UtA blood flow and diameter*	Increased risk of subclinical atherosclerosis

ADMA = asymmetric dimethylarginine; baPWV = brachial-ankle pulse wave velocity; ccIMT = carotid intima media thickness; DC = distensibility coefficient; FMD = flow mediated dilatation; hs-CRP = high=sensitivity C-reactive protein; ICAM-1 = intracellular adhesion molecule-1; IL-6 = interleukin-6; SAA = serum amyloid A; SIM = serum inflammatory markers; UtA = uterine artery; VCAM-1 = vascular cell adhesion molecule-1; vWF = von Willebrand factor.
* $P < 0.05$.

2005; *Mu et al., 2016*; *Santoro et al., 2015*; *Sherer et al., 2010*). Ultimately, if these findings can be replicated through well-designed longitudinal studies, the clinical management of young women with endometriosis may indeed need to extend beyond chronic pain and fertility treatments to account for the considerable impact on long-term cardiovascular health.

Markers of endothelial function can serve to evaluate preclinical and subclinical atherosclerotic risk in women with endometriosis, not only in the peritoneal cavity but also at a systemic level, independent of pathogenic structural changes or traditional cardiovascular risk factors (*Santanam et al., 2002*). One of the earliest markers of subclinical atherosclerosis is ccIMT, yet all of the included studies failed to show any difference, thereby suggesting no increase in subclinical atherosclerosis in women with endometriosis (*Pretta et al., 2007*; *Santoro et al., 2012*, *2014*). However, all authors acknowledged the study population's relatively young age, which is relevant because ccIMT reflects structural vascular damage that occurs later in the atherosclerotic process.

TABLE 4 SUMMARY OF THE RESULTS OF STUDIES USING NON-INVASIVE MEASUREMENTS OF DC, CCIMT, FMD, PWV TO ASSESS THE RISK OF ASCVD/SUBCLINICAL ATHEROSCLEROSIS

Study	DC ($\times 10^{-3}$mmHg^{-1}) Left/right	ccIMT (mm) Left/right	FMD (%)	PWV (cm/s)	UtA PI/RI	UtA d (mm)
Pretta et al. (2007) Endometriosis Controls	4.7 ± 2.1/4.9 ± 0.3 4.4 ± 2.3/5.1 ± 0.2 NS/NS	0.4 ± 0.02/0.5 ± 0.03 0.5 ± 0.02/0.47 ± 0.02 NS/NS	N/A	N/A	N/A	
Kinugasa et al. (2011)	N/A	N/A	Endometriosis versus controls: 8.39 ± 0.43 versus 10.79 ± 0.54 $P < 0.05$	N/A	N/A	
Santoro et al. (2012)	N/A	N/A	Pre- versus post-treatment: −4.62 (95% CI: −6.52,−2.73) $P < 0.05$	N/A	N/A	
Santoro et al. (2014)	N/A	0.03 (95% CI: 0.0, 0.07) NS	Pre versus post-treatment: +5.07 (95% CI: 3.50, 6.63) $P < 0.05$	N/A	N/A	
Tani et al. (2015)	N/A	N/A	N/A	Endometriosis versus controls: 1187.5 ± 142.5 versus 1063.1 ± 12.3 $P < 0.05$	N/A	
Waratani et al. (2017) Ipsilateral side of endometrioma Contralateral side of endometrioma Ipsilateral control group	N/A	N/A	N/A	N/A	High ($P < 0.05$)	3.91 ± 0.15 ($P < 0.05$) 3.50 ± 0.23 3.42 ± 0.15

Values reported as mean ± SD or mean difference (95% CI).

ccIMT = carotid artery intima media thickness; CI = confidence interval; DC = distensibility coefficient; FMD = flow mediated dilatation; N/A = not available; NS = not statistically significant; PWV = pulse wave velocity; UtA = uterine artery pulsatility index (PI) resistance index (RI), diameter (d).

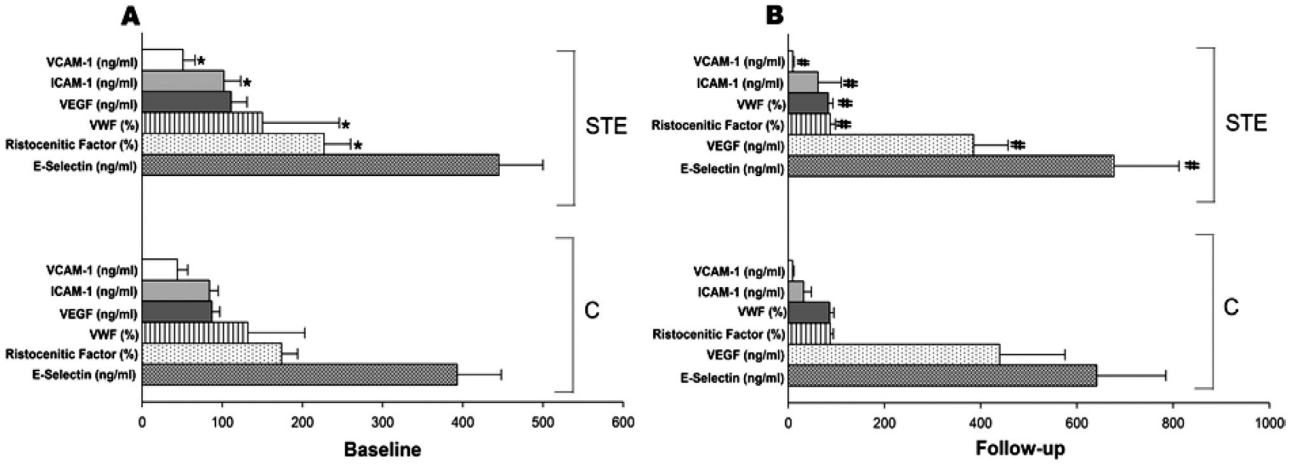

FIGURE 3 Serum levels of endothelial activation parameters investigated at baseline (A) and 2 year follow-up (B) in young women with surgically treated endometriosis and controls (C = control group; STE = surgically treated endometriosis group; *denotes $P < 0.05$). Data reproduced from *Santoro et al. (2014)*.

Conversely, *Santoro et al. (2012)* studied FMD (an indirect measure of endothelial dysfunction independent of traditional cardiovascular risk factors) to overcome the limitation of ccIMT in identifying early ASCVD and reported significantly lower FMD in women with endometriosis after excluding confounding factors that cause endothelial dysfunction (such as diabetes, obesity and hypertension). These results coincide with an earlier study by *Kinugasa et al. (2011)*, which found significantly increased AMDA levels with enhanced inflammation (IL-6, SAA) and lower FMD in women with endometriosis compared with controls. Interestingly, *Antoniades et al. (2011)* also noted that circulating IL-6 levels are positively associated with both ADMA levels and endothelial dysfunction in healthy individuals, even in the absence of atherosclerosis, and that ADMA is a predictor of FMD.

More recently, a follow-up study by Santoro and colleagues assessed the presence of endothelial dysfunction and subclinical atherosclerosis in women with STE (*Santoro et al., 2014*). After a 2-year follow-up, baseline and follow-up ccIMT, FMD, lipids, SIM and EAP were compared. The authors reported that there was a significant improvement in FMD compared with baseline in women with STE, while follow-up EAP were similar among women with STE and controls. This is the only published report showing that therapy leads to improvement of endothelial dysfunction, resulting in decreased subclinical atherosclerosis and ASCVD risk; however, its findings are limited by its small sample size and the use of different laboratories in measuring serum SIM and EAP at baseline and follow-up. Nevertheless, it could be speculated based on these findings that endothelial dysfunction could be reversed after treatment for endometriosis, resulting in decreased cardiovascular risk. However, further longitudinal studies are needed to outline the effects of surgical and medical therapy in ameliorating the development of atherosclerosis and related risks.

This systematic review demonstrates that there is considerable evidence in support of the suggestion that chronic inflammation, among other factors, may lead to subclinical atherosclerosis. Given that chronic inflammation, oxidative stress and endothelial dysfunction are common to the pathogenetic process of both endometriosis and atherosclerosis, it is reasonable to speculate that women with endometriosis may also be at increased risk of ASCVD. Because endometriosis may be present in up to 176 million women worldwide, mitigating the risks of ASCVD in women with endometriosis may reduce overall rates of morbidity and mortality and reduce public health costs. Unfortunately, a recently published joint statement by the American Heart Association (AHA) and American College of Obstetricians and Gynecologists (ACOG) regarding cardiovascular health screening does not discuss the role of endometriosis as a potential risk factor for ASCVD in young women (*Brown et al., 2018*). As presented in this systematic review, this link is supported by a growing body of evidence (*Glavind et al., 2017*; *Leone Roberti Maggiore et al., 2017*; *Saraswat et al., 2017*), which may warrant further discussion in future guidelines for cardiovascular health screening.

This study is the most thorough review to date of the evidence on this topic, evaluating both direct and indirect markers of lifelong atherosclerotic and cardiovascular disease among women with endometriosis. However, the major limitation of this review is the lack of robust prospective studies to evaluate the overall incidence of cardiovascular events in women with endometriosis, despite the fact that the underlying mechanisms have been described and understood for some time. Furthermore, clinical trials linking endometriosis and cardiovascular risk according to the type, stage and severity of endometriosis are very limited, probably owing to the heterogeneous nature of endometriosis and its widely varying clinical presentations, which often result in delays in diagnosis and management. Ultimately, future prospective studies should consider evaluating which subtypes and stages of endometriosis are most highly associated with endothelial dysfunction and subclinical atherosclerosis, whether early diagnosis and treatment of endometriosis will reduce the incidence of future cardiovascular events, and which clinical and preclinical markers hold the strongest prognostic significance for evaluating ASCVD risk. This would invariably help to inform future cardiovascular screening guidelines for stratifying risk in women with endometriosis and determining

whether a multidisciplinary approach involving family practice, gynaecology and cardiology would help in the lifelong management of endometriosis.

Although the actual level of ASCVD risk in women with endometriosis is unknown, the currently available evidence suggests that young women with endometriosis are at increased risk of lifelong cardiovascular disease. This risk may be severely underestimated, given that endometriosis is typically diagnosed in women at a relatively young age. However, this underestimation of risk may lead to substantial healthcare costs and unanticipated disease burden as these women get older. Although more robust studies are still needed to outline the real incidence of cardiovascular events in this population, the relevance of the type and stage of endometriosis, and the effects of surgical and medical therapy in ameliorating cardiovascular risk, currently available evidence is believed to support the potential benefit of specific cardiovascular screening guidelines for young women with endometriosis. These guidelines may entail a multidisciplinary approach to address a potentially increased risk of subclinical and 'accelerated' atherosclerosis and to improve their lifelong health.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2019.05.021.

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