# Association of endometriosis with cardiovascular disease: Genetic aspects (Review)

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**Abstract.** Cardiovascular disease (CVD) comprises a broad spectrum of pathological conditions that affect the heart or blood vessels, including sequelae that arise from damaged vasculature in other organs of the body, such as the brain, kidneys or eyes. Atherosclerosis is a chronic inflammatory disease of the arterial intima and is the primary cause of coronary artery disease, peripheral vascular disease, heart attack, stroke and renal pathology. It represents a leading cause of mortality worldwide and the loss of human productivity that is marked by an altered immune response. Endometriosis is a heritable, heterogeneous, common gynecological condition influenced by multiple genetic, epigenetic and environmental factors, affecting up to 10% of the female population of childbearing age, causing pain and infertility; it is characterized by the ectopic growth of endometrial tissue outside the uterine cavity. Of note, epidemiological data obtained thus far have suggested a link between endometriosis and the risk of developing CVD. The similarities observed in specific molecular and cellular pathways of endometriosis and CVD may be partially explained by a shared genetic background. The present review presents and discusses the shared genetic factors which have been reported to be associated with the development of both disorders.

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**Contents**

1. Introduction
2. Genetics of CVD and endometriosis
3. Influence of the immune system and inflammation on CVD and endometriosis
4. Influence of angiogenesis on CVD and endometriosis
5. Shared susceptibility loci between CVD and endometriosis
6. Current knowledge of biological mechanisms involving the shared genetic loci
7. Conclusions and future perspectives

## 1. Introduction

The cardiovascular system consists of the heart and its blood vessels. Cardiovascular disease (CVD) is a general term that describes a type of disease that affects any of these components. The majority of the anatomical structures that are related to the cardiovascular system display a common tissue organization, with endothelial cells (ECs), smooth muscle cells (SMCs) and myocardial cells being three of the major cell types at the cellular level. In this context, several types of CVD exist, affecting only the blood vessels or the heart, but most commonly, both of these, either simultaneously as result of a common cause or as a sequalae arising, for example, from one condition that leads to other diseases within the group (e.g., coronary vessel disease that leads to ischemic cardiac disease or arrhythmias) (1).

Endometriosis is a common, benign, estrogen-dependent gynecological disease, associated with chronic pelvic pain and subfertility, defined by the presence of ectopic endometrial glands and stroma outside of the uterine cavity on other organs (2,3). It affects 10 to 15% of women of reproductive age, exhibiting varying symptoms such as severe pelvic pain, irregular menstrual bleeding, heavy menstrual pain, urinary tract and gastrointestinal symptoms and pain during intercourse, and can significantly affect the quality of life of

patients (4-6). Notably, endometriosis possesses numerous features that are reminiscent of a benign neoplastic process, which has the potential for malignant transformation. Genetic factors contribute to the development of this condition, in combination with environmental ones, such as toxins and pollution agents (3,7). Although the exact molecular and pathophysiological pathways leading to endometriosis remain unclear, various hypotheses have been suggested thus far, and all cases are not able to be explained by one theory alone (8). There is strong evidence to suggest the contribution of not only hormonal aspects, but also of multiple immune-mediated processes related to chronic inflammation, increased oxidative stress and an atherogenic lipid profile (9,10).

Women with endometriosis, which is a heterogeneous condition, are at a high risk of developing several other chronic diseases, including cancer (11) and various autoimmune diseases, such as systemic lupus erythematosus (SLE), multiple sclerosis, rheumatoid arthritis (RA), Crohn's disease, scleroderma, ulcerative colitis, autoimmune thyroid disorder, Sjögren's syndrome, coeliac disease and ankylosing spondylitis (12-14). Of note, previous findings have suggested that endometriosis can increase the susceptibility for cardiovascular disorders in these women, considering that both conditions share pathogenic mechanisms based on hormonal deviations, as well as aberrant immunology and genetic profiles (15-17). Moreover, studies have reported a similar potential association between endometriosis and atherosclerotic CVD, underlying similar pathogenic mechanisms including coronary microvascular dysfunction, endothelial dysfunction and atherogenic lipid profile (18,19). There is an extended amount of literature focusing on the increased risk that women with endometriosis have for developing myocardial infarction, ischemic heart disease, hypertension, atherosclerosis requiring bypass and angioplasty or stenting procedures (16,20-24). However, CVD in women with endometriosis remains underdiagnosed and, therefore, detailed studies are required to fully understand the clinical relevance, as well as the underlying pathophysiological mechanisms of the interactions between these conditions.

The present review discusses and summarizes the observed increased risk of CVD among women with endometriosis from the genetic point of view, focusing on the potential underlying shared genetic factors that warrant further study. Understanding these associations in depth requires mechanistic and functional genomics research in an effort to determine the causal shared risk factors.

## 2. Genetics of CVD and endometriosis

Recent advances in human genetics, mainly due to the rapid development of genome-wide association studies (GWAS), polygenic risk score and next-generation sequencing (NGS) technologies, have revealed thousands of genetic associations between common DNA sequence variants [e.g., single nucleotide polymorphisms (SNPs)] and complex human diseases or traits, thus leading to a marked increase in the number of risk alleles identified in patients with complex diseases. CVDs are the leading public health problem worldwide (25). Among these, atherosclerosis of the coronary circulation along with its complications of acute coronary syndromes, and ischemic heart failure are the principal entities. Genetic studies have led to a more in-depth knowledge of the pathophysiological processes in coronary artery disease (CAD) and the identification of novel treatment targets (e.g., in lipid metabolism).

The first GWAS for CAD were published in 2007 (26-28). Since then, the appearance of high-throughput genotyping arrays along with advances in statistical methods and large data sets have revolutionized the identification of thousands of disease-associated variants. It is currently well-established that CVDs are characterized by a strong genetic background. This genetic component includes in its minority, genes that are involved in pathways of traditional risk factors. Of note, experimental research has revealed novel, and, in some circumstances surprisingly, non-predictable mechanisms. Three independent pioneer studies in CVD research almost synchronously identified the chromosome 9p21 locus as a risk factor for CVD (26-29). Together with the lipoprotein(a) (*LPA*) locus, they exert the most prominent effect on the risk of developing CAD (30). The 9p21 locus was initially designated as a 'gene desert' as no known genes could be recognized within it. Although the coding genes of the cyclin-dependent kinase (CDK) inhibitors 2A/2B (*CDKN2A*/*CDKN2B*) reside in close proximity, extensive research could not provide evidence for the involvement of these genes (31). On the other hand, long non-coding RNA (lncRNA) *ANRIL* was identified in the same genetic region and genetic variants in that region proved to affect its expression. The increased expression of linear ANRIL was found to enhance atherosclerosis (32), in contrast to circular ANRIL, which was protective (33). Genetic engineering in induced pluripotent stem cells identified that the risk genotype accompanied by an increased *ANRIL* expression, also induced a pro-atherogenic phenotype in vascular SMCs (VSMCs) (34).

Currently, known CAD genes that target the vessel wall and the process of atherosclerosis independently of the genes involved in the regulation of risk factors, can be classified as genes affecting plaque progression and platelet function, although they are not limited to this classification. Genes involved in the pathophysiological process include genes affecting the vascular remodeling (VSMCs), the proliferation/mitosis of angiogenic cells, transcriptional regulation, inflammation, angiogenesis and nitric oxide signaling (35).

Endometriosis is a complex disease and genetic, epigenetic and environmental influences interact with each other, thus leading to the disease phenotype. Apart from the aberrant immunological responses, angiogenesis processes and biochemical alterations leading to the growth of endometrial tissue outside the uterus, which impair fertility, the disease has a strong genetic component, as firstly shown by monozygotic twin-based and family studies performed (36,37). Considering that the association between genetic polymorphisms and clinical disease has long been recognized, 'candidate gene' studies have greatly assisted investigators in identifying causal genetic variants underlying endometriosis over the past decades, taking into account hundreds of genes and SNPs (38,39), while GWAS have succeeded in identifying common genetic variants of moderate effects for various complex diseases (40-44). Currently, the number of novel endometriosis-associated loci is increased due to the developments in NGS techniques, which result in the detection of common or rarer variants conferring a high risk of disease. However, apart from the progress made

in the identification and confirmation of novel SNPs associated with endometriosis, many studies have obtained controversial results, mainly due to the enrolment of small populations and the unclear definition of race and/or ethnicity (38). Thus, some of these endometriosis-associated loci were confirmed in other populations and/or replication studies, while further new loci were also identified through meta-analyses, as presented in a comprehensive analysis by Sapkota *et al* (45). In a meta-analysis conducted by Rahmioglu *et al* (39), involving four GWAS and four replication datasets, a genome-wide level association of SNPs in six out of nine genetic loci was detected for rs12700667 on 7p15.2, rs7521902 near Wingless and Int-1 (Wnt) family member 4 (*WNT4*), rs10859871 near vezatin adherens junctions transmembrane protein (*VEZT*) gene, rs1537377 near CDKN2B antisense RNA 1 (*CDKN2B-AS1*), rs7739264 near inhibitor of DNA binding 4 (*ID4*) gene and rs13394619 in growth regulating estrogen receptor binding 1 (*GREB1*) gene with all these loci; however, *VEZT* SNP exhibited a stronger association with stage III/IV of endometriosis. A further meta-analysis by Sapkota *et al* (44) identified five novel loci significantly (at a genome-wide level) associated with the risk of developing endometriosis, with these genes being involved in sex steroid hormone pathways [fibronectin 1, coiled-coil domain containing 170, estrogen receptor 1 (*ESR1*), spectrin repeat containing nuclear envelope protein 1 and follicle stimulating hormone subunit beta]. Since then, in the largest GWAS and replication meta-analysis of endometriosis that was performed to date, 42 loci (31 novel) were identified. According to that study, these loci explained 5.5% of disease variance with roles in progesterone resistance, cell cycle regulation, oncogenesis and ovarian tissue enhancers (46). Of note, whole exome sequencing (WES) that was used for the first time in family studies allowed for the detection of two genes, UDP glucuronosyltransferase family 2 member B28 (*UGT2B28*) and ubiquitin specific peptidase 17 like family member 2 (*USP17L2*), which are novel endometriosis-associated genes, by investigating a three-generation family from Crete, Greece (47).

## 3. Influence of the immune system and inflammation on CVD and endometriosis

Several well-conducted basic science studies on atherosclerosis and CVD over the past years have undoubtedly established the concept that the deregulation of the immune system plays a major role in its pathophysiology (48-51). The translational confirmation of this concept was provided by the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS study) (52,53) and studies using colchicine in patients with CAD (54,55). These pioneer studies proved that independently of the control of dyslipidemia as a traditional risk factor, targeting inflammatory cytokines reduced cardiovascular complications in high-risk subjects. Data from these studies definitively established the role of inflammation in CVD and several additive experimental evidence [summarized in (56)], is now supported by genetic data. Of particular importance, genetic data from GWAS assigned to the inflammation pathways associated with CAD, do not contain the expected and easily predictable molecules, such as interleukin (IL)-1β (57) or components of the NOD-like receptor protein 3 inflammasome (58) or classic pro-atherogenic chemokines [e.g., chemokine (C-X-C motif) ligand (CXCL)1] (59). Instead of usual suspects, a member of the *CXCL* family, *CXCL12* and IL-6 receptor were identified as CAD genetic risk loci (26,60). As is known, CXCL12 is the ligand for C-X-C motif chemokine receptor 4. Signaling pathways via this receptor play a complex role (61); however, generally, in ECs, it appears to have pro-atherosclerotic properties (62).

Immune and inflammatory cells are not the only players in the inflammation 'game' of atherosclerosis. Although it is well known that subsets of ECs in different tissues and organs have functions, such as alloimmunity, immune cell recruitment, immune tolerance and vascular inflammation (63-65), additive immune functions, typical of immune cells, have been recognized. Co-stimulation and co-inhibition, (66), the induction of apoptosis in other cells (67) and roles as semi-professional-antigen-presenting cells, have all been assigned to ECs.

Of utmost importance, within the past 20 years, new data have confirmed that atherosclerosis is an inflammatory and immune-mediated disease, reducing the rank of traditional risk factors. There is accumulating evidence to suggest that ~40% of individuals with confirmed CVD were never exposed to smoking or diagnosed with diabetes mellitus. On the other hand, it is well established that atherogenesis is accelerated by autoimmune diseases, such as SLE, antiphospholipid syndrome, RA and vasculitis (68). In this context, it is not surprising that a marked improvement in the understanding of the mechanisms regulating the engagement and activation of various immune cells in atherosclerosis and the production of several chemo- and cytokines that regulate these recruitment and process, may serve as a common molecular mechanism explaining the co-occurrence of atherosclerosis in several other diseases with strong inflammatory and immune components, independently of the male sex, older age or other classic risk factors such as endometriosis, known to affect young women without traditional risk factors for CVD (as exactly is the point in SLE).

Taking the aforementioned data into account, endometriosis and CVD may be considered as inflammatory diseases. Inflammatory cytokines, chemokines and growth factors that are involved in the generation of localized inflammation have been found in atherosclerotic plaque and the peritoneal fluid of female patients with endometriosis (10). For example, the deregulated production of interferon-γ has been reported as an underlying mechanism between endometriosis and atherosclerosis, indicating that female patients with endometriosis are at an increased risk of developing microvascular dysfunction and atherosclerosis (69).

Detailed studies have been conducted in an attempt to elucidate the influence of inflammation in endometriosis, thus shedding light on the pathogenetic mechanisms leading to this disorder. The association between inflammation and endometriosis was initially suggested in infertile women, characterized by an extended intra-peritoneal inflammation (70). Endometriosis, highlighted by systemic inflammation in affected organs throughout the body, is caused by a variety of inflammatory factors, such as cytokines, prostaglandins, macrophages, and tumor necrosis factor (TNF). Inflammation is part of the non-specific immune response, playing a key role

in the pathophysiology of the disease, by altering the function of immune cells and increasing the levels of pro-inflammatory mediators in the peritoneal cavity, endometrium and blood. In particular, this marked elevation refers to pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α), while JNK in eutopic endometrial cells from women with endometriosis upregulates the expression of inflammatory cytokines (71). Furthermore, levels of various inflammatory factors, such as intracellular adhesion molecule 1 (ICAM-1), C-reactive protein, IL-1, IL-6, TNF-α and vascular endothelial growth factor (VEGF) have been found to be elevated in the peritoneal fluid and peripheral blood of women with endometriosis (72). In addition, endometriosis has been shown to be accompanied by alterations in the levels and function of inflammatory products, including macrophage migration inhibitory factor, C-C chemokine monocyte chemoattractant protein-1, serum amyloid A and chemokine (C-C motif) receptor (CCR)1 (73).

Of note, Monsanto *et al* (74) reported that the inflammatory profile was significantly altered, both locally and systemically, in women with endometriosis upon surgical lesion removal, thus suggesting that ectopic lesions may drive systemic inflammation in endometriosis. Indeed, endometriosis lesions have been found to produce estrogen themselves, which stimulates mast cells to support the inflammatory process (75). Considering that degranulating mast cells have been found in high quantities in endometriotic lesions, pain and hyperalgesia in endometriosis may be attributed to inflammation due to mast cells (76). Various data have demonstrated that hormonal alterations in endometriosis are related to the inflammatory unbalance characterizing this disease, with steroid hormones promoting the expression and release of pro-inflammatory factors, with inflammation altering hormonal regulation by modulating sex steroid receptors expression (77). Additionally, the deregulation of the inflammasome pathway has been suggested to participate in disease progression through promoting adhesion, invasion and cell proliferation and by preventing cell death (78). In a recent study by Rafi *et al* (17), it was shown that in women with endometriosis, inflammation causes a hypercoagulable status, which leads to the development of atherosclerosis and other cardiac complications. Thus, it can be hypothesized that endometriosis may be a risk factor of cardiovascular disorders in these patients. Furthermore, Bao *et al* (79) demonstrated that multi-layered genomic datasets, based on GWAS data in endometriosis, regulatory genomics and protein interactome, led to the generation of an atlas of genetic target prioritizations in endometriosis, which enhanced the understanding of endometriosis as an inflammatory systemic disease.

## 4. Influence of angiogenesis on CVD and endometriosis

Various studies have significantly associated endometriosis with angiogenesis, lymphangiogenesis and neurogenesis, which may be mediated by the activation of inflammatory cells, thus leading to the ectopic growth of endometrial tissue. Angiogenesis is significantly involved in endometriosis in general. A continuum vascular development results in the development of endometriosis, through the induction of angiogenesis and lymphangiogenesis, while it is well known that endometriotic lesions have lymphangiogenic properties (80,81). Angiogenesis and neurogenesis are activated coordinately, with angiogenesis allowing the maintenance of lesions, supplying them with functional blood vessels, thus forming a dense vascularization (82). Taking into account that pelvic pain represents a usual manifestation of endometriosis, the endometriosis-associated increase in neurogenesis is likely to be a consequence of the observed proximity between mast cells and nerve fibers and, therefore, mast cells may contribute to pain (83). In this framework, it has been suggested that neurogenesis contributes to the growth of nerve fibers, the subsequent peripheral neuroinflammation and the generation of chronic pain (84). Notably, the identification of novel molecular factors associated with angiogenesis and lymphangiogenesis may facilitate the development of novel therapeutic strategies for this disorder. Moreover, in a recent study focusing on the measurement and validation of circulating proteins in predominantly adolescents and young adult women with endometriosis, a significant enrichment and increased activation of proteins that are related to angiogenesis and cell migration pathway was observed (85).

Although in adults the majority of ECs remain quiescent, postnatal angiogenesis can take place under both physiological and pathological stimuli, including reproduction, inflammation, tissue regeneration and tumor growth. In line with this phenomenon, pathological angiogenesis has been implicated in the pathogenesis of numerous diseases, such as cancer, atherosclerosis, ischemic heart disease, hypertension and vascular retinopathies. The mechanisms of angiogenesis are numerous, with angiogenic factors and their corresponding signaling pathways playing a key role in blood vessel growth and morphogenesis (86). In the cascade of angiogenesis and vascular diseases, important functions for ncRNAs have been assigned. ncRNAs can be classified as microRNAs (miRNAs or miRs), circular RNAs, other small RNAs (including tRNAs, 5S and 5.8S ribosomal RNA, small nuclear RNAs and piRNAs) and lncRNAs. Currently, although the functions and mechanisms of miRs in angiogenesis and vascular diseases are well established (87,88), the perspective role of lncRNAs remains unknown. What definitely be concluded about the functional mechanisms of lncRNAs regarding their expression, regulation and roles in angiogenesis and vascular disease, is that central mechanisms predicted from shared genetic background between endometriosis and CVD, are cross-linked in several molecular pathways that are significantly modified by lncRNAs, thus emphasizing the rationale for a detailed description of these mechanisms [reviews on lncRNAs in CVD and therapeutic angiogenesis have been previously provided (89,90)].

The standard sequence of pathogenic events involved in the progression of atherosclerosis has been described, including endothelial dysfunction and endothelial activation as initial events, followed by monocyte/macrophage adhesion, activation and migration, lipid deposition, extracellular matrix synthesis, SMC migration and proliferation and finally, plaque neovascularization (48,91). Specific environments in atherosclerotic areas (relative anoxia, inflammation, oxidative stress) induce angiogenic factors that primarily promote sprouting angiogenesis from pre-existing vasa vasorum (92-97). Neovascularization acts by supplying nutrients and $O_2$ to the

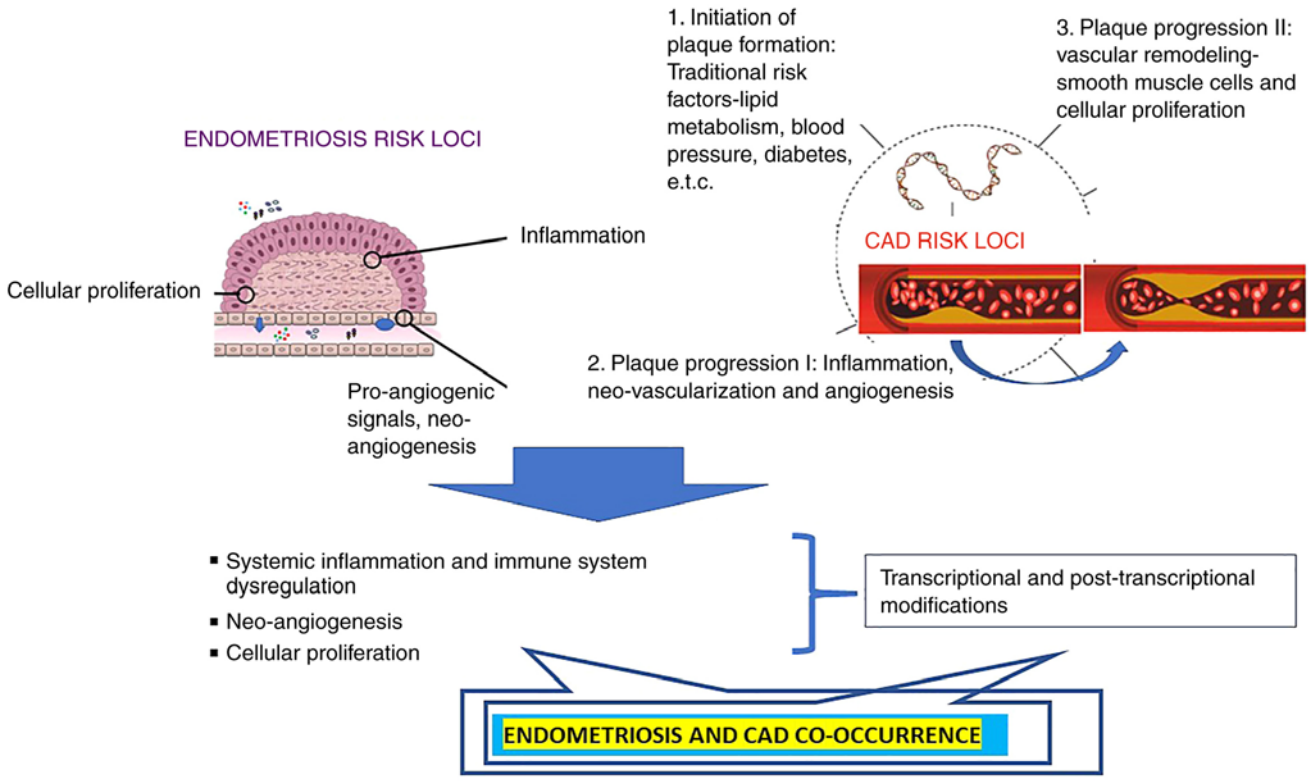


Figure 1. Proposed mechanisms of the endometriosis-cardiovascular interaction. Genetic risk loci associated with coronary artery disease, are classified into major distinct mechanistic pathways, assigned to initiation and plaque progression Major mechanisms include pro-inflammatory, pro-angiogenic, and aberrant immune functions. Common genetic risk loci influence the initiation and progression of endometriosis and are classified in the same three distinct molecular pathways. All these pathways predicted from genetic data, are influenced at the transcriptional and post-transcriptional level, being the cross-link mechanism of the shared genetic background for both diseases. CAD, coronary artery disease.

local microenvironment; however, the incomplete maturation and the fragility of neocapillaries promote intra-plaque hemorrhages that may lead to plaque instability and rupture (98). Indeed, the presence of neocapillaries in atherosclerotic plaques play a role in their progression and complications (93), with the adventitial delivery of VEGF promoting neoangiogenesis and intimal hyperplasia (99), whereas inhibitors of angiogenesis attenuate plaque growth (100).

It appears reasonable that the vascular wall where resident, recruited and circulating cells and lipids interact for the initial formation and proceeding plaque progression, along with increasing evidence of the involvement of immune cells, inflammation [for a detailed overview please see (101), and for an overview of platelets please see (102)] in atherosclerosis, has been subjected to detailed investigations. VSMCs have been already described to influence atherosclerosis via vascular tone and via local processes, including inflammation andvascular remodeling, leading either to the stabilization or destabilization of the plaque. Significant genetic overlap exists between these two functions. The nitric oxide signaling pathway induces vasodilatation via the second messenger cyclic guanosine monophosphate (103) and simultaneously inhibits the migration of VSMCs (104), which itself is a hallmark of athero-progression (105). Another genetic locus affecting VSMC biology is the 9p21 locus (33,34), which will be described in the following sections of the present review. A schematic diagram of the shared pathogenesis of CVDs and endometriosis is presented in Fig. 1.

## 5. Shared susceptibility loci between CVD and endometriosis

Previous findings have suggested an association between endometriosis and an increased risk of developing CVD in various populations (15,17-23), with this observation posing the interesting question regarding the potential role of a shared genetic background on the co-occurrence of endometriosis and CVD. Considering that various genes involved in inflammation are significantly associated with both endometriosis and CVD, it appears reasonable that shared genetic components between these diseases exist. Indeed, recent findings have linked endometriosis to several pathological mechanisms, ranging from systemic inflammation and enhanced oxidative stress to endothelial dysfunction (106). Given the fact that CVD is also a systemic and multifactorial condition, it may be intriguing to further explore the shared mechanisms underlying endometriosis and CVD, by highlighting key clinical evidence that links endometriosis with adverse cardiovascular events. Considering that the aforementioned mechanisms of systemic inflammation and endothelial dysfunction are considered the key mechanisms in the development of atherosclerosis/CVD and that both endometriosis and CVD are characterized by a strong genetic component, as described above, the present review presents current knowledge regarding the potential shared genetic background of these diseases by performing an extensive search of the current literature.

Table I. Overview of genetic polymorphisms related to the development of both endometriosis and CVD, as confirmed by gene association studies and/or GWAS.

| dbSNP ID | Endometriosis and CVD-associated gene | Function | (Refs.) |
|---|---|---|---|
| rs1570360 | *VEGF* | A signaling protein involved in both vasculogenesis and angiogenesis | (108,109) |
| rs3025039 | *VEGF* | A signaling protein involved in both vascularization and angiogenesis | (108,111) |
| rs1800796 | *IL-6* | A pro-inflammatory cytokine; stimulator of osteoclast formation | (114,115) |
| rs1800871 | *IL-10* | An anti-inflammatory cytokine; inhibitor of Th1 differentiation | (116,118) |
| rs11556213 | *IL-16* | A T-cell proinflammatory cytokine; a chemoattractant factor | (9,119) |
| rs9340799 | *ESR1* | A nuclear receptor activated by the sex hormone estrogen | (112,113) |
| rs1801133 | *MTHFR* | A key regulatory enzyme in folate and homocysteine metabolism | (120,121) |
| rs507666 | *ABO* | Blood group determined by the presence of A and B antigens on the surface of the red blood cells | (124,125) |
| rs1042522 | *TP53* | A nuclear phosphoprotein; a tumor suppressor factor | (126,180) |
| rs2812378 | *CCL21* | A cytokine that mediating homing of lymphocytes to secondary lymphoid organs | (122,123) |

CVD, cardiovascular disease; VEGF, vascular endothelial growth factor; IL, interleukin; ESR1, estrogen receptor 1; MTHFR, methylenetetrahydrofolate reductase; CCL21, C-C motif chemokine ligand 21.

The results of the literature research revealed that the *VEGF* rs1570360 and rs3025039 SNPs (107-111), *ESR1* (or *ER-alpha*) rs9340799 (112,113), *IL-6* rs1800796 (114,115), *IL-10* rs1800871 (116-118), *IL-16* rs11556213 (9,16,119), 5,10 methylenetetrahydrofolate reductase (*MTHFR*) rs1801133 (Ala222Val) (120,121), C-C motif chemokine ligand 21 (*CCL21*) rs2812378 (122,123), rs507666 at *ABO*/9q34.2 (124,125) and tumor protein p53 (*TP53*) rs1042522 (126,127) are associated with both diseases under investigation (Table I).

Of note, rs10757272 of *CDKN2B* and rs1333049 of *ANRIL* (128,129), rs10965235 in *CDKN2BAS* (130,131) and rs7865618 in *CDKN2B-AS1* (41,132,133) have also been reported to be associated with both diseases. Moreover, various miRs have been found to be associated with the development of both conditions, including *miR-146a* (rs2920164) and *miR-499* (rs3746444) (134,135), *miR-27a* (rs895819) (136,137), *miR-331* located on 12q22 (44,138), *miR-214* located on 1q24.3 (44,139), *miR-3120* located also on 1q24.3 (44,140), *miR-143* (rs41291957) (135,141), *miR-143* (rs4705342) (142,143), *miR-145* (141), *miR-23B* and *miR-27B* probably located on 9q22.32, *miR-423* (rs6505162) (137,144) and *miR-196a2* (rs11614913) (145,146) (Table II).

With a closer look at these common genetic findings, one can easily conclude that they can be grouped into three major gene groups, representing inflammation and immunity, angiogenesis and cell proliferation and, finally, the group of ncRNAs (either miRs or lncRNAs) that influence several biological pathways by transcriptional and post-transcriptional regulation, cross-linking all the above pathways in one way or another (9,147-150). As it is widely acknowledged that endometriosis is a multifactorial condition involving hormonal, pro-inflammatory, pro-angiogenic, immunological and genetic processes that have been previously extensively reviewed (8,9,106), in the following section, the present review describes in further detail the influence of this common genetic background in the context of possible risk prediction for both diseases and putative implications in therapeutic management, which is the ultimate task in every genetic analysis.

## 6. Current knowledge of biological mechanisms involving the shared genetic loci

VEGF is encoded by the human *VEGF* gene located on chromosome 6p21.3 and it serves as a powerful regulator of angiogenesis, while is also associated with endothelial cell dysfunction. The rs1570360 (-1154G/A) SNP in the promoter region, which is located within a transcription factor binding site (*TFBS*), has been shown to be associated with both coronary heart disease (CHD) (109,151) and endometriosis (152). The rs1570360 SNP in the promoter region, located at -1,154 bp from the transcriptional start site of the *VEGF* gene, has been found to be associated with a number of disease conditions in humans. Of note, the G allele creates four unique potential TFBS, while the A allele creates six potential TFBS (153). VEGF functions as a pro-inflammatory cytokine, strongly induced by hypoxia, representing a potent endothelial cell-specific angiogenic factor (154). Several polymorphisms within the *VEGF* gene have been found to be associated with

Table II. Overview of genetic polymorphisms in non-coding RNAs related to the development of both endometriosis and CVD.

| SNP | Annotation | Chromosome | (Refs.) |
|---|---|---|---|
| rs2910164 | *miR-146A* | 5 | (22,135) |
| rs3746444 | *miR-499A* | 20 | (22,135) |
| rs895819 | *miR-27A* | 19 | (136,137) |
| rs41291957 | *carmn* | 5 | (135,201) |
| | *miR-143*, | | |
| | *miR-145* | | |
| rs4705342 | *carmn* | 5 | |
| | *miR-143* | | (135,142,143) |
| rs6505162 | *miR-423* | 17 | (136,137,144) |
| rs11614913 | *miR-196A2* | 12 | (145,146) |
| | *miR-214* | 1 | (44,139,140,224) |
| | *miR-3120* | | |
| | *miR-331* | 12q22 | (44,138) |
| rs10757272 | *cdkn2b* | 9p21 | (129,190) |
| rs1333049 | *cdkn2b* | 9p21 | (128,129) |
| rs10965235 | *cdkn2bas* | 9p21 | (131,191) |
| rs7865618 | *cdkn2bas* | 9p21 | (41,132) |

CVD, cardiovascular disease; SNP, single nucleotide polymorphism.

alterations in the production of VEGF protein and an increased susceptibility to several disorders, where angiogenesis plays a critical role in their pathogenesis (155,156). Considering that angiogenesis is involved in the development of endometriosis, VEGF substantially promotes neovascularization, which contributes to the implantation of endometrial cells in ectopic sites (157); thus, it can be hypothesized that alterations in VEGF production may be crucial regarding the initiation of endometriosis. Furthermore, both rs1570360 and rs3025039 SNPs have been shown to be associated with altered expression levels of *VEGF* in CHD, and for this reason, they were considered to be ideal candidate genetic biomarkers of this disease (158).

Cytokines modify immune responses and contribute to the maintenance of the balance between pro-inflammatory and anti-inflammatory stimuli in the process of CVD. The *IL-6* gene, located on chromosome 7p21, encodes a multifunctional pro-inflammatory cytokine and represents a physiological link between the endocrine and the immune systems. An association of the *IL-6* promoter region rs1800796 (-634C/G) SNP with the increased susceptibility to both CAD and endometriosis has been reported (114,115). This SNP influences *IL-6* transcription rates *in vitro* and basal *IL-6* levels *in vivo* (159), while elevated levels of IL-6 were assessed in both peritoneal fluid and serum of women with endometriosis (130). Similarly, Lu *et al* (115) reported that the G allele of this SNP may influence the expression of the *IL-6* gene, given that bioinformatics analysis revealed that it is located in a potential transcription factor binding site. It was suggested that this SNP predisposes to CAD, considering that *IL-6* is expressed at relatively high levels in human atherosclerotic plaques (160).

IL-10, produced by Th2 cells and macrophages, is an immunomodulatory, anti-inflammatory cytokine, involved in the ongoing coronary inflammation and may inhibit the activation and function of T-cells, macrophages and monocytes (161). The human *IL-10* gene maps to chromosome 1q31-32. It has been demonstrated that *IL-10* promoter polymorphisms are associated with the production of anti-CA II antibody in patients with endometriosis (162). Previous research on women with endometriosis has demonstrated that allele C of rs1800871 SNP is associated with a 2-fold reduced risk of developing the disease compared with the common TT genotype, while the C allele is associated with higher levels of IL-10 compared with the T allele in women suffering from this condition (163). Furthermore, a significant increase in the IL-10 serum level in patients with CVD has been previously reported (164).

The *IL-16* gene, located at chromosome 15q26.3, is translated into a 631 amino acid precursor protein (165). The IL-16 protein is a T-cell proinflammatory and immunoregulatory cytokine, a chemoattractant factor that is secreted by $CD8^+$ T-lymphocytes, mast cells and B-cells (166). The binding of IL-16 has been found to stimulate monocytes to secrete a series of cytokines, including IL-1β, IL-6 and TNF-α (166). The *IL-16* rs11556218 G/T SNP is located in the exon 6 region of the *IL-16* gene and corresponds to a missense mutation, wherein asparagine is substituted by lysine. This SNP is significantly associated with the risk of both CAD and endometriosis (9,119). The G allele has been found to be strongly associated with the risk of developing CAD in the Chinese population (119). Although IL-16 is closely associated with $CD4^+$ lymphocyte-mediated immunity, with $CD4^+$ T-lymphocytes being closely associated with atherosclerosis, the functions of the *IL-16* gene polymorphism and rs11556218 warrant further clarification regarding their involvement in atherosclerosis and CAD (119). In a recent study conducted by the authors, it was found that rs11556218 was associated with endometriosis in Greek women (9). In particular, allele 'G' of rs11556218 was found to be associated with an increased susceptibility of developing endometriosis. In an attempt to clarify the functional role of this SNP, the authors previously performed a bioinformatics analysis by constructing 3D models and it w concluded that this SNP may result in the aberrant expression of *IL-16*, thus indicating a possible association between the mutation and functional modification of Pro-IL-16 (9). Of note, a previous study demonstrated that the level of IL-16 was found to be elevated in the peritoneal fluid and serum of women with endometriosis but, due to the small number of subjects analyzed, this finding has to be validated in larger studies (167).

The *MTHFR* gene encodes a key regulatory enzyme in folate and homocysteine metabolism, which catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (168). The rs1801133 (Ala222Val) SNP, located in exon 4 of the *MTHFR* gene, has been shown to be significantly associated with endometriosis-associated infertility (121). Thus, it was hypothesized that the dietary folate requirements in women can be modulated by estrogen levels, thus modulating the production of MTHFR. Of note, the variant T allele of the rs1801133 SNP (677C>T polymorphism) has been found to be associated with an increased risk of developing CAD and abnormal lipid levels (120). In particular, this allele was shown

to be associated with elevated levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C). Furthermore, it has been widely reported that the rs1801133 SNP 'T' allele results in elevated plasma homocysteine levels, which has been considered as a CAD risk factor with oxidative stress, endothelial injury and vascular inflammation being involved in the underlying mechanisms in which homocysteine causes CAD (120,169).

The *CCL21* gene, one of several Cys-Cys cytokine genes located on the short arm of chromosome 9, encodes a chemokine that is involved in homing lymphocytes to secondary lymphoid organs. Its function refers to the recruitment of CCR7-expressing lymphocytes and dendritic cells to secondary lymphoid tissues (170). Notably, both CVD and endometriosis are associated with variants of the *CCL21* gene (117,122,123). Angiogenesis, which is dependent on endothelial cell activation, migration and proliferation, is involved in the development of CVD and CCL21 appears to play a pivotal role in the pathophysiological mechanism of these diseases (171). Notably, it has been suggested that CCL21, as well as its receptor, CCR7, may possibly play a role in the development of atherosclerosis through the recruitment of T-cells and macrophages to the atherosclerotic lesions, by mediating inflammatory responses in these cells (172). The role of CCL21 protein in the development of endometriosis remains unknown, although a shift toward a Th1 response may contribute to the increased cytokine/inflammatory profile observed in this condition (173).

Estrogen exerts its effects on tissues upon binding (with high affinity) to and activating estrogen receptors (ERs). ERs are steroid nuclear ligands that are involved in the regulation of the transcription of the estrogen-responsive genes (113). Apart from the initial thoughts that estrogens are hormones involved in female reproduction, it has been found that they are also involved in lipid homeostasis, vascular tissue repair, insulin signaling and CVD (174,175). The e*ESR1* gene, considered the primary receptor for estrogen, is located on chromosome 6q25.1 and consists of eight exons separated by seven introns. The rs9340799 SNP, which is an *Xba*I restriction site polymorphism involving an A-to-G transition in intron-1, has been found in previous studies to increase the risk of developing both CVD and endometriosis (112,113). It has been suggested that the A to G transition of rs9340799 may alter transcription, thus exerting its effect on the gene expression levels as well as ER-related molecular mechanisms (176). In particular, a decreased number of ERs may result in less effective estrogen signaling and, as a consequence, may indirectly influence molecular signaling mechanisms that are related to risk factors for CVD (113). Moreover, numerous studies have shown an association between G allele of rs9340799 SNP and at least one risk factor for CVD, while the GG genotype was reported to increase the risk of developing endometriosis 4-fold (177,178).

The *TP53* gene at 17p13.1 codes for the TP53 nuclear phosphoprotein, a transcription factor that is involved in programmed cell death (apoptosis), cell cycle regulation, angiogenesis and DNA repair, thus playing a crucial role as a tumor suppressor that protects the genome from damage (179). rs1042522 is a functional polymorphism of the *TP53* gene, located within exon 4 (codon 72), leading to the substitution of proline (CCC) to arginine (CGC); it has been reported to be implicated in susceptibility to several clinical diseases, including CAD and endometriosis (126,180). Of note, the arginine allele has been shown to be associated with a greater apoptotic function than proline, which itself appears to be associated more with inflammation and activation of the transcription process (181). In accordance with this finding, it was shown that arginine stimulates apoptosis at least 5-fold more effectively than proline through its better localization of the mitochondria (182).

The ABO blood group is determined by the presence of A and B antigens on the surface of the red blood cells with the frequency of the common ABO phenotypes varying among different populations, probably due to evolutionary selection (183). ABO blood groups have been shown to be associated with various disease phenotypes, including cardiometabolic diseases (184). rs507666 at *ABO*/9q34.2, located within intron 1, has been previously shown to be associated with CVD and, recently, with endometriosis as well (124,141). Various studies have shown that the ABO glycotransferase may result in the development of atherosclerotic CVD by a broader mechanism than simply modulating thrombosis (141). The study by Pare *et al* (185) demonstrated that rs507666, which represents a perfect tag for ABO blood group A1, was associated with decreased levels of circulating soluble ICAM-1 (sICAM-1) when compared to the O allele. Moreover, in a previous meta-analysis, it was found that heterozygotes, as well homozygotes for the minor allele of rs507666 had lower plasma levels of sICAM-1, soluble P-selectin (sP-selectin) and soluble E-selectin (sE-selectin) (186).

Since the first GWAS on CAD, the chr9p21 risk locus has emerged as a top signal in GWAS of atherosclerotic CVD and was shown to increase susceptibility to CAD in carriers of certain alleles of SNPs located within this locus (26,187). This locus codes for an antisense RNA (CDKN2B-AS1 or ANRIL), which is located close to the *CDKN2A-CDKN2B* gene cluster (188). Both the *CDKN2A* and *CDKN2B* genes have been reported to be significantly associated with an increased risk of CAD (26). Thus, rs10757272 of *CDKN2B*, as well as the rs10965235 of *ANRIL* were found to be associated with CAD (189), while rs1333049 of *ANRIL* has been found to be associated with myocardial infarction (128,131,190). Notably, all the aforementioned SNPs have been associated with endometriosis as well (129,191). It has been reported that the majority of genetic variants associated with CAD are located within intronic and flanking sequences of *ANRIL*, which is involved in the regulation of both *CDKN2A* and *CDKN2B* genes (189). This locus mediates its risk at the vessel wall, given that the repression of these genes causes SMC proliferation, which appears at the coronary artery wall during the initial stages of atherosclerosis (192). In this framework, it has also been reported that the genotype of individuals determines the production of atherogenic (linear) over anti-atherogenic *ANRIL* RNA species (circular), thus pointing to the functional role of *ANRIL* regulation in CAD (131). However, the molecular mechanisms through which the genotype of this locus controls the ratio of linear and circular ANRIL are currently unclear (131).

A wide repertoire of miRs have been implicated in vascular pathologies (174). The bicistronic miR-143/145 cluster has been reported to play a role in vessel development and

vascular diseases, including atherosclerosis and pulmonary hypertension, mainly affecting the proliferation of VSMCs and ECs (193-200). Along with these biological properties, a prognostic value in human CVD, of a *miR-143/145* SNP was recently identified as significant, namely, rs41291957. This VSMC-specific miR-SNP-rs41291957 affects *miR-143* and *miR-145* expression and is linked to disease progression in patients with stable CAD (201).

Nimi-Hoveidi *et al* (202) genotyped *miR-143* rs41291957 and rs4705342 SNPs in infertile women with endometriosis and matched healthy subjects. They reported an association between the C allele of rs4705342 and an increased risk of endometriosis. In addition, the A allele of rs41291957 polymorphism was found to be associated with susceptibility to endometriosis (202); the expression level of *miR-145* has also been found to be significantly upregulated in stage I or II of endometriosis (203). Although the exact mechanisms through which miR-143/miR-145 affect endometrial tissue have not yet been fully elucidated, it can hypothesized that their regulatory role in VSMCs and cell proliferation/differentiation is a key mechanism, thus making sense of the common molecular pathways of angiogenesis/cell proliferation between endometriosis and CVD. Cardiac mesoderm enhancer-associated non-coding RNA (CARMN) is a lncRNA implicated in cardiac differentiation (204,205). The initial transcript contains *miR-143/145* cluster, which are considered miRs as regulators of SMC differentiation (86,193,194,197,206,207). In this manner, CARMN maintains VSMC contractile phenotype by directly binding to myocardin (MYOCD) and potentiating MYOCD functions, representing a potential therapeutic target for diseases encompass SMC proliferation (208).

The *miR-146* family has been implicated by recent studies in the innate immune response and immune-mediated diseases like infection (209,210), CVD (211,212) and cancer (213-215). *miR-146b* regulates critical cellular functions, such as cell death (216) and autophagy (217) and its expression significantly upregulated in peritoneal fluid and serum samples of patients with endometriosis. The majority of *miR-146b* targets that have been identified are key regulators of macrophage functions. miR-146b inhibits IL-1 receptor-associated kinase 1 (*IRAK1*) and TNF receptor-associated factor 6 (*TRAF6*) expression by binding to the 3′UTR of *IRAK1* or *TRAF6*, suppressing the TLR-mediated pathway (218).

rs11614913 in *miR-196A2* has been shown to be associated with the development and progression of endometriosis. Genetic variations with a role in ribosome biogenesis that have been assigned to the risk allele, appear to be mediated by regulating the expression of multiple small nucleolar RNAs (snoRNAs) and ribosomal proteins (RPs) and these snoRNAs and RPs are upregulated in endometriotic lesions and thus active ribosome biogenesis in cell nucleoli drives endometriosis (145). The same SNP, rs11614913, in *miR-196a2* has been reported as genetic risk factor of newly developed CAD, but not with its complications such as in-stent coronary restenosis (146). Taking account that stent restenosis involves VSMC proliferation, it can be hypothesized that the *miR-196a2 C/T* rs11614913 SNP interferes with cell cycle progression and the proliferation of cell types differential to VSMCs, such as ECs (promoting neo-angiogenesis) and/or immune cells.

The significant associations of rs895819 in *miR-27A* and rs6505162 in *miR-423* have been recently reported in endometriosis (137). Of note, the *pre-miR-27a* rs895819 polymorphism is associated with myocardial infarction susceptibility in the Chinese Han population (136) with a possible mechanism being its unique role in EC dysfunction (219) and the promotion of angiogenesis (220). On the other hand, the polymorphism rs6505162 C>A is located in pre-*miR-423* region, and it has been reported to promote the expression of mature mir-423 (221). The *miR-423* C>A gene variation has been reported to be associated with susceptibility to CAD (144) and *miR-423* heterozygosity or A/C genotype have been shown to be associated with an increased susceptibility to CAD in the Indian population (143). When *miR-423* is overexpressed, it inhibits the translation of O-GlcNAc transferase (OGT) and catalyzes the addition of O-GlcNAc to proteins and is required for cell division and embryogenesis in cardiomyocyte (222) mRNA, which promotes the apoptosis of cardiomyocytes (223).

Diverse and complex roles of *miR-214* have been described, such as an oncogene, tumor suppressor, protector against $Ca^{2+}$ overload and oxidative damage, mediator of angiogenesis and pathological fibrosis and, as a regulator of osteogenesis, myogenesis and cellular immunity through a vast repertoire of targets, influencing multiple cellular functions and oftentimes contrasting roles, are attributed to particular targets (224). Nevertheless, it is evident that *miR-214* can regulate several aspects of major signaling pathways via the post-transcriptional modifications of critical genes in the immunity/inflammation pathway, cell survival and cell proliferation pathway, including angiogenesis. The implication of this locus in endometriosis, along with the reported functions in CVD (139), may aid in the understanding of how CVD and endometriosis share common genetic pathways that can be translated in common molecular pathways in the pathogenesis of both diseases.

## 7. Conclusions and future perspectives

Based on the aforementioned data, a clear identification of a link between endometriosis and lifelong CVD would necessitate a radical shift in public health management. Although endometriosis remains an enigmatic disease and little is understood about the main causes of the disease, it has been associated with various diseases, including CVD, thus suggesting that women with endometriosis may represent a high-risk group for CVD. Of note, Taskin *et al* (225) pointed out that endometriosis should be considered as a risk factor for CVD, thus requiring specific counseling and prevention. Key questions that arise from these studies refer to whether gynecologists have to recommend women with endometriosis for a cardiology assessment, as well as the possibility of these findings leading to substantial changes in treatment options. However, it should not be under-recognized that other known risk factors for CVD in women, such as diabetes, LDL-C levels, obesity and hypertension, may have a larger combined effect on the risk of CVD compared to endometriosis alone. Evidently, an in-depth understanding of the association between these conditions may enrich the existing knowledge and may provide new insight into the chronic consequences

of endometriosis. Furthermore, given the high prevalence of endometriosis, the development of preventive and early detection guidelines for CVD for women with endometriosis may prove beneficial for public health (226).

Advances in cardiovascular genetics prompted the American Heart Association (AHA) to publish a very recent Scientific Statement for the incorporation of polygenic risk scores to the management of five cardiometabolic diseases (coronary artery disease, hypercholesterolemia, type 2 diabetes, atrial fibrillation, and venous thromboembolic disease) (227). This report summarizes the dogma for the CVD as a multifactorial and complex one. Despite advancements being made, risk prediction remains imprecise with persistently high rates of incident CVD. Currently, such scores are often used in research, one field being the study the inter-relationship between the risk of CAD and other phenotypes. In an attempt to unravel the mechanisms underlying the risk association between endometriosis and CVD, various possible explanations can be suggested. Thus, it can be hypothesized that endometriosis may cause chronic inflammation, considering that inflammation is the precursor to a number of different disease pathologies, including CVD. To this end, various markers of endothelial function (including common carotid intima-media thickness) can be useful for an evaluation of a preclinical and subclinical risk of atherosclerosis in women with endometriosis, not only in the peritoneal cavity, but also at a systemic level (10). Notably, a higher risk of CHD has been observed among women who have had a hysterectomy/oophorectomy than in those who have not undergone this surgical procedure and, as a consequence, this fact has to be taken into account before a decision for this invasive treatment (15). The data presented herein provide evidence of various genetic factors that are shared between endometriosis and CVD, thus demonstrating apparent genetic links between these conditions. Noteworthy, it is beneficial for clinicians to be aware of the possibility of a co-occurrence of these diseases in order to provide suitable medication to women with endometriosis. Given the existing link between endometriosis and early menopause (228), hormone replacement therapy during perimenopause has shown that estrogen therapy is cardioprotective (229). However, although estrogens have been found to be generally cardioprotective in women with early atherogenesis, it has been reported that it is potentially harmful in women with established atherosclerosis (230). In addition, the common treatment of endometriosis by the inhibition of the production of prostaglandins (using drugs such as ibuprofen or naproxen) in an attempt to significantly reduce the symptoms of disease should be avoided, considering that these can lead to an increased cardiovascular risk as an undesirable secondary effect (231).

Future research should attempt to fully unravel the shared molecular pathways underpinning the association between endometriosis and CVD, thus allowing physicians to develop and customize novel therapeutic interventions based on an individual's molecular and clinical profiles.

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VMV, MIZ, EE and GNG designed the present study and drafted the manuscript. GNG, MIZ, DV, LP, DAS and DC searched the literature. DC, EE, DV, DC, LP, MIZ and VMV analyzed and organized the data to be included in the review. DAS, DV, LP and DC critically revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

**Ethics approval and consent to participate**

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**Patient consent for publication**

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**Competing interests**

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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