Accepted Manuscript

The Link Between Endometriosis, Atherosclerotic Cardiovascular Disease, and the Health of Women Midlife

Omur Taskin MD , Kiran Rikhraj , Justin Tan MD , Tara Sedlak MD , Timothy C. Rowe MD , Mohamed A. Bedaiwy MD

PII: S1553-4650(19)30206-7
DOI: https://doi.org/10.1016/j.jmig.2019.02.022
Reference: JMIG 3809

To appear in: *The Journal of Minimally Invasive Gynecology*

Received date: 12 October 2018
Revised date: 14 February 2019
Accepted date: 19 February 2019

Please cite this article as: Omur Taskin MD , Kiran Rikhraj , Justin Tan MD , Tara Sedlak MD , Timothy C. Rowe MD , Mohamed A. Bedaiwy MD , The Link Between Endometriosis, Atherosclerotic Cardiovascular Disease, and the Health of Women Midlife, *The Journal of Minimally Invasive Gynecology* (2019), doi: https://doi.org/10.1016/j.jmig.2019.02.022

Special Article

The Link Between Endometriosis, Atherosclerotic Cardiovascular Disease, and the Health of Women Midlife

Omur Taskin, MD, Kiran Rikhraj, Justin Tan, MD, Tara Sedlak, MD, Timothy C. Rowe, MD, and Mohamed A. Bedaiwy, MD

From the Department of Obstetrics and Gynecology (Drs Taskin, Tan, Rowe, Bedaiwy, and Med.student Rikhraj), and Department of Cardiology (Dr Sedlak), University of British Columbia, Vancouver, BC, Canada.

Corresponding author: Mohamed A. Bedaiwy, MD, Professor and Head, Division of Reproductive Endocrinology and Infertility, British Columbia Women's Hospital & Health Center, University of British Columbia, 4500 Oak Street, Vancouver, BC, Canada, V6H 3N1. E-mail: mohamed.bedaiwy@cw.bc.ca Telephone: 604.875.2000 ext. 4310; Facsimile: 604.875.2725

The authors declare that they have no conflicts of interest.

Abstract

Endometriosis and atherosclerotic cardiovascular disease (ASCVD) are both essentially diseases of inflammation. It is well established that inflammation is the leading mechanism in the initiation and maintenance of vascular injury and in the development and progression of atherosclerosis. Thus, if women with endometriosis do indeed have increased general inflammation, they are at increased risk of developing microvascular dysfunction and atherosclerosis. Currently available evidence suggests that young female patients with proven endometriosis may be at a higher lifetime risk of developing cardiovascular disease; this may be unrecognized owing to the relatively young age of women found to have endometriosis. Other mechanisms proposed to explain the link between endometriosis and ASCVD include similarities in the genetic underpinnings of each condition including microRNA dysfunction and the association between endometriosis and early menopause, a risk for developing ASCVD. While physicians today primarily focus on traditional risk factors when evaluating an individual female patient's risk of developing ASCVD, we believe that a history of endometriosis should be included as a possible risk factor and needs further exploration. A better understanding of the mechanisms linking endometriosis with ASCVD will hopefully guide the implementation of new therapies to mitigate the increased cardiovascular disease burden that patients with endometriosis might face.

Keywords: Endothelial dysfunction; Inflammation; Menopause; Microvascular dysfunction; Vascular injury

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in women, with an incidence that rises sharply after menopause [1]. Typically, the first presentation of ASCVD in women is seen 10 years later than in men and is thought to be related to the decline in ovarian hormone concentrations during the menopausal transition [1]. While both men and women experience the sequelae of ASCVD, they do not have similar risk factors, clinical presentation, comparable treatments, or equivalent clinical outcomes. The population-adjusted risk of cardiovascular mortality is greater for women (20.9%) than men (14.9%) [2] making it essential to recognize risk factors and signs and symptoms as early as possible to improve disease management and outcomes. A recent timely joint statement from the American Heart Association and the American College of Obstetricians and Gynecologists encourages the recognition of ASCVD risk in both young and postmenopausal women and counseling or referral to the appropriate sources with the goal of preventing future cardiovascular events [3]. It does not acknowledge the possibility that endometriosis is also a risk factor for the development of ASCVD. Moreover, a potential link between endometriosis and sex-specific nontraditional risk factors for ASCVD (preterm delivery, hypertensive disorders of pregnancy, autoimmune diseases, depression) is supported by growing evidence [4].

Endometriosis, affecting 6% to 10% of the female population of reproductive age, has been implicated in several chronic diseases including cardiovascular diseases related to systemic inflammation, increased oxidative stress, and an atherogenic lipid profile [5–7]. Two recent large-scale prospective studies using the same cohort showed a higher risk of myocardial infarction, angiographically confirmed angina, coronary artery bypass graft surgery, coronary angioplasty procedure or stenting, or a combination of these, in female patients with laparoscopically confirmed endometriosis [8,9].

A recent systematic review explored the association between endometriosis, markers of atherogenic lipid profiles, endothelial dysfunction, and subclinical atherosclerosis [10]. Although further studies are warranted to investigate the causal relationship between ASCVD and endometriosis, several mechanisms have been proposed to explain the possible relationship between the two chronic conditions: (1) a common pathogenesis of chronic inflammation; (2) genetic similarities; (3) microRNA dysfunction; and (4) the association between endometriosis and early menopause, a well-established risk for developing ASCVD.

Common pathogenesis of chronic inflammation

Endometriosis and ASCVD are both essentially diseases of inflammation. It is well-established that inflammation is one of the leading mechanisms in the initiation and maintenance of vascular injury and in the development and progression of atherosclerosis, the key long-term pathogenic process in ASCVD. The overall concentration of T-lymphocytes and macrophages expressing interferon-gamma (INF-y), a proinflammatory cytokine, has been found to be significantly greater in women with endometriosis [11,12]. Women with endometriosis also show significantly higher markers of endothelial inflammation and activation [13,14]. Importantly, Santanam et al [6] pointed out that both atherosclerotic plaque and the peritoneal fluid of female patients with endometriosis have an abundance of inflammatory cytokines, chemokines and growth factors that are involved in the generation of localized inflammation. Further, women with endometriosis are at increased risk of developing microvascular dysfunction and atherosclerosis [15]. The dysregulated production of IFN-γ has been reported as an underlying association between endometriosis and atherosclerosis [4], leaving female patients with endometriosis at increased risk of developing microvascular dysfunction and atherosclerosis.

Because inflammation plays an important and at least partially reversible role in the development of arterial stiffness, inflammatory markers are useful additional indices in the clinical assessment of cardiovascular risk in women with endometriosis [16]. Combining assessment of arterial stiffness and measurement of inflammatory markers may improve noninvasive early assessment of cardiovascular risk, and reducing inflammation can decrease microvascular dysfunction [11,13,16]. In addition, statins and other cholesterol-reducing agents have beneficial effects and have been shown to have a potential therapeutic role in female patients with endometriosis [17]. Metformin has anti-inflammatory properties, a modulatory effect on ovarian steroid production, and reduces the levels of serum cytokines, thus having potential to inhibit the development of endometriosis [18].

Genetic similarities

There appears to be a genetic link between the development of endometriosis and ASCVD. To date, a total of 24 GWAS/OMIM/DEG genes have been identified as associated with both endometriosis and ASCVD [19] and are involved in the vitamin B metabolic pathway that plays an important role in overall metabolism, genetic and environmental information processing, cellular processes, and human diseases [19]. Endometriosis shares a genetic pathway with myocardial infarction, coronary artery disease, and sleep disorders. As an example, the CDKN2CBAS genetic variants on chromosome 9 are significantly associated with the development of endometriosis and with acute myocardial infarction [20].

Endometriosis, ASCVD and microRNA dysfunction

The discovery of microRNAs opens up new avenues for research about the link between endometriosis and ASCVD. MicroRNAs are small non-coding RNA molecules that can regulate gene expression and thus promote or prevent protein synthesis [21] as well as regulate the

expression of adhesion molecules that are highly expressed in the cardiovascular system. Abnormal levels of expression of some microRNA have been observed in multiple conditions affecting human reproductive organs and processes, including preeclampsia, endometrioid endometrial adenocarcinoma, uterine leiomyomas, ovarian adenocarcinoma, endometriosis, and recurrent pregnancy loss [21] as well as most medical disciplines including reproductive health, cardiovascular health, and neurodegenerative disease. Further research of mitochondrial dysfunction could help clinicians to better understand the shared pathophysiology of seemingly unrelated diseases.

Endometriosis and ovarian function

Early menopause is a well-established risk factor for ASCVD, and females who enter menopause before the average age have been shown to have a greater risk of clinical cardiovascular disease. This is primarily attributed to estrogen deficiency during menopause as estrogen has positive effects on the vascular system prior to menopause because it increases the release of nitric oxide in arterial endothelium (leading to vasodilation), regulates prostaglandin production, and inhibits smooth muscle proliferation [22]. These effects are mediated by estrogen receptor (ER) isoforms, and reduced levels of ERα and ERα polymorphism are linked to the severity and risk of coronary artery disease [23]. Further, overexpression of ERβ in endometriosis suppresses ERα activity, resulting in increased cyclo-oxygenase-2 levels, which contributes to progesterone resistance, inflammation, hypoxia, oxidative stress, and vascular smooth muscle cell proliferation that lead to endothelial dysfunction and consequently ASCVD [24].

Association between endometriosis and early menopause

A number of studies have established the link between endometriosis and early menopause [25–27]. A prospective Japanese study of 49,927 female nurses ≥25 years showed that a past history of endometriosis was significantly associated with earlier onset of menopause, with an odds ratio of 1.32 (95% confidence interval [CI] 1.07-1.64) [25]. These findings were corroborated by a 2011 retrospective case-controlled study of 5,113 postmenopausal women in the United Kingdom [26]. A closer analysis showed that endometriosis causing infertility was significantly associated with earlier onset of menopause, even after adjustment for age, age at menarche, number of pregnancies, smoking before menopause, body mass index, and other causes of infertility (odds ratio 3.06; 95% CI 1.85-5.06) [25]. Thus, while endometriosis itself is associated with earlier menopause, endometriosis causing infertility increases the risk of early menopause further. This may be in part because of the impact of endometriosis and endometriosis-related surgery on ovarian reserve [27].

Hormone replacement therapy (HRT) during perimenopause has shown that estrogen therapy is cardioprotective [28]. However, some studies have reported otherwise owing to the timing of HRT administration because women may be more likely to have established atherosclerosis owing to their age and number of years in an estrogen-deficient state [29,30]. Women receiving HRT early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of cancer or venous thrombosis [31]. Notably, while estrogen is generally cardioprotective in women with early atherogenesis, it is potentially harmful in women with established atherosclerosis [1]. Women who began taking HRT within 10 years of menopause had the 0.76 (95% CI 0.50-1.16) hazard ratio for coronary heart disease, and the estimated absolute excess risk for coronary heart disease was -6 per 10,000 person-years [30]. Furthermore, in a subsequent analysis of women aged 50 to 59 years, a trend toward reduced total mortality with HRT (with or without progestin) was noted in women within the first 10 years after menopause [30]. In postmenopausal women

free of cardiovascular disease who were stratified according to time since menopause and randomly assigned to receive either placebo or estrogen treatment, there was significantly slower progression of coronary artery intima media thickness among women who initiated HRT within six years after menopause [32]. The “timing hypothesis” refers to the concept that the cardiovascular effects of HRT strongly depend on individual vascular health and the time of initiating HRT relative to menopause.

We predict that a history of endometriosis will be shown to be a factor in screening for ASCVD and in considering initiation of HRT during the transition to menopause because of its association with increased ASCVD risk.

Conclusion

Although the actual risk of ASCVD in female patients with endometriosis is unknown, evidence suggests that young women with endometriosis and possibly older women with a previous history of endometriosis may be at higher risk of cardiovascular disease, particularly if early menopause is induced.

Future research is warranted to assess the global risk of ASCVD both at diagnosis of endometriosis and during follow-up. Types and stages of endometriosis associated with higher endothelial disease and subclinical atherosclerosis requiring therapy need to be determined as well as the surgical or medical therapy necessary to improve endothelial disease. It seems important to determine at what point to include a cardiologist in the standard treatment of women with endometriosis. A multidisciplinary approach is needed to improve the life-long health of patients with endometriosis.

References

1. Newson L. Menopause and cardiovascular disease. *Post Reprod Health.* 2018; 24:44–49.

2. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.

3. Brown HL, Warner JJ, Gianos E, 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;137:e843–e852.

4. Glavind MT, Forman A, Arendt LH, Nielsen K, Henriksen TB. Endometriosis and pregnancy complications: a Danish cohort study. *Fertil Steril*. 2017;107:160–166.

5. Bulun SE. Endometriosis. *N Engl J Med*. 2009;360:268–279.

6. Santanam N, Song M, Rong R, Murphy AA, Parthasarathy S. Atherosclerosis, oxidation and endometriosis. *Free Radic Res*. 2002;36:1315–1321.

7. Kvaskoff M, Mu F, Terry KL, Harris HR, Poole EM, Farland L, Missmer SA. Endometriosis: a high-risk population for major chronic diseases? *Hum Reprod Update*. 2015;21:500–516.

8. Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Missmer SA. Endometriosis and risk of coronary heart disease. *Circ Cardiovasc Qual Outcomes*. 2016;9:257–264.

9. Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Forman JP, Missmer SA. Association between endometriosis and hypercholesterolemia or hypertension. *Hypertension*. 2017;70:59–65.

10. Tan J, Taskin O, Bedaiwy M. Risk of cardiovascular disease may be increased in women with endometriosis: a systematic review of the evidence. *Fertil Steril*. 2018;110(4 suppl):e390–e391.

11. Mormile R, Vittori G, Squarcia U. How much truth is there in the association between endometriosis and atherosclerosis? *J Pediatr Endocr Metab*. 2013;26:797–798.

12. Bedaiwy MA, Falcone T, Sharma RK, Goldberg JM, Attaran M, Nelson DR, Agarwal A. Prediction of endometriosis with serum and peritoneal fluid markers: a prospective controlled trial. *Hum Reprod*. 2002;17:426–431.

13. Santoro L, D'Onofrio F, Campo S, et al. Endothelial dysfunction but not increased carotid intima-media thickness in young European women with endometriosis. *Hum Reprod*. 2012;27:1320–1326.

14. Santoro L, D'Onofrio F, Campo S, et al. Regression of endothelial dysfunction in patients with endometriosis after surgical treatment: a 2-year follow-up study. *Hum Reprod*. 2014;29:1205–1210.

15. Capobianco A, Rovere-Querini P. Endometriosis, a disease of the macrophage. *Front Immunol*. 2013;4:9.

16. Mozos I, Malainer C, Horbańczuk J, et al. Inflammatory markers for arterial stiffness in cardiovascular diseases. *Front Immunol*. 2017;8:1058.

17. Gibran L, Maranhao RC, Abrao MS, Baracat EC, Podgaec S. Could statins constitute a novel treatment for endometriosis? Systematic review of the literature. *Eur J Obstet Gynecol Reprod Biol*. 2014;179:153–158.

18. Foda A, Abdel Aal IA. Metformin as a new therapy for endometriosis, its effects on both clinical picture and cytokines profile. *Middle East Fertil Soc J*. 2012;17:262–267.

19. Tarin JJ, Garcia-Perez MA, Hamatani T, Cano A. Infertility etiologies are genetically and clinically linked with other diseases in single meta-diseases. *Reprod Biol Endocrinol*. 2015;13:31.

20. Hirata K, Takahashi A, Nakamura Y, et al. A genome-wide association study identifies genetic variants in the CDKN2BAS locus associated with endometriosis in Japanese. *Nat Genet*. 2010;42:707–710.

21. Santamaria X, Taylor H. MicroRNA and gynecological reproductive diseases. *Fertil Steril.* 2014;101:1545–1551.

22. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women–2011 update: a guideline from the American Heart Association. *Circulation*. 2011;123:1243–1262

23. Deroo BJ, Korach KS. Estrogen receptors and human disease. *J Clin Invest*. 2006;116:561–570.

24. Bulun SE, Monsavais D, Payone ME, et al. Role of estrogen receptor-ß in endometriosis. *Semin Reprod Med*. 2012;30:39–45.

25. Yasui T, Hayashi K, Mizunuma H, et al. Association of endometriosis-related infertility with age at menopause. *Maturitas*. 2011;69:279–283.

26. Pokoradi A, Iversen L, Hannaford PC. Factors associated with age of onset and type of menopause in a cohort of UK women. *Am J Obstet Gynecol*. 2011;205:34.e1–34.e13.

27. Somigliana E, Vigano P, Filippi F, Papaleo E, Benaglia L, Candiani M, Vercellini P. Fertility preservation in women with endometriosis: for all, for some, for none? *Hum Reprod*. 2015;30:1280–1286.

28. Stevenson JC. Long-term benefits and risks of HRT (Section 11): Cardiovascular disease. *Post Reprod Health*. 2016;22:80–82.

29. Santen RJ. Use of cardiovascular age for assessing risks and benefits of menopausal hormone therapy. *Menopause*. 2017;24:589–595.

30. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297:1465–1477.

31. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ*. 2012;345:e6409.

32. Hodis HN, Mack WJ, Henderson VW, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med*. 2016;374:1221–1231.