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JMIG The Journal of Minimally Invasive Gynecology

Letters to the Editor

Regarding: "Link between Endometriosis, Atherosclerotic Cardiovascular Disease, and the Health of Women Midlife"

To the Editor:

Because of the reported association between endometriosis and cardiovascular disease [1,2], Taskin et al [3] suggested that endometriosis should be considered a risk factor for atherosclerotic cardiovascular disease requiring specific counseling and prevention [4]. Both endometriosis and cardiovascular disease are diseases characterized by chronic inflammation, with potentially underlying genetic similarities. The premature menopause in endometriosis might be a cofactor increasing cardiovascular risk. It is surprising that in these excellent articles, the methodologic problems and potential biases are not discussed adequately [1-4].

The conclusion that endometriosis is associated with increased cardiovascular risk should be considered with caution. The conclusions made in these large epidemiologic studies are based on hospital discharge records with the diagnosis of endometriosis. However, the type of endometriosis in these studies is not specified, and the content of subtle, typical, cystic ovarian, and deep endometriosis is variable. In women with pain, the prevalence of subtle, typical, cystic ovarian, and deep endometriosis is estimated at more than 80%, around 50%, less than 20%, and less than 5%, respectively [5]. The recognition of subtle lesions varies with the expertise of the surgeon, but when the pelvis is scrutinized when no other pathology is found, subtle lesions can be found in almost all women with pain and/or infertility. Although it remains unclear whether subtle lesions represent a pathologic or a normal physiologic condition occurring intermittently in all women [6,7], many women with the diagnosis of endometriosis according to hospital records are at risk of having subtle lesions only. This problem in the interpretation of the epidemiology of endometriosis [8,9] and the interpretation of its association with fat intake [10] is well known.

More problematic is that the diagnosis of endometriosis is made during a laparoscopy, which is performed on account of pain or infertility. Therefore, it is highly likely that also laparoscopy and pain and infertility will be found to be statistically associated with the same increased cardiovascular risk as that found with endometriosis. Association studies, moreover, cannot distinguish between the effect of endometriosis and the effect of other factors associated with endometriosis, such as the intake of pain killers, ovulation induction, in vitro fertilization, repetitive surgery, and a higher risk of a hysterectomy often with an ovariectomy. Each of these factors will, therefore, also probably be found to be statistically associated with cardiovascular disease if investigated. We, therefore, suggest that until the mechanisms become apparent, it is premature to conclude that cardiovascular disease and endometriosis are associated. Until appropriate multivariate analysis, and a sufficiently large dataset.

The strength of the association between endometriosis and most factors such as pain, infertility, and pregnancy disorders [11], as well as preeclampsia and small for gestational age babies, increases with the severity of endometriosis. In addition, the genetic risk [12] of developing endometriosis increases with the severity of the disease. Clinically, an increased cardiovascular risk in women with deep endometriosis is not obvious. It, therefore, seems important to check whether the risk of cardiovascular disease increases with the severity of endometriosis.

The authors [3] appropriately discuss genetic similarities between the pathophysiology of endometriosis and cardiovascular disease to explain the observed link. This discussion is consistent with the genetic-epigenetic pathophysiology of endometriosis [12], which suggests that endometriosis-associated pregnancy problems are caused by common genetic factors transmitted at birth, increasing the susceptibility for developing endometriosis, and increasing the risk of placentation problems and hypertensive disease. It is therefore not surprising that endometriosis-associated pregnancy problems do not disappear after the resection of deep endometriosis. Because we can assume that most endometriosis lesions are surgically treated during the laparoscopy conducted to make the diagnosis, the association based on hospital discharge records similarly suggests that removal of endometriosis does not eliminate the risk. This argument suggests that eventual cardiovascular risks could be caused by hereditary and genetic similarities. However, it can equally be explained as an effect caused by one of the endometriosis-associated treatments and by the stress caused by the diagnosis of "endometriosis." Adding cardiovascular risk to the stress already caused by the prospects of infertility, chronic pain, surgery, more hysterectomies, and by the disease often considered chronic and recurrent, might even increase the stress and cardiovascular risk.

In conclusion, the presence of many uncertainties should make us prudent enough to exercise caution before

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concluding that endometriosis is associated with cardiovascular disease. We need to keep an open mind for all other factors that might cause this apparent statistical association. A common genetic-epigenetic constitution and the susceptibility to oxidative stress might offer an explanation. However, hitherto unrecognized cardiovascular risks of (repetitive) surgery, pain killers, infertility therapies, the decreased quality of life, and the chronic stress caused by the diagnosis of endometriosis cannot be excluded.

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https://doi.org/10.1016/j.jmig.2019.09.785