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Establishing a Comprehensive Framework for Future Explorations: An Endometriosis and Cardiovascular Disease Literature Review

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Abstract
Endometriosis is one of the most prominent gynecological disorders often associated with several cardiovascular repercussions. Although no conclusive mechanism has been found, previous literature indicates potential links between endometriosis and atherosclerosis, a vital indicator of cardiovascular disease (CVD). However, with the majority of previous studies overlooking the impact of critical confounding variables and testing for only certain biomarkers, a strong argument towards a link cannot be made. Existing literature was thoroughly analyzed to identify major confounding variables that were unaccounted for to compile a list of vital biomarkers indicative of CVD in women with endometriosis. The stage and severity of the disease, surgery, hormone therapy, and presence of endometriosis in the control group were found to be major confounding variables that should be statistically accounted for. From previous literature, biomarkers that were shown to be highly indicative of CVD included lipid profile, arterial stiffness measures, as well as additional measures of vascular function and structure.
Encapsulating vital confounding variables and biomarkers, a comprehensive framework was established for a longitudinal study design. This paper provides a narrative review of the common weaknesses and limitations of past investigations exploring the link between endometriosis and CVD and suggests methods to overcome these considerations. Although existing literature has significantly contributed to the surface-level understanding of the link between endometriosis and CVD, knowledge gaps persist. As a result, repercussions are experienced by women with endometriosis worldwide. To ensure better healthcare for women with endometriosis, greater CVD intervention and prevention is critical. Through the holistic longitudinal study design proposed, improved treatment plans considering the potential CVD risks that women with endometriosis are at a greater likelihood of developing can be implemented.

Keywords: endometriosis; atherosclerosis; cardiovascular disease; biomarkers; menstrual disorder; women's health; longitudinal study

Introduction

Defining Endometriosis

Affecting approximately 15% of reproductive age women around the world, endometriosis is a common estrogen-dependent gynecological disorder, characterized by the presence of endometrium-like tissue outside the uterine cavity [1]. Common symptoms of endometriosis include chronic pelvic and abdominal pain, dysmenorrhea, hypermenorrhea and reduced fertility [2]. As a result, it significantly decreases the quality of life of symptomatic women [3].

According to the American Fertility Society, endometriosis can be classified into four distinct stages: stage I (minimal), stage II (mild), stage III (moderate) and stage IV (severe) [4]. Examination of the patient's endometrial lesions and adhesions are conducted by health care professionals, arbitrarily scored and then compared to a weighted point system to determine the stage of endometriosis. Although there are several theories behind the pathogenesis of endometriosis, implantation is the most commonly recognized [5]. Implantation involves an early lesion in the uterus which serves as a focal point, a nidus, for bacteria accumulation and endometrial tissue proliferation [6]. Endometriosis lesions can be white, red or black. The red lesions are indicative of a high level of vascularization. The white lesions are later stages of red lesions that have undergone fibrosis and a process of inflammation. The most common, black lesions are a result of the healing of the scar tissue [6].

There are a variety of ways to diagnose endometriosis, including a laparotomy, laparoscopy, and imaging [1]. However, imaging techniques such as magnetic resonance imaging and computerized tomography are seldom used as they lack the adequate resolution to diagnose the disease, while laparotomy is considered far too invasive [7]. As a

result, laparoscopy is considered the gold standard of an endometriosis diagnosis [8].

Defining Cardiovascular Disease (CVD)

Cardiovascular disease is the leading cause of death of women in the United States, and worldwide, CVD accounts for more than 17.9 million deaths annually [9]. CVD is most prevalent among women of older age, as after menopause, hypoestrogenism increases the risk of oxidative stress and chronic inflammation [10]. However, menstrual conditions such as endometriosis also increase the likelihood of developing CVD at an earlier age and thus put pre-menopausal women at an increased risk.

Atherosclerosis is the precursor of several acute cardiovascular events including myocardial infarction, stroke and sudden cardiac death [11]. Consequently, the research in this paper aims to look at these preliminary stages of cardiovascular disease by using atherosclerosis as the main indicator. A variety of typical cardiovascular risk factors are linked with the formation of atherosclerosis. This includes hypertension, elevated plasma concentration of low-density lipoprotein cholesterol and insulin resistance. Atherosclerosis is characterized by an accumulation of fatty deposits known as plaque in the arteries [12]. It is a slowly progressing disease with a multitude of risk factors including elevated cholesterol and triglyceride levels, diabetes mellitus, and smoking [13].

With atherosclerotic risk factors appearing to have a greater impact on women as compared to men, early detection and intervention are critical [13]. Likewise, the American Heart Association and the American College of Obstetricians and Gynecologists recently released a statement encouraging recognition of atherosclerosis risk factors in young and postmenopausal women [13]. Recent research suggests that women with endometriosis have a higher risk of developing atherosclerosis, with many potential underlying links.

Exploring Proposed Mechanisms for the Pathogenesis of Cardiovascular Disease from Endometriosis

Many studies suggest an underlying link between endometriosis and atherosclerosis, with various proposed mechanisms. Commonly, studies detail the factors shared by endometriosis and atherosclerosis in their pathogenesis and development [11]. For instance, inflammation, a pathophysiological factor in atherosclerosis development and a result of endometriosis, is commonly suggested as a linking cause between the two conditions [11,14,15]. Furthermore, oxidative stress, a condition characterized by the imbalance of reactive oxygen species and antioxidants involved in the pathophysiology of both diseases, may promote the development of atherosclerosis in endometriosis [11].

Furthermore, previous studies have revealed increased plasma asymmetric dimethylarginine (ADMA) levels in women with endometriosis as a potential link [14,16]. ADMA is an endogenous inhibitor of nitrogen oxide

synthase, an enzyme responsible for the production of nitric oxide (NO). Likewise, endothelial dysfunction, which is partly characterized by low levels of NO, is very common in women with endometriosis [16]. Nitric oxide is released by endothelial cells, which relaxes the surrounding smooth muscle to allow for vasodilation to occur [17]. Thus, it promotes blood flow and reduces blood pressure. In contrast, the absence of NO leads to higher blood pressure and the development of hypertension. High blood pressure degrades the artery walls, making them more vulnerable to plaque buildup. This plaque results in the narrowing of arteries, also known as atherosclerosis.

Moreover, studies have found that women with a family history of endometriosis are generally more susceptible to endometriosis [18]. This suggests that genetic factors potentially play a role in the etiology of the disorder. Presently, the Genome-Wide Association Studies (GWAS), the Online Mendelian Inheritance in Man catalogue and differentially expressed genes have shown a genetic connection between endometriosis and atherosclerosis [19]. Certain genes, identified through the GWAS, influence the vitamin B metabolic pathway which plays a vital role in the overall metabolism of the body, cellular processes and human disease control. More specifically, endometriosis has the same genetic pathway as several other atherosclerosis risk factors such as myocardial infarction and coronary artery disease (CAD). For instance, the CDKN2BAS genetic variants on chromosome 9 influence the development of endometriosis as well as acute myocardial infarction, a major risk of atherosclerosis [19]. They both also share some pathogenic similarities such as the activation of inflammatory genes, cytotoxicity, and recruitment/retention of macrophages [20].

Literature Gap

Despite an abundance of studies investigating the link between endometriosis and various risk factors of cardiovascular disease, no conclusive mechanism has been proposed. Nevertheless, the mentioned research strongly supports the existence of the relationship between conditions, which is why it is critical to explore whether women with endometriosis have a higher chance of developing atherosclerosis.

Likewise, to better determine if a correlation exists, various prospective research studies have examined whether women with endometriosis have a higher chance of developing atherosclerosis compared to women without endometriosis [16,18,20]. These studies utilized various testing methods and parameters to identify different biomarkers that could link endometriosis to cardiovascular disease. However, to our knowledge, no studies have taken a holistic approach to examine the link, as most examine only a limited range of biomarkers. Moreover, tests and measures examining the impact of critical confounding variables are often not taken, which renders the results of many of these studies as generalizations.

Most commonly, the data utilized to examine whether women with endometriosis have a higher chance of developing atherosclerosis is from pre-existing longitudinal studies. For instance, the pivotal 2016 paper by Mu et al. utilized data from the multi-decade Nurses' Health Study II [18]. Thus, since there is no singular focus on endometriosis initially, information on certain factors that would be critical for finding a proper correlation between endometriosis and CVD is not collected. Likewise, the biggest weakness of utilizing data from these longitudinal studies is that they do not test for and control critical confounding variables. Thus, by recognizing these weaknesses and designing a study where these variables are tested for, a definitive link between endometriosis and CVD can be identified.

Purpose

Even though prospective studies are limited in their ability to make conclusive links between endometriosis and atherosclerosis, as correlation does not imply causation, they are critical first steps in identifying whether a link between these two disease states exists. However, if study design neglects critical confounding variables and tests for only certain biomarkers, then a strong argument towards such a link cannot be made. Therefore, this review aims to propose a holistic methodology to better address the question of whether individuals with endometriosis have a greater chance of developing atherosclerosis, and ultimately, CVD. This entails analyzing critical confounding variables and discussing testing methods for vital biomarkers. Likewise, not only does this paper provide a narrative review of common weaknesses and limitations of past investigations exploring the link between endometriosis and CVD, but it suggests methods to overcome these considerations. Finally, this paper provides a cumulative design for future longitudinal studies which entails testing for multiple vital biomarkers.

Importance/Implications

Endometriosis is one of the most prominent and severe gynecological disorders with several repercussions, especially cardiovascular ones. As such, further investigation into whether women with endometriosis a higher chance of developing atherosclerosis have is a step in ensuring better cardiovascular health of premenopausal women. This review provides researchers designing future longitudinal studies with insight into other information that should be collected to overcome prior study limitations. For instance, it is important for longitudinal studies that already investigate cardiovascular health to consider incorporating specific biomarkers of endometriosis. This research provides clinicians with a proactive approach to prevent cardiovascular disease in women with endometriosis.

Narrative Review with Discussion
Biomarkers and Tests Indicative of Atherosclerosis

Lipid Profile

One of the most commonly tested collections of biomarkers for cardiovascular disease is the lipid profile, measuring total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides [21]. It is crucial to test for all of these biomarkers as they are vital indicators of cardiovascular health. Many studies have found unfavourable lipid profiles in women with endometriosis, with the most alarming one being the extremely high LDL levels [11]. Often referred to as "bad cholesterol," LDL makes up a significant part of our total cholesterol. However, a buildup of LDL, as frequently observed in women with endometriosis, can result in its accumulation on blood vessel walls. As this plaque increases overtime, narrowing of the vessels impairs blood flow, heightening the risk of certain cardiovascular events such as angina [22]. The alarming prevalence of pro-atherogenic lipid profiles for women with endometriosis emphasizes the need for these biomarkers to be tested [7]. All the biomarkers mentioned within the lipid profile can be easily tested using a minimally invasive blood test.

Arterial Stiffness

Arterial stiffness is one of the most common measures of vascular structure and function [23]. Relative to other biomarkers, arterial stiffness has shown to be a vital predictor of cardiovascular events, independent of traditional risk factors [24]. Arterial stiffness may also help identify atherosclerosis and cardiovascular events in asymptomatic individuals and helps identify at-risk patients at an early stage [25]. Although there are several indices and methods for testing arterial stiffness, the cardio-ankle vascular index , and ankle-brachial index have shown to be most useful. These testing methods help detect the presence of atherosclerosis via arterial stiffness in a non-invasive, cost-effective, and efficient manner [26,27]. In addition, both cardio-ankle vascular index and ankle-brachial index can be done at the same time which helps save time and increase the rate at which the longitudinal study can be conducted.

1. Cardio-Ankle Vascular Index (CAVI)

The CAVI is a measure of arterial stiffness independent of blood pressure. It is indicative of the stiffness from the ascending aorta to the ankle arteries. In the last decade, it has gained widespread recognition as playing a major role as a predictive factor for atherosclerosis and other related diseases [25]. CAVI uses recordings from blood pressure cuffs placed on both arms and ankles along with a microphone attached to the chest. It is also operator-independent and does not require the probing of the neck or the groin [28]. As such, compared to other testing methods such as the standard arterial stiffness measuring tool, carotid-femoral pulse wave velocity, CAVI is relatively less invasive and results in less participant discomfort. Additionally, in comparison to the widely used pulse wave velocity method, the CAVI index is not

susceptible to hampering by changes in blood pressure [29]. This increases the accuracy of the CAVI index. As such several cross-sectional studies have supported the use of CAVI as a comprehensive marker of systemic arterial stiffness [28]. Apart from aiding in the detection of atherosclerosis, CAVI also aids in monitoring the progression of the disease and the effectiveness of the treatment the patient undergoes [29].

2. Ankle-Brachial Index (ABI)

Similar to CAVI, ABI is a non-invasive determinant of the initial stages of atherosclerosis, at times when other signs or symptoms are not present. ABI is the measure of the ratio of the ankle to the brachial systolic blood pressure (SBP) [30]. Clinicians may choose to use different sonography/ultrasound instruments to measure ABI. For example, a 2020 study by Maeda et al. investigated atherosclerosis-related biomarkers in women with endometriosis, where they used a VaSera VS-1000 vascular screen system. Using this equipment, they measure the SBP of the upper (brachial arterial) and lower (tibial arterial) SBP, dividing ankle SBP by brachial SBP to calculate the ABI index value [31]. It is often recommended that repeated measures of the ABI should be taken, preferably over an extended period prior to diagnosis. However, its simplicity, cost-effectiveness, and usefulness for early detection make it a great tool and test to readily implement.

Additional Measures of Vascular Function and Structure
All of the tests outlined below are minimally invasive and provide a holistic understanding of atherosclerotic health, which is critical to help examine the link between endometriosis and cardiovascular health.

1. Flow Mediated Dilation (FMD)

As a functional parameter of atherosclerosis, FMD measures the vasodilation of arteries when blood flows through them and is primarily caused by the release of nitric oxide by endothelial cells [9-11]. Many studies have found that women with endometriosis have significantly lower values of FMD when compared with the women in the control groups [9,12,14]. Women with endometriosis have low levels of NO production by their endothelial cells, which results in decreased vasodilation of the arteries and hence, lower levels of FMD.

2. Distensibility Coefficient (DC)

Distensibility is the inverse of arterial stiffness as it refers to the ability of an artery to expand in response to pulse pressures. Cross-sectional studies performed in the past have repeatedly observed a link between decreased distensibility and cardiovascular risk factors, explaining that decreased distensibility is reflective of increased arterial stiffness [10]. This study found that the DC of arteries, specifically the common carotid artery, did not differ significantly between women with and without endometriosis, referring to

insufficient sensitivity of DC measurements in detecting minuscule differences in subclinical atherosclerosis between both groups. Nonetheless, determining the DC of arteries is a minimally invasive, time-efficient procedure that provides substantial insight into cardiovascular health and hence, should be determined to gain a holistic understanding of the patient's health.

3. Carotid Intima-Media Thickness (cIMT)

By determining the thickness between the intima and media, two layers of the carotid artery using a non-invasive ultrasound examination of the carotid artery, the cIMT is a measure of the extent of atherosclerotic vascular disease [32]. Maeda et al., 2020, found cIMT levels were significantly increased in women with endometriosis using oral contraceptives for an extended period. This is representative of arterial wall thickening, indicating an elevated risk for atherosclerosis [31]. As mentioned, the administration of hormonal therapy as part of a treatment plan for women with endometriosis for extended periods increases the risk of developing atherosclerosis and by extension cardiovascular disease due to the consequential increase in oxidative stress. As such, using a non-invasive ultrasound procedure to obtain cIMT measurements provides a greater understanding of the patient's atherosclerotic health.

Asymmetric Dimethylarginine (ADMA) and Symmetric Dimethylarginine (SDMA)
ADMA is another biomarker that is indicative of cardiovascular health. As an endogenous inhibitor of NO synthase, increased ADMA levels in patients result in decreased NO levels, which is reflective of both endothelial dysfunction and cardiovascular health. In 2011, Kirusaga et al. reported that ADMA levels were significantly higher for women with endometriosis when compared with women in the control group, coinciding with the findings of multiple other studies [14]. Through the inhibition of NO synthase and consequent reduction of NO, elevated ADMA levels result in an enhanced state of inflammation, increasing the likelihood of the development of cardiovascular disease. Moreover, the reduction in NO interferes with the ability of blood vessels to undergo vasodilation, further heightening the risk of CVD. Furthermore, SDMA levels also provide insight into cardiovascular health as they lack NO synthase inhibitory activity. Both ADMA and SDMA levels can be determined through the use of high-performance liquid chromatography. Overall, both provide substantial insight into the cardiovascular health of women with endometriosis compared to those without endometriosis.

Serum C-Reactive Protein level (hs-CRP)
Another critical biomarker of CVD is hs-CRP as elevated levels are reflective of inflammation, specifically in the arteries of the heart [33]. Among the various baseline laboratory markers of cardiovascular disease, hs-CRP is "the

strongest predictor of the risk of cardiovascular events" [20]. Multiple studies have observed elevated hs-CRP levels in women with endometriosis. A 2011 study by Kirusaga et al. revealed a negative correlation between FMD and hs-CRP [14]. This was a central finding as it highlighted that the heightened CRP production could be impeding normal vascular function in women with endometriosis.

Inflammatory Markers: Interleukin 1, 6 & Tumour Necrosis Factor-Alpha

Often reported collectively in past studies, interleukin 1, interleukin 6 and tumour necrosis factor-alpha are three key biomarkers, more specifically pro-inflammatory cytokines, that have increased expression during endometriosis [14]. Interleukin 1 is a common inflammatory cytokine that contributes to the regulation of inflammatory and immune responses [34] and interleukin 6 is another pro-inflammatory cytokine that "plays a pathological effect on chronic inflammation," [35]. Macrophages secrete tumour necrosis factor-alpha in response to signals from the body to induce inflammatory responses. A characteristic symptom of endometriosis is the inflammation it causes, which is a potential explanation for the link between it and atherosclerosis. Through enzyme immunoassays, studies in the past determined the quantity of these biomarkers in women with and without endometriosis, consistently observing elevated levels in women with endometriosis. This implied increased inflammation in women with endometriosis, supporting the notion that the inflammatory pathways of both endometriosis and atherosclerosis can explain the link between the two.

Analysis of Previous Studies: Unaccounted Confounding Variables

As mentioned previously, there is uncertainty surrounding the pathogenesis of atherosclerosis as a result of endometriosis. It is difficult to pinpoint if endometriosis itself leads to atherosclerosis, or if confounding variables related to atherosclerosis are responsible for this relationship. Thus, in addition to testing for vital biomarkers, studies must collect information required to minimize the effects of confounding variables to better establish a relationship between endometriosis and CVD.

Endometriosis and Stage/Severity of Disease

As previously mentioned, endometriosis can be classified into four distinct stages: stage I (minimal), stage II (mild), stage III (moderate) and stage IV (severe) [4]. A prior systematic review indicated that very few studies link the stage and severity of endometriosis with atherosclerosis [16]. Instead, papers lacking information regarding the specific stage of endometriosis statistically adjust for endometriosis clinical severity. For instance, a 2016 study by Mu et al. utilized potential indicators of hysterectomy as indicators of severity, which were then statistically adjusted for [36]. Nevertheless, the majority of papers did not account for stage

and severity at all, with most classifying all women with endometriosis into the same group. This is likely the result of the heterogeneous nature of endometriosis, as it often has very diverse clinical presentations [16].

Nevertheless, knowing the stage and severity of the women with endometriosis in these prospective studies is critical as the risk of atherosclerosis may be correlated with the stage of endometriosis. A 2007 study looked at the relationship between serum paraoxonase-1 activity in women with endometriosis and its relationship with the stage of the disease [37]. Serum paraoxonase-1 (PON-1), a high-density lipoprotein enzyme, prevents "oxidative modification of [LDL]" [37]. As previously mentioned, oxidative stress has been shown to play a significant role in the development and progression of atherosclerosis. On a similar note, low levels of PON-1 may contribute to an increased risk of atherosclerotic development [37]. The study found that reduced serum PON-1 activity was significantly lower in women with severe endometriosis as compared to those with mild endometriosis and the control group, with an overall significant negative correlation concluded. This article highlights why knowing the stage and severity of endometriosis is critical, as it may have a significant effect on the development of atherosclerosis. However, it should be noted that a 2013 observational study exploring the same relationship found no correlation between PON-1 and severity of the disease [38]. Similar to Verit et al.'s study with 87 women, Melo et al. also examined a small group with the study consisting of 80 women. However, unlike Verit et al., the study had no control group. Melo et al. hypothesized that the difference in results was due in part to the younger age of patients in their study. As well, the proposed variation in PON-1 activity between individuals may be due to differences in HDL levels, a factor neither study accounted for. Thus, although there is no definitive consensus regarding the correlation between this biomarker and endometriosis, there is enough evidence to warrant further investigation into how the stage and severity of endometriosis impacts atherosclerosis.

Furthermore, a 2010 study by Melo et al. regarding unfavourable lipid profiles in women with endometriosis also highlighted the importance of looking at severity when determining associations with atherosclerosis [14]. Holistically, the study found that women with endometriosis have increased HDL and LDL cholesterol levels as compared to women without endometriosis. The study went on to compare their results with a similar investigation conducted by Verit et al. which compared lipid profiles of women with endometriosis to those without this condition. Opposite to the study by Melo et al., Verit et al. found that women with endometriosis had lower HDL levels [37]. However, while 75% of women in Melo et al.'s case group consisted of women with severe endometriosis and 25% with moderate endometriosis, half of the women in Verit et al.'s case group had mild endometriosis. Moreover, it should be noted that while Melo et al. did not consider mild

endometriosis at all, Verit et al. did. These contrasting results further highlight the importance of considering the stage of endometriosis, as it could ultimately have a significant effect on the development of atherosclerosis [14].

Holistically, the few studies evaluating the effect of stage and severity of endometriosis mentioned have concluded that the stage of endometriosis had a significant effect on the several biomarkers for CVD. This strongly supports the necessity of evaluating the stage and severity of endometriosis and factoring it into the statistical analysis when looking at how endometriosis impacts atherosclerotic development. Moreover, in the future, if screen guidelines identifying atherosclerosis risk for women with endometriosis are developed, knowing the effect of stage and severity will be especially critical [39]. Overall, when future longitudinal studies laparoscopically confirm the presence of endometriosis, the severity and stage should be recorded as well. Specifically, utilizing standards such as those provided by the American Fertility Society to determine the stage and severity of the disease is recommended [40].

Presence of Endometriosis in the Control Group
For the case group (i.e., women with endometriosis), the majority of previous studies went forward to confirm the presence of endometriosis in individuals rather than relying solely on self-reporting measures. Often, these tests were conducted subsequently after subjects reported symptoms of endometriosis such as infertility and pelvic pain [14]. Most often, endometriosis was confirmed laparoscopically, the gold standard of an endometriosis diagnosis [8]. However, to our knowledge, no study utilized testing measures to confirm the absence of endometriosis for women in the control group.

It is possible that women in the control group had undiagnosed endometriosis. In fact, 2-22% of women who do not present any symptoms of endometriosis are diagnosed with endometriosis if they undergo video laparoscopy [14]. A 2017 study by Tissot et al. which examined 465 women wanting to undergo tubal sterilization by laparoscopy found a 10% prevalence of endometriosis in asymptomatic women [41]. Furthermore, the World Endometriosis Society reports that endometriosis affects an average of 1 in 10 women during their reproductive years worldwide [42]. Given these statistics, it is likely that in many studies, women in control groups had undiagnosed endometriosis. Unfortunately, this uncontrolled variable has the potential to compromise the internal validity of the results unless accounted for.

Unfortunately, performing laparoscopy to rule out endometriosis in the control group is unrealistic. Although minimally invasive, laparoscopy is still a surgery, and thus performing it to confirm endometriosis if the subject displays no symptoms is unwarranted. As a solution, it was found that some studies statistically adjusted for unexampled diagnosis by stratifying analysis, as done in a 2015 study by Hopeman et al. [43]. Overall, the presence of endometriosis in the control group is a major uncontrolled variable, and likewise, it is recommended that future studies statistically account for

the presence of undiagnosed endometriosis in the control group to mitigate the effects it may have on results.

Surgery and Endometriosis
As treatments for endometriosis, hysterectomies or oophorectomies are occasionally performed. A hysterectomy is the surgical removal of the uterus, while an oophorectomy is the surgical removal of one or both ovaries. Endometriosis does not have a cure, so these procedures are performed to help relieve symptoms of pain [44]. In the United States, 18% of hysterectomies are performed as a result of endometriosis [45]. Women with endometriosis are not only more likely to undergo these surgeries but also more likely to receive them at a younger age [7]. As a result of these surgeries, menopause is induced at a younger age. Substantial research has found that post-menopausal women are at a greater risk of developing heart disease [42]. Similarly, a substantial amount of research suggests that hysterectomies and oophorectomies are linked to heart disease, [46] thus positioning these surgeries as major confounding variables.

Examining the impact of hysterectomies on CVD risk, a 2018 study by Laughlin-Tommaso et al. found that women who had undergone hysterectomies are at an increased long-term risk of cardiovascular conditions. This association is especially prominent in those women who underwent a hysterectomy at 35 years of age or younger [46]. It has been proposed that this link is the result of the decrease in endogenous sex hormone levels that follow these procedures, which subsequently can accelerate the development of heart disease [47]. Moreover, another 2018 study which was conducted by Ding et al. with 1 million patients found a significant association between hysterectomy and CAD, even after the study had adjusted statistically for baseline CAD risk factors [47]. A 2005 study also found women who had undergone this surgery had a higher risk profile, prevalence and incidence of CVD. However, the multivariate models utilized in the study suggest that the higher prevalence of CVD is a result of the adverse initial risk profiles of the women who underwent surgeries as opposed to the risk of the surgery itself. Thus, while there is research suggesting that hysterectomies increase the risk of CVD, it is important to note that the results are not completely conclusive.

Regarding whether oophorectomies affect cardiovascular disease, there are also conflicting results. A 2010 study by Rivera et al. found a significantly increased cardiovascular mortality in women who underwent oophorectomy at a young age [48]. On the other hand, another study conducted by researchers Jacoby et al. in the same year found no relationship between oophorectomy and CVD risk [21].

A 2016 study by Mu et al. investigating the effect of endometriosis on the risk of coronary heart disease (CHD) examined both the effect of hysterectomies and oophorectomies. This study found that women who had

undergone these procedures had higher rates of CHD, with statistical controls for age. However, they also found that adjusting for heart disease risk factors caused by hysterectomy and oophorectomy did not decrease the association between endometriosis and CHD [24].

Holistically, even though research regarding the effect of hysterectomies and oophorectomies on CVD is inconclusive, there is enough evidence to suggest these procedures may be confounding variables. Likewise, future longitudinal studies should collect information at baseline regarding whether subjects underwent these surgeries. As well, researchers should statistically compare the risk of atherosclerosis between the control group, women with endometriosis, and women who have had a hysterectomy or an oophorectomy.

Hormone Therapy and Endometriosis
Hormone therapy is a commonly adopted course of treatment by clinicians for women suffering from an array of symptoms associated with menstrual cycle conditions [24]. Hormonal therapy involves administering drugs that interfere with or suppress the production of certain hormones [49] and may be used during treatment for endometriosis to relieve associated pain [49].

In 2006, Pretta et al. conducted a case-control study comparing levels of subclinical atherosclerosis in women with and without endometriosis [20]. Amidst factors such as age, body mass index (BMI) and smoking habits, this investigation took into consideration whether participants had received hormonal treatments in the past. A majority of women in the case group of women with endometriosis reported previous hormonal treatment usage A commonly prescribed treatment involves gonadotropin-releasing hormone (GnRH) analogues which control the release of follicle-stimulating hormone and luteinizing hormone, both of which play a crucial role in the regulation of the menstrual cycle. Another common medication used is danazol, which is used in the treatment process by shrinking the endometrial tissue present outside the uterine cavity.

To study the relationship between endometriosis and atherosclerosis, the intima-media thickness and distensibility coefficient in both groups was investigated. Overall, the control group had lower levels of intima-media thickness and higher DC values, revealing increased arterial stiffness in women with endometriosis [20]. A significant portion of women with endometriosis had received hormonal therapy prior to the study and researchers cited this as a potential explanation behind these women having a greater risk of developing atherosclerosis. Hormonal therapies, such as GnRH analogs and danazol, are used in the treatment for endometriosis and may suppress estrogen levels, contributing to the increased development of atherosclerosis as supported by their results. Holistically, the results of the study suggest that hormonal therapy may have an effect on the development and progression of both endometriosis and atherosclerosis.

Dienogest (DNG) and oral contraceptives are two of the most common hormone therapies prescribed by clinicians for women suffering from endometriosis. Maeda et al. tested for various biomarkers to determine the impact of these two hormone therapies on the development of atherosclerosis [31]. The biomarkers hs-CRP and diacron-reactive oxygen metabolites levels were the highest in women on oral contraceptive therapy. Heightened levels of these two biomarkers are indicative of an increased risk of developing atherosclerosis, thus supporting that oral contraceptives increase atherosclerosis risk. Results from this study correspond with those of past ones that frequently concluded that hormonal contraceptive use in healthy women can increase the risk of developing atherosclerosis. Flow-mediated dilation significantly decreases as the duration of hormonal contraceptive use increases. Furthermore, oral contraceptive use has been found to increase oxidative stress in healthy women.

Numerous studies in the past have arrived at a consensus that a longer duration of oral contraceptive administration increases oxidative stress in healthy women [31]. Although the mechanism through which oral contraceptive use increases oxidative stress is unknown, this is one of the potential mechanisms linking endometriosis and atherosclerosis. Thus, hormone therapy may be a precursor to atherosclerosis. However, it is important to be cognizant of the limitations of these studies themselves. Often, studies were conducted with an unrepresentative sample size and lacked sufficient baseline data, restricting the ability to arrive at a general conclusion on the influence of hormone therapy on endometriosis and atherosclerosis [17]. Although this impairs the validity of the conclusions reached by these studies, it still sheds light on the potential influence hormone therapy may have on the development and progression of endometriosis and atherosclerosis, calling for increased research on this topic.

A substantial amount of literature surrounding endometriosis and atherosclerosis utilizes hormone therapy as a part of the study's exclusion criteria, disregarding the impact it may have on the development and progression of endometriosis and by extension atherosclerosis. To our knowledge, these are the only studies that have referenced the potential influence of hormone therapy in women with endometriosis on the development of atherosclerosis, warranting further investigation into the topic.

Recommendations for Study Design
Type of Study
To explore how endometriosis increases the risk of developing atherosclerosis, a prospective longitudinal study design is recommended over a retrospective design. Research done by Song and Chung reveals that the primary disadvantage of a retrospective study design is the limited control the researcher has over data collection. This often results in incomplete or inaccurate information. Contrastingly prospective studies are designed with specific

data collection and as a result has the advantage of being bespoke for specific data exposure [50]. Moreover, a longer period for analysis allows for the necessary biomarkers to be tested prior to the onset of atherosclerosis or cardiovascular disease. A study conducted by Husby et al. (2003) determined that after the onset of symptoms associated with endometriosis, it may take anywhere from 3-11 years for an affirmative diagnosis, with the average time of diagnosis being 5 years. [51] Since the pathogenesis of endometriosis spans a large time range, it is important for the study to last a sufficient amount of time to ensure significant and accurate results are obtained.

Thus, it is recommended that this study is conducted for a minimum of 5-10 years, although a longer period is encouraged for more insightful results. The recommended study design for a prospective longitudinal investigation evaluating the effect of endometriosis on atherosclerosis is a case-control study. In this design, individuals with the disease of interest, endometriosis, are known as cases and are compared with the controls, individuals without endometriosis. Specifically, a matched case-control study design is recommended to reduce the impact of confounding variables. This entails selecting a control to match the characteristics of each case with endometriosis in the study. For matching criteria, it is recommended to look at the presence of other health conditions (e.g., diabetes), age, socioeconomic, geographic and racial characteristics, and similar anthropometric characteristics. A notable anthropometric characteristic to include is BMI. If possible, more specific matching criteria is recommended, but its implementation is at the investigator's discretion given that increased specificity can restrict the pool of potential participants. Overall, this study design provides a comprehensive understanding and allows the progression of risk factors to be monitored for better insight into the development of atherosclerosis from endometriosis.

Study Criteria
It is encouraged that longitudinal studies follow strict criteria when selecting the individuals to include in the control and case groups. This is critical as it minimizes the effects of confounding variables. The criteria can be divided into three categories: information collected at baseline, inclusion criteria, and exclusion criteria.

Baseline Characteristics
All women should be surveyed to determine their age, anthropometric characteristics, menstrual health history, and family history of severe disease or illness with a focus on conditions related to menstrual/reproductive health and cardiovascular health. Geographic, racial, ethnic, and socioeconomic backgrounds should also be collected as they have a substantial impact on lifestyle, health, and quality of healthcare available [19]. With a match case-controlled study design, knowing these characteristics are critical to

finding an appropriate control match for individuals in the case group.

Inclusion Criteria
The inclusion criteria for women can be further divided into two parts, the control group and the cases. For the case group, the women have a laparoscopically confirmed diagnosis of endometriosis and are within the reproductive age of 18-49 years. The control group must also fall within the same reproductive age range, have a regular menstrual cycle and be screened for any potential symptoms of endometriosis, as discussed previously.

Exclusion Criteria (Control and Case)
Exclusion criteria would include pregnancy, hypertension, pelvic inflammatory disease, diabetes mellitus or an autoimmune disorder. Moreover, women with other coagulation, menstrual, and endocrine disorders should also be excluded. While it is recommended that smokers be excluded as smoking increases the risk of atherosclerosis, [52] studies may include women who smoke if they statistically adjust for these. If they do so, they should match cases that smoke with controls who also smoke.

Statistical Analysis
As with any longitudinal study, appropriate statistical tests must be conducted. Due to the widespread benefits of multivariate statistical analysis, Santoro et al. [11], among many other researchers, made use of this test to strengthen their conclusions. The use of multivariate statistical analysis in future longitudinal studies is encouraged as it not only adjusts for major confounding variables outlined previously, but also provides an understanding of which biomarkers have a more profound impact on the link between endometriosis and atherosclerosis.

Pathways for Future Investigations
The proposed study design takes a holistic approach to examining the link between endometriosis and cardiovascular disease. The various confounding factors and biomarkers considered in this longitudinal study design allows for a plethora of relationships to be further investigated.

To begin, further insight into the links between endometriosis, atherosclerosis and various confounding variables can be made. One prominent area that can be further investigated is whether surgical treatment for endometriosis increases the risk of cardiovascular disease. Moreover, given that information regarding the stage and severity of endometriosis should be collected, then the relationship between stage and severity of endometriosis and atherosclerosis can be determined statistically. Finally, the relationship between hormone therapy, endometriosis and cardiovascular disease can also be examined.

In addition, following a potential study conducted with this proposed design, the effectiveness and reliability of the biomarkers can also be determined by examining which

biomarkers are better indicators of cardiovascular disease in women with endometriosis. Thus, this further insight can improve diagnostic measures and by extension aid in timely detection of cardiovascular disease in this clinical population.

Furthermore, this research can be used to address several other research questions beyond the original investigation. For instance, the question of at what age do women with endometriosis develop cardiovascular disease can be answered. Moreover, this longitudinal study design also opens up an opportunity for research into the role time of intervention plays in both reducing the risk of cardiovascular disease and treatment plans for women with endometriosis.

Conclusion

Previous studies that have investigated the relationship between endometriosis and cardiovascular disease have greatly contributed to our basic understanding of the mechanisms potentially explaining the link between the two conditions. However, much of the research done can be considered preliminary as there is variability in the potential links proposed by these studies, leading to significant knowledge gaps. Rather than looking at the holistic link between endometriosis and cardiovascular disease, many studies approached the topic through a narrow lens. Although taking a focused approach allows for a stronger understanding of the influence of specific biomarkers, it significantly inhibits the ability to draw definitive mechanistic conclusions regarding the overall link between endometriosis and cardiovascular disease. The repercussions are experienced by women with endometriosis around the world as there is no concrete treatment plan considering the potential cardiovascular risk.

Past studies often did not take critical confounding variables into account, specifically the stage and severity of endometriosis, previous surgeries such as oophorectomies and hysterectomies and previous use of hormonal therapy. After extensive research, it was determined that these specific variables must be taken into consideration and be adjusted for during statistical analysis so that a more holistic understanding of the link between endometriosis and cardiovascular health can be determined. Moreover, the majority of existing literature takes into accounted limited biomarkers, further impeding the ability to definitively determine the mechanism linking endometriosis and cardiovascular disease.

As such, the proposed methodology in this paper has been designed after a critical and thorough reflection of the present literature. This proposal not only takes into account the strengths of present studies but also considers the methodology that overcomes the limitations of existing literature. Through suggesting a framework that encompasses a collection of minimally invasive tests to be conducted, suggested confounding variables to account for, and biomarkers to be tested for, longitudinal studies that

incorporate this methodology into their research will be equipped with sufficient information to strengthen our understanding of the link between endometriosis and atherosclerosis, thus by extension, cardiovascular disease.

Presently, there is no cure for endometriosis, and likewise, current treatment plans only consist of symptom mitigation [53]. The insufficient understanding between endometriosis and cardiovascular disease is an obstacle for early cardiovascular disease detection and intervention for women with endometriosis. Thus, through gaining a more holistic understanding by incorporating the proposed methodology of this paper into future longitudinal studies, clinicians will be equipped with the necessary information needed to improve treatment plans and quality of life for women with endometriosis.

List of Abbreviations
ABI: ankle-brachial index
ADMA: asymmetric dimethylarginine
BMI: body mass index
CAD: coronary artery disease
CAVI: cardio-ankle vascular index
CHD: coronary heart disease
cIMT: carotid intima-media thickness
CVD: cardiovascular disease
DC: distensibility coefficient
DNG: dienogest
FMD: flow-mediated dilation
GWAS: genome-wide association studies
GnRH: gonadotropin-releasing hormones
HDL: high-density lipoprotein
hs-CRP: high sensitivity C-reactive protein
LDL: low-density lipoprotein
LH: luteinizing hormone
NO: nitric oxide
PON-1: paraoxonase-1
SBP: systolic blood pressure
SDMA: symmetric dimethylarginine

Conflicts of Interest
The authors declare no conflicts of interest.

Ethics Approval and/or Participant Consent
As this paper is a review, no ethics approval was required. However, for future studies that choose to implement the longitudinal design, following the latest Tri-Council Policy Statement on ethical conduct for research involving humans is critical.

References
[1] Parasar P, Ozcan P, Terry KL. Endometriosis: Epidemiology, Diagnosis and Clinical Management. Curr Obstet Gynecol Rep. 2017 Mar;6(1):34–41. https://doi.org/10.1007%2Fs13669-017-0187-1
[2] Mu Fan, Rich-Edwards Janet, Rimm Eric B., Spiegelman Donna, Forman John P., Missmer Stacey A. Association Between Endometriosis and Hypercholesterolemia or Hypertension. Hypertension. 2017 Jul 1;70(1):59–65. https://doi.org/10.1161/HYPERTENSIONAHA.117.09056
[3] Iii MHA, Yoder N, Taylor HS. The Systemic Effects of Endometriosis. Semin Reprod Med. 2017 May;35(03):263–70. https://doi.org/10.1016/j.jogoh.2017.05.003
[4] Revised American Fertility Society Classification of Endometriosis: 1985. Fertil Steril. 1985 Mar 1;43(3):351–2. https://doi.org/10.1016/s0015-0282(16)48430-x
[5] Burney RO, Giudice LC. Pathogenesis and Pathophysiology of Endometriosis. Fertil Steril [Internet]. 2012 Sep;98(3). https://doi.org/10.1016/j.fertnstert.2012.06.029
[6] Alimi Y, Iwanaga J, Loukas M, Tubbs RS. The Clinical Anatomy of Endometriosis: A Review. Cureus [Internet]. 2018 Sep;10(9). https://doi.org/10.1016/j.jogoh.2017.05.003
[7] Zanelotti A, DeCherney AH. Surgery and Endometriosis. Clinical Obstetrics Gynecology. 2017 Sep;60(3):477–84. https://doi.org/10.1016/j.jogoh.2017.05.003
[8] HSU A, Khachikyan I, Stratton P. Invasive and non-invasive methods for the diagnosis of endometriosis [Internet]. 2010 June;53(2):413-419. https://doi.org/10.1097/GRF.0b013e3181db7ce8
[9] Cardiovascular diseases [Internet]. [cited 2020 Dec 21]. Available from: https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1
[10] Yazdanyar A, Newman AB. The Burden of Cardiovascular Disease in the Elderly: Morbidity, Mortality, and Costs. Clin Geriatr Med. 2009 Nov;25(4):563–vii. https://doi.org/10.1016/j.jogoh.2017.05.003
[11] Santoro L, D'Onofrio F, Flore R, Gasbarrini A, Santoliquido A. Endometriosis and atherosclerosis: what we already know and what we have yet to discover. Am J Obstet Gynecol. 2015 Sep;213(3):326–31. https://doi.org/10.1016/j.jogoh.2017.05.003
[12] Atherosclerosis [Internet]. www.heart.org. [cited 2020 Dec 21]. Available from: https://www.heart.org/en/health-topics/cholesterol/about-cholesterol/atherosclerosis
[13] Brown Haywood L., Warner John J., Gianos Eugenia, Gulati Martha, Hill Alexandria J., Hollier Lisa M., et al. Promoting Risk Identification and Reduction of Cardiovascular Disease in Women Through Collaboration With Obstetricians and Gynecologists: A Presidential Advisory From the American Heart Association and the American College of Obstetricians and Gynecologists. Circulation. 2018 Jun 12;137(24):e843–52. https://doi.org/10.1016/j.jogoh.2017.05.003
[14] Melo AS, Rosa-e-Silva JC, Rosa-e-Silva ACJ de S, Poli-Neto OB, Ferriani RA, Vieira CS. Unfavorable lipid profile in women with endometriosis. Fertil Steril. 2010 May 1;93(7):2433–6. https://doi.org/10.1016/j.jogoh.2017.05.003
[15] Hughes CL, Foster WG, Agarwal SK. The Impact of Endometriosis across the Lifespan of Women: Foreseeable Research and Therapeutic Prospects [Internet]. BioMed Research International. Hindawi. 2015; 93(7):2433-2436. https://doi.org/10.1155/2015/158490
[16] Tan J, Taskin O, Iews M, Lee AJ, Kan A, Rowe T, et al. Atherosclerotic cardiovascular disease in women with endometriosis: a systematic review of risk factors and prospects for early surveillance. Reprod Biomed Online. 2019 Dec 1;39(6):1007–16. https://doi.org/10.1016/j.jogoh.2017.05.003
[17] Staff E. The Best Way to Maintain Heart-Healthy Nitric Oxide Levels [Internet]. Health and Wellness Alerts. 2018 [cited 2020 Dec 21]. Available from: https://www.healthandwellnessalerts.berkeley.edu/topi

cs/heart-health/the-best-way-to-maintain-heart-healthy-nitric-oxide-levels/

[18] Taskin O, Rikhraj K, Tan J, Sedlak T, Rowe TC, Bedaiwy MA. Link between Endometriosis, Atherosclerotic Cardiovascular Disease, and the Health of Women Midlife. J Minim Invasive Gynecol. 2019 Aug;26(5):781–4. https://doi.org/10.1016/j.jogoh.2017.05.003

[19] Satoko U, Hitoshi Z, Akira H, Atsushi T, Michiaki K, Tomoko A, Daisuke A, Nayouki K, Koichi H, Yusuke N. Genome-wide association study identifies genetic variants in the CDKN2BAS locus associated with endometriosis in Japanese. Nature Genetics. [Internet]. 2019 Aug;42(8):707-10. https://doi.org/10.1038/ng.612

[20] Pretta S, Remorgida V, Abbamonte LH, Anserini P, Ragni N, Del Sette M, et al. Atherosclerosis in women with endometriosis. Eur J Obstet Gynecol Reprod Biol. 2007 Jun;132(2):226–31. https://doi.org/10.1016/j.jogoh.2017.05.003

[21] JACOBY VL, GRADY D, SAWAYA GF. Oophorectomy as a Risk Factor for Coronary Heart Disease. Am J Obstet Gynecol. 2009 Feb;200(2):140.e1-140.e9. https://doi.org/10.1016/j.jogoh.2017.05.003

[22] CDC. LDL and HDL Cholesterol: "Bad" and "Good" Cholesterol [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 Dec 21]. Available from: https://www.cdc.gov/cholesterol/ldl_hdl.htm

[23] Quinn U, Tomlinson LA, Cockcroft JR. Arterial stiffness. JRSM Cardiovasc Dis [Internet]. 2012 Sep 30;1(6). https://doi.org/10.1258/cvd.2012.012024

[24] Mayo Clinic Staff. Hormone therapy: Is it right for you? [Internet]. Mayo Clinic. [cited 2020 Dec 21]. Available from: https://www.mayoclinic.org/diseases-conditions/menopause/in-depth/hormone-therapy/art-20046372

[25] Miyoshi T, Ito H, Horinaka S, Shirai K, Higaki J, Orimio H. Protocol for Evaluating the Cardio-Ankle Vascular Index to Predict Cardiovascular Events in Japan: A Prospective Multicenter Cohort Study. Pulse. 2017 Jan;4(Suppl 1):11–6. https://doi.org/10.1159/000448464

[26] Miyoshi T, Ito H. Assessment of Arterial Stiffness Using the Cardio-Ankle Vascular Index. Pulse. 2016 Jul;4(1):11–23. https://doi.org/10.1159/000445214

[27] Itoga NK, Minami HR, Chelvakumar M, Pearson K, Mell MM, Bendavid E, et al. Cost Effectiveness Analysis of Asymptomatic Peripheral Arterial Disease Screening with the ABI Test. Vasc Med Lond Engl. 2018 Apr;23(2):97–106. https://doi.org/10.1016/j.jogoh.2017.05.003

[28] Kunihiro Matsushita, Ning Ding, Esther D. Kim, Matthew Budoff, Julio A. Chirinos, Bo Fernhall, et al. Cardio-ankle vascular index and cardiovascular disease: Systematic review and meta-analysis of prospective and cross-sectional studies. The Journal of Clinical Hypertension - Wiley Online Library [Internet]. 2019; 21(1):16-24. https://doi.org/10.1111/jch.13425

[29] Sun C-K. Cardio-ankle vascular index (CAVI) as an indicator of arterial stiffness [Internet]. Vol. 6, Integrated Blood Pressure Control. Dove Press; 2013; p. 27–38. https://doi.org/10.2147/IBPC.S34423

[30] Beth D Weatherley, Lloyd E Chambless, Gerardo Heiss, Diane J Catellier, Curtis R Ellison. The reliability of the ankle-brachial index in the Atherosclerosis Risk in Communities (ARIC) study and the NHLBI Family Heart Study (FHS). BMC Cardiovsc Discord [Internet]. 2006 Feb; 6(7). https://doi.org/10.1186/1471-2261-6-7

[31] Maeda E, Koshiba A, Mori T, Ito F, Kataoka H, Okimura H, et al. Atherosclerosis-related biomarkers in women with endometriosis: The effects of dienogest and oral contraceptive therapy. Eur J Obstet Gynecol Reprod Biol X. 2020 Jul 1;7:100108. https://doi.org/10.1016/j.eurox.2020.100108

[32] Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB. Carotid-Wall Intima–Media Thickness and Cardiovascular Events. N Engl J Med. 2011 Jul 21;365(3):213–21. https://doi.org/10.1056/NEJMoa1012592

[33] Robin Donovan. C-Reactive Protein Test: Purpose, Procedure, and Results [Internet]. [cited 2020 Dec 21]. Available from: https://www.healthline.com/health/c-reactive-protein

[34] Kaneko N, Kurata M, Yamamoto T, Morikawa S, Masumoto J. The role of interleukin-1 in general pathology. Inflamm Regen. 2019 Jun 6;39(1):12. https://doi.org/10.1186/s41232-019-0101-5

[35] Tanaka T, Narazaki M, Kishimoto T. IL-6 in Inflammation, Immunity, and Disease. Cold Spring Harb Perspect Biol [Internet]. 2014 Oct;6(10). https://doi.org/10.1101/cshperspect.a016295

[36] Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Missmer SA. Endometriosis and Risk of Coronary Heart Disease. Circ Cardiovasc Qual Outcomes. 2016 May;9(3):257–64. https://doi.org/10.1161/CIRCOUTCOMES.115.002224

[37] Verit FF, Erel O, Celik N. Serum paraoxonase-1 activity in women with endometriosis and its relationship with the stage of the disease. Hum Reprod Oxf Engl. 2008 Jan;23(1):100–4. https://doi.org/10.1093/humrep/dem340

[38] Bragatto F, Barbosa C, Christofolini D, Peluso C, Santos A, Mafra F, et al. There is no relationship between Paraoxonase serum level activity in women with endometriosis and the stage of the disease: An observational study. Reprod Health. 2013 Jun 22;10:32. https://doi.org/10.1186/1742-4755-10-32

[39] Kianpour M, Nematbakhsh M, Ahmadi SM. Asymmetric dimethylarginine (ADMA), nitric oxide metabolite, and estradiol levels in serum and peritoneal

fluid in women with endometriosis. Iran J Nurs Midwifery Res. 2015 Aug;20(4):484–9. https://doi.org/10.4103/1735-9066.160997

[40] Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. Fertil Steril. 2010 Oct;94(5):1609–15. https://doi.org/10.1016/j.fertnstert.2009.09.035

[41] Tissot M, Lecointre L, Faller E, Afors K, Akladios C, Audebert A. Clinical presentation of endometriosis identified at interval laparoscopic tubal sterilization: Prospective series of 465 cases. J Gynecol Obstet Hum Reprod. 2017 Oct;46(8):647–50. https://doi.org/10.1016/j.jogoh.2017.05.003

[42] World Endometriosis Society. FACTS about endometriosis [Internet]. 2015 [cited 2020 Dec 21]. Available from: http://endometriosis.ca/Facts-about-endometriosis.pdf

[43] Margaret M. Hopeman, Joan K. Riley, Antonina I. Frolova, Hui Jiang, Emily S. Jungheim. Serum Polyunsaturated Fatty Acids and Endometriosis [Internet]. 2015 Dec;22:183-1087. https://doi.org/10.1177%2F1933719114565030

[44] A Sandström, M Bixo, M Johansson, T Bäckström, S Turkmen. Effect of hysterectomy on pain in women with endometriosis: a population-based registry study. An International Journal of Obstetrics & Gynaecology. [Internet]. 2020 May; 127(13): 1628-1635. https://doi.org/10.1111/1471-0528.16328

[45] Alternatives to Hysterectomy: Myomectomy, Endometrial Ablation, Uterine Fibroid Embolization [Internet]. [cited 2020 Dec 21]. Available from: https://www.webmd.com/women/guide/alternatives-to-hysterectomy#1

[46] Laughlin-Tommaso SK, Khan Z, Weaver AL, Smith CY, Rocca WA, Stewart EA. Cardiovascular and metabolic morbidity after hysterectomy with ovarian conservation: a cohort study. Menopause N Y N. 2018 May;25(5):483–92. https://doi.org/10.1097/GME.0000000000001043

[47] Ding D-C, Tsai I-J, Hsu CY, Wang J-H, Lin S-Z. Hysterectomy is associated with higher risk of coronary artery disease. Medicine (Baltimore) [Internet]. 2018 Apr 20;97(16). https://doi.org/10.1097/MD.0000000000010421

[48] Rivera CM, Grossardt BR, Rhodes DJ, Brown RD, Roger VL, Melton LJ, et al. Increased cardiovascular mortality following early bilateral oophorectomy. Menopause N Y N. 2009;16(1):15–23. https://doi.org/10.1097/gme.0b013e31818888f7

[49] Healthwise Staff. Endometriosis: Should I Use Hormone Therapy? [Internet]. [cited 2020 Dec 21]. Available from: https://myhealth.alberta.ca:443/Health/Pages/conditions.aspx?hwid=tv7240.

[50] Song JW, Chung KC. Observational Studies: Cohort and Case-Control Studies. Plast Reconstr Surg. 2010 Dec;126(6):2234–42. https://doi.org/10.1097/PRS.0b013e3181f44abc

[51] Husby GK, Haugen RS, Moen MH. Diagnostic delay in women with pain and endometriosis. Acta Obstet Gynecol Scand. 2003 Jul;82(7):649–53. https://doi.org/10.1034/j.1600-0412.2003.00168.x

[52] Howard G, Wagenknecht LE, Burke GL, Diez-Roux A, Evans GW, McGovern P, et al. Cigarette smoking and progression of atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study. JAMA. 1998 Jan 14;279(2):119–24. https://doi.org/10.1001/jama.279.2.119

[53] Healthwise Staff. Endometriosis [Internet]. HealthLink BC. [cited 2020 Dec 21]. Available from: https://www.healthlinkbc.ca/health-topics/hw102998

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