Exploring the Link between Chronic Inflammation and Atherosclerosis-Endometriosis Association

Anastasia V. Poznyak [1,*], Vasily N. Sukhorukov [2], Igor A. Sobenin [2], Vladimir P Ofitserov [3], Alexander L Golovyuk [4], Dmitriy Yu Serdyukov [5], Anton Y. Postnov [2], Alexander N. Orekhov [2,*]

Abstract

Background: Atherosclerotic cardiovascular disease (ASCVD) and endometriosis are both inflammatory diseases with significant implications for clinical practice and public health. Evidence Acquisition: To examine the clinical question regarding the relationship between ASCVD and endometriosis, we gathered data from various sources, including research studies and subsequent reference searches of retrieved articles. Our research strategies focused on identifying high-quality evidence through comprehensive study time periods and rigorous methods for quality assessment and article inclusion. Results: Our review of the literature reveals significant findings regarding the interplay between ASCVD and endometriosis. Both conditions share inflammation as a key factor in their pathophysiology. Inflammation not only contributes to the initiation and progression of vascular damage in ASCVD but also plays a role in the development and persistence of endometriosis. Women with endometriosis demonstrate higher levels of inflammatory markers and endothelial activation. Conclusions: Based on the available evidence, we conclude that there is a likely genetic link between ASCVD and the development of endometriosis. Additionally, the influence of estrogen on ASCVD varies depending on the stage of atherosclerosis. While estrogen may be protective in women with early artery blockages, it can pose a potential risk to those with established atherosclerosis. Clinicians should consider these factors when managing patients with ASCVD and endometriosis to optimize care.

Keywords: Curcumin; Natural compound; Phytotherapy; Atherosclerosis; Cardiovascular disease.

Introduction

Endometriosis is a prevalent and chronic non-malignant gynecological condition where tissue similar to the lining of the uterus is found outside the uterine cavity. Due to the fact that many cases of endometriosis in combination with other pathologies have been identified, interest in its study has grown greatly. For example, based on common pathogenetic features, one of the recent studies studied the possible coexistence of cardiovascular diseases in patients with endometriosis (Smolarz et al., 2021).

Although endometriosis was first discovered over a century ago, there is still a lack of comprehensive understanding regarding its underlying causes and mechanisms. The widely accepted theory is Sampson's theory of retrograde menstruation, which suggests that menstrual blood flows backward into the pelvis, leading to the development of endometrial tissue outside the uterus. However, successful implantation and growth of this misplaced tissue in

---

Significance | Understanding shared inflammation mechanisms in atherosclerosis and endometriosis informs innovative interdisciplinary treatments, enhancing patient care and outcomes comprehensively.

*Correspondence.

Anastasia V. Poznyak, Institute for Atherosclerosis Research, Osennyaya 4-1-207, 121609 Moscow, Russia; And Alexander N. Orekhov, Laboratory of Cellular and Molecular Pathology of Cardiovascular System, Federal State Budgetary Scientific Institution «Petrovsky National Research Centre of Surgery» (FSBSI "Petrovsky NRCS"), Abrikosovsky per., 2, Moscow, 119991, Russia. E-mail: tehhy_85@mail.ru, alexandernikolaevichorekhov@gmail.com

ectopic areas require additional changes in various biological processes, particularly the creation of a more immunotolerant peritoneal environment (Gruber and Mechsner, 2021).

Currently, endometriosis is regarded as a complex condition influenced by multiple factors, including hormones, immune responses, anatomy, genetics, and the environment. For many years, studies have been conducted on the immunological/inflammatory features of endometriosis (Laganà et al., 2019).

In the context of endometriosis, several key factors contribute to its initiation, maintenance, and progression. These factors include the degradation of the main extracellular matrix, resistance to apoptosis, and the promotion of neoangiogenesis (Hogg et al., 2020).

Peritoneal macrophages have been identified as significant contributors in these processes. As the main producers of cytokines and growth factors, they play a crucial role in promoting the ectopic growth of endometrial tissue fragments that have survived phagocytosis. Additionally, the reduced phagocytic capacity of macrophages and the absorption of their own residues further contribute to this process (Wilke et al., 2011).

Moreover, certain mediators released by macrophages attract additional inflammatory immune cells, such as neutrophils, type 17 T helper cells, and regulatory T cells. This influx of immune cells exacerbates the already excessive inflammatory microenvironment associated with endometriosis (Kokot et al., 2021).

It is important to note that endometriosis is not limited solely to the abdominal cavity, as it is associated with a state of systemic subclinical inflammation. This is supported by the elevated levels of serum cytokines and biomarkers, including C-reactive protein and carbohydrate antigen 125. Based on extensive research, endometriosis is now recognized as a chronic systemic inflammatory disease. At the same time, local inflammation is considered the main cause of pelvic pain and infertility (Kokot et al., 2021).

The main component of inflammation that is associated with endometriosis is an increased oxidative process. Possibly, retrograde menstruation transfers a number of well-known inducers of oxidative stress into the abdominal cavity: erythrocytes, endometrial apoptotic tissue and cellular debris (in addition to pelvic macrophages). Also, pro-oxidant and pro-inflammatory substances are hemoglobin and its toxic products: iron and heme. The production of reactive oxygen species in the abdominal cavity may be involved in inflammation, which is associated with endometriosis, as well as by regulating the expression of numerous inflammatory genes (Rudzitis-Auth et al., 2020).

In this review, we aim to examine the underlying mechanisms responsible for the development of two specific conditions: endometriosis and atherosclerosis. We performed the comprehensive analysis of existing literature to answer the question: what are the shared mechanisms of these two pathologies?

Evidence Acquisition

The search strategy for our study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The primary objective of our search was to investigate the linkage between atherosclerosis and endometriosis, with a focus on chronic inflammation as a common factor between the two pathologies.

Criteria for Eligibility:

1. Study Characteristics: We included articles published from 2018 onwards to ensure the relevance of the research in the contemporary context. No language or publication status restrictions were imposed.

2. Report Characteristics: Studies reporting on the association between atherosclerosis and endometriosis, with an emphasis on chronic inflammation, were considered for eligibility.

Selection Process:

1. Screening: Initially, we conducted a preliminary search utilizing the PubMed database, using the keywords "atherosclerosis" and "endometriosis" in various combinations with the Boolean operator "AND." The search was limited to papers published from 2018 onwards. The search results were imported into a reference management software for further analysis.

2. Eligibility: In the second stage, we expanded our search to include additional sources by incorporating a search in Google Scholar. We introduced the keyword "inflammation," with or without the term "chronic," and combined it with the two initial keywords, "atherosclerosis" and "endometriosis."

Electronic Search Strategy (Example using PubMed):

((atherosclerosis [Title/Abstract]) AND (endometriosis [Title/Abstract])) AND ("2018/01/01"[Date - Publication]: "3000/12/31"[Date - Publication])

The above strategy reflects the combination of the keywords "atherosclerosis" and "endometriosis" and limits the search to articles published from January 1, 2018, to December 31, 3000. The Boolean operator "AND" ensures that both terms are present in the retrieved articles.

Lately, there has been growing attention to the influence of genetic predisposition in the onset of endometriosis. Endometriosis has polygenic inheritance (prevalence in relatives of the first degree from 4 to 9%). Furthermore, a variety of gene polymorphisms have been identified that govern the production of different components,

including estrogen receptors, detoxification enzymes, extracellular matrix remodeling enzymes, cytokines, and immunomodulatory proteins. Simultaneously, it's important to note that certain variations among these options could result in a more unfavorable prognosis and a heightened likelihood of endometriosis recurrence (Vassilopoulou et al., 2019).

Endometriosis: epidemiology, symptoms, diagnosis, and treatment

It has been reported that approximately 10% of women in their reproductive age experience endometriosis. However, the exact figures remain unclear due to historical reliance on laparoscopy as the primary diagnostic method and more recent implementation of multimodal imaging techniques. Consequently, misdiagnosis remains prevalent, often causing significant delays in obtaining a proper diagnosis. Currently, endometriosis is estimated to affect anywhere between 5% to 50% of infertile women, 2% to 11% of asymptomatic women, and 5% to 21% of women experiencing pelvic pain (Muhaidat et al., 2021). The most commonly observed indications and symptoms of endometriosis include dyspareunia, infertility, chronic pelvic pain, and dysmenorrhea. It is worth noting that asymptomatic cases may also occur. In the future, fatigue, decreased labor productivity, high consumption of analgesics, decreased quality of life and depression are observed. Endometriosis, like diabetes, is expensive, the estimated annual cost per patient is 9,579 euros (Missmer et al., 2021). This condition presents various phenotypes that are commonly associated with it. These include ovarian endometriomas, superficial lesions on the peritoneum, deep infiltrating endometriosis, and extragenital manifestations. The extragenital areas affected can involve peripheral nerves, as well as localizations in the rectum, diaphragm, and pleural regions (Guerriero et al., 2020).

The diagnosis of endometriosis remains complex and time-consuming due to its varying degrees of severity, ranging from asymptomatic cases to severe conditions. The typical symptoms of dysmenorrhea, chronic pelvic pain, and dyspareunia are not specific and can overlap with other conditions that impact the urinary and digestive systems (Parasar et al., 2017). Based on the family history of endometriosis, during interviews with patients, key signs of endometriosis can be identified, including the cyclical nature of pelvic pain, a weak reaction or lack of reaction to analgesics, severe primary dysmenorrhea in adolescence and infertility. Physical examination does not exclude endometriosis (Verket et al., 2019). Simultaneously, when examining the pelvic organs and rectum, it is possible to identify areas of infiltration and sensitivity that impact the pelvic cavity, including the vagina, rectovaginal septum, uterosacral ligaments, and Douglas sac, which can be palpated. It is also worth noting that the effectiveness of physical examinations may be higher during menstruation. Non-invasive imaging methods, such as transvaginal ultrasound and magnetic resonance imaging, are considered crucial in the diagnostic process. The diagnosis of endometriosis should rely on thorough examination, visualization, and patient interviews (Riazi et al., 2019). Surgical intervention should be reserved for cases of diagnostic uncertainty and persistent symptoms, even after optimal drug therapy. Presently, available therapeutic options consist of non-hormonal drug treatments (such as nonsteroidal anti-inflammatory drugs) and hormonal methods (including combined oral contraceptives, progestins, and gonadotropin-releasing hormone analogues), as well as surgical interventions (both conservative and definitive) and assisted reproductive technologies for individuals experiencing infertility associated with endometriosis (van Barneveld et al., 2020).

Common Pathogenesis of Chronic Inflammation

ASCVD (atherosclerotic cardiovascular disease) and endometriosis are both inflammatory conditions. Inflammation plays a crucial role in initiating and sustaining vascular damage, as well as in the progression of atherosclerosis, a major underlying process in long-term cardiovascular disease (CVD). Studies have revealed that women diagnosed with endometriosis exhibit significantly higher levels of T-lymphocytes and macrophages expressing interferon-g, a proinflammatory cytokine (Taskin et al., 2019). Also, women with endometriosis have higher markers of endothelial inflammation and activation. In their study, Santanam et al. found that both atherosclerotic plaques and peritoneal fluid of women with endometriosis encompasses a wide array of inflammatory cytokines, chemokines, and growth factors that contribute to the onset of localized inflammation. Furthermore, women with endometriosis face a heightened likelihood of experiencing microvascular dysfunction and atherosclerosis, which poses additional risks (Santanam et al., 2002). Dysregulation of interferon-g production is the main association between endometriosis and atherosclerosis. As a result, women diagnosed with endometriosis face an elevated risk of developing microvascular dysfunction and atherosclerosis (Li et al., 2021). Considering the significant contribution of inflammation, which can be partly reversed, in arterial stiffness progression, incorporating inflammatory markers into the clinical evaluation of cardiovascular risk proves beneficial for women with endometriosis. By combining assessments of arterial stiffness and measuring inflammatory markers, noninvasive early detection of cardiovascular risk can be enhanced. And reducing inflammation can reduce microvascular dysfunction (Mozos et al., 2017). In the management of endometriosis, statins and other cholesterol-lowering medications exhibit positive effects and could potentially serve as a therapeutic intervention for women with this condition. Notably, metformin possesses anti-inflammatory properties, while

also modulating ovarian steroid production and reducing serum cytokine levels. These combined effects make it a potential inhibitor in the progression of endometriosis (Kimber-Trojnar et al., 2022).

An analysis of existing reviews and studies on the efficacy and safety of statins in managing inflammation reveals promising results. Statins have been shown to exert anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and promoting the release of anti-inflammatory mediators. These mechanisms suggest a potential role for statins in reducing inflammation in conditions such as atherosclerosis, rheumatoid arthritis, and even some forms of cancer. However, while some studies have demonstrated positive effects on inflammatory markers and disease progression, the overall clinical benefit of using statins as anti-inflammatory agents remains a topic of debate. Concerns have been raised about the inconsistency of results across studies, potential side effects, and the need for further research to establish clear guidelines for their use in an anti-inflammatory context.

Similarly, the use of metformin as an anti-inflammatory agent has been an area of interest in the medical community. Metformin's anti-inflammatory properties are linked to its ability to modulate various signaling pathways involved in inflammation, such as AMP-activated protein kinase (AMPK) and nuclear factor-kappa B (NF-kB) pathways. Studies have suggested that metformin may have potential benefits in reducing inflammation associated with conditions like diabetes, obesity, and even certain cancers. However, conflicting results have been reported regarding the efficacy of metformin in directly targeting inflammation, with some studies showing modest effects on inflammatory markers while others have not observed significant changes. Additionally, concerns have been raised about the optimal dosages, duration of treatment, and potential side effects associated with using metformin for its anti-inflammatory properties.

Overall, while both statins and metformin show promise as potential therapeutic interventions for managing inflammation in clinical practice, the current evidence is not definitive. Further well-designed clinical trials and meta-analyses are needed to elucidate their true efficacy, optimal dosages, safety profiles, and long-term effects in different patient populations. Additionally, considering the complex nature of inflammation and its role in various diseases, a personalized medicine approach may be necessary to determine which patients are most likely to benefit from anti-inflammatory treatments with statins and metformin. Close monitoring of patients for potential adverse effects and regular reassessment of treatment strategies based on evolving research findings will be crucial in maximizing the benefits of these interventions while minimizing risks.

Genetic Similarities

It is highly likely that there exists a genetic connection between ASCVD (atherosclerotic cardiovascular disease) and the onset of endometriosis. Current research has identified various genes, including those found through Genome-Wide Association Studies (GWAS), Online Mendelian Inheritance in Man (OMIM), and differentially expressed (DEG) genes, that are associated with both endometriosis and ASCVD. These genes are involved in the vital vitamin B metabolic pathway, which plays a crucial role in overall metabolism, genetic and environmental information processing, cellular processes, and human diseases. Notably, endometriosis shares a common genetic pathway with sleep disorders, myocardial infarction, and coronary heart disease. For instance, genetic variants of CDKN2CBAS located on chromosome 9 have been linked to the development of both endometriosis and acute myocardial infarction (Lalami, et al., 2021).

Endothelial Nitric Oxide Synthase (eNOS) Pathway: The eNOS gene (NOS3) encodes the enzyme responsible for producing nitric oxide (NO) in endothelial cells. NO is a vasodilator and anti-inflammatory molecule that plays a central role in maintaining vascular homeostasis. Variants in the NOS3 gene have been associated with endothelial dysfunction and impaired NO production, which can contribute to the development of atherosclerosis. Functional polymorphisms in NOS3 have been linked to increased cardiovascular risk, highlighting the importance of this pathway in vascular health.

Estrogen Receptor (ER) Signaling Pathway: Estrogen exerts its effects through binding to estrogen receptors, particularly ERα (ESR1) and ERβ (ESR2). Polymorphisms in these genes can influence estrogen sensitivity and signaling efficiency in endothelial cells. Genetic variations in ESR1 and ESR2 have been associated with altered endothelial function, inflammation, and atherosclerosis susceptibility. The functional significance lies in the differential responses to estrogen among individuals with distinct genotypes, which can impact cardiovascular outcomes.

Inflammatory Pathways: Inflammation is a key driver of atherosclerosis and endothelial dysfunction. Genetic polymorphisms in genes encoding pro-inflammatory cytokines (e.g., TNF-α, IL-6) and adhesion molecules (e.g., VCAM-1, ICAM-1) can amplify the inflammatory response within the vascular wall. Variants in these genes have been linked to increased risk of atherosclerosis progression and adverse cardiovascular events. The functional significance lies in the dysregulation of inflammatory pathways, promoting endothelial dysfunction and atherogenesis.

Lipid Metabolism Pathways: Dysregulation of lipid metabolism is a hallmark of atherosclerosis. Genetic variations in genes involved in lipid transport and metabolism, such as APOE, PCSK9, and LDLR, have been implicated in the development of atherosclerotic plaques. Mutations in these genes can affect lipid levels, leading to accelerated plaque formation and increased cardiovascular risk.

The functional significance lies in the impact of genetic variants on lipid homeostasis, plaque stability, and atherosclerosis progression. Understanding the genetic pathways involved in estrogen signaling, endothelial dysfunction, and atherosclerosis provides insights into the molecular mechanisms underlying cardiovascular disease susceptibility. Personalized approaches that take into account genetic variations may offer tailored strategies for risk assessment, prevention, and treatment of vascular disorders. Further research into these genetic pathways and their functional significance holds promise for precision medicine interventions targeting the intersection of estrogen-related pathways, endothelial function, and atherosclerosis.

Endometriosis, ASCVD, and MicroRNA Dysfunction

The discovery of microRNAs has opened up new avenues in exploring the connection between ASCVD (atherosclerotic cardiovascular disease) and endometriosis. microRNAs are small RNA molecules that do not code for proteins but play a role in regulating gene expression. They have the ability to influence protein synthesis and regulate the expression of adhesion molecules that are highly present in the cardiovascular system. Abnormal levels of certain microRNAs have been observed in various conditions affecting human reproductive organs and processes, such as endometrioid adenocarcinoma of the endometrium, preeclampsia, ovarian adenocarcinoma, uterine leiomyomas, repeated pregnancy loss, and endometriosis (Bjorkman and Taylor, 2019). By further studying mitochondrial dysfunction, researchers and clinicians may gain deeper insight into the underlying pathophysiology of seemingly unrelated diseases in the future.

MicroRNAs (miRNAs) are increasingly recognized as pivotal regulators of gene expression and are playing important roles in the development of various diseases, including atherosclerosis and endometriosis.

In atherosclerosis, miRNAs have shown promise as potential biomarkers due to their stability in blood and their altered expression patterns in patients with cardiovascular disease. Specific miRNAs, such as miR-21, miR-126, miR-155, and miR-33, have been found to influence processes like inflammation, lipid metabolism, and endothelial dysfunction. Profiling these atherosclerosis-associated miRNAs in blood samples could aid in early disease detection, risk assessment, and monitoring disease progression.

Moreover, miRNAs are also being investigated as therapeutic targets in atherosclerosis. Targeting atherosclerosis-related miRNAs through antimiRs or miRNA mimics represents a novel approach for treating the disease. By modulating the expression of miRNAs such as miR-33 or miR-126, which are involved in crucial pathways associated with atherosclerosis development, we may have the potential to stabilize plaques, reduce inflammation, and

enhance vascular function, therefore providing new avenues for therapy.

When it comes to endometriosis, miRNAs have been implicated in its pathogenesis, a chronic gynecological disorder characterized by the growth of endometrial-like tissue outside the uterus. Dysregulation of specific miRNAs, including members of the miR-200 family, miR-21, and miR-145, has been linked to processes such as cell proliferation, inflammation, and angiogenesis in endometriosis. Detecting altered miRNA expression profiles in endometrial tissues and blood samples could have diagnostic and prognostic value for this condition.

In the realm of endometriosis therapy, manipulating miRNA levels is being explored as a potential therapeutic strategy. By targeting miRNAs known to be oncogenic, like miR-21, or restoring the expression of tumor-suppressive miRNAs such as those in the miR-200 family, we might be able to regulate pathways critical for the development and growth of endometriotic lesions. miRNA-based therapies, including miRNA inhibitors or mimics, may offer novel approaches for managing inflammation, inhibiting angiogenesis, and promoting apoptosis in endometriotic tissues.

In summary, miRNAs have the potential to serve as both biomarkers and therapeutic targets in atherosclerosis and endometriosis. Understanding the roles of miRNAs in disease pathophysiology and leveraging their diagnostic and therapeutic potentials is crucial for improving early detection, risk assessment, and personalized treatment approaches for these complex conditions. Advancing research into disease-specific miRNA signatures and developing miRNA-based therapeutic interventions is essential for advancing precision medicine in the management of atherosclerosis and endometriosis.

Endometriosis and Ovarian Function

Early menopause is a well-known factor that increases the risk of cardiovascular disease (CVD). Studies have revealed that women experiencing menopause at a younger age are more prone to developing clinical cardiovascular conditions. This can be attributed to the decline in estrogen levels during menopause. Estrogen plays a crucial role in maintaining vascular health prior to menopause by enhancing the release of nitric oxide in the arterial endothelium, which promotes vasodilation. Additionally, estrogen inhibits the proliferation of smooth muscle cells and regulates prostaglandin production (Leuzzi et al., 2012). These beneficial effects are mediated by estrogen receptor (ER) isoforms, and reduced levels of ERα as well as ERα polymorphism are associated with increased severity and risk of coronary heart disease. In endometriosis, overexpression of ERβ suppresses ERα activity, resulting in elevated levels of cyclooxygenase-2. The increased cyclooxygenase-2 levels contribute to progesterone resistance, inflammation, hypoxia, oxidative stress, and proliferation of

smooth muscle cells in blood vessels, ultimately leading to endothelial dysfunction and the development of CVD (Eldafira et al., 2021).

Association between Endometriosis and Early Menopause

According to the results of the conducted research, a link between early menopause and endometriosis was revealed. A study conducted in Japan followed 49,927 female nurses aged 25 years and older. The results revealed that women with a history of endometriosis had a higher likelihood of experiencing early menopause, with an odds ratio of 1.32 (95% confidence interval 1.07-1.64) (Thombre Kulkarni et al., 2022). These findings were corroborated by a retrospective study conducted in the United Kingdom involving 5,113 postmenopausal women. Further analysis demonstrated that endometriosis causing infertility was significantly associated with early onset of menopause, even after adjusting for factors such as age, age at menarche, number of pregnancies, body mass index, smoking before menopause, and other causes of infertility (odds ratio 3.06; 95% confidence interval 1.85-5.06). So, it becomes clear that endometriosis, which causes infertility, further increases the risk of early menopause. The impact of endometriosis and related surgeries on ovarian reserve contributes partly to the observed effects (Upson and Missmer, 2020). Studies on hormone replacement therapy (HRT) during perimenopause have shown divergent results in terms of cardioprotection. Some studies suggest that early administration of estrogen therapy in menopausal women reduces the risk of myocardial infarction, heart failure, or mortality (Reslan and Khalil, 2012), without a significant increase in the risk of cancer or venous thrombosis. However, it is important to note that while estrogen may have a cardioprotective effect in women with early atherogenesis, it could be potentially harmful for those with existing atherosclerosis. For women who began HRT within 10 years after menopause, the risk factor for coronary heart disease was estimated to be 0.76 (95% confidence interval, 0.50-1.16), with an absolute excess risk of -6 per 10,000 person-years (Iorga et al., 2017). Subsequent research involving women aged 50 to 59 years within the first 10 years after menopause indicated a trend towards reduced overall mortality with HRT (with or without progestin). Among postmenopausal women without pre-existing cardiovascular diseases, those who started HRT within 6 years after menopause showed significantly slower progression of coronary artery intima thickness compared to those on placebo (Maas et al., 2021). The "time hypothesis" suggests that the cardiovascular effects of HRT depend on individual vascular conditions and the timing of HRT initiation relative to menopause. In the future, the presence of endometriosis in medical history may serve as a factor in screening for atherosclerotic cardiovascular disease (ASCVD) and when considering the initiation of HRT during the menopausal

transition, given its association with an increased risk of ASCVD (Chapron et al., 2022).

The intricate relationship between estrogen signaling, endothelial dysfunction, and atherosclerosis involves complex molecular mechanisms that influence cardiovascular health. Estrogen plays a crucial role in maintaining vascular homeostasis by exerting both genomic and non-genomic effects on endothelial cells. Estrogen receptors, particularly ERα and ERβ, are expressed in endothelial cells and contribute to the regulation of genes involved in vascular tone, inflammation, and oxidative stress. Estrogen promotes the production of nitric oxide (NO) by endothelial nitric oxide synthase (eNOS), leading to vasodilation and inhibition of platelet aggregation and smooth muscle cell proliferation.

However, in conditions of estrogen deficiency, such as menopause or certain endocrine disorders, the protective effects of estrogen on the endothelium are diminished. This imbalance in estrogen signaling can lead to endothelial dysfunction, characterized by reduced NO bioavailability, increased oxidative stress, inflammation, and impaired vascular repair mechanisms. Endothelial dysfunction sets the stage for the initiation and progression of atherosclerosis, a chronic inflammatory disorder of the arteries characterized by the accumulation of lipid-rich plaques. In the context of atherosclerosis, the dysfunctional endothelium becomes more permeable to circulating lipids, particularly low-density lipoprotein (LDL), which infiltrate the arterial wall and undergo modification, triggering an inflammatory response. Inflammatory cytokines and adhesion molecules further promote the recruitment of immune cells, such as macrophages, to the site of lipid deposition. Ultimately, this leads to the formation of atherosclerotic plaques that may progress to unstable lesions prone to rupture, thrombosis, and vascular events like myocardial infarction or stroke.

The interplay between estrogen signaling, endothelial dysfunction, and atherosclerosis underscores the importance of maintaining vascular health through the modulation of hormonal balance, lifestyle factors, and targeted therapies. Strategies aimed at preserving endothelial function, reducing inflammation, and promoting lipid metabolism may offer therapeutic avenues for preventing and managing atherosclerotic cardiovascular disease in populations at risk, especially in the context of altered estrogen signaling dynamics.

Endometriosis and cardiovascular risk factors

Cardiovascular risk factors are becoming more prominent in their correlation with endometriosis (Mu et al., 2016). We proposed the scheme of association between endometriosis and atherosclerosis in Figure 1.

Hypertension

In their research, Mu et al. discovered a strong link between hypertension and endometriosis. They conducted a prospective study involving 116,430 nurses aged 25 to 42 years, observing them for 20 years. Out of the participants, 4244 women were diagnosed with confirmed endometriosis through laparoscopy (Mu et al., 2016; Mu et al., 2017; Marchandot et al., 2022). After adjusting for other factors, the study found that women with endometriosis had a relative risk (RR) of 1.14 (95% confidence interval [CI] 1.09–1.18) for developing hypertension. Conversely, women with arterial hypertension had an RR of 1.29 (95% CI 1.18–1.41) for having laparoscopically confirmed endometriosis. This has led to various hypotheses, with inflammation being a key component in the pathogenesis of hypertension, which is also associated with endometriosis (Marchandot et al., 2022). According to the results of the studies, it also became clear that 30% of the reported cases of association between hypertension and endometriosis were due to the effects of treatment. Namely, an earlier period of surgery and hysterectomy /ovariectomy. It has been established that the risk of hypertensive disorders in women increases due to a decrease in the production of sex hormones or after ovariectomy. It is worth noting that the use of nonsteroidal anti-inflammatory drugs (NSAIDs), which are commonly prescribed to alleviate pelvic pain, has been found to elevate blood pressure and can serve as a significant confounding factor (Blue et al., 2018). In a study conducted by Okoth et al., they observed 56,090 women with endometriosis and compared them to a control group of 223,669 individuals. After adjusting for other variables, they identified an adjusted odds ratio (aOR) of 1.12 (95% CI 1.07–1.17) for hypertension among women with endometriosis. This suggests that endometriosis independently contributes to an increased risk of gestational hypertension and preeclampsia (Okoth et al., 2020).

Dyslipidaemia

Observational studies have provided substantial evidence showcasing a robust association between an elevated atherogenic lipid profile and endometriosis. In particular, these data are described in detail in the work of Mu et al. The focus of this study was on the health of nurses II (NHSII; n = 116,430). The findings revealed a 25% higher risk of hypercholesterolemia in women with endometriosis (95% CI 1.21-1.30), as well as a 22% increased risk of laparoscopically confirmed endometriosis in women with hypercholesterolemia (95% CI 1.15-1.31). Another Nurses' Health Survey conducted in Japan involving 49,927 women (2001-07) confirmed a 30% increase in the likelihood of hypercholesterolemia in women with endometriosis (95% CI 1.15-1.47). It is worth noting that in the course of this work, an adjustment for related factors was not taken into account (Melo et al., 2010; Mu et al., 2017).

In a cross-sectional study conducted by Melo et al., the lipid profile of 120 women was examined, with 40 of them having confirmed endometriosis through laparoscopy. The results indicated elevated levels of total cholesterol, LDL cholesterol, triglycerides, and HDL cholesterol (Mu et al., 2017). In the course of additional studies of the lipid profile in endometriosis, contradictory results were obtained. Tan et al. effectively reviewed the results of nine studies investigating RRS dyslipidemia in women with endometriosis. It is important to approach their findings with caution due to several factors. Firstly, the study included a relatively small sample size of patients. Additionally, there were variations in the parameters measured and the timing of these measurements, which may impact the interpretation of the results (Tan and Almaria, 2018).

In the course of preclinical studies, a change in the lipid profile of blood serum in mice with endometriosis was revealed. The following reports also confirmed that a key role in the pathogenesis of endometriosis is played by impaired metabolism of phospholipids and sphingolipids (Chen et al., 2021). Sphingolipids play crucial roles in various cellular processes such as proliferation, maturation, and apoptosis. In a study by Lee et al., they demonstrated significant alterations in the metabolic flow of sphingolipids in women with endometriosis. The researchers observed increased regulation of specific sphingolipid enzymes (sphingomyelin synthase 1, sphingomyelinase 3, and glucosylceramide synthase) in endometriotic residues. This corresponded to elevated levels of glucosylceramide, decreased levels of sphingomyelin, and reduced apoptosis in the endometrium. Ceramides, which serve as secondary mediators in the apoptotic cascade and precursors for other sphingolipids, were found to be elevated in the peritoneal fluid of infertile women with endometriosis. This causes the formation of reactive oxygen species and leads to cytotoxicity (Lee et al., 2014; Sanvicens and Cotter, 2006). Other studies have also demonstrated the key role of sphingolipids in the pathogenesis of stroke, hypertension, myocardial infarction and diabetes. Thanks to the data obtained, it can be assumed that sphingolipids can function as intermediaries of inter-organ and intercellular communication. Moving forward, it becomes crucial to investigate the involvement of sphingolipids in endometriosis and determine if sphingolipids affected by endometriosis contribute to a systemic pro-inflammatory and pro-oxidant cascade. This cascade, in turn, may lead to dysfunction in various organs, including those related to the cardiovascular system (Alessenko et al., 2018; Borodzicz et al., 2015).

Obesity

Although a correlation has been observed between endometriosis and lower body mass index (BMI), a few limited studies have hinted at the contrary. The clinical manifestation of a low BMI in women with endometriosis can be attributed to significant factors such as the depletion of fat stem cells, anorexigenic effects resulting from
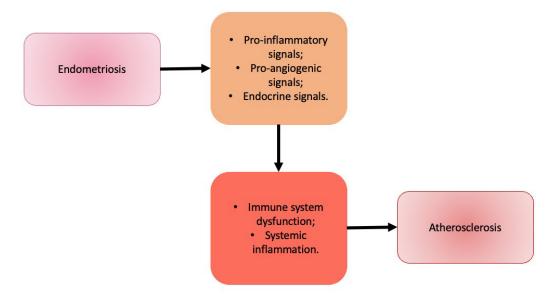
Figure 1. Potential association between endometriosis and atherosclerosis.

alterations in liver gene expression, and the initiation of lipid dysfunction and fat loss (Zolbin et al., 2019; Goetz et al., 2016).

Smoking, air pollution exposure, and diabetes

Although tobacco smoking is widely recognized as a risk factor for coronary heart disease, there is ongoing debate regarding its connection to endometriosis. Also, some studies have suggested that smoking may reduce the risk of endometriosis, but in subsequent studies, the link between endometriosis and tobacco smoking habits has been refuted. Also, the connection between endometriosis and exposure to pollutants remains presumptive. Only one NHSII study did not show an increased risk of endometriosis. as for the effects of air pollution (Helbig et al., 2021). At the moment, there has not been a proven link between diabetes and endometriosis, even despite the potential coincidence of molecular pathways between them. Based on the analysis conducted in NHSII, there was no identified link between laparoscopically confirmed endometriosis and the development of type 2 diabetes, as determined through multivariate analysis. However, there is ongoing controversy regarding the potential risk of gestational diabetes mellitus in women with endometriosis (Farland et al., 2021).

Results

To establish and maintain endometriotic lesions, several cardiovascular drugs were tested on animal models. But despite the fact that the results were promising in animal models, their use in human clinical trials was severely limited.

Statins are recognized for their ability to lower cholesterol levels and their anti-inflammatory effects. In relation to endometriosis, research conducted on human endometriosis stromal cell cultures has demonstrated that statins can influence cell signaling. By undergoing statin therapy, apoptosis (cell death) is increased, while proliferation is reduced. Moreover, the therapy also hampers cell adhesion and mobility, along with diminishing angiogenesis and impeding stromal cell invasion (Taylor et al., 2017). Recent studies have highlighted the significant involvement of platelets in both the overall development of endometriosis and specifically in fibrogenesis. It was found that antiplatelet therapy prevents the progressive development of endometriosis. epithelial-mesenchymal transition, transdifferentiation of fibroblasts into myofibroblasts and metaplasia of smooth muscles (Xiao et al., 2020). Consequently, a reduction in the size of endometriotic lesions and fibrogenesis has been observed. Recently, researchers have suggested the use of low-dose aspirin in preclinical studies as a potential treatment for infertility associated with endometriosis. This is attributed to its ability to combat progesterone resistance.

Moreover, women with endometriosis often experience heightened psychological stress, which contributes to tumor growth and metastasis. In a mouse model, the blockade of Beta-adrenergic receptors effectively eliminated the stimulating effect of chronic stress, leading to the suppression of ADRB2 and CREB activation (Long et al., 2016). As a result, angiogenesis and proliferation were suppressed. Another study demonstrated that perioperative administration of propranolol in a mouse model significantly impeded the growth of intentionally neglected residual endometriotic lesions following the initial operation. Similarly, the use of telmisartan inhibited vascularization, reduced immune cell activity, and hindered the growth of endometriosis-like lesions in mice.

Limitations

One limitation pertains to the predominantly observational nature of the studies included in the analysis. The reliance on observational data may introduce biases and confounding variables that could influence the strength and direction of the reported associations. Additionally, the generalizability of findings from observational studies to broader populations or diverse demographic groups may be limited.

Another constraint to be mindful of is the potential for publication bias within the literature reviewed. Studies with positive findings are more likely to be published, leading to an overrepresentation of significant results in the analysis. This bias could skew the overall interpretation of the relationship between chronic inflammation, endometriosis, and atherosclerosis.

The review may also be constrained by the availability and quality of the studies included. Variability in study methodologies, sample sizes, outcome measures, and reporting standards across the literature could impact the robustness and reliability of the conclusions drawn in the review. Moreover, the potential for heterogeneity among the included studies may limit the ability to perform meta-analyses or draw definitive conclusions.

Furthermore, the review's scope may be constrained by the existing body of literature on the topic. Limited research focusing specifically on the interconnection between chronic inflammation, endometriosis, and atherosclerosis may restrict the depth of analysis and comprehensive understanding of the mechanisms underlying these associations.

Lastly, given the evolving nature of research in this field, the review's findings and conclusions may be subject to change as new studies are published and novel insights emerge. Continued updates and revisions to the review may be necessary to incorporate the latest evidence and address emerging limitations.

Despite these constraints, the review serves as a valuable synthesis of current knowledge on the complex interplay between chronic inflammation, endometriosis, and atherosclerosis, highlighting areas for further investigation and potential clinical applications.

In addition to the limitations already discussed, it is important to acknowledge that the inclusion of studies published only in the last few years may introduce a potential bias towards recent findings, overlooking important earlier research. By favoring more recent studies, the review may inadvertently neglect valuable insights and foundational research that could provide critical context and historical perspective on the link between chronic inflammation, endometriosis, and atherosclerosis.

Conclusion

Atherosclerosis is a multifactorial pathology, and endometriosis is also a complex pathology. Inflammation is a cornerstone of both disorders. In this review, we observed the adherent points of endometriosis and atherosclerosis, which is not limited to inflammation itself, but with numerous associated molecules, mechanisms, and even risk factors. Dysregulation of interferon-g production is the main association between endometriosis and atherosclerosis, that is confirmed by the range of studies. Furthermore, women diagnosed with endometriosis have a higher likelihood of experiencing microvascular dysfunction and developing atherosclerosis.

The main limitation of this study is the fact that this review is narrative, not systematic. Our goal was to overview the broad range of potential connections at different levels. Also, it is worth mentioning, that further studies are needed to understand the details of vascular aspects of endometriosis, and the inflammatory processes underlie the linkage of two pathologies.

Understanding the relationship between endometriosis and an increased risk of microvascular dysfunction and atherosclerosis suggests integrating assessments of arterial stiffness and inflammatory markers in the clinical evaluation of women with endometriosis. This holistic approach can aid in early detection of cardiovascular risk and guide preventive measures.

The review indicates that statins, cholesterol-lowering medications, and metformin could hold promise in managing endometriosis by leveraging their anti-inflammatory properties, hormone modulation effects, and cytokine reduction capabilities. Investigating the efficacy of these medications as therapeutic interventions for endometriosis is a pivotal area for future research. Delving into the genetic connections between atherosclerotic cardiovascular disease and endometriosis offers insights into shared genes and pathways, potentially leading to tailored treatments for individuals with both conditions. Further exploration of common genetic pathways could pave the way for personalized therapeutic strategies.

The role of microRNAs in regulating gene expression and their impact on both endometriosis and atherosclerosis opens new avenues for diagnostic and therapeutic approaches. Understanding how microRNA dysfunction contributes to the pathophysiology of these conditions may unveil novel targeted treatments.

Recognizing the impact of endometriosis on ovarian function and its association with early menopause has implications for hormone replacement therapy (HRT) decisions in women with endometriosis during the menopausal transition. Considering the cardiovascular risks linked to early menopause in individuals with endometriosis can inform treatment choices.

Exploring the links between endometriosis and cardiovascular risk factors like hypertension, dyslipidemia, obesity, and lifestyle factors such as smoking, air pollution exposure, and diabetes provides a comprehensive understanding of the interplay of these factors in the overall health of individuals with endometriosis.

In conclusion, further research probing the mechanisms connecting chronic inflammation, endometriosis, and atherosclerosis is vital for advancing our understanding of these intricate conditions and devising targeted interventions to enhance patient outcomes. An interdisciplinary approach to studying these connections presents opportunities for innovative treatments and comprehensive care strategies. By integrating perspectives and expertise from diverse fields such as cardiology, gynecology, immunology, and molecular biology, researchers can explore the interconnected pathways and mechanisms underlying both diseases. This collaborative approach allows for a more holistic examination of how chronic inflammation, hormonal factors, genetic predispositions, and lifestyle choices contribute to the development and progression of atherosclerosis and endometriosis. By leveraging the insights and methodologies of different disciplines, researchers can uncover novel connections, identify common risk factors, and develop more effective diagnostic tools and treatment strategies that address the complex interplay between these conditions. Embracing an interdisciplinary perspective not only enriches the scientific discourse but also paves the way for innovative research initiatives and personalized healthcare approaches that consider the intricate web of factors influencing the pathogenesis and management of atherosclerosis and endometriosis.

Author contribution

A.V.P. conceptualized, V.N.S., M.A.P., Y.S.C., A.Y.P., A.N.O. wrote, drafted, reviewed, edited, prepared the graph of the article. All authors have read and agreed to the published version of the manuscript.

Competing financial interests
The authors have no conflict of interest.

References

Alessenko, A. V., Lebedev, А. Т., & Kurochkin, I. N. (2018). Rol' sfingolipidov v serdechno-sosudistykh patologiiakh [The role of sphingolipids in cardiovascular pathologies]. Biomeditsinskaia khimiia, 64(6), 487–495. https://doi.org/10.18097/PBMC20186406487

Bjorkman, S., & Taylor, H. S. (2019). MicroRNAs in endometriosis: biological function and emerging biomarker candidates†. Biology of reproduction, 100(5), 1135–1146. https://doi.org/10.1093/biolre/ioz014

Blue, N. R., Murray-Krezan, C., Drake-Lavelle, S., Weinberg, D., Holbrook, B. D., Katukuri, V. R., Leeman, L., & Mozurkewich, E. L. (2018). Effect of ibuprofen vs acetaminophen on postpartum hypertension in preeclampsia with severe features: a double-masked, randomized controlled trial. American journal of obstetrics and gynecology, 218(6), 616.e1–616.e8. https://doi.org/10.1016/j.ajog.2018.02.016

Borodzicz, S., Czarzasta, K., Kuch, M., & Cudnoch-Jedrzejewska, A. (2015). Sphingolipids in cardiovascular diseases and metabolic disorders. Lipids in health and disease, 14, 55. https://doi.org/10.1186/s12944-015-0053-y

Chapron, C., Lafay-Pillet, M. C., Santulli, P., Bourdon, M., Maignien, C., Gaudet-Chardonnet, A., Maitrot-Mantelet, L., Borghese, B., & Marcellin, L. (2022). A new validated screening method for endometriosis diagnosis based on patient questionnaires. EClinicalMedicine, 44, 101263. https://doi.org/10.1016/j.eclinm.2021.101263

Chen, Z., Wang, C., Lin, C., Zhang, L., Zheng, H., Zhou, Y., Li, X., Li, C., Zhang, X., Yang, X., Guan, M., & Xi, Y. (2021). Lipidomic Alterations and PPARα Activation Induced by Resveratrol Lead to Reduction in Lesion Size in Endometriosis Models. Oxidative medicine and cellular longevity, 2021, 9979953. https://doi.org/10.1155/2021/9979953

Eldafira, E., Prasasty, V. D., Abinawanto, A., Syahfirdi, L., & Pujianto, D. A. (2021). Polymorphisms of Estrogen Receptor-α and Estrogen Receptor-β Genes and its Expression in Endometriosis. Turkish journal of pharmaceutical sciences, 18(1), 91–95. https://doi.org/10.4274/tjps.galenos.2019.94914

Farland, L. V., Degnan, W. J., Harris, H. R., Tobias, D. K., & Missmer, S. A. (2021). A prospective study of endometriosis and risk of type 2 diabetes. Diabetologia, 64(3), 552–560. https://doi.org/10.1007/s00125-020-05347-6

Goetz, T. G., Mamillapalli, R., & Taylor, H. S. (2016). Low Body Mass Index in Endometriosis Is Promoted by Hepatic Metabolic Gene Dysregulation in Mice. Biology of reproduction, 95(6), 115. https://doi.org/10.1095/biolreprod.116.142877

Gruber, T. M., & Mechsner, S. (2021). Pathogenesis of Endometriosis: The Origin of Pain and Subfertility. Cells, 10(6), 1381. https://doi.org/10.3390/cells10061381

Guerriero, S., Conway, F., Pascual, M. A., Graupera, B., Ajossa, S., Neri, M., Musa, E., Pedrassani, M., & Alcazar, J. L. (2020). Ultrasonography and Atypical Sites of Endometriosis. Diagnostics (Basel, Switzerland), 10(6), 345. https://doi.org/10.3390/diagnostics10060345

Helbig, M., Vesper, A. S., Beyer, I., & Fehm, T. (2021). Does Nutrition Affect Endometriosis?. Geburtshilfe und Frauenheilkunde, 81(2), 191–199. https://doi.org/10.1055/a-1207-0557

Hogg, C., Horne, A. W., & Greaves, E. (2020). Endometriosis-Associated Macrophages: Origin, Phenotype, and Function. Frontiers in endocrinology, 11, 7. https://doi.org/10.3389/fendo.2020.00007

Iorga, A., Cunningham, C. M., Moazeni, S., Ruffenach, G., Umar, S., & Eghbali, M. (2017). The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. Biology of sex differences, 8(1), 33. https://doi.org/10.1186/s13293-017-0152-8

Kimber-Trojnar, Ż., Dłuski, D. F., Wierzchowska-Opoka, M., Ruszała, M., & Leszczyńska-Gorzelak, B. (2022). Metformin as a Potential Treatment Option for Endometriosis. Cancers, 14(3), 577. https://doi.org/10.3390/cancers14030577

Kokot, I., Piwowar, A., Jędryka, M., Sołkiewicz, K., & Kratz, E. M. (2021). Diagnostic Significance of Selected Serum Inflammatory Markers in Women with Advanced Endometriosis. International journal of molecular sciences, 22(5), 2295. https://doi.org/10.3390/ijms22052295

Laganà, A. S., Garzon, S., Götte, M., Viganò, P., Franchi, M., Ghezzi, F., & Martin, D. C. (2019). The Pathogenesis of Endometriosis: Molecular and Cell Biology Insights. International journal of molecular sciences, 20(22), 5615. https://doi.org/10.3390/ijms20225615

Lalami, I., Abo, C., Borghese, B., Chapron, C., & Vaiman, D. (2021). Genomics of Endometriosis: From Genome Wide Association Studies to Exome Sequencing. International journal of molecular sciences, 22(14), 7297. https://doi.org/10.3390/ijms22147297

Lee, Y. H., Tan, C. W., Venkatratnam, A., Tan, C. S., Cui, L., Loh, S. F., Griffith, L., Tannenbaum, S. R., & Chan, J. K. (2014). Dysregulated sphingolipid metabolism in endometriosis. The Journal of clinical endocrinology and metabolism, 99(10), E1913–E1921. https://doi.org/10.1210/jc.2014-1340

Leuzzi, C., Marzullo, R., & Modena, M. G. (2012). La menopausa è un fattore di rischio per la cardiopatia ischemica? [Is menopause a risk factor for ischemic heart disease in women?]. Giornale italiano di cardiologia (2006), 13(6), 401–406. https://doi.org/10.1714/1073.11757

Li, P. C., Yang, Y. C., Wang, J. H., Lin, S. Z., & Ding, D. C. (2021). Endometriosis Is Associated with an Increased Risk of Coronary Artery Disease in Asian Women. Journal of clinical medicine, 10(18), 4173. https://doi.org/10.3390/jcm10184173

Long, Q., Liu, X., Qi, Q., & Guo, S. W. (2016). Chronic stress accelerates the development of endometriosis in mouse through adrenergic receptor β2. Human reproduction (Oxford, England), 31(11), 2506–2519. https://doi.org/10.1093/humrep/dew237

Maas, A. H. E. M., Rosano, G., Cifkova, R., Chieffo, A., van Dijken, D., Hamoda, H., Kunadian, V., Laan, E., Lambrinoudaki, I., Maclaran, K., Panay, N., Stevenson, J. C., van Trotsenburg, M., & Collins, P. (2021). Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists. European heart journal, 42(10), 967–984. https://doi.org/10.1093/eurheartj/ehaa1044

Marchandot, B., Curtiaud, A., Matsushita, K., Trimaille, A., Host, A., Faller, E., Garbin, O., Akladios, C., Jesel, L., & Morel, O. (2022). Endometriosis and cardiovascular disease. European heart journal open, 2(1), oeac001. https://doi.org/10.1093/ehjopen/oeac001

Melo, A. S., Rosa-e-Silva, J. C., Rosa-e-Silva, A. C., Poli-Neto, O. B., Ferriani, R. A., & Vieira, C. S. (2010). Unfavorable lipid profile in women with endometriosis. Fertility and sterility, 93(7), 2433–2436. https://doi.org/10.1016/j.fertnstert.2009.08.043

Missmer, S. A., Tu, F. F., Agarwal, S. K., Chapron, C., Soliman, A. M., Chiuve, S., Eichner, S., Flores-Caldera, I., Horne, A. W., Kimball, A. B., Laufer, M. R., Leyland, N., Singh, S. S., Taylor, H. S., & As-Sanie, S. (2021). Impact of Endometriosis on Life-Course Potential: A Narrative Review. International journal of general medicine, 14, 9–25. https://doi.org/10.2147/IJGM.S261139

Mozos, I., Malainer, C., Horbańczuk, J., Gug, C., Stoian, D., Luca, C. T., & Atanasov, A. G. (2017). Inflammatory Markers for Arterial Stiffness in Cardiovascular Diseases. Frontiers in immunology, 8, 1058. https://doi.org/10.3389/fimmu.2017.01058

Mu, F., Rich-Edwards, J., Rimm, E. B., Spiegelman, D., & Missmer, S. A. (2016). Endometriosis and Risk of Coronary Heart Disease. Circulation. Cardiovascular quality and outcomes, 9(3), 257–264. https://doi.org/10.1161/CIRCOUTCOMES.115.002224

Mu, F., Rich-Edwards, J., Rimm, E. B., Spiegelman, D., Forman, J. P., & Missmer, S. A. (2017). Association Between Endometriosis and Hypercholesterolemia or Hypertension. Hypertension (Dallas, Tex. : 1979), 70(1), 59–65. https://doi.org/10.1161/HYPERTENSIONAHA.117.09056

Mu, F., Rich-Edwards, J., Rimm, E. B., Spiegelman, D., Forman, J. P., & Missmer, S. A. (2017). Association Between Endometriosis and Hypercholesterolemia or Hypertension. Hypertension (Dallas, Tex. : 1979), 70(1), 59–65. https://doi.org/10.1161/HYPERTENSIONAHA.117.09056

Muhaidat, N., Saleh, S., Fram, K., Nabhan, M., Almahallawi, N., Alryalat, S. A., Elfalah, M., & Elfalah, M. (2021). Prevalence of endometriosis in women undergoing laparoscopic surgery for various gynaecological indications at a Jordanian referral centre: gaining insight into the epidemiology of an important women's health problem. BMC women's health, 21(1), 381. https://doi.org/10.1186/s12905-021-01530-y

Okoth, K., Chandan, J. S., Marshall, T., Thangaratinam, S., Thomas, G. N., Nirantharakumar, K., & Adderley, N. J. (2020). Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review. BMJ (Clinical research ed.), 371, m3502. https://doi.org/10.1136/bmj.m3502

Parasar, P., Ozcan, P., & Terry, K. L. (2017). Endometriosis: Epidemiology, Diagnosis and Clinical Management. Current obstetrics and gynecology reports, 6(1), 34–41. https://doi.org/10.1007/s13669-017-0187-1

Reslan, O. M., & Khalil, R. A. (2012). Vascular effects of estrogenic menopausal hormone therapy. Reviews on recent clinical trials, 7(1), 47–70. https://doi.org/10.2174/157488712799363253

Riazi, H., Tehranian, N., Ziaei, S., Mohammadi, E., Hajizadeh, E., & Montazeri, A. (2015). Clinical diagnosis of pelvic endometriosis: a scoping review. BMC women's health, 15, 39. https://doi.org/10.1186/s12905-015-0196-z

Rudzitis-Auth, J., Huwer, S. I., Scheuer, C., Menger, M. D., & Laschke, M. W. (2022). The ischemic time window of ectopic endometrial tissue crucially determines its ability to develop into endometriotic lesions. Scientific reports, 12(1), 5625. https://doi.org/10.1038/s41598-022-09577-z

Santanam, N., Song, M., Rong, R., Murphy, A. A., & Parthasarathy, S. (2002). Atherosclerosis, oxidation and endometriosis. Free radical research, 36(12), 1315–1321. https://doi.org/10.1080/1071576021000049908

Sanvicens, N., & Cotter, T. G. (2006). Ceramide is the key mediator of oxidative stress-induced apoptosis in retinal photoreceptor cells. Journal of neurochemistry, 98(5), 1432–1444. https://doi.org/10.1111/j.1471-4159.2006.03977.x

Smolarz, B., Szyłło, K., & Romanowicz, H. (2021). Endometriosis: Epidemiology, Classification, Pathogenesis, Treatment and Genetics (Review of Literature). International journal of molecular sciences, 22(19), 10554. https://doi.org/10.3390/ijms221910554

Tan, D. A., & Almaria, M. J. G. (2018). Postmenopausal endometriosis: drawing a clearer clinical picture. Climacteric : the journal of the International Menopause Society, 21(3), 249–255. https://doi.org/10.1080/13697137.2018.1450855

Taskin, O., Rikhraj, K., Tan, J., Sedlak, T., Rowe, T. C., & Bedaiwy, M. A. (2019). Link between Endometriosis, Atherosclerotic Cardiovascular Disease, and the Health of Women Midlife. Journal of minimally invasive gynecology, 26(5), 781–784. https://doi.org/10.1016/j.jmig.2019.02.022

Taylor, H. S., Alderman Iii, M., D'Hooghe, T. M., Fazleabas, A. T., & Duleba, A. J. (2017). Effect of simvastatin on baboon endometriosis. Biology of reproduction, 97(1), 32–38. https://doi.org/10.1093/biolre/iox058

Thombre Kulkarni, M., Shafrir, A., Farland, L. V., Terry, K. L., Whitcomb, B. W., Eliassen, A. H., Bertone-Johnson, E. R., & Missmer, S. A. (2022). Association Between Laparoscopically Confirmed Endometriosis and Risk of Early Natural Menopause. JAMA network open, 5(1), e2144391. https://doi.org/10.1001/jamanetworkopen.2021.44391

Upson, K., & Missmer, S. A. (2020). Epidemiology of Adenomyosis. Seminars in reproductive medicine, 38(2-03), 89–107. https://doi.org/10.1055/s-0040-1718920

van Barneveld, E., Veth, V. B., Sampat, J. M., Schreurs, A. M. F., van Wely, M., Bosmans, J. E., de Bie, B., Jansen, F. W., Klinkert, E. R., Nap, A. W., Mol, B. W. J., Bongers, M. Y., Mijatovic, V., & Maas, J. W. M. (2020). SOMA-trial: surgery or medication for women with an endometrioma? Study protocol for a randomised controlled trial and cohort study. Human reproduction open, 2020(1), hoz046. https://doi.org/10.1093/hropen/hoz046

Vassilopoulou, L., Matalliotakis, M., Zervou, M. I., Matalliotaki, C., Krithinakis, K., Matalliotakis, I., Spandidos, D. A., & Goulielmos, G. N. (2019). Defining the genetic profile of endometriosis. Experimental and therapeutic medicine, 17(5), 3267–3281. https://doi.org/10.3892/etm.2019.7346

Verket, N. J., Falk, R. S., Qvigstad, E., Tanbo, T. G., & Sandvik, L. (2019). Development of a prediction model to aid primary care physicians in early identification of women at high risk of developing endometriosis: cross-sectional study. BMJ open, 9(12), e030346. https://doi.org/10.1136/bmjopen-2019-030346

Wilke, C. M., Bishop, K., Fox, D., & Zou, W. (2011). Deciphering the role of Th17 cells in human disease. Trends in immunology, 32(12), 603–611. https://doi.org/10.1016/j.it.2011.08.003

Xiao, F., Liu, X., & Guo, S. W. (2020). Platelets and Regulatory T Cells May Induce a Type 2 Immunity That Is Conducive to the Progression and Fibrogenesis of Endometriosis. Frontiers in immunology, 11, 610963. https://doi.org/10.3389/fimmu.2020.610963

Zolbin, M. M., Mamillapalli, R., Nematian, S. E., Goetz, T. G., & Taylor, H. S. (2019). Adipocyte alterations in endometriosis: reduced numbers of stem cells and microRNA induced alterations in adipocyte metabolic gene expression. Reproductive biology and endocrinology : RB&E, 17(1), 36. https://doi.org/10.1186/s12958-019-0480-0