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Article

Inflammation Indexes PLR, SII, AISI, MLR, NLPR and MCVL in Peripartum Treated Thrombophilia Patients Undergoing Cesarean Section at Term-STROBE Compliant

Catalina Filip [1], Roxana Covali [2,*], Demetra Socolov [3], Ingrid Andrada Vasilache [3], Alexandru Carauleanu [3], Mona Akad [4,*], Ioana Sadyie Scripcariu [3], Tudor Butureanu [5], Gabriela Dumachita-Sargu [5], Lucian Vasile Boiculese [6], Alina Melinte [5] and Razvan Socolov [5]

[1] Department of Vascular Surgery, General Medicine Faculty, Grigore T. Popa University of Medicine and Pharmacy Iasi, 700115 Iasi, Romania; filipcatalina20@gmail.com
[2] Department of Radiology, Elena Doamna Obstetrics and Gynecology University Hospital, Iasi, Biomedical Engineering Faculty, Grigore T. Popa University of Medicine and Pharmacy Iasi, 700115 Iasi, Romania
[3] Department of Obstetrics and Gynecology, Cuza Voda Obstetrics and Gynecology University Hospital, Iasi, General Medicine Faculty, Grigore T. Popa University of Medicine and Pharmacy, 700115 Iasi, Romania; socolov@hotmail.com (D.S.); tanasaingrid@yahoo.com (I.A.V.); acarauleanu@yahoo.com (A.C.); isscripcariu@gmail.com (I.S.S.)
[4] Department of Obstetrics and Gynecology, Elena Doamna Obstetrics and Gynecology University Hospital, Iasi, General Medicine Faculty, Grigore T. Popa University of Medicine and Pharmacy, 700115 Iasi, Romania
[5] Department of Obstetrics and Gynecology, Elena Doamna Obstetrics and Gynecology University Hospital, Iasi, General Medicine Faculty, Grigore T. Popa University of Medicine and Pharmacy Iasi, 700115 Iasi, Romania; tudorandreib@gmail.com (T.B.); sargu_gabriela@yahoo.com (G.D.S.); melinte555@yahoo.com (A.M.); socolovr@yahoo.com (R.S.)
[6] Department of Statistics, Grigore T. Popa University of Medicine and Pharmacy Iasi, 700115 Iasi, Romania; lboiculese@gmail.com
* Correspondence: rcovali@yahoo.com (R.C.); akad.mona@yahoo.com (M.A.); Tel.: +40-232-210-390/275 (R.C.); +40-232-210-390/233 (M.A.)

Abstract: (1) Background: Thrombophilia is a tendency towards hypercoagulability, and it is increased by pregnancy, peaking around delivery. Research question: does thrombophilia stimulate the inflammatory state of the patient, already suppressed by pregnancy? (2) Methods: Eighty thrombophilia patients admitted for delivery between 1/10/2017 and 1/12/2021 were prospectively studied, together with eighty age- and para-matched control patients. Patients were admitted for delivery at term by means of cesarean section. The inflammation indexes from the complete blood count values analysis during both the 24 hours before and after labor—extracted from the hospital's medical records—were calculated and then correlated with uterine involution. (3) Results: Except for the PLR, most of the numerous inflammation indexes studied were not significantly different in treated thrombophilia patients, before and after delivery, compared to non-thrombophilia patients. Only when we split the patients, based on the uterine haematometra in the first 24-48 hours postpartum, we found out that the few treated thrombophilia patients with haematometra (14 with haematometra out of 79 with treated thrombophilia) had elevated SII and AISI antepartum. In pregnant patients treated for thrombophilia, MLR is higher in patients without the Rh factor than in those with the Rh factor. In non-thrombophilia patients, MCVL and NLPR increased with age and before labor, while SII and AISI increased with age postpartum. (4) Conclusions: Thrombophilia did not stimulate the inflammatory state of the patient, already suppressed by pregnancy.

Keywords: thrombophilia; pregnancy; postpartum uterine ultrasonographic scale; SII; AISI; MLR; PLR; MCVL; NLPR; Rh factor

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1. Introduction

Rationale: inflammation generates increased coagulation, but nobody studied if increased coagulation, that is thrombophilia, has an underlying inflammatory substrate. After treating thrombophilia, with anticoagulants, does this inflammatory state exist? Research question: does thrombophilia stimulate the inflammatory state of the patient, already suppressed by pregnancy [1–3]? Study aim: to determine which inflammation indexes are modified in treated thrombophilia patients, before and after delivery, compared to non-thrombophilia patients. Reason: Inflammation during pregnancy is associated with an increased risk of neurodevelopmental disorders, including autism spectrum disorders [4,5] and child attention-deficit/hyperactivity disorder (ADHD) [6] and changes in the neuroimmune environment of offspring that persist into adulthood [4]. Systemic inflammation during pregnancy is also associated with shorter duration of any and exclusive breastfeeding [7].

Thrombophilia is a tendency towards hypercoagulability, and it is caused by genetic or acquired hemostasis conditions [2]. Pregnancy by itself favors hypercoagulability [9], which accelerates during pregnancy and reaches its highest point peripartum [10]. Thrombophilia alters pregnancy outcomes due to hypercoagulability, stasis, and placental modifications [11–15]. The administration of low-molecular-weight heparin (LMWH) is adapted to each pregnant patient. The treatment stops when labor pain occurs or 6 hours before the planned cesarean section, and it restarts after delivery [16]. They report a protective effect of LMWH on miscarriage in patients with a history of unexpected recurrent pregnancy losses due to thrombophilia [17–20]. Other studies contest it: high-dose thromboprophylaxis did prevent thrombosis antepartum; still, neonatal outcomes were worse among mothers with thrombophilia [21–28].

In a previous article [29], we demonstrated that postpartum uterine involution only correlated with postpartum neutrophil and postpartum platelet counts. Neutrophils and platelet originate from the same bone marrow [30]. Pathogen-induced platelet activation leads to systemic thrombosis [31]. Inflammation and coagulation are connected. Blood retention into the uterus may elicit inflammation, the more blood in the uterus, the higher risk of endometritis, even higher in cesarean sections than in vaginal deliveries [32]. High concentrations of citokines in pregnancy are associated with postpartum hemorrhage [33,34].

Therefore, we considered that there may be an underlying inflammatory state that persisted despite treatment, especially in patients with uterine haematometra, and we further analyzed it within the same group of patients. We calculated all the inflammation indexes that we could, derived from the routine haematological parameters. We considered that, when there are so many variables explored, the probability of getting some significance was very high. The inflammation indexes studied were the neutrophil–lymphocyte ratio, derived neutrophil–lymphocyte ratio, monocyte–lymphocyte ratio, platelet–lymphocyte ratio, systemic inflammatory index, systemic inflammatory response index, aggregate index of systemic inflammation, mean corpuscular volume–lymphocyte ratio, and cumulative inflammatory index.

2. Materials and Methods

We studied 160 pregnant patients. There were 80 pregnant treated thrombophilia patients in the study group, and we chose another 80 patients who had similar age and parity. Patients were referred to our hospital for delivery at term by means of cesarean section between 1/10/2017 and 1/12/2021. Hospital policy required that patients already diagnosed with thrombophilia will be provided cesarean section at 38 weeks gestational age. So were the study group patients. This was a prospective study. All thrombophilia patients already had their diagnosis established. Treatment with low-molecular-weight heparin is ongoing. Our hospital cannot supply thrombophilia screening tests; thus, the control group had their blood sent for screening to specialized laboratories, yielding negative results. The exclusion criteria are as follows: patients suffering from thrombocytopenia (n=2), patients with deep vein thrombosis (n=0), and patients with cerebral thrombosis (n=0) [29].

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Table 1. Thrombophilia mutations identified in the study group [29].

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%

MTHFR = methylene tetrahydrofolate reductase.

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

Table 2. Thrombophilia mutations in the control group [29].

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%

MTHFR = methylene tetrahydrofolate reductase.

Table 3. Patients' characteristics: mean, median, standard deviation and quartiles 1 and 2 values [29].

Patients	Thrombophilia patients (n = 80)	Non-thrombophilia patients (n =80)	Significance, p
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

The non-parametric Mann-Whitney test was used for comparisons.

Every patient received a sonogram during the first 1-2 days after cesarean section, and the uterine evaluation was interpreted with the use of the PUUS scale (Postpartum Uterine Ultrasonographic Scale). This scale [35,36] counts the quarters of missing uterine vacuum lines, which could be due to blood or debris presence, as follows:

In grade 0, the uterine cavity is completely empty.

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In grade 1, there is a small amount of blood or debris occupying less than one-quarter of the vacuum line.

In grade 2, there is a slightly larger amount of blood or debris occupying less than two-quarters of the vacuum line.

In grade 3, there is a large amount of blood or debris occupying less than three-quarters of the vacuum line.

In grade 4, there is a large amount of blood or debris occupying more than three-quarters of the vacuum line [35,36].

In these cases, debris means that there could be blood or retained trophoblastic tissue. Blood is mobile and has no Doppler signal, while retained trophoblastic tissue is not mobile, is delineated in one or more areas and has Doppler signal. In this group of patients, we had no one with retained trophoblastic tissue. We further referred to these debris as "uterine haematometra".

In a previous study [29] on the same group of patients, we presented the demographic, maternal and fetal outcomes.

The values and characteristics of the patients' blood following analysis were extracted from the hospital's medical records. For this study, the complete blood count values—the first count is obtained postpartum and the last count is obtained antepartum—were considered. Hospital policy requires blood analyses both 24 hours before and after labor [29]. From these values, we calculated inflammation indexes NLR, dNLR, MLR, PLR, SII, SIRI, AISI, MCVL, NLPR, and IIC as follows:

NLR= number of neutrophils/number of lymphocytes. MLR= number of monocytes/number of lymphocytes. PLR= number of platelets/number of lymphocytes. dNLR= number of neutrophils/difference between the number of white blood cells and number of neutrophils. SII= number of neutrophils x number of platelets/number of lymphocytes. SIRI= number of neutrophils x number of monocytes/number of lymphocytes. AISI= number of neutrophils x number of monocytes x number of platelets/number of lymphocytes. MCVL= mean corpuscular volume/number of lymphocytes. IIC= mean corpuscular volume x width of erythrocyte distribution x number of neutrophils/one thousand times the number of lymphocytes. NLPR= neutrophils/ (number of lymphocytes x number of platelets) [37].

We performed the blood analysis using MAN-HEMATO Laboratory Equipment.

We performed the data analysis via SPSS version 18 (PASW Statistics for Windows, Chicago: SPSS Inc., Chicago, IL, USA). We determined mean and median values, standard deviations, and quartiles. We also used the nonparametric Mann–Whitney U test and Spearman's correlation. We considered $p<0.05$ as significant [29].

3. Results

One patient with thrombophilia had incomplete data; thus, she was removed from this study, leaving 79 patients with thrombophilia and 80 patients without thrombophilia; all pregnant patients were at term.

3.1. Inflammation indexes in Pregnant Patients and the Postpartum Period

The PLR index is significantly higher in healthy, non-thrombophilia patients compared to treated thrombophilia patients. The other inflammatory indexes are not significantly different between the two groups of treated thrombophilia or non-thrombophilia patients, either pregnant or postpartum.

Still, some patients had uterine haematometra within the first 24 hours postpartum, while others had not. We further analyzed the situation via the postpartum uterine ultrasonographic scale (PUUS).

3.2. Inflammation Indexes in Different PUUS Categories of Patients

In thrombophilia patients, because there are only 14 thrombophilia patients with a PUUS of 1-4 and 65 patients with PUUS 0, we divided the patients into two groups: PUUS=0 (without uterine haematometra) and PUUS ≥1 (with uterine haematometra, in various degrees). Moreover, we

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compared the inflammation indexes among them (Table 4). The same was carried out for non-thrombophilia patients. Because there were only 11 non-thrombophilia patients with a PUUS of 1-4 and 69 patients with PUUS 0, we divided the patients into two groups: PUUS=0 (without uterine haematometra) and PUUS ≥1 (, with uterine haematometra, in various degrees).

Table 4. Inflammation indexes: mean numbers in the first row and median numbers in the second row. In brackets: standard deviation in the first row and quartiles 1 and 3 in the second row of every index for pregnant treated thrombophilia patients at term compared to pregnant non-thrombophilia patients at term.

Inflammation indexes and median (mean) values	Pregnant Treated thrombophilia patients at term n=79	Pregnant Non-thrombophilia patients at term n=80	Significance, *P*
NLR	2.23 (±.98) 2.08 (1.62, 2.85)	2.34 (±.93) 2.35 (1.69, 2.78)	.375
dNLR	1.3 (±.69) 1.23 (.83, 1.68)	1.31 (±.59) 1.23 (.94, 1.63)	.623
MLR	.87 (±.46) .73 (.59, 1.06)	.95 (±.72) .75 (.50, 1.15)	.762
PLR	100.9 (±35.61) 96.36 (78.66, 117.08)	109.27 (±29.66) 103.64 (89.42, 130.85)	.031
SII	571.61 (±289.67) 518.65 (360.40, 777.72)	620.24 (±276.87) 598.64 (429.60, 735.26)	.224
SIRI	4.53 (±2.47) 3.98 (3.01, 5.31)	4.98 (±4.11) 4.00 (2.74, 5.92)	.888
AISI	1152.24 (±748.28) 990.62 (684.06, 1399.34)	1321.89 (±1103.44) 1017.99 (618.54, 1517.14)	.586
MCVL	33.53 (±8.64) 32.23 (26.70, 36.95)	34.81 (±10.9) 33.77 (27.81, 40.67)	.507
IIC	2.534 (±1.018) 2.372 (1.9, 3.238)	2.645 (±1.056) 2.623 (1.968, 3.055)	.446
NLPR	0.0089 (±0.0043) 0.0084 (0.0056, 0.0108)	0.0091 (±0.0041) 0.0087 (0.0062, 0.0116)	.705

NLR: Neutrophil–lymphocyte ratio; dNLR: derived neutrophil–lymphocyte ratio; MLR: monocyte–lymphocyte ratio; PLR: platelet–lymphocyte ratio; SII: systemic inflammatory index; SIRI: systemic inflammatory response index; AISI: aggregate index of systemic inflammation; MCVL: mean corpuscular volume–lymphocyte ratio; IIC: cumulative inflammatory index; NLPR: neutrophils-to-lymphocytes and platelets ratio.

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In pregnant treated thrombophilia patients, the patients with uterine haematometra within the first 24-48 hours (PUUS≥1) had significantly higher SII and AISI inflammation indexes than those without uterine haematometra (PUUS=0). (Table 5)

Table 5. Inflammation indexes: mean numbers in the first row and median numbers in the second row. In brackets: standard deviation in the first row and quartiles 1 and 3 in the second row of every index for **pregnant** treated **thrombophilia** patients at term without uterine haematometra (PUUS=0) or with uterine haematometra (PUUS≥1).

Inflammation indexes and median (mean) values	**PUUS≥1**	**PUUS=0**	**Significance, *P***
NLR	2.52 (±.73) 2.54 (1.93, 3.11)	2.17 (±1.02) 2.07 (1.589, 2.81)	.103
dNLR	1.42 (±.48) 1.38 (.94, 1.80)	1.27 (±.73) 1.20 (.78, 1.68)	.180
MLR	.79 (±.25) .79 (.59, 1.00)	.88 (±.49) .73 (.60, 1.18)	.964
PLR	112.49 (±29.51) 107.91 (85.97, 125.83)	98.40 (±36.51) 92.93 (78.30, 111.73)	.070
SII	716.47 (±280.34) 680.79 (480.61, 861.16)	540.41 (±284.12) 488.82 (346.65, 719.35)	.036
SIRI	5.39 (±2.47) 5.03 (3.61, 6.12)	4.34 (±2.45) 3.88 (2.97, 4.83)	.074
AISI	1388.84 (±595.12) 1382.85 (903.55, 1593.69)	1101.28 (±771.74) 913.78 (645.32, 1274.79)	.025
MCVL	34.51 (±11.94) 31.51 (25.46, 43.86)	33.32 (±7.85) 32.23 (28.14, 36.85)	.748
IIC	2.923 (±.846) 2.987 (2.152, 3.604)	2.450 (±1.038) 2.244 (1.831, 3.116)	.081
NLPR	0.0098 (±0.0045) 0.0088 (0.0065, 0.0119)	0.0091 (±0.0042) 0.0086 (0.0059, 0.0119)	0.532

NLR: neutrophil–lymphocyte ratio; dNLR: derived neutrophil–lymphocyte ratio; MLR: monocyte–lymphocyte ratio; PLR: platelet–lymphocyte ratio; SII: systemic inflammatory index; SIRI: systemic inflammatory response index; AISI: aggregate index of systemic inflammation; MCVL: mean corpuscular volume–lymphocyte ratio; IIC: cumulative inflammatory index; NLPR: neutrophils-to-lymphocytes and platelets ratio.

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In postpartum treated thrombophilia patients, as well as in non-thrombophilia patients, pregnant or postpartum, there was no significant difference in the inflammation indexes of patients with uterine haematometra within the first 24-48 hours (PUUS≥1) compared to those without uterine haematometra (PUUS=0).

3.3. Correlations between Inflammation Indexes and Age

There was no correlation between inflammation indexes and age before or after birth in treated thrombophilia patients. In non-thrombophilia patients, there was a correlation in pregnant patients between MCVL and age and also between NLPR and age. There was a correlation between P SII and age and also between P AISI and age in postpartum non-thrombophilia patients. (Table 6)

Table 6. Nonparametric (Spearman's) correlation between inflammation indexes and age in **pregnant non-thrombophilia** patients at term **and postpartum non-thrombophilia patients.**

Inflammation indexes in pregnant non-thrombophilia patients	**Correlation (Significance 2-tailed)**	**Inflammation indexes in postpartum non-thrombophilia patients**	**Correlation (Significance 2-tailed)**
NLR	0.093 (0.409)	P NLR	-0.122 (0.304)
dNLR	0.067 (0.552)	P dNLR	-0.145 (0.221)
MLR	0.008 (0.942)	P MLR	-0.050 (0.672)
PLR	0.014 (0.900)	P PLR	-0.160 (0.177)
SII	-0.169 (0.131)	P SII	**-0.260 (0.027)**
SIRI	-0.097 (0.391)	P SIRI	-0.186 (0.116)
AISI	-0.216 (0.054)	P AISI	**-0.243 (0.039)**
MCVL	**0.396 (< 0.01)**	P MCVL	0.227 (0.054)
IIC	0.045 (0.687)	P IIC	-0.134 (0.259)

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NLPR	**0.304 (< 0.01)**	P NLPR	0.059 (0.625)

NLR: Neutrophil–lymphocyte ratio; dNLR: derived neutrophil–lymphocyte ratio; MLR: monocyte–lymphocyte ratio; PLR: platelet–lymphocyte ratio; SII: systemic inflammatory index; SIRI: systemic inflammatory response index; AISI: aggregate index of systemic inflammation; MCVL: mean corpuscular volume–lymphocyte ratio; IIC: cumulative inflammatory index; NLPR: neutrophils-to-lymphocytes and platelets ratio. P NLR: postpartum neutrophil–lymphocyte ratio; P dNLR: postpartum derived neutrophil–lymphocyte ratio; P MLR: postpartum monocyte–lymphocyte ratio; P PLR: postpartum platelet–lymphocyte ratio; P SII: postpartum systemic inflammatory index; P SIRI: postpartum systemic inflammatory response index; P AISI: postpartum aggregate index of systemic inflammation; P MCVL: postpartum mean corpuscular volume–lymphocyte ratio; P IIC: postpartum cumulative inflammatory index; P NLPR: postpartum neutrophils-to-lymphocytes and platelets ratio.

3.4. Correlations between Inflammation Indexes and Blood Groups (ABO and Rh Factor)

There was no correlation between inflammation indexes and ABO blood groups before or after birth in treated thrombophilia patients, nor in non-thrombophilia patients. There was no correlation between inflammation indexes and the Rh blood factor before or after birth in non-thrombophilia patients.

In pregnant treated thrombophilia patients, MLR is higher in patients without Rh factor (Rh-negative patients) than in those with the Rh factor (Rh-positive patients): median (1.30 versus .72) and mean values (1.14 versus .83). (Table 7)

Table 7. Comparisons (Mann-Whitney test) between **i**nflammation indexes grouped by Rh blood factor in **pregnant** treated **thrombophilia** patients at term **and postpartum treated thrombophilia patients.**

Inflammation indexes in pregnant treated thrombophilia patients	**Significance (2-tailed)**	**Inflammation indexes in postpartum treated thrombophilia patients**	**Significance (2-tailed)**
NLR	0.740	P NLR	0.525
dNLR	0.413	P dNLR	0.925
MLR	0.049	P MLR	0.142
PLR	0.478	P PLR	0.680
SII	0.793	P SII	0.492
SIRI	0.284	P SIRI	0.057

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AISI	0.700	P AISI	0.096
MCVL	0.459	P MCVL	0.959
IIC	0.988	P IIC	0.719
NLPR	0.677	P NLPR	0.430

NLR: Neutrophil–lymphocyte ratio; dNLR: derived neutrophil–lymphocyte ratio; MLR: monocyte–lymphocyte ratio; PLR: platelet–lymphocyte ratio; SII: systemic inflammatory index; SIRI: systemic inflammatory response index; AISI: aggregate index of systemic inflammation; MCVL: mean corpuscular volume–lymphocyte ratio; IIC: cumulative inflammatory index; NLPR: neutrophils-to-lymphocytes and platelets ratio. P NLR: postpartum neutrophil–lymphocyte ratio; P dNLR: postpartum derived neutrophil–lymphocyte ratio; P MLR: postpartum monocyte–lymphocyte ratio; P PLR: postpartum platelet–lymphocyte ratio; P SII: postpartum systemic inflammatory index; P SIRI: postpartum systemic inflammatory response index; P AISI: postpartum aggregate index of systemic inflammation; P MCVL: postpartum mean corpuscular volume–lymphocyte ratio; P IIC: postpartum cumulative inflammatory index; P NLPR: postpartum neutrophils-to-lymphocytes and platelets ratio.

3.5. Correlations between Inflammation Indexes and Maternal Features (Height, Weight, BMI)

There was no correlation between inflammation indexes and maternal features (height, weight, BMI) before or after birth in treated thrombophilia patients, nor was in non-thrombophilia patients. Still, there was a close to significant (p=0.51) correlation between postpartum dNLR and BMI in treated thrombophilia patients. (Table 8)

Table 8. Nonparametric (Spearman's) correlation between **i**nflammation indexes and maternal BMI in **pregnant** treated **thrombophilia** patients at term **and postpartum treated thrombophilia patients.**

Inflammation indexes in pregnant treated thrombophilia patients	**Correlation (Significance 2-tailed)**	**Inflammation indexes in postpartum treated thrombophilia patients**	**Correlation (Significance 2-tailed)**
NLR	-0.078 (0.496)	P NLR	-0.190 (0.102)
dNLR	-0.094 (0.410)	P dNLR	-0.226 (0.051)
MLR	0.008 (0.944)	P MLR	0.004 (0.976)
PLR	0.049 (0.671)	P PLR	-0.088 (0.451)

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SII	-0.103 (0.366)	P SII	-0.196 (0.091)
SIRI	-0.045 (0.692)	P SIRI	-0.120 (0.307)
AISI	-0.078 (0.496)	P AISI	-0.094 (0.421)
MCVL	-0.001 (0.993)	P MCVL	-0.109 (0.351)
IIC	-0.050 (0.659)	P IIC	-0.144 (0.219)
NLPR	-0.038 (0.742)	P NLPR	-0.179 (0.123)

NLR: Neutrophil–lymphocyte ratio; dNLR: derived neutrophil–lymphocyte ratio; MLR: monocyte–lymphocyte ratio; PLR: platelet–lymphocyte ratio; SII: systemic inflammatory index; SIRI: systemic inflammatory response index; AISI: aggregate index of systemic inflammation; MCVL: mean corpuscular volume–lymphocyte ratio; IIC: cumulative inflammatory index; NLPR: neutrophils-to-lymphocytes and platelets ratio. P NLR: postpartum neutrophil–lymphocyte ratio; P dNLR: postpartum derived neutrophil–lymphocyte ratio; P MLR: postpartum monocyte–lymphocyte ratio; P PLR: postpartum platelet–lymphocyte ratio; P SII: postpartum systemic inflammatory index; P SIRI: postpartum systemic inflammatory response index; P AISI: postpartum aggregate index of systemic inflammation; P MCVL: postpartum mean corpuscular volume–lymphocyte ratio; P IIC: postpartum cumulative inflammatory index; P NLPR: postpartum neutrophils-to-lymphocytes and platelets ratio.

3.6. Correlations between Inflammation Indexes and Fetal Features (Weight, Apgar Score)

There was no correlation between inflammation indexes and fetal features (weight, Apgar score) before or after birth in treated thrombophilia patients, nor was in non-thrombophilia patients.

4. Discussion

Thrombophilia did not stimulate the inflammatory state of the patient, already suppressed by pregnancy. Except for the PLR, most of the numerous inflammation indexes studied were not significantly different in treated thrombophilia patients, before and after delivery, compared to non-thrombophilia patients. The PLR index was significantly higher in healthy, non-thrombophilia patients compared to treated thrombophilia patients. This is in accordance with other authors who observed that patients with a non-immunological disease had an increased PLR baseline value [38].

Only when we split the patients, based on the uterine haematometra in the first 24-48 hours postpartum, we found out that the few treated thrombophilia pregnant patients with haematometra (14 with haematometra out of 79 with treated thrombophilia) had elevated SII and AISI antepartum. SII and AISI increase relative to inflammation and infection according to many studies: SII and SIRI are more reliable biomarkers than other inflammation parameters in hidradenitis suppurativa patients [39]. The SII index showed high accuracies for the prediction of deep neck infection complications [40]. The SII value was significantly higher in non-survivors than that of survivors, and it was identified as an independent predictor of sepsis mortality [41]. In children presenting with

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abdominal pain, high SIRI and SII values alone support the diagnosis of acute appendicitis at a rate of 95% [42]. The systemic immune inflammation index was significantly higher in the severe COVID-19 and pregnant patient group than in the mild COVID-19 and pregnant patient group [43]. SII proved to be a good predictor of inflammation and abortion in those with ongoing pregnancy [44,45]. An inflammatory state was observed in cases of late uterine involution [46]. This proved our working hypothesis: there is an underlying inflammatory state, which persisted despite treatment in few patients, therefore the uterine haematometra within the first 24-48 hours. There was no reason for increased SII and AISI antepartum found in the hospital records, therefore we considered thrombophilia as a possible cause.

As for AISI, in patients with COVID-19, increased values upon admission predict severe or fatal evolution [47]; therefore, determining the AISI value upon admission can help triage the patients with a bad prognosis [48]. In patients with hemophagocytic lymphohistiocytosis, the aggregate index of systemic inflammation (AISI) was also an independent risk factor for 28-day mortality [49]. After aortic valve replacement, AISI was a statistically significant independent factor associated with in-hospital death [50]. This also proved our working hypothesis: there is an underlying inflammatory state, and it persisted despite treatment in some patients. Moreover, in adults with hypertension, elevated AISI levels are significantly associated with an increased risk of cardiovascular mortality [51]. This means that a cardiovascular factor may also be involved in the delay in uterine involution in few treated thrombophilia patients.

In other studies [52], in women at risk for venous thrombosis and thromboprophylaxis, postpartum hemorrhage was common and higher doses of thromboprophylaxis may increase obstetric bleeding complications, therefore they are not recommended. [53] We do not report postpartum hemorrhage. LWMH thromboprophylaxis was recommended only in women with high-risk thrombophilia or in women with low risk thrombophilia and previous venous thrombosis, as stated in the literature [54,55]

In postpartum treated thrombophilia patients, there was no significant difference between the postpartum inflammation indexes in patients with uterine haematometra within the first 24-48 hours (PUUS≥1) compared to those without uterine haematometra (PUUS=0). This is reasonable because, as discovered in [56], only a few patients had severe complications after cesarean section, and delays in eliminating uterine haematometra are not a complication.

In pregnant and postpartum non-thrombophilia patients, there was no significant difference between the inflammation indexes in patients with uterine haematometra within the first 24-48 hours (PUUS≥1) compared to those without uterine haematometra (PUUS=0). Other factors that may have been involved primarily include the following: number of gestations, number of parity, etc.

There was no correlation between inflammation indexes and age before or after birth in treated thrombophilia patients. In non-thrombophilia patients, there was a correlation between MCVL and age in pregnant patients. This correlation has not been reported before. There was also a correlation between NLPR and age in non-thrombophilia pregnant patients. Nor has this correlation been reported before. There was also a correlation between postpartum SII and age and between postpartum AISI and age in postpartum non-thrombophilia patients. These findings have not been previously reported.

Patients with group O blood (a blood group with lower baseline levels of von Willebrand factor) have a lower risk of COVID-19 infection and disease severity compared to other ABO blood groups [57]; therefore, coagulation characteristics and early fibrinogenesis may vary between ABO groups [58]. There was no correlation between inflammation indexes and ABO blood groups before or after birth in treated thrombophilia patients or non-thrombophilia patients. This means that thrombophilia treatment was appropriate.

In pregnant treated thrombophilia patients, MLR is higher in patients without the Rh factor than in those with the Rh factor. There was no correlation between inflammation indexes and the Rh blood factor before or after birth in non-thrombophilia patients. MLR may serve as a potential indicator for predicting the progression of hematoma after cerebral contusion [59]. The MLR was significantly higher in the HELLP group than in the normal pregnant patient control group at the delivery time

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[60]. The monocyte value and monocyte/lymphocyte value (MLR) were significantly higher in the cesarean pregnancy group than in the control group [61]. There have been no reports of higher MLR values in pregnant Rh-negative treated thrombophilia patients so far.

The main limitation of this study is the small number of patients treated in this research topic. The second limitation is that we did use the blood parameters data that we already gathered for the previous article, without calculating the sample size specifically for the inflammation indexes. The third limitation is that we could not apply a multivariable model analysis, since the major covariates of interest did not exist (There were no intraoperative complications, no postpartum hemorrhage, no Hayman or B-Lynch sutures required, no peripartum fever reported, no chorionoamnionitis reported, no COVID-19 infection reported, all the COVID-19 positive patients were admitted to deliver in a separate building and were not performed examination by PUUS scale, few chronic illnesses and very few with type 2 diabetes) and the output was normal (all children were in normal range of weight, normal Apgar score).

5. Conclusions

Thrombophilia did not stimulate the inflammatory state of the patient, already suppressed by pregnancy. Except for the PLR, most of the numerous inflammation indexes studied were not significantly different in treated thrombophilia patients, before and after delivery, compared to non-thrombophilia patients.

Only when we split the patients, based on the uterine haematometra in the first 24-48 hours postpartum, we found out that the few treated thrombophilia pregnant patients with haematometra (14 with haematometra out of 79 with treated thrombophilia) had elevated SII and AISI antepartum.

In pregnant treated thrombophilia patients, the MLR is higher in patients without the Rh factor than in those with the Rh factor. In non-thrombophilia patients, there was a correlation between MCVL and age, and another correlation between NLPR and age in pregnant patients. There was also a correlation between postpartum SII and age and between postpartum AISI and age in postpartum non-thrombophilia patients.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies.***

	Page No	**Recommendation**
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	2	State specific objectives, including any prespecified hypotheses
Methods		
Study design	3	Present key elements of study design early in the paper
Setting	3	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	3	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		(*b*) For matched studies, give matching criteria and the number of controls per case

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Variables	3	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	3	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	12	Describe any efforts to address potential sources of bias
Study size	3	Explain how the study size was arrived at
Quantitative variables	4	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	4	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how matching of cases and controls was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	4-10	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	4-10	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	4-10	Report numbers in each exposure category, or summary measures of exposure
Main results	4-10	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	4-10	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	10	Summarise key results with reference to study objectives
Limitations	12	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

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Interpretation	10-12	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	10-12	Discuss the generalisability (external validity) of the study results
Other information		
Funding	12	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls. **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Author Contributions: Conceptualization, Catalina Filip and Roxana Covali; Data curation, Ioana Sadyie Scripcariu and Tudor Butureanu; Formal analysis, Ingrid Andrada Vasilache; Funding acquisition, Catalina Filip; Investigation, Mona Akad and Gabriela Dumachita-Sargu; Methodology, Alexandru Carauleanu; Project administration, Razvan Socolov; Software, Lucian Vasile Boiculese; Supervision, Razvan Socolov; Validation, Demetra Socolov and Alina Melinte; Visualization, Mona Akad; Writing—original draft, Catalina Filip and Roxana Covali; Writing—review & editing, Demetra Socolov and Alexandru Carauleanu.All authors have read and agreed to the published version of the manuscript.

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