HJOG An Obstetrics and Gynecology International Journal

Review

HJOG 2020, 19 (2), 65-76

Revealing the enigma of coagulation in endometriosis: the risk of thrombosis and the role of antithrombotic treatment

Theoni Kanellopoulou

Department of Clinical Hematology, Blood Bank, Hemostasis, Onassis Cardiac Surgery Center, Greece

Corresponding Author

Theoni Kanellopoulou, MD, PhD, Onassis Cardiac Surgery Center 356, Andra Syggrou ave.
176 74 Kallithea-Attiki, Greece, Tel: +30-2109493953, Fax:+30-2109493867, Email: theokanel@gmail.com

Abstract

Endometriosis is a chronic inflammatory disease of women of reproductive age that is defined by the presence of ectopic endometrium. The pathophysiology of the disease is poorly understood, however platelet activation play a crucial role in initiation of inflammation and fibrinogenesis, which in term further activate the coagulation cascade. The relationship between inflammation and coagulation motivated researchers to study whether patients are in a hypercoagulable state and if endometriosis represent an independent risk factor for venous thromboembolism or cardiovascular risk. This review article focuses on the role of coagulation, the risk of thrombosis and a possible beneficial effect of antithrombotic-treatment.

Key words: Endometriosis, inflammation, platelets, thrombosis, antithrombotic treatment

Introduction

Endometriosis is a chronic disease defined as the presence of endometrial tissue outside the uterus. It is an estrogen-dependent disease, affecting roughly 6–10% of women of reproductive age. It is a major contributing cause for dysmenorrhoea, pelvic pain and infertility impacting negatively on the quality of life Three clinically different phenotypes have been described: Endometriotic implants on the surface of the pelvic peritoneum (PE), ovarian endometrioma (OE) and deep infiltrating endometriosis (DIE), the latter being the most severe form of the disease[1].

The pathophysiology of endometriosis is poorly understood and endometriotic lesions can be viewed as wounds that undergo repeated tissue injury and repair, ultimately leading to fibrosis[2].It has recently been proposed that women with endometriosis may be in an inflammatory and hypercoagulable state and even though inflammation and coagulation are separate entities is increasingly evident that interact each other[3,4].Due to the major role of coagulation in disease development, in this review article we study the actual thrombotic risk in women with endome-

triosis and discuss a feasible role of antithrombotic treatment in disease remission.

Pathophysiology: the role of coagulation

The activation of coagulation in women with endometriosis is actually consistent with the notion that endometriotic lesions undergo cyclic bleeding resulting in repeated tissue injury and repair, which in turn causes platelet activation and aggregation[4]. The activated platelets promote the release of other procoagulant factors like von Willebrand factor, thromboxan A2 (TXA2) causing further platelet aggregation and activation of coagulation cascade. Once the platelets are activated and aggregated, they promote angiogenesis and cellular proliferation, causing smooth muscle metaplasia and ultimately fibrosis[5]. The activated platelets could also induce the release microparticles (MPs). Studies in other diseases have shown that platelet-MPs play major role in coagulation, as they are highly thrombogenic and elevated MPs have been found in almost all thrombotic diseases and conditions associated with inflammation, cellular activation and angiogenesis. Munros et al. provided data showing higher levels of total MPs in patients with DIE compared with OE or without endometriosis. The higher MPs levels in patients with DIE may represent the more intense grade of inflammation and angiogenesis in this more aggressive type[6].

After tissue injury, platelets release angiogenic proteins to promote wound healing. In later stage of healing, pro-angiogenic proteins are compensated by the release of angiogenic suppressors from stromal cells and platelets in order to prevent uninhibited growth. Endometriotic stromal cells have elevated expression of tissue factor (TF), and the peritoneal fluid from women with endometriosis has higher concentration of TF as well as thrombin, which is a potent inducer of platelet activation[4]. Following vascular disruption, perivascular TF binds to circulating factor VIIa to mediate the activation of both factor IX and X and ultimately to generate thrombin[7]. An altered expression of several components of the fibrinolytic system in the endometrium and peritoneal fluid of women with the disease has been suggested as a key factor in the establishment of the endometriotic lesions. There is evidence of increased fibrinolytic activity in the eutopic endometrium of these women, resulting in endometrial fragments with a high potential to enable implantation. Proteolytic status is determined by the imbalance between plasminogen activators and plasminogen activator inhibitors, which are expressed differently depending on the type of lesion considered and the stage of the disease[8].

The risk of thrombosis

Coagulation Factors

Review of the literature disclosed many clinical studies investigating a possible impact of activation of the coagulation during disease development on laboratory clotting tests. Wu et al. reported that women with OE had a significantly shortened both activated partial thromboplastin time (APTT) and thrombin time (TT) and elevated fibrinogen (FIB) levels as compared with controls, although most of the results were within the normal range. Moreover, the co-occurrence of DIE or PE and more severe stage appeared to further decrease APTT, nevertheless the difference was not statistical significant[3]. In line with the previous study, Vigano et al. also documented a statistically significant shortening of the APTT in women with OE[9] and Lin et al. found that the levels of PT and TT in patients with OE were significantly shorter and levels of FIB and D-dimer significantly higher than those with benign ovarian cysts[10]. Ding et al. showed that women with OE had a significantly higher platelet activation rate and platelet aggregation rate, elevated plasma D-dimer, FIB, fibrinogen

degradation products (FDPs), as well as shortened TT. However, no difference was observed in PT, APTT[11].

All previous studies published positive results in patients with OE. It should be considered that an endometrioma contains free iron, proteolytic enzymes, and inflammatory molecules in concentrations notably higher than those present in peripheral blood or in other types of benign cysts. Sanchez et al. showed that concentrations of some coagulation parameters such as plasminogen activator inhibitor-1 (PAI-1), PAI-2, and urokinase plasminogen activator were found to be in the same range or even much higher in the endometrioma fluid compared to malignant tumors, and it is reasonable to think that this content may leak from the cyst and be absorbed through the peritoneum[12]. The large amounts of coagulation-related products present in ovarian endometrioma is remarkably described in a case of endometriotic cyst rupture that caused a rapid but transient elevation in plasma D-dimer levels[13].

Genes of thrombotic risk

Due to genetic predisposition, there was a concern whether patients share similar genes of high thromboembolic risk. However, no association between inherited thrombophilia and endometriosis has been reported so far, in order to support costly and time-consuming thrombophilia-screening tests in this group of patients.

In a small study, screening for thrombophilia showed that the prevalence of prothrombin G20210A mutation and hyperhomocysteinemia in patients with endometriosis was not different from that of the general population and prevalence of factor V-Leiden mutation, was found with a lower prevalence[14]. In another study in which emphasis was given in fibrinolysis and plasminogen activator inhibitor-1 (PAI-1) gene, endometriosis was more likely in patients with 4G/5G or 4G/4G which are associated with hypofibrinolysis compared with 5G/5G PAI-1 genotype[15].Nevertheless, the existence of 4G allele alone does not represent an independent high risk factor of thromboembolic disease.

Thromboembolic Risk Factor

It is a great concern if the activation of coagulation not only result to progression of the disease but also increases the thromboembolic risk. However, there are no published data to support a possible association and there are only anecdotal reports of patients who experienced deep vein thrombosis (DVT) in the presence of other risk factors like immobilization or hormonal therapy[16].

Special attention should be kept at the rare localization of endometriosis that could involve the femoral and iliac veins either with extrinsic compression or infiltration. This situation could cause cyclical leg swelling, coincidental with menstruation[17-20] and a possible complication due to this localization could be thrombosis[21-25].

Hormonal Therapy

The therapeutic suppression of ovulation and menstruation with hormonal treatment is an effective conservative management of controlling the disease and its associated symptoms. Combined hormonal contraceptives (COC) constitute the most common long-term treatment to control the disease with the best profile in terms of long-term safety, adherence and cost. However, the main concern is a slight increase of the relative risk of venous thromboembolism and arterial thrombosis. Both thrombotic events are associated with estrogen dose, while progestin-only preparations confer no increased risk. Progressively, during the 1970s, the estrogenic content of COC has been was gradually lowered from 150 to 20 μg, with a parallel reduction of venous thrombosis risk from more than 10-fold to only a 4-fold increase among users of formulations containing less than 50 mg of estrogen[26].

Second line treatment include gonadotropin-releasing hormone analog (GnRHa). This drug acts by inhibiting the ovarian production of estrogen. However, there is no clear evidence of increase in either venous thrombosis incidence or cardiovascular risk. Yamaguti et. al showed that in patients treated with GnRHa, there was a 6% increase in antithrombin III, 29% reduction in D-dimers, and 19% increase in tissue plasminogen activator (tPA). Consequently, taking into consideration the coagulation parameters studied there, there was no association with a procoagulant profile[27].

Third-line and less tolerated treatment consists of danazol. Ford et al. investigated the effects of treatment with danazol on hemostatic function and showed that plasma FIB levels fell significantly, the PT shortened but remained within normal limits, and there were no significant changes in factors VII, VIIa, or fibrinopeptide A. No significant changes were found in platelet function even if there was an increase in their count. Functional levels of protein C, protein S, and antithrombin III, all rose significantly, above the normal range. Authors concluded that the observed changes might be considered beneficial in the context of venous thromboembolism. The only concern was an increase in whole blood viscosity during treatment that remained significantly elevated during follow-up. The rheological effects, however, indicate a degree of caution in the use of the drug in individuals considered being at risk from arterial cardiovascular disease[28,29].

Atherosclerosis and Cardiovascular Disease

In the last few years, a possible development of accelerated atherosclerosis in patients with endometriosis has been hypothesized due to systemic chronic inflammation and increased oxidative stress. Moreover, several studies have documented the presence of a pro-atherogenic lipid profile in women with endometriosis. Moreover, another aspect to take into account when considering the cardiovascular risk of women affected by endometriosis is the frequent use of a variety of medications, including no-steroidal anti-inflammatory drugs (NSAIDs) and/or COC or therapeutic menopause[30,31].

The risk of cardiovascular events in patients under treatment with COC increases with estrogen dosage whereas treatment with progestins alone or GnRH analogues (GnRHa) does not increase the risk[26]. Ferreira et al. compared the cardiovascular risk factors of patients that were treated either with levonorgestrel intrauterine system (LNG-IUS) or GnRHa. In the LNG-IUS group, after six months of treatment there was a significant reduction in lipid leverls whereas in the GnRHa group, the lipid profile did not show any statistical difference. The impact on the lipid profile with LNG-IUS could lead to a favorable effect on long-term treatment[32].

In addition, treatment of endometriosis with hysterectomy and/or oophorectomy may confer one more risk factor inducing menopause at a younger age. In a large prospective study including 116430 patients with a 20-year follow-up, laparoscopically confirmed endometriosis was associated with a significantly increased risk of coronary heart disease and the increased risk was greatest among younger women. It is possible that the observed risk was associated with surgical menopause from hysterectomy and/or oophorectomy among women with endometriosis[33]. However, in previous smaller case-control studies that included patients of young age with small follow-up, endometriosis was not associated with atherosclerosis[34,35].

Perioperative Risk – Postoperative period

Concerning the perioperative risk, there is no evidence that patients with endometriosis are at increased risk in comparison with patients that undergo same operation for benign no endometriotic lesions. Ageno et al. studied the incidence of venous

thromboembolism after gynecologic laparoscopy for benign lesions and found no episodes in a group of 266 patients in which 21% had endometriosis[36]. However, particular attention should be given not only for DVT but also for other rare thrombosis in the postoperative period in order to be early identified. Single cases of ovarian vein thrombosis have also been reported[37,38].

Wu et al. reported that one month after the surgical removal of endometriotic lesions, the extent of platelet activation in the peripheral blood is significantly reduced, probably resulting from the reduction or removal of endometriotic foci that are inducers of platelet activation[3] Ding et al. reported that nearly all coagulation parameters return back to the normal levels three months after surgical removal of endometriotic lesions[11]. Thus, surgical management of endometriosis could result in reducing the hypercoagulable state of affected women by diminishing the inflammatory burden of the disease.

Pregnancy

A critical and well-known characteristic of endometriosis is the marked relief of pain that affected women experience during pregnancy possibly due to lack of hormonal fluctuations that typically characterize a menstrual cycle. Accordingly, chronic inflammation process should be suppressed. Instead, it is well known that pregnancy and post-partum period is associated with increased risk of VTE due to activated coagulation. Therefore, it is a great concern if endometriosis might trigger VTE especially in this group of patients who suffer from subfertility and may follow in vitro fertilization (IVF) treatment.

There are only single cases of patients with endometriosis that experienced a thrombotic event during pregnancy[39]. However, in a recent study in Japan, there is evidence that endometriosis could represent a novel independent VTE risk factor and this is the first study that ever showed positive results. This study included 103,070 pregnancies and the frequency of VTE was 7.5 per 10,000 pregnancies. Even if the incidence of VTE was similar to that in Caucasian population, the results support a positive association because VTE has been speculated to be less frequent in the Japanese population due to the fact that no factor V Leiden and prothrombin mutations are found[40].

Another important issue is the thrombotic risk in women after ovarian stimulation for IVF. Most of reported cases concerning thrombosis have been described in this group of patients with endometriosis related to pregnancy. Thrombosis is not only in common sites like DVT but could also include uncommon sites[41,42]. Except for vein thrombosis there are also single cases concerning arterial thrombosis like thrombotic stroke[43]. Nevertheless, it is well known that high levels of endogenous estradiol due to ovarian hyperstimulation may result in a hypercoagulable state causing thrombosis. Consequently, since there are no cross-sectional studies about the risk of thrombosis during IVF, endometriosis could not be implicated as a risk factor.

The role of antithrombotic treatment

Antiplatelet treatment & Platelet depletion

The hypercoagulability apparently resulting from endometriosis suggests that anticoagulation or antiplatelet therapy could be promising treatment options. Therefore, several preclinical studies in animal models focus on new treatment approaches targeting the hypercoagulative state responsible for fibrinogenesis and development of the disease. Most experiments are designed targeting on the role of platelets and the beneficial effect either of platelet depletion or antiplatelet treatment in disease remission.

Acetylsalicylic acid (Aspirin) is the most common used antiplatelet agent, widely available, inexpensive and is generally regarded as safe. The experimental

results of Saad-Hossne et al. showed that intralesional aspirin injection resulted in elimination of gross and histological areas of endometriotic tissue, leaving only fibrosis, necrosis, and apoptosis in their place with a good safety profile. As the scar tissue can negatively impact on local tissue function and culminate in clinical manifestations, further investigations should examine the real scar tissue formation rate and its clinical implications, such as fertility, after intralesional aspirin injection[44]. Siquiera et al. issued also encouraging results with intralesional injection with aspirin in endometriotic lesions in rabbits[45].

Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit platelet cyclooxygenase in a reversible way in contrast to aspirin. Therefore, their use may not be limited for pain management but could also be beneficial in fibrosis inhibition. Efstathiou et al. studied in murine models the effects of celecoxib. Although significant reductions in disease burden were observed when celecoxib was begun immediately after the induction of endometriosis, this effect was not seen when treatment was delayed. These findings show that treatment, while effective on lesion establishment and growth, had no effect on the size of fully established lesions. This suggests that celecoxib inhibits disease development in this model but does not regress established lesions[46].

Another study evaluated the efficacy of Ozagrel treatment, which is an antiplatelet agent inhibiting TXA2 synthesis. Low and high dose Ozagrel treatment resulted in significant reduction in lesion area along with improved hyperalgesia in mice with surgically induced endometriosis. As expected, Ozagrel treatment nearly suppressed platelet aggregation, and significantly reduced expression of other inflammatory markers. Targeting platelet depletion, pre-emptive depletion of platelets prior to the endometriosis induction reduced the lesion growth, suggesting that platelets also play a critical role in the initiation of endometriosis. The observation that later platelet depletion is as effective as the early depletion in reducing lesion weight strongly suggests that platelets play important roles not only in the initiating stage of the development of endometriosis but also in later stages as well[47]. In agreement to previous study, research in adenomyosis with either Ozagrel treatment or platelet depletion suppressed myometrial infiltration and slowed down the process of fibrogenesis with a dose-dependently manner[48]. Like Ozagrel, treatment with a recombinant P-selectin can effectively reduce lesion area in murine models of endometriosis[4,47].

Research has also been performed with herbals with known antiplatelet action. Tanshinone-IIA (TAN) is a plant used in traditional Chinese medicine and has been demonstrated that inhibits platelet aggregation and fibrogenesis. Zhang et al. induced endometriotic lesions in mice and TAN injection provided in vivo evidence of inhibition of disease progression, resulting in reduced lesion size and extent of fibrosis[49]. Scutellarin is an herbal flavonoid with multiple pharmacological activities including antithrombotic, antioxidant and anti-inflammatory effects. Scutellarin also reduced the peripheral-activated platelets rate and resulted in significantly reduced platelet aggregation, cellular proliferation, angiogenesis, and the extent of fibrosis[50].

Heparin

Targeting coagulation in a different manner, there is one preclinical study revealed that endometriotic stromal cell (ECSC)-mediated gel contraction was significantly diminished in the presence of heparin in a dose-dependent manner suppressing the ECSC attachment to collagen fibers. Therefore, heparin could represent a promising agent for the treatment of endometriosis-associated fibrosis[51].

The use of heparin could represent a challenging tool for better healing and decreasing the severity of adhesions. Preliminary data also present heparin to

diminish adhesion prevention in combination with humidification and dexamethasone during peritoneal full conditioning[52].

Antiplatelet Treatment and Fertility

Another important aspect is the role of antithrombotic treatment in improving fertility. The role of aspirin in improving fertility or live births is controversial, however taking into consideration the encouraging results about beneficial effect in women with other inflammatory diseases, maybe could represent another treatment that could improve pregnancy rates in women with endometriosis[53]. Martinez-Zamora et al. studied women attempting conception with elevated CRP and prior pregnancy loss and found that low dose aspirin may increase clinical pregnancy and live birth rates compared with women without inflammation and reduce CRP elevation during pregnancy[54]. However, in most studies that investigated the effect of preconception initiated low dose aspirin, patients with known endometriosis were excluded.

Experiments in rats showed that endometriosis treated with intraperitoneal indomethacin resulted in better reproductive performance than in animals treated with other methods. Microsurgery and danazol therapy both were effective in preventing residual endometriosis, but the animals tended to be less fertile after treatment. In rats treated with indomethacin, persistent endometriotic cysts were invariably smaller near the site of intraperitoneal injection suggesting a local antiprostaglandin effect[55] and clinical and experimental evidence showed an increased concentration of prostaglandins in peritoneal fluid in cases of endometriosis[56].

DISCUSSION

Endometriosis is a chronic pelvic inflammatory condition which activates platelets and the coagulation cascade. Consequently, women with endometriosis appear to be in a hypercoagulable state. The activation of platelets and of coagulation cascade faces severe concerns, about a possible increase in thromboembolic risk in patients with endometriosis. There are not available data to support a possible association and most reported cases in the literature correspond to patients with other known thrombophilia risk factors or topical infiltration of femoral and iliac veins.

It is crucial to be clarified if women with endometriosis have an additional thromboembolic risk factor in order to consider different approach during increased risk situations like the postoperative period, pregnancy/postpartum or under hormonal treatment. However, there are insufficient data to support a possible association. Remarkably, some studies have shown that platelet and coagulation activation is improved after surgery or hormonal treatment due to elimination of disease burden[3,11,32]. Up to now, patients were not supposed to be in higher risk of thrombosis during pregnancy or postpartum than women without endometriosis. Nevertheless, a recent study showed that endometriosis could represent an independent risk factor of VTE in Japanese population[40]. However, more studies are needed during pregnancy in order to generalize the previous finding because the overall thrombotic risk differs in Japanese population from other populations like Caucasians.

A systematic laboratory testing for thrombophilia factors does not seem justified in patients with endometriosis before initiation of hormonal treatment or during pregnancy. These tests should be targeted to selected patients with first-degree relatives with a diagnosis of venous thromboembolism or cardiovascular event in young age. Concerning the use of COC preparations with the lowest possible estrogen dose should constitute the first-line choice, considering that the estrogen content affects the risk of both venous and arterial thrombosis. Progestins are

increasingly used even as monotherapy, and since they do not increase the thrombotic risk, their use can be safely suggested in many women with contraindications to estrogens as well as in those with other known thrombophilia factors including past history of thromboembolic event, positive family history, smoking, obesity, presence of gross varicose veins, hypertension, diabetes and age >35 years.

The demonstration that platelets are involved in the pathogenesis of the disease provides a motivation for the use of anti-coagulants to treat endometriosis, and opens prospects for developing novel biomarkers for diagnostic or prognostic purposes. Platelet depletion or suppression of platelet aggregation is an interesting approach and preclinical studies are running. Primary results with intralesional aspirin injection[44,45] or other antiplatelets are encouraging by effectively reducing lesion growth and the extent of fibrosis[46,50].

Conclusion

Endometriosis is a benign disease and certainly not life-threatening. Therefore, it places higher premium on best treatment approach as compared with other life-threatening diseases. More research is needed to determine the actual thrombotic risk and if antithrombotic treatment could represent an effective treatment in inhibition of disease progression balancing on the hemorrhagic risk and the risk of damage to normal endometrial mucosa, with potential consequences to fertility.

Conflicts of interest and funding

None to declare

References

1. Vercellini P, Viganò P, Somigliana E, et al. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 2014;10:261-75.
2. Burney RO. The genetics and biochemistry of endometriosis. Curr Opin Obstet Gynecol. 2013;25:280-6.
3. Wu Q, Ding D, Liu X, et al. Evidence for a Hypercoagulable State in Women With Ovarian Endometriomas. Reprod Sci. 2015;22:1107-14.
4. Ding D, Liu X, Duan J, et al. Platelets are an unindicted culprit in the development of endometriosis: clinical and experimental evidence. Hum Reprod. 2015;30:812-32.
5. Zhang Q, Duan J, Liu X, et al. Platelets drive smooth muscle metaplasia and fibrogenesis in endometriosis through epithelial mesenchymal transition and fibroblast-to-myofibroblast transdifferentiation. Mol Cell Endocrinol. 2016;428:1-16.
6. Munrós J, Martínez-Zamora MA, Tàssies D, et al. Total circulating microparticle levels are increased in patients with deep infiltrating endometriosis. Hum Reprod. 2017;32:325-331.
7. Krikun G, Lockwood CJ, Paidas MJ. Tissue factor and the endometrium: from physiology to pathology. Thromb Res. 2009;124:393-6.
8. Gilabert-Estelles J, Ramon LA, España F, et al. Expression of the fibrinolytic components in endometriosis. Pathophysiol Haemost Thromb. 2006;35:136-40.
9. Viganò P, Ottolina J, Sarais V, et al. Coagulation Status in Women With Endometriosis. Reprod Sci. 2018;25:559-565.
10. Lin Q, Ding SJ, Zhu TH, et al. [Role and clinical significance of coagulation and inflammatory factors in moderate and severe ovarian endometriosis]. Zhonghua Fu Chan Ke Za Zhi. 2018;53:167-171 [Abstract].
11. Ding D, Liu X, Guo SW. Further Evidence for Hypercoagulability in Women With Ovarian Endometriomas. Reprod Sci. 2018;25:1540-8.
12. Sanchez AM, Viganò P, Somigliana E, et al. The distinguishing cellular and molecular features of the endometriotic ovarian cyst: from pathophysiology to the potential endometrioma-mediated damage

to the ovary. Hum Reprod Update. 2014;20:217-30.
13. Fujiwara H, Kosaka K, Hamanishi S, et al. Acute elevation of plasma D-dimer levels associated with rupture of an ovarian endometriotic cyst: Case report. Hum Reprod. 2003;18:338-41.
14. Paradisi R, Ferrini G, Matteucci C, et al. Does exist a correlation between endometriosis and thrombophilic disorders? A pilot study. Taiwan J Obstet Gynecol. 2017;56:371-373.
15. Bedaiwy MA, Falcone T, Mascha EJ, et al. Genetic polymorphism in the fibrinolytic system and endometriosis. Obstet Gynecol. 2006;108:162-8.
16. Sueta D, Akahoshi R, Okamura Y, et al . Venous Thromboembolism Due to Oral Contraceptive Intake and Spending Nights in a Vehicle -A Case from the 2016 Kumamoto Earthquakes. Intern Med. 2017;56:409-412.
17. Recalde AL, Majmudar B. Endometriosis involving the femoral vein. South Med J. 1977;70:69.
18. Ju MH, Keldahl ML, Rodriguez HE. Chronic common femoral vein occlusion secondary to endometriosis. J Vasc Surg Venous Lymphat Disord. 2014;2:197-9.
19. Zamurovic M. Rare extrapelvic endometriosis on iliac vein wall--diagnosis and treatment. Clin Exp Obstet Gynecol. 2014;41:349-50.
20. Rosengarten AM, Wong J, Gibbons S. Endometriosis causing cyclic compression of the right external iliac vein with cyclic edema of the right leg and thigh. J Obstet Gynaecol Can. 2002;24:33-5.
21. Chiaramonte R, Castorina S, Castorina EG, et al. Thrombosis of iliac vessels, a rare complication of endometriosis: Case report and review of literature. J Adv Res. 2017;8:1-5.
22. Sharma RP, Delly F, Marin H, et al. Endometriosis causing lower extremity deep vein thrombosis - case report and review of the literature. Int J Angiol. 2009;18:199-202.
23. Li M, Chen K, Fong YF. A rare case of endometriosis invading external iliac vein causing deep vein thrombosis. Am J Obstet Gynecol. 2019;220:113-114.
24. Ianieri MM, Buca DIP, Panaccio P, et al. Retroperitoneal endometriosis in postmenopausal woman causing deep vein thrombosis: case report and review of the literature. Clin Exp Obstet Gynecol. 2017;44:148-150.
25. Nawroth F, Schmidt T, Foth D, et al. Menorrhagia and adenomyosis in a patient with hyperhomocysteinemia, recurrent pelvic vein thromboses and extensive uterine collateral circulation treatment by supracervical hysterectomy. Eur J Obstet Gynecol Reprod Biol. 2001;98:240-3.
26. Vercellini P, Buggio L, Berlanda N, et al. Estrogen-progestins and progestins for the management of endometriosis. Fertil Steril. 2016;106:1552-1571.
27. Yamaguti EM, Brito MB, Ferriani RA, et al. Comparison of the hemostatic effects of a levonorgestrel-releasing intrauterine system and leuprolide acetate in women with endometriosis: a randomized clinical trial. Thromb Res. 2014;134:1193-7.
28. Ford I, Li TC, Cooke ID, et al. Changes in haematological indices, blood viscosity and inhibitors of coagulation during treatment of endometriosis with danazol. Thromb Haemost. 1994;72:218-21.
29. Alvarado RG, Liu JY, Zwolak RM. Danazol and limb-threatening arterial thrombosis: two case reports. J Vasc Surg. 2001;34:1123-6.
30. Santoro L, D'Onofrio F, Flore R, et al. Endometriosis and atherosclerosis: what we already know and what we have yet to discover. Am J Obstet Gynecol. 2015;213:326-31.
31. Tani A, Yamamoto S, Maegawa M, et al. Arterial stiffness is increased in young women with endometriosis. J Obstet Gynaecol. 2015;35:711-5.
32. Ferreira RA, Vieira CS, Rosa-E-Silva JC, et al. Effects of the levonorgestrel-releasing intrauterine system on cardiovascular risk markers in patients with endometriosis: a comparative study with the GnRH analogue. Contraception. 2010;81:117-22.

33. Mu F, Rich-Edwards J, Rimm EB, et al. Endometriosis and Risk of Coronary Heart Disease. Circ Cardiovasc Qual Outcomes. 2016;9:257-64.
34. Pretta S, Remorgida V, Abbamonte LH, et al. Atherosclerosis in women with endometriosis. Eur J Obstet Gynecol Reprod Biol. 2007;132:226-31.
35. 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;27:1320-6.
36. Ageno W, Manfredi E, Dentali F, et al. The incidence of venous thromboembolism following gynecologic laparoscopy: a multicenter, prospective cohort study. J Thromb Haemost. 2007;5:503-6.
37. O'Hagan S, Andronikou S, Truter R, et al. Ovarian vein thrombosis – a rare but important complication of hysterectomy and oophorectomy. South African Journal of Obstetrics and Gynaecology 2013;19: 86-87.
38. Al-Achmar SN, Stavrou S, Protopapas A, et al. Ovarian vein thrombosis after total laparoscopic hysterectomy with unilateral adnexectomy: A case report. Int J Surg Case Rep. 2017;41:1-4.
39. Panaych KPS, Hazarika A, Hazarika B, et al. Cerebral Venous Thrombosis: A Complicated Anaesthetic Scenario for Caesarean Section. J Anesth Clin Res 2016;7:661.
40. Sugiura-Ogasawara M, Ebara T, Matsuki T, et al; and the Japan Environment & Children's Study (JECS) Group. Endometriosis and Recurrent Pregnancy Loss as New Risk Factors for Venous Thromboembolism during Pregnancy and Post-Partum: The JECS Birth Cohort. Thromb Haemost. 2019;119:606-17.
41. Belaen B, Geerinckx K, Vergauwe P, et al. Internal jugular vein thrombosis after ovarian stimulation. Hum Reprod. 2001;16:510-2.
42. Hirata M, Yano H, Taji T, Shirakata Y. Mesenteric vein thrombosis following impregnation via in vitro fertilization-embryo transfer. World J Gastrointest Surg. 2017;9:209–13.
43. Chua N, Wang J, Loh S, et al. Thrombotic stroke in association with ovarian hyperstimulation and early pregnancy rescued by thrombectomy. Case Reports in Perinatal Medicine 2012 ;1: 43-5.
44. Saad-Hossne R, Barretto AB, Siqueira JM, et al. Evaluation of peritoneal endometriosis treatment using intralesional acetylsalicylic acid injection in rabbits. Acta Cir Bras. 2016;31:227-34.
45. Siqueira JM, Barreto AB, Saad-Hossne R. Treatment of endometriosis with local acetylsalicylic acid injection: experimental study in rabbits. J Minim Invasive Gynecol. 2011;18:800-6.
46. Efstathiou JA, Sampson DA, Levine Z, et al. Nonsteroidal anti-inflammatory drugs differentially suppress endometriosis in a murine model. Fertil Steril. 2005;83:171-81.
47. Guo SW, Ding D, Liu X. Anti-platelet therapy is efficacious in treating endometriosis induced in mouse. Reprod Biomed Online. 2016;33:484-499.
48. Zhu B, Chen Y, Shen X, et al. Anti-platelet therapy holds promises in treating adenomyosis: experimental evidence. Reprod Biol Endocrinol. 2016;14:66.
49. Zhang Q, Liu X, Guo SW. Progressive development of endometriosis and its hindrance by anti-platelet treatment in mice with induced endometriosis. Reprod Biomed Online. 2017;34:124-136.
50. Ding D, Cai X, Zheng H, et al. Scutellarin Suppresses Platelet Aggregation and Stalls Lesional Progression in Mouse With Induced Endometriosis. Reprod Sci. 2018 [Epub ahead of print].
51. Nasu K, Tsuno A, Hirao M, et al. Heparin is a promising agent for the treatment of endometriosis-associated fibrosis. Fertil Steril. 2010;94:46-51.
52. Koninckx PR, Corona R, Timmerman D, et al. Peritoneal full-conditioning reduces postoperative adhesions and pain: a randomised controlled trial in deep endometriosis surgery. J Ovarian Res. 2013;6:90.

53. Sjaarda LA, Radin RG, Silver RM, et al. Preconception Low-Dose Aspirin Restores Diminished Pregnancy and Live Birth Rates in Women With Low-Grade Inflammation: A Secondary Analysis of a Randomized Trial. J Clin Endocrinol Metab. 2017;102:1495-1504.
54. Martínez-Zamora MA, Tàssies D, Reverter JC, et al. Increased circulating cell-derived microparticle count is associated with recurrent implantation failure after IVF and embryo transfer. Reprod Biomed Online. 2016;33:168-73.
55. Golan A, Dargenio R, Winston RM. The effect of treatment on experimentally produced endometrial peritoneal implants. Fertil Steril. 1986;46:954-8.
56. Dargenio R, Corbucci MG, Lamanna MA, et al. Indomethacin and fertility in experimental endometriosis. Acta Eur Fertil. 1992;23:85-8.

Received 16-12-19
Revised 05-04-20
Accepted 11-04-20