


RESEARCH ARTICLE

The postpartum uterine ultrasonographic scale in assessment of uterine involution after cesarean section in treated thrombophilia pregnant patients at term

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Abstract

Background: Pregnancy is a prothrombotic condition which can be abnormally exaggerated in women with thrombophilia.

Methods: In a prospective study, patients who delivered at term, by cesarean section, between 1 October 2017 and 1 December 2021, who already had a diagnosis of thrombophilia before coming to our hospital, were included in the study group ($n = 80$). A similar number of nonthrombophilia patients ($n = 80$) without any history of thrombotic events, age- and para-matched with the study group, were included in the control group. The postpartum uterine ultrasonographic scale (PUUS) values, in the first 24–48 h, were correlated with the patients' data.

Results: The P-LCR (platelet large cell ratio), was significantly higher in the treated thrombophilia group ($p = 0.042$). There was no correlation between PUUS and complete blood count values, coagulation factors, maternal characteristics, or fetal outcomes, except for postpartum neutrophils ($p = 0.047$) and postpartum platelet count ($p = 0.046$).

Conclusions: Postpartum uterine involution was not significantly different, after cesarean section, between treated thrombophilia patients and nonthrombophilia patients. Involution correlated only with postpartum neutrophils and postpartum platelet count.

KEYWORDS

cesarean section, coagulation factors, complete blood count, fetal outcomes, maternal characteristics, postpartum uterine ultrasonographic scale, thrombophilia, uterine involution

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1 | INTRODUCTION

The pregnancy-induced shift in coagulation, as an adaptation to prevent postpartum bleeding, can be abnormally exaggerated in women with thrombophilia,¹ especially after cesarean section, which doubles the risk of thrombotic events compared with vaginal deliveries.² Thrombophilia is a group of genetic disorders that cause the blood to clot abnormally and is linked to adverse pregnancy outcomes.^{3–5} Therefore, antithrombotic treatment in pregnant patients with previous adverse fetal outcomes, and especially thrombophilia, is recommended.⁶

Recurrent pregnancy loss is generated mainly by acquired thrombophilia (antiphospholipid antibody syndrome), according to Alesandru,⁷ while, according to Gandone,⁸ inherited thrombophilia (factor V Leiden) is mostly involved.

The risk of venous thromboembolism is five times higher in pregnant patients, than in nonpregnant ones, up to 20 times higher immediately after labor, and even higher in thrombophilia pregnant patients, and persists until nearly 12 weeks postpartum.⁹ Still, Lafalla¹⁰ could not correlate patient thrombophilia with placenta-mediated pregnancy complications; moreover, in patients undergoing low-molecular-weight heparin treatment and/or acid acetylsalicylic fetal outcomes improved, acting both as protective factors. The low-molecular-weight heparin may be effective in patients who had pre-eclampsia, or other pathologic vascular processes.¹¹ On the contrary, according to Intzes,¹² in patients having thrombophilia, the benefit of low-molecular-weight heparin for a live birth does not exist.

Assuming that uterine involution could be similar in treated thrombophilia patients and healthy patients, but different in non-treated thrombophilia patients, this work aimed to study whether there is any difference in the postpartum uterine involution, assessed in a numerical fashion, after cesarean section, between treated thrombophilia patients at term and nonthrombophilia patients, as well as to elucidate the relationship of this involution with maternal and fetal characteristics. The aim of the work is focused on the instrumental aspect (the ultrasonographic assessment), not on the laboratory values.

2 | MATERIALS AND METHODS

Patients admitted in the Elena Doamna Obstetrics and Gynecology University Hospital in Iasi for delivery at term by cesarean section between 1 October 2017 and 1 December 2021 were prospectively studied. We included in the study group patients who delivered at term and who already had a diagnosis of thrombophilia before coming to our hospital. We included only thrombophilic patients identified on laboratory tests outside our hospital. We had no other symptomatic patients during the study period. The laboratory in our hospital cannot perform screening for thrombophilia patients, therefore we only included patients who already came with thrombophilia diagnosis established by specialized laboratories.

We compared them with a similar number of healthy patients who delivered by cesarean section, in our hospital, in the same period of time, who were age- and para-matched with the study group, without any history of thrombotic events or symptoms suggesting thrombotic events, and we sent their blood samples to the same external laboratory to determine any thrombophilia mutations; there were none. Thrombophilia patients who delivered vaginally were excluded from this study. Patients with thrombocytopenia, deep vein thrombosis, or cerebral thrombosis peripartum were also excluded from the study. There were 160 patients studied, with 80 patients in each group. Since all of the thrombophilia patients were already diagnosed before delivering in our hospital, they were also already receiving anticoagulant treatment. None of the thrombophilia patients had any vascular symptoms during the current hospitalization; all of them previously had recurrent pregnancy losses, which raised the suspicion of thrombophilia, and their blood samples were sent to specialized laboratories for thrombophilia screening.

All patients were examined postpartum by ultrasonography, in the first 24–48 h postpartum, and the PUUS scale was used. The PUUS scale (Postpartum Uterine Ultrasonographic Scale) has previously been described, but briefly, and it is a visual scale that evaluates the number of quarters of the endometrial length occupied by blood or debris, ranging from 0 to 4, as follows:

Grade 0: No blood or debris in the uterine cavity.

Grade 1: Less than a quarter of the endometrial length occupied by blood or debris.

Grade 2: Less than a half of the endometrial length occupied by blood or debris.

Grade 3: Less than three quarters of the endometrial length occupied by blood or debris.

Grade 4: Over three quarters of the endometrial length occupied by blood or debris.

The PUUS scale was used because it is faster than laboratory findings, and evaluates exactly, in a numerical fashion, the uterine involution.

The values and characteristics of the patients' blood following analysis were extracted from the hospital's medical records. For this work, the complete blood count values—the last ones antepartum and the first ones postpartum—were considered. The coagulation factors were harvested only antepartum. Hospital policy required that blood analysis was performed in both the 24 h before and the 24 h after labor.

The MAN-HEMATO Laboratory Equipment was used for the complete blood count, and the RAYTO RT-2201C Coagulation Analyzer for the coagulation factors.

This study was approved by the Ethics Committee of Elena Doamna Obstetrics and Gynecology University Hospital (approval number 9; 17 September 2017). Informed written consent was obtained from each patient.

Data were analyzed using SPSS version 18 (PASW Statistics for Windows, Chicago: SPSS Inc., Chicago, IL, USA). Descriptive measures were point-estimated for both categorical and numerical variables. The absolute and relative frequencies, averages, standard

deviations, median and quartiles were computed. Due to the fact that a lot of the distributions of the variables did not follow a normal curve, we applied comparisons using the nonparametric Mann–Whitney *U*-test and for correlation the Spearman formula. We have also applied the Student's *t*-test when data follows a normal distribution. The standard significance level was 0.05 as a cutoff for statistical hypothesis decisions.

3 | RESULTS

The mutations of thrombophilia identified in the study group are described in Table 1. The antiphospholipid syndrome includes one or more of the following three factors: anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, lupus anticoagulant present in plasma, and anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma.^{13,14} We only had one patient in the study group with lupus anticoagulant.

There were no thrombophilia mutations identified in the control group (Table 2).

These results were in accordance with Gulino,¹⁵ who found MTHFR gene mutation in most infertile patients selected for thrombophilia screening. The number of mutations for each patient is not detailed, since, according to Patounakis,¹⁶ outcomes cannot be predicted by the cumulative number of thrombophilic mutations present in the patient.

In the study group, there were 6 Rh incompatibility cases (7.5%), 2 of them (33.33%) tested negative for anti-Rh positive antibodies, the other 4 were not tested, and all 6 of them (100%) were administered anti-D immunoglobulin.

There was no significant difference ($p = 0.366$) between the PUUS grade in the two groups. There was no significant difference in blood values between the two groups, except for postpartum P-LCR, which was significantly higher in group 1 (treated thrombophilia group) ($p = 0.042$). There was no correlation between PUUS and the complete blood count values, either antepartum or postpartum, or the antepartum coagulation factors, except for postpartum neutrophils ($p = 0.047$) and postpartum platelet count ($p = 0.046$), whose mean values were not significantly different between the two groups.

TABLE 1 Thrombophilia mutations identified in the study group

Thrombophilia mutations identified in the study group	Number	Percent
Gene MTHFR	43	53.75%
Factor V Leiden	17	21.25%
Plasminogen activator inhibitor	11	13.75%
Protein C	4	5.00%
Prothrombin G20210A	3	3.75%
Lupus anticoagulants	1	1.25%
Antithrombin	1	1.25%
Total	80	100%

Abbreviation: MTHFR, methylene tetrahydrofolate reductase.

TABLE 2 Thrombophilia mutations in the control group

Thrombophilia mutations identified in the control group	Number	Percent
Gene MTHFR	0	0%
Factor V Leiden	0	0%
Plasminogen activator inhibitor	0	0%
Protein C	0	0%
Prothrombin G20210A	0	0%
Lupus anticoagulants	0	0%
Antithrombin	0	0%
Protein S	0	0%
Factor XIII V34L	0	0%
Anticardiolipin antibodies	0	0%
Antibeta-2-glycoprotein 1 antibodies	0	0%
Antiphospholipid antibodies	0	0%
Total	0	0%

Abbreviation: MTHFR, methylene tetrahydrofolate reductase.

3.1 | Patients' characteristics

Though patients in the control group were selected to be age- and para-matched to the study group, gestation number was significantly higher in the thrombophilia group as a consequence of previous miscarriages generated by thrombophilia (Table 3). Gestational age was 38.13 weeks in the thrombophilia group and 38.50 weeks in the non-thrombophilia group ($p = 0.912$), and they were all at term pregnancies.

3.2 | PUUS values

There was no significant difference ($p = 0.366$) between the PUUS grade in the two groups (Table 4). Uterine involution was not significantly different.

There was no PUUS 4 value in these groups; therefore, value 4 for PUUS was removed in the next tables, and only values 0–3 were written.

3.3 | Complete blood count and coagulation factors

There was no significant difference in these values between the two groups, except for postpartum P-LCR, which was significantly higher in group 1 (treated thrombophilia group) ($p = 0.042$).

3.4 | Correlation between PUUS and complete blood count and coagulation factors

There was no correlation between PUUS and complete blood count values, either antepartum or postpartum, or antepartum coagulation factors, except for postpartum neutrophils ($p = 0.047$) and

Patients	Thrombophilia patients (n = 80)	Nonthrombophilia patients (n = 80)	Significance, <i>p</i>
Age (years)	30 (±5) 30 (27–34)	30 (±5) 30 (27–34)	0.944
Gestation (number)	3 (±1) 3 (2–3)	2 (±1) 2 (1–2)	<0.001
Parity (number)	2 (±1) 2 (1–2)	2 (±1) 2 (1–2)	0.213

Note: The nonparametric Mann–Whitney test was used for comparisons.

TABLE 4 PUUS values in the two groups

PUUS value	Thrombophilia patients (n = 80)	Nonthrombophilia patients (n = 80)
0	65 (81.25%)	69 (86.25%)
1	7 (8.75%)	6 (7.50%)
2	5 (6.25%)	4 (5%)
3	3 (3.75%)	1 (1.25%)
4	0 (0%)	0 (0%)
Total	80 (100%)	80 (100%)

postpartum platelet count ($p = 0.046$), whose mean values were not significantly different between the two groups (Table 5).

3.5 | PUUS and maternal blood group

There was no significant difference between the maternal blood groups ($p = 0.413$) in the two groups. The PUUS distribution is shown in Table 6.

Due to the lack of consistency, a Chi-square test could not be used to determine associations between PUUS and the blood groups.

3.6 | PUUS and the Rh factor

There was no significant difference between the Rh factor distribution ($p = 0.79$) in the two groups. The PUUS distribution is shown in Table 7.

Due to the lack of consistency, a Chi-square test could not be used to determine correlations between PUUS and the Rh factor.

3.7 | PUUS and fetal outcomes

There were no significant differences between the fetal outcomes in the two groups: weight ($p = 0.571$) or Apgar score ($p = 0.303$). There was no correlation between PUUS and fetal outcomes (Table 8).

3.8 | PUUS and fetal gender

Fetal gender was not significantly different between the two groups ($p = 0.627$). The PUUS distribution is shown in Table 9.

TABLE 3 Patients' characteristics: mean, median, standard deviation and quartiles 1 and 2 values

Due to the lack of consistency, a Chi-square test could not be used to determine the correlation between PUUS and fetal gender.

3.9 | PUUS and maternal characteristics

There was no significant differences between the maternal characteristics in the two groups: height, weight, BMI ($p = 0.376$; 0.239 and 0.085 respectively). There was no correlation between PUUS grade and maternal characteristics (Table 10).

4 | DISCUSSION

Though there was a worldwide agreement about the benefits of low molecular weight heparin in patients having low risk thrombophilia, there was no agreement about dosage in patients at high risk.¹⁷ Despite this lack of consensus, the above results showed that treated thrombophilia pregnant patients had similar characteristics and outcomes to nonthrombophilia pregnant patients.

For Stamou,¹⁸ the use of low-molecular-weight heparin and/or acid acetylsalicylic was not related to live birth rates or late obstetric complications, nor was the etiology of thrombophilia; the only factor inversely related to live birth rates was age above the cutoff value of 35.5 years ($p = 0.049$). This was true for our patients, since we considered the thrombophilia patients altogether, and the results were similar to those of the nonthrombophilia patients; we only had 15 patients aged over 35, but their results did not differ to the results of the other patients.

There was also no difference in the chromosomal aberration rate between the factors for recurrent pregnancy loss, with or without thrombophilia, and antithrombotic therapy; only advancing maternal age was significantly correlated with increased embryo chromosomal aberration rates.¹⁹ On the contrary, according to Kurodawa,²⁰ the live birth rate in thrombophilia patients treated with low-dose aspirin increased in all patients, except for those older than 40 years old. Our patients were treated with low-molecular-weight heparin, not aspirin, but there was no difference regarding age.

Heparin-derived compounds significantly contribute to the prevention and treatment of thrombotic events in pregnancy, respiratory inflammation, renal diseases, sepsis, and pancreatitis, among others.²¹ Low-molecular-weight heparin also has a positive effect on thrombophilia IVF patients,²² because it decreases coagulation in

small blood vessels and increases trophoblast development.²³ This is in accordance with what we found, that treated thrombophilia patients had the same outcomes as normal patients.

Ultrasonography is the mainstay in the initial imaging evaluation of a postpartum patient, with occasional progression to computed body tomography, magnetic resonance imaging, or angiography.²⁴ Ucci²⁵ tried to standardize the postpartum involution of the endometrial thickness, Levinson²⁶ used Doppler to classify the risk of retained products of conception, and Vyas²⁷ associated endometrial

thickness and lack of Doppler signal in uterine mucosa and muscular layer to positive maternal outcomes. However, all of these methods are time-consuming. The PUUS method is easier and can be adapted to a patient's body size.

During postpartum uterine involution, the majority of the endometrium is regenerated to replace the tissue that is shed postpartum, but the particular role of putative stem cells is poorly understood.²⁸ Bone marrow-derived progenitors have been found to provide a novel nonhematopoietic cellular contribution to postpartum uterus remodeling.²⁹ Freshly isolated bone marrow-derived cells (including hematopoietic progenitor cells) induce the greatest degree of regeneration of the endometrium.³⁰ We found a correlation between the PUUS scale and postpartum neutrophils and platelet count, which supported these statements, since hematopoietic stem cells divide into increasing specialized cells and eventually lead to mature leukocytes, erythrocytes, and platelets.³¹

Fibrinogen was considered an important part of a scale for pregnant women who need blood transfusion,³² together with prothrombin time and antithrombin III, among other factors. Fibrinogen was also considered part of a logistic regression model to evaluate the risk of thrombophilia in pregnant women, together with activated partial thromboplastin time, among others.³³ Gris³⁴ tried to establish two quantitative scores as references for coagulation assays performed for thrombophilia screening, prescribed according to guidelines, after a first venous thromboembolic event. We found no correlation between the PUUS scale and coagulation factors in the treated thrombophilia patients.

In patients receiving heparin, coagulation function is assessed by determining APTT or, less frequently, anti-activated factor X,³⁵ with similar sensibility.³⁶ Low-dose unfractionated heparin prophylaxis decreases the incidence of venous thromboembolism in hospitalized patients, but increases the risk of bleeding events; therefore, patients who develop a prolonged activated partial thromboplastin time while on low-dose unfractionated heparin may be at higher risk of bleeding complications.³⁷ We reported no patient with prolonged activated partial thromboplastin time while treated with low-dose unfractionated heparin.

We reported significantly higher postpartum P LCR in treated thrombophilia patients than in normal patients. Generally, the platelet-large cell ratio (P-LCR) increased with age,³⁸ but in the case of postpartum patients, a higher value of P LCR can be interpreted

TABLE 5 Patients' characteristics correlated with PUUS: mean values (and standard deviations)

Patients' characteristics	Thrombophilia patients (n = 80)	Nonthrombophilia patients (n = 80)	Significance, p
P NEUT	7.59 (±3.03)	8.01 (±3.64)	0.891
P PLT	223.01 (±64.57)	242.33 (±63.49)	0.089

Abbreviations: P NEUT, postpartum neutrophils; P PLT, postpartum platelet count.

TABLE 6 PUUS values as regards maternal blood group in the two groups

Blood group	PUUS grade	Thrombophilia patients (n = 80)	Nonthrombophilia patients (n = 80)
O	0	20 (87.0%)	20 (90.9%)
	1	1 (4.3%)	2 (9.1%)
	2	1 (4.3%)	0 (0.0%)
	3	1 (4.3%)	0 (0.0%)
A	0	28 (80%)	33 (82.5%)
	1	4 (11.4%)	4 (10%)
	2	2 (5.6%)	3 (7.5%)
	3	1 (2.9%)	0 (0.0%)
B	0	13 (72.2%)	10 (90.9%)
	1	2 (11.1%)	0 (0.0%)
	2	2 (11.1%)	1 (9.1%)
	3	1 (5.6%)	0 (0.0%)
AB	0	4 (100%)	6 (85.7%)
	1	0 (0.0%)	0 (0.0%)
	2	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	1 (14.3%)

TABLE 7 PUUS values as regards the Rh factor in the two groups

PUUS value	Thrombophilia patients (n = 80)		Nonthrombophilia patients (n = 80)	
	Rh+	Rh-	Rh+	Rh-
0	57 (80.28%)	8 (88.88%)	61 (84.72%)	8 (100%)
1	6 (8.45%)	1 (11.11%)	6 (8.33%)	0 (0%)
2	5 (7.04)	0 (0%)	4 (5.55%)	0 (0%)
3	3 (4.22%)	0 (0%)	1 (1.38%)	0 (0%)
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	71 (100%)	9 (100%)	72 (100%)	8 (100%)

Fetal outcomes correlated with PUUS	Thrombophilia patients (n = 80)	Nonthrombophilia patients (n = 80)
Weight	-0.082	0.021
Apgar	-0.014	-0.09

Note: All correlations were nonsignificant.

TABLE 8 Correlation coefficient between PUUS values and fetal outcomes in the two groups

PUUS value	Thrombophilia patients (n = 80)		Nonthrombophilia patients (n = 80)	
	M	F	M	F
0	36 (76.59%)	29 (87.87%)	44 (88%)	25 (83.33%)
1	4 (8.51%)	3 (9.09%)	3 (6%)	3 (10%)
2	5 (10.63%)	0 (0%)	2 (4%)	2 (6.66%)
3	2 (4.25%)	1 (3.03%)	1 (2%)	0 (0%)
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	47 (100%)	33 (100%)	50 (100%)	30 (100%)

TABLE 9 PUUS values as regards the fetal gender in the two groups

TABLE 10 Correlation coefficient between the PUUS values and maternal characteristics in the two groups

Maternal characteristics correlated with PUUS	Thrombophilia patients (n = 80)	Nonthrombophilia patients (n = 80)
Height	-0.028	-0.061
Weight	0.013	0.046
BMI	0.049	0.048

Note: Correlations were nonsignificant.

Abbreviation: BMI, body mass index.

as the presence of a high percentage of new platelets characterized by a greater size,³⁹ since young platelets are larger and more active than mature cells,⁴⁰ and contain greater amounts of thromboxane A1 and beta-thromboglobulin.^{41,42} This means that labor triggered the release of more numerous young platelets and an increase in P-LCR, but only in thrombophilia patients.

The PUUS scale demonstrated that postpartum uterine involution in treated thrombophilia patients was the same as in healthy patients, therefore the PUUS scale can be an easy method to assess, in a numerical fashion, the uterine involution immediately postpartum in treated thrombophilia patients. Further studies to assess the uterine involution during the follow up of thrombophilia patients, with or without treatment, would be interesting".

This study has several weaknesses. First, a larger study would be necessary to confirm these results. Second, a correlation between PUUS grade and the dose of low-molecular-weight heparin, requiring more patients, should follow this study. Third, it only included treated thrombophilia pregnant patients at term, while patients who were untreated, with miscarriages or preterm birth, were not studied. Though the assessment of PUUS may seem to have no clinical value in treated thrombophilia patients, the results might be totally different in patients who have not been treated yet. Fourth, a larger study to compare the different types of

thrombophilia and the uterine involution evaluated by the PUUS scale might show some significant differences. Fifth, a larger study would be useful to evaluate the diffusion of the single mutation of MTHFR Factor in general population, as a reason for an increasing risk of thrombophilia.

5 | CONCLUSIONS

Postpartum uterine involution was not significantly different between treated thrombophilia patients and nonthrombophilia patients. Involution correlated only with postpartum neutrophils and postpartum platelet count.

AUTHOR CONTRIBUTIONS

Conceptualization, Catalina Filip and Roxana Covali; data curation, Mona Akad; formal analysis, Lucian Boiculescu; funding acquisition, Catalina Filip; investigation, Alexandru Carauleanu and Madalina Irina Ciuhodaru; methodology, Ioana Pavaleanu and Demetra Socolov; project administration, Răzvan Socolov; resources, Mona Akad; software, Lucian Boiculescu; supervision, Răzvan Socolov; validation, Demetra Socolov and Sadyie Scripcariu; visualization, Demetra Socolov; writing—original draft, Roxana Covali and Tudor Butureanu; writing—review and editing, Alexandru Carauleanu, Sadyie Scripcariu and Ingrid Andrada Tanasa. All authors read and agreed to the published version of the article.

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None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data can be obtained from the corresponding author upon reasonable request.

INSTITUTIONAL REVIEW BOARD STATEMENT

This study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Elena Doamna Obstetrics and Gynecology University Hospital (Approval number 9; 17 September 2017).

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study.

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