European Journal of Obstetrics & Gynecology and Reproductive Biology 204 (2016) 99–103

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Dysfunctional coagulation and fibrinolysis systems due to adenomyosis is a possible cause of thrombosis and menorrhagia

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ARTICLE INFO

Article history:
Received 12 April 2016
Received in revised form 12 July 2016
Accepted 26 July 2016

Keywords:
Adenomyosis
Coagulation
Fibrinolysis
Menstruation
Menorrhagia

ABSTRACT

Objective: To study the effects of adenomyosis on the coagulation and fibrinolysis system during menstruation and the relationship between dysfunction of the coagulation and fibrinolysis system and the symptoms and complications of adenomyosis.
Study design: Concentrations of thrombin–antithrombin complex (TAT) and soluble fibrin (SF) as markers of coagulation, D-dimer (DD) as a marker of both coagulation and fibrinolysis, and plasmin-alpha 2-plasmin inhibitor complex (PIC) as a marker of fibrinolysis in the peripheral blood of eight patients with adenomyosis were measured daily from the first to fifth day of menstruation. Associations between levels of these markers during menstruation and patient characteristics, history of thrombotic disorder, and hemoglobin loss during menstruation were investigated.
Results: TAT, SF, DD and PIC increased in 5, 2, 3 and 1 of the 8 patients, respectively. TAT increased in 5 of the 6 patients with an adenomyotic uterus ≥100 cubic centimeters. Patients with elevated DD, SF and/or PIC were among patients with elevated TAT. DD was only increased in 3 patients with a past history of small cerebral infarction or pulmonary thromboembolism and/or hemoglobin loss >2.0 g/dl during menstruation. SF was increased only in 2 patients with a past history of cerebral infarction or pulmonary thromboembolism. PIC increased in 1 of the 2 patients with hemoglobin loss >2.0 g/dl during menstruation.
Conclusion: Adenomyosis patients with a uterus volume ≥100 cubic centimeters are at risk of having an activated coagulation system. These patients, particularly those with elevated SF and DD, may be at risk of thrombotic disorders. Fibrinolysis is activated in a portion of patients with activated coagulation during menstruation. Activated fibrinolysis during menstruation may contribute to menorrhagia in patients with adenomyosis, as only patients with activated fibrinolysis suffered menorrhagia, even though patients with an adenomyotic uterus ≥100 cubic centimeters without activated fibrinolysis did not. These results suggest extensive adenomyosis confers a potential risk of infarction and thrombosis and exacerbates menorrhagia via activation of coagulation and fibrinolysis during menstruation.

Introduction

Adenomyosis is defined as the intramyometrial presence of ectopic endometrial glands and stromal cells surrounded by reactive, hypertrophic myometrium [1,2]. Patients with adenomyosis suffer from menorrhagia [3–5], attributed to an enlarged uterine cavity and dysfunctional contractility of the outer myometrium and/or endometrial interface during menstruation [3]. However, Naftalin et al. found no significant association between adenomyosis and menorrhagia when adenomyosis was assessed as a binary outcome [6]. Because only a part of adenomyosis causes menorrhagia and other does not, no statistical association was found. Furthermore, some non-symptomatic patients with pain display menorrhagia, even with comparatively extensive adenomyosis. Clearly, not all the mechanisms underlying the development of menorrhagia in adenomyosis have been clarified.

Inflammation and hemorrhage are known as potential causes of dysfunctional coagulation and fibrinolysis [7–9]. In adenomyotic tissue, inflammation and infinitesimal hemorrhages occur during

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http://dx.doi.org/10.1016/j.ejogrb.2016.07.499
0301-2115/

menstruation. Adenomyosis can thus cause dysfunctional coagulation and fibrinolysis. In fact, some case reports have described adenomyosis causing severe conditions related to abnormal coagulation and fibrinolysis, such as infarction, thrombotic disorder and disseminated intravascular coagulation (DIC) [10–13]. This raises the question of whether adenomyosis often causes dysfunctional coagulation and fibrinolysis during menstruation and whether such dysfunction contributes to the symptoms and/or complications of adenomyosis.

To clarify the effects of adenomyosis on coagulation and fibrinolysis during menstruation, the present study measured coagulation- and fibrinolysis-related factors in peripheral blood during menstruation in patients with adenomyosis. The results revealed activation of coagulation and fibrinolysis in a proportion of extensive adenomyosis cases, representing a possible cause of thrombosis and menorrhagia. These findings offer new insights into the pathophysiology of adenomyosis.

Material and methods

All experimental procedures were approved by the ethics committees of Shiga University of Medical Science. A total of 8 patients treated at Shiga University of Medical Science for adenomyosis from June 2006 to June 2014 were enrolled in this study after providing written informed consent for participation in this study. Age, parity, gravidity, body mass index, and past history were obtained from the medical records. Adenomyosis was diagnosed by the presence of either diffuse or focal thickening of the inner myometrium or an ill-defined myometrial nodule of low signal intensity on T2-weighted magnetic resonance imaging (MRI) [14,15]. Patients with complications of endometrial polyps and/or submucous myoma detected on ultrasonography or MRI were excluded, as were patients taking any medicine considered to affect coagulation or fibrinolysis. Uterine volume was calculated from MRI using previously reported methods [16]. The region of adenomyosis involvement in the uterus was estimated based on T2-weighted MRI. Adenomyosis was also divided into 4 subtypes according to the criteria reported by Kishi et al. [17], as follows: subtype I, adenomyosis with an intimate relationship with inner structural components of the uterus, such as the endometrium and the junctional zone; subtype II, adenomyosis arising in the outer shell of the uterus disrupting serosa but not affecting the inner components; subtype III, adenomyosis residing solitarily in the myometrium; and subtype IV, adenomyosis categorized to none of subtypes I–III.

To evaluate the coagulation and fibrinolysis systems during menstruation, the patient underwent daily blood sampling from day 1 (within 24 h after start of menstruation) to day 5 of menstruation. Serum samples were frozen until assayed. Thrombin–antithrombin complex (TAT) and soluble fibrin (SF), as markers of coagulation, D-dimer (DD) as a marker of coagulation and fibrinolysis, and plasmin-alpha 2-plasmin inhibitor complex (PIC) as a marker of fibrinolysis were measured using chemiluminescent enzyme immunoassay (STACIA CLEIA TAT; LSI Medience, Tokyo, Japan), latex photometric immunoassay (IATRO SF; LSI Medience), latex photometric immunoassay (LPIA ACE D-D dimer II; LPI Medience), and latex photometric immunoassay (LPIA ACE PPI II; LPI Medience), respectively. The hemoglobin (Hb) level in peripheral blood was also measured and Hb loss was defined as the difference in levels between the first and fifth days of menstruation. Relationships between activation of the coagulation and fibrinolysis systems and the characteristics of patient, characteristic of adenomyosis, past history of thrombotic disorder and Hb loss were assessed.

Results

Age, parity, gravidity, body mass index, and characteristics of adenomyosis (including size, region, subtype and multiple high signal spots on T2-weighted MRI) for patients are shown in Table 1. Representative results of T2-weighted MRI are shown in Fig. 1. Age ranged from 33 to 43 years. Uterine size was ≥300 cubic centimeters in 2 patient (Case 1 and 8), ≥200 in 2 (Cases 2, 3), ≥100 in 2 (Cases 5 and 6), ≤100 in 2 (Case 4 and 7). Adenomyosis was located at the anterior wall in 2 patients (Cases 3 and 5), at the posterior wall in 2 (Cases 2, 4) and at both walls in 4 (Cases 1, 6, 7 and 8). Adenomyosis was classified as subtype I in 3 patients (Cases 5, 6, 8), II in 1 (Case 4) and IV in 4 (Cases 1–3 and 7). Multiple signal-hyperintense spots were detected on T2-weighted MRI in 4 (Cases 1–3 and 5).

TAT levels are shown in Fig. 2A, and exceeded the upper reference value (3.0 ng/ml) in 5 of the 8 patients (Cases 1–3, 5 and 8). Three patient clusters were seen for peak TAT levels: 2 patients peaked on day 1 (Cases 2 and 5), 2 on day 4 (Cases 3 and 8) and 1 on day 5 (Case 1).

SF levels are shown in Fig. 2B, and exceeded the upper reference value (1.0 μg/ml) in 2 of the 8 patients; from days 3–5 in Case 3 and only on day 1 in Case 5. In both cases, levels were more than 4-fold higher than the upper reference value.

DD levels are shown in Fig. 3A, and exceeded the upper reference value (3.0 μg/ml) in 3 of the 8 patients. All 3 patients were among the 5 patients with elevated TAT. Peak DD level corresponded to the peak of TAT in Cases 3 and 5, but occurred a day after peak TAT in Case 2.

PIC levels are shown in Fig. 3B, and exceeded the upper reference value (1.0 μg/ml) only in Case 3.

Past history of thrombotic disorder, Hb loss and elevations of the assessed blood parameters are shown in Table 2. Two patients had a past history of thrombotic disorder, in the form of a small cerebral infarct in Case 3, and pulmonary thromboembolism in Case 5 while taking an oral contraceptive. Two patients showed Hb loss >2.0 g/dl (Cases 2 and 3).

Table 1
Patient background demographics and characteristics of adenomyosis.

Case	Age (y.o.)	BMI (kg/m^2)	Gravidity	Parity	Adenomyosis			
					Size (cm^3)	Region	Subtype	Multiple high signal spots
1	37	21.8	1	0	392.2	Both anterior and posterior	IV	+
2	34	22.1	0	0	233.1	Posterior	IV	+
3	38	16.0	0	0	271.6	Anterior	IV	+
4	43	20.9	0	0	62.8	Both anterior and posterior	II	
5	33	20.9	1	0	138.4	Anterior	I	+
6	38	21.2	1	1	160.1	Posterior	I	
7	37	18.5	1	1	72.6	Both anterior and posterior	IV	
8	33	20.9	0	0	304.9	Both anterior and posterior	I	

+: Multiple high signal spots were detected.