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Coagulation Status in Women With Endometriosis

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Abstract

Subtle alterations in coagulation and fibrinolysis have been recently reported in patients with endometriosis supporting a potential hypercoagulable status associated with the disease. This cross-sectional study aimed at evaluating some variables of coagulation status and inflammatory markers in women with endometriosis. A total of 314 women who underwent surgery were considered. The case group (n = 169) included patients with a surgical diagnosis of endometriosis, at any stage of disease. The control group (n = 145) included women with a surgical diagnosis of benign gynecologic pathology. No difference was found for thrombin time, International Normalized Ratio (INR), platelet count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio (PLR) between women with endometriosis and controls. Conversely, patients with endometriosis had significantly shortened activated partial thromboplastin time (APTT) when compared to controls (1.08 ± 0.06 and 1.12 ± 0.19, respectively; $P < .01$). In the subgroup analysis, women with ovarian endometriosis had significantly shortened APTT values in comparison to women without this form and women with stage I to II endometriosis had significantly shorter APTT values and higher PLR than those with stage III to IV disease. In multivariate logistic regression analysis, after controlling for potential confounders, a shortened APTT remained associated with the disease. Activated partial thromboplastin time is shorter in women with endometriosis but still in the normal range. The evidence is insufficient to foresee a possible use of APTT as a diagnostic marker and to claim a crucial role of a systemic hypercoagulable state in the origin of the disease. A role of the local coagulation system in the pathogenesis of the disease cannot be excluded.

Keywords

coagulation, endometriosis, activated partial thromboplastin time, platelet, platelet–lymphocyte ratio, thrombin time, INR

Introduction

Recently, increased cardiovascular morbidity in terms of myocardial infarction, angina, and coronary bypass graft intervention has been recognized in women with endometriosis.[1,2] The relative risk of combined coronary heart disease events was 1.62 (95% confidence interval: 1.39-1.89) after adjustment for confounders.[1] Factors contributing to this increased risk have not been deeply investigated. A portion of this association could be explained by treatment factors associated with endometriosis such as hormonal therapy and hysterectomy/oophorectomy.[3,4] On the other hand, it is worthwhile noting that subtle alterations in coagulation and fibrinolysis parameters have also been recently identified in affected patients supporting a potential hypercoagulable status associated with the disease.[5] A single contribution has reported that patients with ovarian endometriomas have significantly shortened activated partial thromboplastin time (APTT), thrombin time (TT), and elevated fibrinogen levels, although most of the parameters were in the normal range. Moreover, the percentage of activated platelets was shown to be significantly higher in patients with ovarian endometriotic cysts and to be reduced by their surgical removal.[5] Albeit evidence is controversial, some studies also documented an increased platelet-to-lymphocyte ratio (PLR) in women with endometriosis.[6-8] Finally, other factors involved in the coagulation cascade such as tissue factor (TF) and proteinase-activated receptors have also been reported to be altered in endometriosis, although their involvement has not been portrayed in the context of coagulation per se but, rather, in the context of angiogenesis or inflammation.[9,10] Indeed,

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some general inflammatory markers including the neutrophil-to-lymphocyte ratio (NLR) have been suggested to be increased in women with endometriosis compared to controls.[6-8,11,12]

Normal hemostasis is characterized by a dynamic equilibrium between procoagulant and anticoagulant components of the hemostatic system. Therefore, blood hypercoagulability may be considered as a state of hemostatic imbalance as well as a shift of the equilibrium toward thrombogenesis occurring either because of an increase in procoagulant potential or reduction in antithrombotic capability of the blood.[13] If this imbalance progresses to a critical level, it may lead to onset of adverse vascular events. It is also important to underlie in this context that endometriomas are characterized by clotting factor changes favoring a particular degradative capacity of the endometrioma fluid that might be supportive of some consumption activity within the cyst.[14]

In the present cross-sectional study, we aimed at gaining more insights into the relation between endometriosis and clotting abnormalities. Specifically, we report on levels of coagulation and inflammatory factors in a large series of reproductive-age women scheduled for gynecological surgery.

Materials and Methods

This cross-sectional study was carried out retrospectively querying our prospective surgical database at San Raffaele Scientific Institute in Milan. This database contains clinical, pathologic, surgical, and follow-up data regarding more than 500 consecutive patients who underwent gynecologic pelvic surgery. Patients who underwent surgery between January 2013 and December 2015 were considered. All patients had a surgical indication for gynecologic disease and a histopathological diagnosis after either laparotomic or laparoscopic surgery. All participants met the following inclusion criteria: nonpregnant reproductive-age women, normal hepatic and renal function tests, and a surgical indication for endometriosis or other pelvic diseases. Women whose data on the coagulation status were absent were excluded. All women routinely provided informed consent for their clinical data and anonymized records to be used for researches purposes. A specific institutional review board was obtained (End01).

For each patient, age, signs and symptoms, body mass index (BMI), obstetric and medical history, duration of infertility, previous in vitro fertilization cycles, smoking status, diameter of masses, operation type, lateralization, reoperation, surgical features, and histopathological diagnosis following surgery were retrieved. A preoperative transvaginal ultrasonographic examination was performed in all women. The case group included all patients with a diagnosis of endometriosis, at any stage of disease. The stage of endometriosis was established according to the revised classification of the American Society for Reproductive Medicine.[15] Both the surgical and the histopathological examinations confirmed that no stage of endometriosis was present in the control group. The control group included women with a surgical diagnosis of uterine leiomyomas, tubal pathology, and ovarian benign cysts. Both case and control patients were excluded if they have taken oral contraceptives, steroid hormones, antiplatelet drugs, or other medications in the last 3 months before surgery. Patients were also excluded if a diagnosis of malignancy was present. According to the abovementioned selection criteria, 314 women were included, 169 had a diagnosis of endometriosis, and 145 had a diagnosis of other benign gynecologic diseases.

The routine preoperative included complete blood count parameters, NLR, PLR, TT ratio, APTT ratio, and International Normalized Ratio (INR). Peripheral blood sample (2 mL) was obtained from the median cubital vein of each patient and mixed with 3.2% citric acid for anticoagulation purpose. All blood analyses were obtained at a maximum of 1 month before surgery. The NLR was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count, while the PLR was obtained dividing by the absolute platelets count by the absolute lymphocyte count. CA125 and fibrinogen levels were partially reported in our database, but we established not to include these variables for data incompleteness. All blood analyses were done during either the follicular or the luteal phase before surgery.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version Chicago 21.0. The Shapiro-Wilk test was used to ascertain whether continuous variables had normal distribution. Continuous and normally distributed variables were presented as mean (stardard deviation) and intragroup differences were investigated using the student *t* test. Categorical variables were expressed as percentages (%), and differences were valuated using the χ^2 test. A univariate linear regression analysis was conducted in order to evaluate the association of each variable with different phenotypes of endometriosis that were included in the regression analysis as n−1 dummy variables. Regression coefficients (*B*) for "ovarian endometriosis" and "peritoneal endometriosis" represent the difference in the mean values compared to the reference category "deep endometriosis" that was indicated by $B = 0$. Multivariate analyses were performed using logistic regression analyses in order to determine independent predictors of endometriosis disease. *P* values of <.05 were considered statistically significant.

The sample size was calculated focusing on APTT as the primary outcome. The expected mean (standard deviation) of this variable in the control group was 1.0 ± 0.1. Setting type I and II errors at 0.05 and 0.10, respectively, and stating as clinically relevant a 5% difference, the required sample size was at least 85 women per group. The available database could well satisfy this estimated sample size. We did not stop recruitment at the precise scheduled sample size to allow for more robust subgroup analyses.

Results

Baseline characteristics of patients with and without endometriosis are shown in Table 1. Of the 169 affected women, 45 were stages I to II, whereas the remaining 124 were stages III to

Table 1. Baseline Characteristics of Controls and Patients With Endometriosis.

Characteristics	Endometriosis	Controls	*P*
Number of patients	169	145	
Age, years	35.8 ± 5.9	36.9 ± 6.5	.4
BMI, kg/mq	22.8 ± 3.3	22.9 ± 3.6	.5
Smoking	25.6%	17.7%	.08
Previous delivery	18.3%	27.1%	.055
Infertility	14.5%	13.9%	.6
Cycle phase: proliferative; secretory	56.8%; 43.2%	53.1%; 46.9%	.7

Abbreviation: BMI, body mass index.

IV. The concomitant presence of other gynecological benign pathologies was observed in 44 (26%) cases and were as follows: ovarian dermoids (n = 4), seromucinous ovarian cysts (n = 7), tubal pathology (n = 21), and myomas (n = 12). Endometriosis could not be detected in 145 women. These cases were used as controls. The main diagnoses of this group were as follows: ovarian dermoids (n = 13), tubal pathology (n = 37), seromucinous ovarian cysts (n = 21), paraovarian cysts (n = 8), and myomas (n = 54), and normal pelvis (n = 12).

As previously reported,[16,17] the concentration of none of the molecules tested appears to be influenced by the phase of the cycle. In proliferative and secretory phase controls, TT ratio was 1.00 ± 0.9 and 0.970 ± 0.10, INR was 0.99 ± 056 and 0.98 ± 0.16, APTT ratio was 1.12 ± 0.19 and 1.13 ± 0.15, platelet count was 250.00 ± 55.8 10^9/L and 262.20 ± 63.4 10^9/L, neutrophil count was 3.76 ± 1.34 10^9/L and 4.31 ± 1.89 10^9/L, lymphocyte count was 2.04 ± 0.56 10^9/L and 1.87 ± 0.52 10^9/L, respectively.

We found no difference in TT ($P = .74$), INR ($P = .87$), platelet count ($P = .63$), neutrophil count ($P = .78$), lymphocyte count ($P = .78$), NLR ($P = .94$), and PLR ($P = .76$) between women with endometriosis and controls. Conversely, we found that patients with endometriosis had significantly shortened APTT when compared to controls ($P = .04$; Figure 1). This difference was maintained in both phases of the menstrual cycles. In proliferative phase, APTT was 1.12 ± 0.19 and 1.08 ± 0.06 ($P = .01$), respectively, in controls and patients with endometriosis, while in the secretory phase, it was 1.13 ± 0.15 and 1.08 ± 0.06 ($P = .05$), respectively. No differences were observed in coagulation parameters among subgroups of controls (ovarian dermoids, tubal pathology, seromucinous ovarian cysts, and myomas).

When we considered the various manifestations of endometriosis separately (Table 2), we found that women with ovarian disease had shortened APTT values ($P = .04$) in comparison to women without this form (controls and women with peritoneal and deep endometriosis); moreover, a significant between-group difference emerged in NLR, as women with peritoneal lesions had lower NLR if compared to patients without this form ($P = .01$). In addition, women with stage I to II endometriosis had slightly shorter APTT values and higher PLR than those with stage III to IV disease, and the differences reached statistical significance ($P = .01$ and $P = .005$, respectively). If compared to controls, women with stage III to IV had statistical significantly shorter APTT values as well ($P = .04$, data not shown).

In multivariate logistic regression analysis, after controlling for potential confounders (age, parity, BMI, and smoking), APTT retained significant predictive value for endometriosis disease ($P = .04$; Table 3).

Discussion

In this study, we failed to document an important relation between endometriosis and the peripheral coagulation system. A statistically significant shortening of the APTT emerged in women with endometriosis, but the magnitude of the difference was modest. Moreover, in the subanalysis according to the various forms of the disease, a shortened APTT was found to be associated with the presence of ovarian cysts only. This result is in line with previous evidence by Wu et al who indeed demonstrated a shorten APTT in women with ovarian endometriosis.[5] On the other hand, we could not confirm alterations in other coagulation variables such as TT which were previously claimed to be altered in affected women.

Importantly, although patients with endometriosis had significantly shortened APTT when compared to controls, these concentrations remain in the normal range and this of course poses some doubts about the clinical relevance of this finding. Moreover, although in multivariate logistic regression analysis APTT retained significant predictive value for endometriosis disease, given the small difference detected, a diagnostic usefulness of this parameter is unlikely.

A short APTT can be used as a surrogate marker for elevated levels of coagulation factors (except factor VII) and seems suitable to reflect any hemostatic balance in favor of a prothrombonic state. The underlying mechanism for increased thrombonic risk with shortened APTT has not been completely elucidated, but it is known that a short APTT is associated with hemostatic activation as evidenced by elevations in prothrombin fragment 1,2, thrombin–antithrombin complexes, D-dimers, and factor VIII coagulant activity, all markers for increased thrombin generation in plasma.[18] The reason for the observed alteration in APTT in women with endometriosis without the involvement of any other coagulation factor is unknown.

Endometriosis is characterized by a sterile, local inflammation occurring in the peritoneal cavity of women affected and an altered function of immune-related cells occurs in the peritoneal environment.[19] Moreover, based on studies at the systemic level, the disease can be recognized as a local affliction with relevant consequences also systemically.[19-23] Indeed, it induces the expression of genes in peripheral leukocytes already identified in nongynecologic chronic inflammatory diseases. In this regard, there is an increasing evidence that an extensive cross-talk between the systems of coagulation and inflammation exists, whereby inflammation leads to activation of coagulation and coagulation also markedly affects

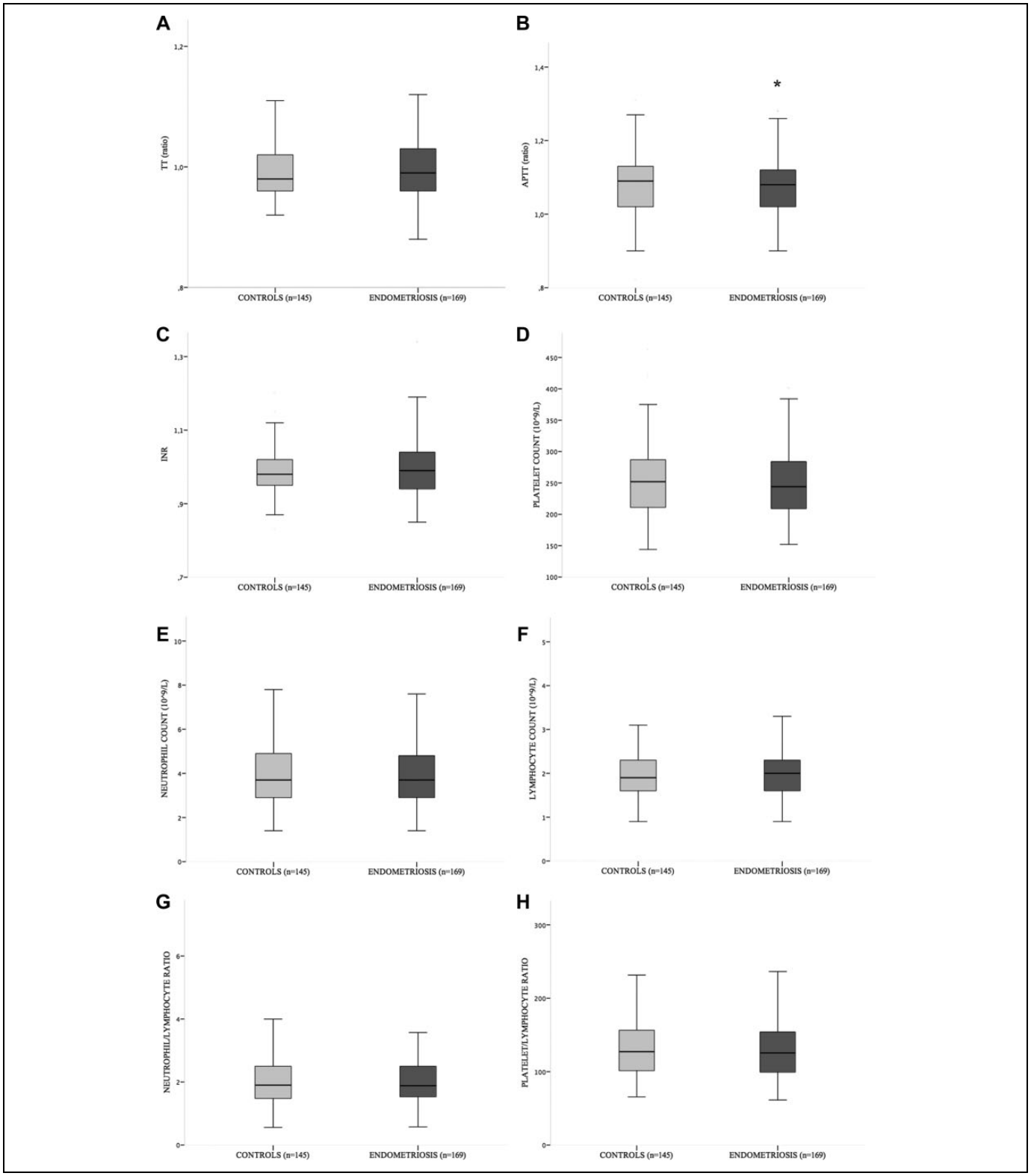

Figure 1. Boxplots of levels of coagulation parameters (A: TT, B: APTT, C: INR; D: Plateler count; H: platelet/lymphocyte ratio) and systemic inflammatory response markers (E: neutrophil count; F: lymphocyte count; G: neutrophil/lymphocyte ratio) in patients with endometriosis and controls (*$P < .05$ vs controls). APTT indicates activated partial thromboplastin time; TT, thrombin time; INR, International normalized ratio.

Table 2. Coagulation Parameters and Systemic Inflammatory Response Markers According to the Presence of the Different Forms of Endometriosis.

Diagnosis	TT (Ratio)	APTT (Ratio)	INR	P, 10^9/L	N, 10^9/L	L, 10^9/L	NLR	PLR
Endometrioma								
Present (n = 98)	0.99 ± 0.06	1.08 ± 0.07	0.99 ± 0.71	254.5 ± 61.47	3.9 ± 1.62	2.02 ± 0.66	2.08 ± 1.01	135.18 ± 68.69
Absent (n = 145)	0.99 ± 0.09	1.14 ± 0.07	0.99 ± 0.11	254.7 ± 58.62	3.99 ± 1.6	1.97 ± 0.55	2.16 ± 1.25	130.65 ± 52.8
P	.901	**.040**	.741	.637	.245	.691	.522	.209
Peritoneal endometriosis								
Present (n = 58)	1.00 ± 0.06	1.07 ± 0.06	1.00 ± 0.06	257.9 ± 62.8	3.98 ± 1.64	2.01 ± 0.54	2.10 ± 0.98	137.27 ± 77.68
Absent (n = 145)	0.99 ± 0.09	1.14 ± 0.07	0.99 ± 0.11	254.7 ± 58.62	3.99 ± 1.6	1.97 ± 0.55	2.16 ± 1.25	130.65 ± 52.8
P	.641	.068	.108	.364	.493	.965	**.019**	.319
Deep endometriosis								
Present (n = 69)	0.99 ± 0.06	1.06 ± 0.11	0.99 ± 0.11	248.02 ± 48.23	3.96 ± 1.88	2.04 ± 0.62	2.17 ± 1.68	130.8 ± 49.87
Absent (n = 145)	0.99 ± 0.09	1.14 ± 0.07	0.99 ± 0.11	254.7 ± 58.62	3.99 ± 1.6	1.97 ± 0.55	2.16 ± 1.25	130.65 ± 52.8
P	.954	.099	.719	.581	.251	.711	.757	.943
Endometriosis (all forms)								
Stage I-II (n = 45)	1.00 ± 0.08	1.05 ± 0.15	1.01 ± 0.07	253.21 ± 72.75	4.01 ± 1.74	1.91 ± 0.56	2.43 ± 2.19	153.09 ± 90.92
Stage III-IV (n = 124)	0.99 ± 0.06	1.07 ± 0.07	0.99 ± 0.07	250.59 ± 55.01	4.05 ± 1.67	2.07 ± 0.66	2.08 ± 0.95	129.57 ± 42.6
P	.228	**.012**	.590	.538	.202	.538	.213	**.005**

Abbreviations: APTT, activated partial thromboplastin time; INR, International normalized ratio; L, lymphocyte count; N, neutrophil count; N/L, neutrophil/lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; P, platelet count; P/L, platelet/lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TT, thrombin time.
Note: Statistically significant P values are indicated in bold.

Table 3. Multivariate Logistic Regression of Variables Predicting Endometriosis Disease.

Variable	B coefficient	SE	OR	*P*
TT (ratio)	0.166	14.08		.991
APTT (ratio)	−1.31	1.07	0.267	**.042**
INR	1.683	10.92		.878
Platelets (10^9/L)	−0.005	0.005		.345
Neutrophils (10^9/L)	0.039	0.228		.863
Lymphocytes (10^9/L)	0.418	0.533		.433
Neutrophil/lymphocyte ratio	−0.108	0.368		.768
Platelet/lymphocyte ratio	−0.007	0.008		.406

Abbreviations: APTT, activated partial thromboplastin time; INR, International normalized ratio; TT, thrombin time.
Note: Statistically significant P values are indicated in bold.

inflammatory activity.[24] Tissue factor plays a central role in the initiation of inflammation-induced coagulation,[25] since, on exposure to blood, it starts a reaction cascade that culminates in the generation of thrombin. Since endometriotic cells express TF,[9] we cannot exclude that the alteration demonstrated herein represents the subtle manifestation of the activation of the TF pathway at the level of endometriotic lesions. Differences among studies in coagulation parameters might thus be related to disease variability among patients. In other words, the weak and clinically debatable evidence emerging from our study tends to rule out a role of the coagulation system in the origin of the disease. Endometriosis would not develop more commonly in women with a shorter APTT. On the other hand, our data cannot be used to deny a relevant role of the coagulation system in the pathogenesis of endometriosis. The mild variations captured at the peripheral levels may reflect a more relevant local alteration. Perturbation of the coagulation system may occur at some time during the pathogenetic process and may have a crucial role in the establishment or progression of the disease.

In this regard, it is noteworthy that women with a more severe disease do not seem to have a shorter APTT, and the alteration seems to be associated with the presence of the endometriotic cyst. In this context, it should be considered that an endometrioma contains free iron, reactive oxygen species, proteolytic enzymes, and inflammatory molecules in concentrations from tens to hundreds of times higher than those present in peripheral blood or in other types of benign cysts.[14,26] 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 peritoneal surface. Similar to what happens in slowly evolving disseminated intravascular coagulation (DIC), APTT values may actually become shorter than normal in plasma, probably because of the increased presence of activated coagulation factors in the plasma (Guidelines for the diagnosis and management of disseminated intravascular coagulationD 2009).[27] The large amounts of coagulation-related products present in the endometrioma is evident in case of cyst rupture that can cause the rapid elevation in plasma D dimer to levels higher than those reported in cases of acute leukemia or with a major embolism.[28,29]

We have also found a significantly lower NLR in women with peritoneal lesions compared to patients without this form. Again, the magnitude of the difference observed is however small, and we have serious concerns about any clinical significance. Data in the literature on NLR in endometriosis are

inconsistent with some contributions reporting higher levels in women affected and others reporting no difference.[6] Finally, although the platelet count was similar between patients with endometriosis and controls and in the various subanalyses, PLR resulted significantly reduced in patients with stages III to IV endometriosis than in those with stage II to III disease. Two studies have addressed the relationship between PLR and endometriosis, one reporting increased and the other similar levels of PLR between women with and without endometriosis.[7,8] Severe forms resulted to have even higher levels in one report and similar levels in the other. The great variability in endometriosis manifestations and forms is likely to explain all these inconsistencies.

This study has some limitations: (1) the retrospective design of the study that could have influenced the interpretation of our findings and (2) the presence of only 1 type of controls, the surgical population. For these reasons, the results should be taken with caution. On the other hand, all the participants considered had a laparoscopic diagnosis, were not on oral contraceptives, and we could include a large sample size with a great variety of forms and manifestations of the disease. Moreover, a consistent number of coagulation variables have been evaluated.

In summary, we confirm the presence of a shorter, but still in the normal range, APTT in women with ovarian endometriomas compared to a control population. The evidence is insufficient to foresee a possible use of APTT as a diagnostic marker and to claim a crucial role of a systemic hypercoagulable state in the origin of the disease. However, our evidence does not exclude a role of the local coagulation system in the pathogenesis and progression of endometriosis. Further evidence is required to investigate this possibility, possibly evaluating more coagulation parameters or inflammatory markers.

Declaration of Conflicting Interests

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