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Short Communication

Does exist a correlation between endometriosis and thrombophilic disorders? A pilot study

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ABSTRACT

Objective: At present, there is growing evidence of the existence of a genetic predisposition in both thrombophilic disorders and endometriosis. The aim of our study was to evaluate for the first time the prevalence of some thrombophilic disorders in patients with endometriosis.
Materials and methods: We conducted a retrospective study on 138 patients with endometriosis and 278 healthy control women. All women were subjected to a blood examination testing for thrombophilic screening and the variables examined were: hyperhomocysteinemia, factor V Leiden and factor II prothrombin G20210A mutations in heterozygosis and homozigosis.
Results: A significant reduced prevalence ($p < 0.05$) of factor V Leiden mutation in endometriosis patients was found, whereas no significant differences ($p = NS$) for factor II and hyperhomocysteinemia were observed.
Conclusion: Our preliminary data do not show any association between thrombophilic condition and endometriosis. Before assuming hormonal therapies, a thrombophilic plasmatic screening seems to be unnecessary in patients affected by endometriosis.

Introduction

A genetic predisposition has been demonstrated for both endometriosis and thrombophilic disorders [1,2]. In the thrombophilic diseases thrombohemorrhagic balance is maintained by complex interactions among coagulation and fibrinolytic systems, platelets and the vessel wall. Thrombophilic states can be divided into heritable and acquired types. In caucasian population, the incidence of factor II prothrombin G20210A and factor V Leiden mutation was approximately 2% and 2–3%, respectively [3,4]. Caucasian population is also characterized by increased plasma homocysteine levels (>15 mmol/L), due to a mutation in methylenetetrahydrofolate reductase gene, in 5–10% of cases [5]. The incidence of adverse events was relatively low in contrast to the incidence of thrombophilic abnormalities in the general population. Factor V Leiden and factor II prothrombin mutations were present in approximately 10% [6] and 18% [7] of patients with venous thrombosis, respectively. Hyperhomocysteinemia was associated with >2-fold increased risk of venous thromboembolism [5].

Endometriosis is a common gynecologic disorder characterized by the displacement of endometrial tissue at ectopic locations [8]. It is a chronic disease affecting 10–15% of women in their reproductive years, responsible for symptoms which can heavily impact a patient's quality of life such as non-menstrual pain, dysmenorrhea and dyspareunia [8]. Although the predisposition to endometriosis is likely multifactorial, a genetic component appears evident. While specific genes involved in the pathology have yet to be identified, endometriosis-associated genes involved in steroid signaling, matrix degradation, inflammation and detoxification have been reported [8]. Moreover, evidence for a potential link between endometriosis and autoimmune disease with genetic transmission has been found [9,10].

Since thrombophilic disorders have a genetic component, and so does endometriosis, patients with endometriosis could be at higher risk of thrombophilia? No studies on this association are reported. Aim of the study is to define for the first time the prevalence of the main genetic thrombophilic disorders (factor V Leiden mutation, factor II prothrombin G20210A mutation, hyperhomocysteinemia) in patients with endometriosis.

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Materials and methods

From December 2012 to December 2014 we retrospectively evaluated a cohort of 138 consecutive women with endometriosis who referred to our center. All patients after performing pelvic bimanual examination and transvaginal sonography (TVS) received a clinical diagnosis of endometriosis. TVS is considered today the first-line imaging technique in the diagnosis of ovarian and/or deep infiltrating endometriosis because of its accuracy, low cost and patient acceptability. Clinicians are recommended to perform TVS to diagnose or to exclude an ovarian endometrioma [11] and ultrasound examination was performed by sonographers at least 6 years experienced in endometriosis. Studies reported that the high specificity of TVS would make it a useful test for confirming DIE. In particular, an ultrasonographic diagnosis of DIE could be used to reduce the need for diagnostic laparoscopy [12].

Each patient underwent a blood test for thrombophilic screening, which was analyzed by the Department of Angiology of our institution. Blood was collected from antecubital vein and plasma was prepared by centrifugation for 20 min at 2,000 g at room temperature; plasma aliquots for DNA extraction were frozen and stored at −70 °C until analysis. Thrombophilia screening included the following tests: homocysteine levels, DNA analysis for factor V mutation and the presence of G20210A mutation of the prothrombin gene in heterozygosis and homozigosis. A cohort of 278 age, height and weight-matched healthy women evaluated at the Department of Angiology of our institution was also used as control group. Inclusion criteria for endometriosis group were: ultrasound diagnosis of superficial, ovarian or deep infiltrating endometriosis and age between 18 and 45 years. Exclusion criteria for all subjects examined were: hormonal treatment in the three months before the blood examination and various causes of hyperhomocysteinemia such as taking medications (methotrexate, phenytoin, carbamazepine, isoniazid) and the presence of some chronic systemic illness, such as hypothyroidism, lupus erythematosus rheumatoid arthritis and, psoriasis. The study was approved by the Institutional Review Board of the Department of Obstetrics, Gynecology and Reproductive Biology of the University of Bologna. All subjects (study and control groups) gave their informed consent for all the investigations. All procedures were in accordance with the Helsinki declaration of 1975.

The normally distributed continuous variables were expressed in terms of mean ± standard deviation (SD), and were analyzed by unpaired student's t test. Grouping variables were described in terms of proportions or percentages and differences were investigated by Fisher's exact test. A p value <0.05 was accepted as statistically significant.

Results

Patients characteristic and data regarding the incidence of thrombophilic disease in the two groups of subjects were detailed in Table 1. No significance differences in terms of age, body mass index (BMI), prevalence of factor II mutation and hyperhomocysteinemia in the two groups of subjects were evidenced. Only a significant reduced prevalence ($p < 0.05$) of factor V Leiden mutation in endometriosis patients was observed.

Table 1
Characteristics and incidence of thrombophilic mutations in patients with endometriosis and control women.

	Endometriosis group (n. 138)	Control group (n. 278)	p value
Age (mean ± SD)	36.0 ± 6.3	35.0 ± 5.8	0.108
BMI (mean ± SD)	22.3 ± 3.4	21.7 ± 3.5	0.097
Factor V Leiden n. (%)	2 (1.5)	19 (6.8)	0.017[a]
Factor II prothrombin G20210A n. (%)	4 (2.9)	16 (5.7)	0.234
Hyperhomocysteinemia n. (%)	12 (8.7)	11 (3.9)	0.065
Mutations in homozygosis n. (%)	0 (0)	0 (0)	

[a] Significant by Fisher's exact test.

Discussion

Thrombophilia is an heritable or acquired defect in blood coagulation that leads to a predisposition towards thrombosis. Thrombus is a solid mass of blood components that can fragment and block the downstream vessels. Physiological blood coagulation is a complex mechanism that is mediated through the interaction of numerous plasma proteins. Heritable thrombophilia is caused most commonly by mutations in the genes for coagulation factors II and V. Factor V Leiden and prothrombin G20210A mutation are genetic thrombophilic disorders associated with increased procoagulant activity.

Endometriosis is a chronic disease defined as the presence of endometrial-like tissue outside the uterus. The pathophysiology of endometriosis remains a subject of debate, however, a genetic component has been hypothesized [8]. Both genetic and environmental factors may be involved in the disease. The risk for first-degree relatives of women with severe endometriosis is six times higher than that for relatives of unaffected women [8]. Endometriosis has been associated with inflammation, attenuated progesterone action at the endometrium level and neoangiogenesis and the association between these processes and specific genes has been advanced [8]. Endometriosis mimics several aspects typical of various autoimmune diseases, including elevated cytokines levels and cell-mediated abnormalities [9]. An association between endometriosis and autoimmune disease with genetic transmission such as bowel diseases (Crohn's disease and ulcerative colitis), thyroid diseases (Graves' disease and Hashimoto's thyroiditis) and celiac disease have been reported [9,10].

Based on these considerations, this preliminary study investigated for the first time the screening for thrombophilia in a population of childbearing women suffering from endometriosis and showed that the prevalence of factor II mutation and hyperhomocysteinemia in patients with endometriosis was not different from that of the general population. Regarding prevalence of factor V, we found a lower prevalence of the factor V mutation in the endometriosis group compared to controls and at the moment we are unable to explain this finding. Therefore, a systematic thrombophilic serum screening does not seem justified in patients with endometriosis and endometriosis itself does not appear to increase thrombophilic risk.

To date there is no permanent cure for endometriosis and conservative management for this condition consists of hormonal therapy. Often it is necessary a long hormonal treatment with the goal of maximizing the medical therapy avoiding surgery. Estroprogestins and progestins were shown to be effective in treating pain in women affected by endometriosis. Thus the continuous use of these drugs to improve the main symptoms of endometriosis were considered to date the first-line medical therapy for this disease [13,14]. Another important role of this therapy is also to delay possible recurrences for as long as possible [14].

A slight increase of the relative risk of venous thromboembolism in women using combined hormonal contraceptives (COC) has been reported [5]. In particular, among women with thrombogenic mutations (as mutation of factor V Leiden and factor II, hyperhomocysteinemia), COC users have two to twenty-fold higher risk of thrombosis than non-users [15,16]. On the other hand,

thrombophilia screening is expensive, time-consuming and must be targeted to selected patients with prior history of venous thromboembolism or to their first-degree relatives [5,17]. These preliminary data suggest that even in patients with endometriosis who must be subjected to long-term treatment with COC, universal thrombophilia screening is not supported by current evidence, but further studies are needed.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

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