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Endometriosis and Cardiovascular Disease: A Systematic Review

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ABSTRACT

Introduction: Endometriosis is a chronic condition characterized by the aberrant distribution of functional tissue outside of the uterus, such as endometrial ducts and stroma. It is dependent on estrogen. Cardiovascular disease may be more prevalent in women who have endometriosis.

Materials/Methods: Using the following keywords: "atherosclerosis," "cardiovascular disease," "cardiovascular risk," "chronic inflammation," "dyslipidaemia," "endometriosis," and "endothelial dysfunction," we searched for publications published between 2017 and 2022. A thorough literature search was conducted using a variety of search engines, such as PubMed, Cochrane, Springer, Science Direct, Nature, and Google Scholar. The literature selection was conducted using the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)..

Results: In women with endometriosis, four studies reported an elevated risk and incidence of cerebrovascular disease and cardiovascular disease. A study reported a substantial increase in the lipid profile value of patients with endometriosis, a known risk factor for the development of atherosclerosis.

Conclusion: Cardiovascular disease is more likely to strike women who have endometriosis.

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INTRODUCTION

Endometrial glands and stroma, which are histological components, proliferate and reside in organs and sites outside the uterus in endometriosis, a chronic gynaecologic disorder. The chief clinical signs of the condition are often infertility and persistent pelvic pain [1]. Endometriosis impacts around 10-15% of women in their reproductive years and is present in 70% of women with persistent pelvic discomfort. The lesions may manifest as peritoneal lesions, superficial implants, ovarian cysts, or deep infiltrating illness [2].

Globally, cardiovascular disease (CVD) is a significant contributor to mortality and impairment [3]. Stratified statistical analysis, focusing on age and sex, has consistently shown a drop in mortality from cardiovascular disease (CVD) among individuals aged 55 years and older. Nevertheless, there has been a deceleration in the decline rate among individuals below the age of 55, specifically among women [4]. It is often observed that women tend to acquire cardiovascular disease approximately ten years later than men.

This phenomenon is thought to be associated with the decline in ovarian hormone levels that occurs with the transition to menopause. Cardiovascular disease impacts both males and females, yet they exhibit distinct risk factors, clinical presentations, therapy, and clinical outcomes. When considering demographic disparities, women had a higher likelihood of dying from cardiovascular disease (20.9%) compared to men (14.9%). Hence, it is imperative to recognize the risk factors and implement preventative actions to combat cardiovascular disease [5,6].

Recent epidemiological studies have established a connection between endometriosis and cardiovascular disease. This connection is based on shared pathogenic mechanisms, including systemic chronic inflammation, heightened oxidative stress, impaired function of the small blood vessels in the heart (coronary microvascular dysfunction), dysfunction of the cells lining the blood vessels (endothelial dysfunction), and an unhealthy lipid profile that promotes the development of fatty deposits in the arteries (atherogenic lipid profile) [7].

A thorough analysis revealed that female patients with endometriosis confirmed laparoscopically are at a markedly higher risk of myocardial infarction, angina proven angiographically, coronary artery bypass graft surgery, coronary angioplasty, or stenting, or any combination of these [8]. This systematic study seeks to examine the association between endometriosis and cardiovascular disease.

MATERIALS/METHODS

Literature Search

Articles published between 2017 and 2022 discussing related topics were searched, with keywords including "atherosclerosis," "cardiovascular disease," "cardiovascular risk," "chronic inflammation," "dyslipidemia," "endometriosis," and "endothelial dysfunction." A literature search was done using many search engines, including Google Scholar, PubMed, Cochrane, Springer, Science Direct, and Nature. After doing a literature search, we examined the papers to determine which ones did not fit the requirements for the systematic review before analyzing the abstract and the full text. The recommended reporting items for systematic review and meta-analysis procedures guidelines (PRISMA-P) were used to guide the selection of publications for this systematic review.

Eligibility Criteria

The following eligibility criteria have to be met to select the appropriate articles to compose the systematic review: (i) experimental, observational, or qualitative studies published between the years 2017 to 2021, (ii) including participants with endometriosis diagnosis, (iii) studying the link between endometriosis and cardiovascular disease, (iv) enrolling women of reproductive age, and (v) published in English. Articles that had poor abstract or article quality were systematic reviews, conference abstracts, and case reports, which only included expert opinion or news information and excluded exclusively presented epidemiological data.

Definition

A laparoscopic visual examination and, ideally, histological confirmation are how endometriosis is identified. Ectopic implantation of functional tissue lining the uterus outside of the uterine cavity is the hallmark of this chronic illness. Heart failure, ischemic heart disease, and cerebrovascular illnesses, including acute ischemia or hemorrhagic stroke, are examples of cardiovascular diseases.

Data Extraction

Data from the research were extracted and recorded in a Microsoft Excel application format. Before data collection, the authors analyzed the titles and abstracts of the retrieved articles to select the appropriate literature. Studies that had titles and abstracts that matched the appropriate topics were then retrieved for a full paper review related to the eligibility criteria for the study. The initial author's name, the year of publication, the number of samples, the age range of the participants, the length of time the data was collected, the location, the study design, and the conclusions of the research findings were among the research data that the authors retrieved.

RESULTS

Two thousand five hundred seventy articles were obtained from the six search engines. Of the 2570 articles, 243 were obtained by screening the title and eliminating duplication of articles. After screening the abstracts, 219 articles were excluded, and 24 were obtained. The 24 articles were subsequently reviewed. Nineteen articles were then excluded. Five articles met the inclusion criteria, as depicted in Fig.1.

Research Characteristics

The combined number of individuals involved in the relevant research was 493,363. The number of participants varied from 643 to 279,579 individuals. Three of the research covered in this review are population-based cohort studies conducted in Taiwan. Research was conducted in the United Kingdom using a population-based cohort study design. Cross-sectional research was conducted in Italy. The age range of the subjects involved in the study was between 16 and 64 years old. The participants were females of childbearing age. The data-gathering period they spanned from 1995 to 2018.

Cardiovascular Disease (CVD) Risk in Women with Endometriosis

All five studies included in this systematic review demonstrated an increased incidence and risk of cardiovascular disease in women with endometriosis [9–13]. A recent research conducted in the UK found that the yearly occurrence of endometriosis has steadily risen

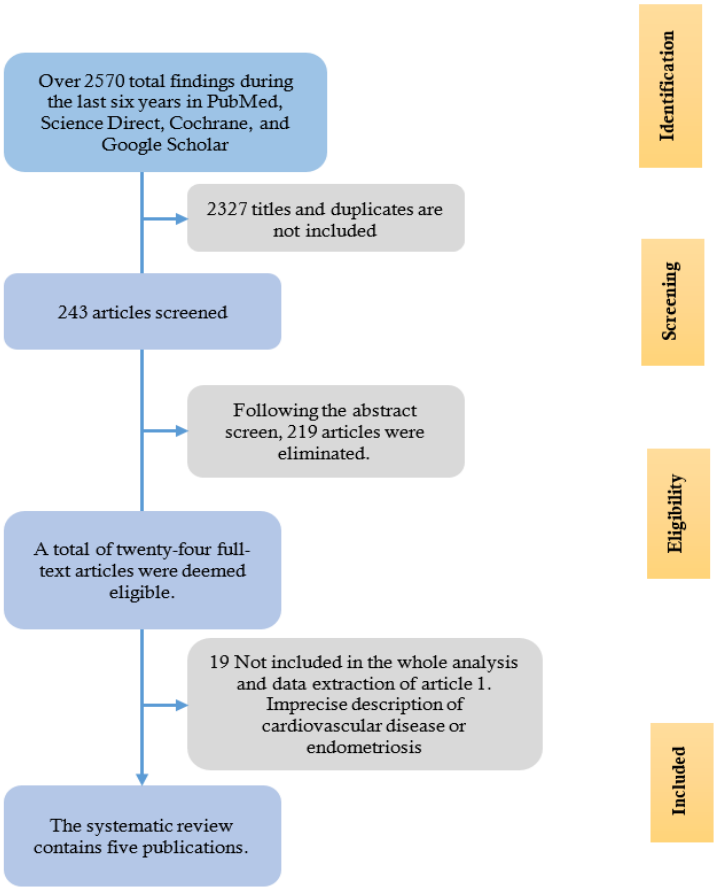

Fig.1. PRISMA Flowchart

from 119.7 cases per 10,000 people in 1998 to 201.3 cases per 10,000 people in 2017. The age group of women between 26 and 35 years old had the greatest occurrence of endometriosis, with a rate of 16.1 cases per 10,000 person-years for those aged 26 to 30 and a rate of 15.1 cases per 10,000 person-years for those aged 31 to 35. Among women with endometriosis, the crude incidence rate of composite cardiovascular disease (CVD) was 1.60 per 1000 person-years, whereas among women without endometriosis, it was 1.36 per 1000 person-years. In the modified model, which took into account demographic factors, lifestyle features, hypertension, diabetes mellitus, and reproductive history, endometriosis was shown to be significantly linked with an increased risk of composite cardiovascular disease (adjusted hazard ratio [aHR] 1.24; 95% confidence interval [CI] 1.14–1.37; P < 0.001) [9].

During the follow-up period, a population-based cohort research conducted in Taiwan revealed a greater incidence rate of endometriosis in the study group compared to the control group (1.8 per 1000 person-years versus 1.3 per 1000 person-years). The hazard ratio (HR) for coronary artery disease (CAD) was 1.52, with a 95% confidence range of 1.23-1.87 (p<0.001), after controlling for demographic variables, comorbidities, surgical procedures, frequency of outpatient visits, and medicines. Stratified analysis showed that individuals between the ages of 20 and 39 had a greater risk of coronary artery disease (CAD) compared to other age groups (40-49, 50-54, and above 55 years). The adjusted hazard ratio (aHR) for this sub-group was 1.73, with a 95% confidence interval (CI) of 1.16-2.59, and a p-value of 0.008 [10].

Chiang et al. (2021) analyzed the association between endometriosis and MACCE (major adverse cardiovascular and cerebrovascular events) in Taiwanese women. The study had a median follow-up length of 9.2 years. The MACCE was categorized into two distinct disease categories, namely cardiovascular disease (CVD) and cerebrovascular accident (CVA). Major cardiovascular diseases (CVD) include acute myocardial infarction (AMI) or heart failure (HF). CVA refers to the occurrence of either an acute ischemic or haemorrhagic stroke. The study found that patients with endometriosis had a 1.2-fold greater risk of MACCE

(95% CI 1.05-1.29; P = 0.0053) and a higher cumulative incidence of MACCE than the general population [11].

A further population-based cohort research conducted in Taiwan showed the same findings, indicating a greater occurrence of coronary artery disease (CAD) in the endometriosis cohort compared to the comparator cohort (5.96 vs. 4.38 per 1000 person-years; adjusted hazard ratio [95% confidence interval], 1.34 [1.22, 1.47]). In individuals with hypertension, endometriosis was shown to increase the risk of coronary artery disease (CAD) by 1.24 times (95% confidence interval: 1.04-1.48) compared to the control group [12].

Cirillo et al. (2021) examined metabolic parameters and indirect endothelial markers associated with atherosclerosis in women with endometriosis. Through the analysis of biohumoral parameters, researchers observed a significant increase in total cholesterol (p = 0.01), LDL-C (p = 0.01), triglycerides (p = 0.05), and homocysteinase (p = 0.04) levels in women with stage III/IV endometriosis compared to those without endometriosis. Additionally, lower values of vitamin B6 and folate (p = 0.07 and p = 0.03, respectively) were observed, along with higher concentrations of high-sensitive C reactive protein (p = 0.05) in women with endometriosis [13]. These results highlight the need to recognize endometriosis as a separate cardiovascular risk factor.

DISCUSSION

Endometriosis is a common condition that affects women in their reproductive years and is regulated by the hormone estrogen [14]. Our findings align with the results of the Nurses' Health Study II (NHS II) done in the United States, which showed that the highest prevalence of laparoscopically confirmed endometriosis was seen in women aged 25 to 29 and decreased beyond the age of 40 [15].

Our extensive investigation suggests that endometriosis may be a potential predisposing factor for cardiovascular disease. The results are consistent with a previous narrative systematic study that investigated the association between endometriosis and atherosclerotic cardiovascular disease (CVD). The systematic review included two population-based research done within the NHS II Cohort in the United States. The NHS II prospective cohort studies found that women with endometriosis had a higher risk of developing composite ischemic heart disease and hypertension compared to those without endometriosis [8,16].

Endometriosis is a complex condition that arises from several sources and manifests as a widely varied disease. Several hypotheses have been proposed; however, none can fully explain the underlying mechanisms of endometriosis and its various manifestations. Studies suggest that immune cells, adhesion molecules, extracellular matrix metalloproteinase, and pro-inflammatory cytokines promote the peritoneal environment, allowing ectopic endometrial cells to differentiate, attach, multiply, and survive. Endometriosis may develop due to these mechanisms, which include gradual alterations to the physiological processes of the endometrium. These modifications include alterations in hormonal physiology and regulating the interplay between endometriosis and the inflammatory response. Inflammation, particularly, has a significant impact on the development and progression of atherosclerosis, suggesting a possible link with endometriosis [17,18]

A recent extensive investigation investigated the relationship between endometriosis, markers of atherogenic lipid profile, endothelial dysfunction, and subclinical atherosclerosis. Additional research is necessary to determine the causal relationship between endometriosis and cardiovascular disease. Numerous methods have been proposed to clarify the probable connection between these two persistent conditions: (1) Chronic inflammation frequently originates from a common underlying factor; (2) There are genetic similarities among individuals; (3) Malfunction in microRNA contributes to the issue; and (4) Endometriosis is associated with early menopause, which is a widely acknowledged risk factor for the development of cardiovascular disease [7].

The documented correlation between endometriosis and increased cardiovascular risk might be attributed to many physiological causes. Firstly, chronic inflammation results in impaired functioning of the endothelium. Several studies have shown increased levels of pro-inflammatory markers in the peritoneal fluid and serum of women with endometriosis, suggesting the existence of systemic inflammation linked to the illness [9]. Furthermore, persistent inflammation might lead to the incidence of ventricular arrhythmias. This may occur via direct modulation of the heart's electrical activity and indirectly by accelerating the progression of ischemic heart disease [19].

Moreover, it has been shown that individuals with endometriosis have elevated levels of markers indicating oxidative stress [20]. Prolonged exposure to oxidative stress has been linked to dysfunction in the blood vessels and heart muscle cells, leading to irregular heart rhythms caused by the formation of cardiac fibrosis, disturbances in ion-channel conduction, and abnormal electrical activity occurring at different stages of the heart's electrical cycle [21,22]. Furthermore, several investigations have shown a link between endometriosis and elevated levels of atherogenic low-density lipoproteins [8]. In addition, the oxidation hypothesis

may help in understanding the link between reproductive risk factors, such as endometriosis, and an increased vulnerability to cardiovascular disease (CVD). The concept posits that low-density lipoprotein (LDL) is not intrinsically atherogenic. Atherosclerosis specifically occurs when reactive oxygen species oxidize low-density lipoprotein (LDL), resulting in the formation of cells, dysfunction of the endothelium, and finally, the development of atherogenesis [23].

Observational studies have shown a significant association between endometriosis and an elevated atherogenic lipid profile [24]. In the Nurses' Health Study II (NHSII; n = 116 430), Mu et al. discovered that women diagnosed with endometriosis had a 25% increased likelihood (95% CI 1.21-1.30) of having hypercholesterolemia. In addition, researchers found that women with hypercholesterolemia had a 22% higher risk (95% CI 1.15-1.31) of having laparoscopically confirmed endometriosis [16]. Melo et al. (2010) conducted a study including 120 women and discovered increased levels of total cholesterol, LDL-cholesterol, triglycerides, and HDL-cholesterol. Out of these ladies, 40 were diagnosed with endometriosis during laparoscopy. Endometriosis development is associated with an aberrant control of phospholipid and sphingolipid metabolism [25]. Lee et al. (2014) identified aberrant sphingolipid metabolism in the bloodstream, peritoneal fluid, and endometrial tissue of people diagnosed with endometriosis. The endometriotic debris identified increased activity of certain enzymes related to sphingolipid metabolism (sphingomyelin synthase 1, sphingomyelinase 3, and glucosylceramide synthase). As a result, there was a rise in glucosylceramide concentrations, a decline in sphingomyelin concentrations, and a reduction in endometrial apoptosis [26].

Mu et al. (2017) discovered a strong link between hypertension and endometriosis, which aligns with the findings of our systematic study. For 20 years, a group of 116,430 people between the ages of 25 and 42 were observed. Among them, 4,244 women were diagnosed with endometriosis with laparoscopic confirmation. After accounting for confounding factors, the relative risk (RR) of hypertension in women with endometriosis was found to be 1.14, with a 95% confidence interval (CI) of 1.09-1.18. Several explanations have been proposed to elucidate these associations, starting with the inflammatory process linked to endometriosis, which has long been recognized as a significant component in the development of hypertension [27].

It is important to consider the constraints of our review. The review's primary emphasis on Taiwanese and Caucasian European women restricted the extent to which the findings could be applied to other ethnic groups. These reports will unavoidably have inconsistencies because of both identifiable and unidentified factors, despite attempts to synchronize these databases. The study showed considerable variations in the definitions of cardiovascular diseases (such as acute myocardial infarction, coronary stenosis, etc.) and endometriosis (such as surgically proven, clinical suspicion, etc.). This difference in terminology heightened the uncertainty around cardiovascular outcomes.

CONCLUSION

Based on the findings of this extensive investigation, women with endometriosis may have a higher vulnerability to cardiovascular illness compared to those without the disorder. Enhanced comprehension of the connection between endometriosis and cardiovascular disease would indeed facilitate the development of novel therapies aimed at reducing the heightened cardiovascular burden in individuals with endometriosis. To prevent cardiovascular disease (CVD) in women with endometriosis, doctors should get a comprehensive reproductive history. A collaborative strategy including gynaecologists, cardiologists, and primary care doctors is necessary to accurately evaluate and supervise the cardiovascular disease risk in women with endometriosis.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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Table 1. Summaries Included Studies

Author, Year	Sample Size	Subject Age (year-old)	Research Duration	Geographical Setting	Study Design	Findings
Okoth et al., 2021 [9]	56,090 (case) 223,669 (control)	16-50	1995-2018	United Kingdom	Population-based cohort study	Endometriosis composite outcome: IHD, HF, cerebrovascular disease (aHR, 1.24; 95% CI 1.13–1.37) IHD (aHR 1.40; 95% CI 1.22–1.61); cerebrovascular disease (aHR, 1.19; 95% CI 1.04–1.36); arrhythmia (aHR, 1.26; 95% CI 1.11–1.43)
Wei et al., 2021 [10]	13,988 (case) 13,988 (control)	> 20	2000-2013	Taiwan	Population-based cohort study	The adjusted Hazard Ratio (aHR) of CAD for the endometriosis group was 1.52 with a 95% CI (1.23-1.87, p<0.001)
Chiang et al., 2021 [11]	17,543 (case) 70,172 (control)	18-50	1997-2013	Taiwan	Population-based cohort study	1.2-fold increased risk of MACCE (95% CI 1.05-1.29; P = 0.0053) in the endometriosis group
Li et al., 2021 [12]	19,454 (case) 77,816 (control)	≤ 64	2000-2012	Taiwan	Population-based cohort study	Higher incidence of CAD in the endometriosis group (5.96 vs 4.38 per 10,000 person-years, aHR 1.34; 95% CI 1.22-1.47
Cirillo et al., 2021 [13]	92 (case) 551 (control)	-	2017-2018	Italy	Cross-sectional study	Significant increased total cholesterol (p = 0.01), LDL-C (p = 0.01), triglycerides (p = 0.05) and homocysteinaemia (p = 0.04), lower vitamin B6 and folate (p = 0.07 and p = 0.03, respectively) values, and higher high-sensitive C reactive protein (p = 0.05) concentrations in the endometriosis group