
The Predictive Value of RDW-CV in Pregnant Patients with Treated Thrombophilia Who Delivered via Cesarean Section at Term

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Article

The Predictive Value of RDW-CV in Pregnant Patients with Treated Thrombophilia Who Delivered via Cesarean Section at Term

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Abstract: (1) Background: The RDW-CV has predictive value in many pregnancy-related conditions. Research question: Can the RDW-CV be utilized predictively in pregnant patients with thrombophilia? Aim of the study: To carry out a detailed analysis of the RDW-CV in pregnant patients with treated thrombophilia as compared with pregnant patients without thrombophilia who delivered via cesarean section at term. (2) Methods: We studied 160 pregnant patients, including 80 pregnant patients with treated thrombophilia in the study group, and another 80 patients of a similar age and parity. The patients were referred to our hospital for delivery at term by means of a cesarean section between 1/10/2017 and 1/12/2021. Every patient received a sonogram during the first 1–2 days after the cesarean section, and their uterine evaluation was interpreted using the PUUS (Postpartum Uterine Ultrasonographic Scale). (3) Results: Our PUUS \geq 1 pregnant and postpartum patients with treated thrombophilia were the only group with an RDW-CV value over 14. No deep vein thrombosis was observed during hospitalization, showing that the anticoagulant treatment was necessary and effective. An RDW-CV of 14.5 was the highest value in the Rh-negative group of pregnant patients with treated thrombophilia. An RDW-CV of 14.48 was the highest level in the Rh-negative postpartum patients with treated thrombophilia. (4) Conclusion: An RDW-CV of \geq 14 can predict uterine hematometra (PUUS \geq 1). The RDW-CV values were higher in Rh-negative patients.

Keywords: RDW-CV; thrombophilia; pregnancy; cesarean section; Rh-factor; postpartum; uterine; ultrasonography; scale

1. Introduction

The RDW-CV has predictive value in many pregnancy-related conditions (preeclampsia, recurrent pregnancy loss, preterm labor, anemia, gestational diabetes). The red blood cell distribution width is calculated as the standard deviation of the erythrocyte volume (RDW-SD) divided by the mean corpuscular volume, times one thousand (RDW-CV). The values of the RDW-CV vary during the three trimesters of pregnancy and can change in conditions like recurrent pregnancy loss, preterm labor, preeclampsia, or anemia [1].

In preeclampsia patients, the values of the RDW-CV are markedly higher than those in healthy pregnant patients [2–5]. RDW levels are significantly increased in patients with severe preeclampsia when compared to patients with mild preeclampsia [6,7]. The RDW is also increased in potential preterm labor patients [8], and in patients with previous pregnancy loss [9,10].

The RDW is significantly higher in maternal blood from COVID-19 seropositive anemic pregnant women compared to seronegative pregnant women, and it is associated with COVID-19-related hypoxia [11–15]. After treatment for anemia, the RDW-SD value increased in pregnant women [16,17]. The RDW-SD, but not the RDW-CV, can be used as a diagnostic index of iron deficiency anemia for pregnant women [18,19].

At low altitudes, the RDW increases with the gestational trimester and is higher than that in non-pregnant women [20], while at high altitudes, the RDW does not change [21]. In acute pancreatitis in pregnancy, the RDW is also markedly elevated and is predictive of severity [22,23].

The aim of this work was to study whether there was any difference in the RDW-CV values in pregnant patients with treated thrombophilia as compared with pregnant patients without thrombophilia who delivered via cesarean section at term.

2. Materials and Methods

We included 160 pregnant patients in this study, with 80 pregnant patients with treated thrombophilia in the study group, and another 80 patients of a similar age and parity. The patients were referred to our hospital for delivery at term by means of a cesarean section between 1/10/2017 and 1/12/2021. Hospital policy required that patients already diagnosed with thrombophilia be provided a cesarean section at 38 weeks gestational age, and these patients comprised the study group. This was a prospective study. All of the patients with thrombophilia already had established diagnoses. Treatment with low-molecular-weight heparin was ongoing. Thrombophilia screening tests were not available at the study hospital; thus, the control group had their blood sent for screening to specialized laboratories, and were included following a negative result. The exclusion criteria were as follows: patients suffering from thrombocytopenia (n=2), patients with deep vein thrombosis (n=0), and patients with cerebral thrombosis (n=0) [24].

Table 1. Thrombophilia mutations identified in the study group [24].

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 [24].

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. Patient characteristics: mean, median, standard deviation, and quartile 1 and 2 values [24].

Patients	Thrombophilia patients (n = 80)	Non-thrombophilia 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

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 PUUS (Postpartum Uterine Ultrasonographic Scale). This scale [25,26] counts the quarters of missing uterine vacuum lines, which could be due to the presence of blood or debris, as follows:

In grade 0, the uterine cavity is completely empty.

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 [25,26].

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 a Doppler signal. In this group of patients, none had retained trophoblastic tissue. We further referred to this debris as “uterine haematometra”.

In a previous study [24] 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 was obtained antepartum and the last count was obtained postpartum—were considered. Hospital policy required blood analyses both 24 hours before and after labor.

We performed the blood analysis using MAN-HEMATO laboratory equipment.

We performed the data analysis using SPSS version 18 (PASW Statistics for Windows, Chicago: SPSS Inc., Chicago, IL, USA). We determined the mean and median values, standard deviations, and quartiles. We also used the nonparametric Mann–Whitney U test and Spearman’s correlation. We considered $p < 0.05$ to indicate significance [24].

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. Pregnant Patients

As shown previously [24], there was no significant difference between the simple values of the RDW-CV in pregnant patients with treated thrombophilia compared to those without. We further aimed to elucidate whether there was any difference in the involution of the uterine cavity postpartum, using the PUUS. Because we had few patients with PUUS grade 1–4, and we could not perform a detailed comparison with grade 1 or 2 or 3 in the group with treated thrombophilia as compared to the non-thrombophilia group, we considered $PUUS \geq 1$ to indicate any uterine cavity that did not close during the first 48 hours postpartum, and we compared these with uterine cavities that did close, designated $PUUS=0$, to simplify comparison between two groups of $PUUS=0$ and $PUUS \geq 1$ and their values for the RDW-CV.

There was no significant difference between the RDW-CV values in patients whose uterine cavities closed in the first 48 hours ($PUUS=0$) as compared to those whose did not ($PUUS \geq 1$), neither in pregnant patients with treated thrombophilia nor in the non-thrombophilia patients (Table 4). However, the $PUUS \geq 1$ pregnant patients with treated thrombophilia were the only group with $RDW-CV \geq 14$.

Table 4. The value of the RDW-CV in treated-thrombophilia patients and non-thrombophilia patients, with a closed uterine cavity within 24-48 hours ($PUUS=0$) or not ($PUUS=1$). The upper line represents the mean values with the standard deviation; the lower line represents the median values with quartiles 1 and 3.

RDW-CV in pregnant patients with	PUUS=0	PUUS \geq 1	Significance, P
Treated thrombophilia	13.77 \pm 1.60 13.51 (12.73; 14.65)	14.06 \pm 1.77 14.02 (13.27; 14.26)	.546
Non-thrombophilia	13.77 \pm 1.30 13.47 (12.84; 14.38)	13.43 \pm 1.15 13.59 (13.19; 14.23)	.917

PUUS, postpartum uterine ultrasonographic scale.

There was a weak negative correlation between the RDW-CV and age in the non-thrombophilia pregnant patients (Table 5): the RDW-CV decreased with the increasing age of the pregnant patient.

Table 5. The correlation coefficients between the RDW-CV and age of the patients.

Pregnant patients	Correlation coefficient	Significance, P
Treated thrombophilia	-0.11	.30
Non-thrombophilia	-0.288	.009

There was no correlation between the RDW-CV and number of gestations of the patients (Table 6).

Table 6. The correlation coefficients between RDW-CV and number of gestation of the patients.

Pregnant patients	Correlation coefficient	Significance, P
Treated thrombophilia	0.10	0.34
Non-thrombophilia	-0.06	0.57

There were no significant differences in the RDW-CV values of the four ABO blood groups (Table 7). There was no correlation between the RDW-CV and the ABO blood group.

Table 7. The value of the RDW-CV in treated-thrombophilia patients and non-thrombophilia patients, according to ABO blood group. The upper line represents the mean values with standard deviations; the lower line represents the median values and the lowest line quartiles 1 and 3.

RDW-CV in pregnant patients with	OI	AII	BIII	ABIV	Significance, P
Treated thrombophilia	14.00±1.65	13.53±1.41	14.05±1.93	14.26±1.85	0.818
	13.70 (13.04; 14.53)	13.29 (12.12; 14.47)	13.38 (12.83; 15.35)	13.58 (12.98; 16.22)	
Non-thrombophilia	13.58±1.23	13.75±1.19	14.00±1.83	13.56±0.97	0.952
	13.42 (12.82; 14.30)	13.58 (12.89; 14.33)	12.96 (12.55; 15.53)	13.19 (13.13; 13.88)	

There was no significant difference between the RDW-CV in the two Rh blood groups (Table 8). There was no correlation between the RDW-CV and the Rh blood groups. However, the Rh-negative pregnant patients with treated thrombophilia had the highest value of the RDW at 14.5.

Table 8. The value of the RDW-CV in treated-thrombophilia patients and non-thrombophilia patients, according to the Rh blood factor. The upper line represents the mean values with standard deviations; the lower line represents the median values with quartiles 1 and 3.

RDW-CV in pregnant patients with	Rh-positive	Rh-negative	Significance, P
Treated thrombophilia	13.73±1.56	14.50±1.96	.291
	13.58 (12.76; 14.45)	14.54 (12.77; 16.17)	
Non-thrombophilia	13.70±1.29	13.90±1.17	.671
	13.48 (12.85; 14.30)	13.68 (12.83; 14.84)	

Then, we calculated the correlation coefficient between the RDW-CV and maternal features (height, weight, body mass index) (Table 9). There was a weak correlation between the RDW-CV and BMI in the pregnant patients with treated thrombophilia (Table 9), indicating that the RDW-CV increased with increasing BMI among the pregnant patients with treated thrombophilia.

Table 9. The correlation coefficients between the RDW-CV and maternal features.

Pregnant patients	Feature	Correlation coefficient	Significance, P
Treated thrombophilia	Height	-0.094	0.409
	Weight	0.168	0.139
	BMI	0.236	0.037
Non-thrombophilia	Height	0.140	0.215
	Weight	0.117	0.302
	BMI	0.039	0.731

BMI=body mass index.

Then, we calculated the correlation coefficient between the RDW-CV and fetal outcomes (fetal weight, Apgar score) (Table 10). There was no correlation between the fetal outcomes and RDW-CV values.

Table 10. The correlation coefficients between the RDW-CV and fetal outcomes.

Pregnant patients	Fetal outcome	Correlation coefficient	Significance, P
Treated thrombophilia	Weight	0.203	0.073
	Apgar score	-0.017	0.883
Non-thrombophilia	Weight	0.176	0.118

Apgar score	-0.038	0.740
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3.2. Postpartum Patients

After calculating the above values, for the antepartum patients, we determined whether there was any correlation between the postpartum RDW-CV values and other values. Although the distribution was significantly different from normal (Table 11), there was no significant difference between the RDW-CV values in the two groups.

Table 11. The value of the postpartum RDW-CV in treated-thrombophilia patients and non-thrombophilia patients.

RDW-CV in postpartum patients with	Mean RDW-CV	Median RDW-CV	Shapiro Wilk test significance
Treated thrombophilia	13.97±1.78	13.61 (12.80; 14.68)	.001
Non-thrombophilia	13.77±1.33	13.47 (12.89; 14.54)	.001

There is significance. Distribution is different from normal.

There was no significant difference between the postpartum RDW-CV values in patients whose uterine cavities closed in the first 48 hours (PUUS=0) as compared to those whose did not (PUUS≥1), neither in the postpartum patients with treated thrombophilia nor in the non-thrombophilia patients (Table 12). The PUUS grade did not depend on the RDW-CV.

Table 12. The value of the postpartum RDW-CV in treated-thrombophilia patients and non-thrombophilia patients, whose uterine cavities closed within 24–48 hours (PUUS=0), or not (PUUS=1). The upper line represents the mean values with standard deviations; the lower line represents the median values with quartiles 1 and 3.

RDW-CV in postpartum patients with	PUUS=0	PUUS=1	Significance, P
Treated thrombophilia	13.96±1.80 13.53 (12.72; 15.08)	14.04±1.76 13.72 (13.11; 14.59)	.765
Non-thrombophilia	13.80±1.37 13.26 (12.87; 14.55)	13.60±1.13 13.67 (13.20; 14.40)	.742

PUUS, postpartum uterine ultrasonographic scale.

There was a weak negative correlation between the postpartum RDW-CV and age in the non-thrombophilia postpartum patients (Table 13), indicating that the RDW-CV decreased with increasing age among the non-thrombophilia postpartum patients.

Table 13. The correlation coefficients between the postpartum RDW-CV and age of the patients.

Postpartum patients	Correlation coefficient	Significance, P
Treated thrombophilia	-0.11	0.33
Non-thrombophilia	-0.35	0.002

There was no correlation between the postpartum RDW-CV and number of gestations of the patients (Table 14).

Table 14. The correlation coefficients between the postpartum RDW-CV and number of gestations of the patients.

Postpartum patients	Correlation coefficient	Significance, P
Treated thrombophilia	0.05	0.62
Non-thrombophilia	-0.05	0.64

There was no significant difference between the postpartum RDW-CV values in the four ABO blood groups (Table 15). There was no correlation between the postpartum RDW-CV and the ABO blood group.

Table 15. The value of the postpartum RDW-CV in treated-thrombophilia patients and non-thrombophilia patients, according to ABO blood group. The upper line represents the mean values with standard deviations; the lower line represents the median values with quartiles 1 and 3.

RDW-CV in postpartum patients with	OI	AII	BIII	ABIV	Significance, P
Treated thrombophilia	14.10±1.69	13.73±1.79	14.23±2.01	14.29±1.78	0.751
	13.67 (12.80; 14.83)	13.26 (12.17; 14.67)	13.52 (13.15; 15.55)	13.58 (13.12; 16.17)	
Non-thrombophilia	13.66±1.30	13.76±1.26	14.06±1.91	13.73±1.07	1.000
	13.48 (12.77; 14.50)	13.57 (12.86; 14.53)	13.14 (12.83; 15.20)	13.22 (13.15; 14.57)	

There was no significant difference between the postpartum RDW-CV in the two Rh blood groups (Table 16). There was no correlation between the postpartum RDW-CV and the Rh blood group.

Table 16. The value of the postpartum RDW-CV in treated-thrombophilia patients and non-thrombophilia patients, according to the Rh blood factor. The upper line represents the mean values with standard deviations; the lower line represents the median values with quartiles 1 and 3.

RDW-CV in postpartum patients with	Rh-positive	Rh-negative	Significance, P
Treated thrombophilia	13.91±1.74	14.48±2.18	.566
	13.61 (12.80; 14.67)	14.09 (12.42; 16.59)	
Non-thrombophilia	13.76±1.35	14.01±1.25	.577
	13.47 (12.86; 14.53)	13.78 (12.98; 14.81)	

There was a weak correlation between the postpartum RDW-CV and BMI in the postpartum patients with treated thrombophilia (Table 17), indicating that the postpartum RDW-CV increased with increasing BMI in the postpartum patients.

Table 17. The correlation coefficients between the postpartum RDW-CV and maternal features.

Postpartum patients	Feature	Correlation coefficient	Significance, P
Treated thrombophilia	Height	-0.052	0.656
	Weight	0.217	0.061
	BMI	0.279	0.015
Non-thrombophilia	Height	0.108	0.365
	Weight	0.132	0.269
	BMI	0.076	0.525

BMI=body mass index.

There was no correlation between the fetal outcomes and postpartum RDW-CV values (Table 18).

Table 18. The correlation coefficients between the postpartum RDW-CV and fetal outcomes.

Postpartum patients	Fetal outcome	Correlation coefficient	Significance, P
Treated thrombophilia	Weight	0.154	0.188
	Apgar score	-0.005	0.969
Non-thrombophilia	Weight	0.225	0.057
	Apgar score	-0.123	0.302

4. Discussion

The RDW-CV demonstrates anisocytosis [27]. The higher the RDW-CV value, the more serious the anisocytosis. The RDW-CV increases in many diseases. A decreased value means that the cells are mostly uniform in size.

Red blood cells transport oxygen. In hypoxia-generating situations, red blood cells change shape, flexibility, dimensions, and adherence. Pregnancy generates hypoxia. In patients with pre-existing thrombophilia, pregnancy will favor the variability of the red blood cell dimensions, represented by the RDW-CV, and will also increase hypercoagulability, or thrombophilia. In recent years, increasingly developed proteomics and metabolomics technologies have become powerful tools for studying mature enucleated erythrocytes, significantly contributing to clarifying how hypoxia affects erythrocytes [28]. The shunt of the glycolysis pathway in oxygen transport is also involved in erythrocyte metabolism, and the deformability of erythrocytes influences erythrocyte aggregation and adhesion [28]. Red blood cells have a specific metabolomic signature in patients with a confirmed diagnosis of deep vein thrombosis or pulmonary embolism that distinguishes them from other acutely diseased patients, as represented by 20 significantly higher metabolites and four lower metabolites [29]. Three months after venous thromboembolism, plasma metabolomic profiling identified 512 metabolites, forming 62 biological clusters, while multivariate analysis revealed a panel of 21 metabolites capable of predicting venous thromboembolism status [30].

Febra [31] demonstrated a significant association between an early high RDW and the diagnosis of acute unprovoked deep vein thrombosis. An RDW of $\geq 14\%$ was an independent predictor of unprovoked venous thromboembolism in adult patients. Our PUUS ≥ 1 pregnant patients with treated thrombophilia had an average RDW of 14.06 (Table 4), and they were the only group with an RDW value over 14. The postpartum group, like the postpartum patients with treated thrombophilia, had an RDW-CV of 14.04 (Table 12), and remained the only group with an RDW-CV over 14, even after delivery. Nevertheless, they showed no deep vein thrombosis during hospitalization, suggesting that their anticoagulant treatment was necessary and effective.

An RDW-CV of 14.5, the highest value, occurred in the Rh-negative pregnant patients with treated thrombophilia (Table 8), indicating that Rh-negative is a potential predictor of deep vein thrombosis in pregnant patients with thrombophilia. An RDW-CV of 14.48 was the highest value in the postpartum group, occurring specifically in the Rh-negative postpartum patients with treated thrombophilia, and an RDW-CV of 14.01 was the highest value in the Rh-negative non-thrombophilia postpartum patients (Table 16).

There was a weak negative correlation between the RDW-CV and age in the non-thrombophilia pregnant patients; the RDW-CV decreased with increasing age of the pregnant patient. Anisocytosis decreased with increasing age of the pregnant patient, which has not been previously reported.

In pregnant women with obesity, the RDW is lower, indicating that a larger maternal body size during pregnancy generates more and smaller erythrocytes [32]. In our study, the RDW-CV increased with increasing BMI of the pregnant patients with treated thrombophilia and was not influenced by BMI in the non-thrombophilia pregnant patients, showing that either the condition or treatment of thrombophilia, associated with a higher BMI, generated anisocytosis.

5. Conclusions

Our PUUS ≥ 1 pregnant patients with treated thrombophilia had an RDW of 14.06, and they were the only group with an RDW over 14. Postpartum, in the same patients with treated thrombophilia, the RDW-CV was 14.04, and they remained the only group with an RDW-CV over 14 even after delivery. However, no deep vein thrombosis was recorded during hospitalization, suggesting that their anticoagulant treatment was necessary and effective.

An RDW-CV of 14.5, the highest value, occurred in the Rh-negative pregnant patients with treated thrombophilia, indicating that Rh-negative status is a potential predictor of deep vein thrombosis in pregnant patients with thrombophilia. An RDW-CV of 14.48, the highest value postpartum, occurred in the Rh-negative postpartum patients with treated thrombophilia. An RDW-CV of 14.01 was obtained in the Rh-negative non-thrombophilia postpartum patients.

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Informed Consent Statement: Written informed consent has been obtained from all subjects involved in the study.

Data Availability Statement: Data from this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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