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Factor deficiency in pregnancy and the role of the delta hemoglobin indices

Gebelikte kalıtsal faktör eksiklikleri ve delta hemoglobin indekslerinin rolü

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Abstract

Objective: To evaluate the bleeding degree with objective indices and treatment interventions in the delivery of inherited factor deficiency pregnancies.

Materials and Methods: The presented case-control study was conducted with pregnancies with factor deficiencies. Maternal obstetrical history, disease characteristics (factor levels, duration of disease, and bleeding history), and treatment features during pregnancy were evaluated. Obstetric (delivery mode, antepartum/postpartum bleedings) and neonatal outcomes (birth weights, birth weeks, APGAR scores) of the study group were compared to those of the control group. The Delta hemoglobin/hematocrit (prepartum - postpartum hemoglobin/hematocrit), and hemoglobin and hematocrit % change [(prepartum - postpartum hemoglobin/hematocrit)/prepartum hemoglobin/hematocrit] indices were used to assess the extent of bleeding during delivery.

Results: None of the patients had an early postpartum hemorrhage. The delta hemoglobin and hematocrit values were increased in the factor deficiency group, with p-values of 0.019 and <0.001. The hemoglobin and hematocrit percentage changes were also found to increase, associated with p-values of <0.001 and 0.010. Three of the patients (16.7%) had postpartum complications. Gestational age at birth, APGAR scores at 1 and 5 minutes were lower in the factor deficiency group with p-values of 0.016, <0.001, and <0.001, respectively. There was one stillbirth. Most patients received peripartum tranexamic acid treatment, with factor derivatives and desmopressin in required cases.

Conclusion: Hemoglobin/hematocrit delta and change rate indices were increased, although none of the patients were recorded as having early peripartum hemorrhage or needing transfusion. New delta bleeding indices are promising for objectively identifying bleeding and regulating treatment in clinical practice. The experience of this clinical study might guide future studies.

Keywords: Inherited factor deficiency, postpartum hemorrhage, obstetric complications, von Willebrand factor

Öz

Amaç: Bu çalışmanın amacı kalıtsal faktör eksikliği olan gebeliklerin doğumunda kanama derecesini objektif indeksler ve tedavi müdahaleleriyle değerlendirmektir.

Gereç ve Yöntemler: Sunulan olgu kontrol çalışması faktör eksikliği olan gebeliklerle yürütülmüştür. Annenin obstetrik öyküsü, hastalık özellikleri (faktör düzeyleri, hastalık süresi ve kanama öyküsü) ve gebelik sırasındaki tedavi özellikleri değerlendirilmiştir. Obstetrik (doğum şekli, doğum öncesi/doğum sonrası kanamalar) ve neonatal sonuçlar (doğum ağırlıkları, doğum haftaları, APGAR skorları) kontrol grubuyla karşılaştırılmıştır. Delta hemoglobin/

PRECIS: We thoroughly evaluated inherited factor deficiency during pregnancy and objectively assessed the degree of bleeding during delivery using objective indices.

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hematokrit (doğum öncesi - doğum sonrası hemoglobin/hematokrit), hemoglobin ve hematokrit % değişimi [(doğum öncesi - doğum sonrası hemoglobin/hematokrit)/doğum öncesi hemoglobin/hematokrit] indeksleri doğumdaki kanama derecesini değerlendirmek için kullanılmıştır.

Bulgular: Hastaların hiçbiri erken postpartum kanama yaşamadı. Delta hemoglobin ve hematokrit değerleri faktör eksikliği grubunda artmıştı, p-değerleri 0,019 ve <0,001 idi. Hemoglobin ve hematokrit % değişimlerinin de p-değerleri <0,001 ve 0,010 değerleri ile arttığı bulundu. Hastaların üçünde (%16,7) doğum sonrası komplikasyonlar görüldü. Doğum haftası, APGAR 1 ve 5 faktör eksikliği grubunda daha düşüktü, p-değerleri sırasıyla 0,016, <0,001 ve <0,001 idi. Bir hasta intrauterin eksitus oldu. Çoğu hasta peripartum traneksamik asit tedavisi aldı, gerekli durumlarda faktör türevleri ve desmopressin aldı.

Sonuç: Hemoglobin/hematokrit delta ve değişim oranı indeksleri artmıştı, ancak hastaların hiçbirinde erken postpartum kanama gelişmedi veya transfüzyon ihtiyacı olmadı. Yeni delta kanama indeksleri klinik uygulamada kanamayı objektif olarak belirlemek ve tedaviyi düzenlemek için umut vericidir. Bu klinik çalışmanın gelecekteki ileri çalışmalara rehberlik edebileceğine inanıyoruz.

Anahtar Kelimeler: Kalıtsal faktör eksikliği, doğum sonrası kanama, obstetrik komplikasyonlar, von Willebrand faktör

Introduction

Inherited factor deficiencies increase bleeding complications in the obstetric patient. Women with inherited factor deficiency have an increased risk of pregnancy-related obstetric and neonatal complications such as peripartum hemorrhage (PPH), placental abruption, retained placenta, abortion, and stillbirth[1]. Studies on prophylactic or therapeutic interventions in pregnancy for this valuable group are limited, and guidance protocols are heavily based on the results of case reports and a small number of studies.

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, and it may be accompanied by mild thrombocytopenia. Its clinical presentation varies according to the degree of deficiency of von Willebrand factor (VWF), factor VIII, and platelet levels[1]. Mild thrombocytopenia could result from biological stressors such as inflammation and pregnancy[2]. The risk of PPH with VWD was reported to be 15-60% in the literature[3]. VWF levels physiologically increase and reach about 50-60% above baseline at the time of delivery and decline rapidly after, reaching a nadir one to three weeks after delivery[4]. The recommended target plasma VWF level is accepted as greater than >50 IU/dL for delivery. However, physiological increases in levels of VWF during pregnancy and mean plasma VWF levels of healthy pregnancies, which were found to be >150 IU/dL, make this recommendation questionable[5]. Factor VIII levels also physiologically increase in pregnancy. However, patients with factor VIII deficiency have an increased risk for PPH, with a reported incidence of about 20% in the literature[6].

Factor V, VII, and XI deficiencies are rare conditions. Factor V deficiency incidence is 1 in 1,000,000, and the actual risk of bleeding in this population remains undetermined[7]. Some studies reported high PPH, reaching 60% in vaginal deliveries, although other studies reported lower bleeding rates[8,9]. Factor VII deficiency incidence is 1 in 500,000, and levels increase during pregnancy[10]. The literature reported the PPH rate as 10-13%[11]. Factor XI deficiency incidence is 1 in 1,000,000 individuals, and levels are mostly variable in pregnancy. Although there is a high risk for PPH, bleeding symptoms do not correlate with factor XI levels[7,12].

Peripartum bleeding evaluations in the literature were mainly subjective or based on only postpartum hemoglobin/hematocrit values. Therefore, since these evaluations had not adequately captured clinical details, indices showing the amount of bleeding were defined as relatively new methods. Delta hemoglobin/hematocrit calculations and hemoglobin/hematocrit change rate indices were used in various studies to predict PPH[13-18].

In the presented study, obstetric and neonatal outcomes were evaluated. The delta hemoglobin/hematocrit and hemoglobin/hematocrit change rate indices were used to assess the tendency to bleed in pregnancies with inherited factor deficiencies. The study aimed to evaluate the usefulness of these new indices in an objective context.

Materials and Methods

The presented case-control study was conducted on pregnant women diagnosed with congenital factor deficiencies and delivered between October 2019 and 2023. Patient data were obtained retrospectively from the hospital database and patient files. All patients who met the inclusion criteria for the study were consecutively included, and the control group consisted of low-risk pregnant women who delivered during the same period. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. The study was approved by the Ankara Bilkent City Hospital Ethics Committee (approval number: E2-23-5850, date: 06.12.2023).

Eligibility criteria for the study included having a singleton pregnancy, maternal age between 18 and 45 years, and no chronic systemic diseases except for congenital factor deficiencies. Patients with oncological diagnoses, liver failure, and anticoagulant use were not included in the study, and other diagnoses of coagulopathies were carefully excluded. Low-risk pregnancy was defined as having no chronic disease and not using any anticoagulant medication.

Maternal obstetrical history (gravidity, parity, abortion, and living children), age, disease characteristics (factor levels, duration of disease, and bleeding history), and treatment received in pregnancy (medications, treatment trimesters, and transfusions) were recorded for all participants. The treatments of all patients were arranged by the hematology department.

During pregnancy, complete blood count and coagulation parameter tests were done monthly or in cases of obstetric necessity, such as antepartum vaginal bleeding, epistaxis, and gum bleeding. All patients had their first, second, and third

trimesters and postpartum blood parameters were recorded and compared with the control group. The last hematological variables recorded before labor were considered third-trimester blood parameters.

All participants had prophylactic carbetosine administration at birth. The lowest hemoglobin/hematocrit parameters 24-48 hours postpartum were recorded as postpartum blood parameter measurements since hemoglobin concentration in the early period after bleeding could be measured falsely higher[19]. Delta hemoglobin (prepartum - postpartum hemoglobin) and delta hematocrit (prepartum - postpartum hematocrit) indices were used to compare peripartum blood loss between the factor deficiency group and control group[13-16]. Hemoglobin % change was calculated as (prepartum - postpartum hemoglobin)/ prepartum hemoglobin, and hematocrit % change was calculated as (prepartum - postpartum hematocrit)/prepartum hematocrit, as defined in the recent studies[17,18].

Birth weights, gestational ages at birth, APGAR scores at the first and fifth minutes, neonatal intensive care unit admissions, delivery mode, cesarean section (c/s) indications, antepartum bleeding, and postpartum bleeding events were recorded as neonatal and obstetric outcomes. All patients were kept under close observation for the occurrence of late PPH for 4-6 weeks. Early PPH was defined as more than 500 mL bleeding in vaginal delivery and more than 1000 mL bleeding for cesarean section. Experienced midwives and doctors evaluated PPH[20]. Delivery mode and time decisions were based on obstetric indications and hematology department advice.

The main hematological parameters were determined: VWF, factor levels, and platelet levels for factor deficiency subgroups. These hematological parameters were measured at baseline and in the third trimester, and level changes were reported according to the literature study[1].

Statistical Analysis

The statistical analyses used the Statistical Package for the Social Sciences version 23. Due to the inconsistency with a normal distribution, descriptive statistics were presented as the median and interquartile range. The Mann-Whitney U test was used to compare the parameters between the groups. The chi-square test was used to compare independent variables between groups. Wilcoxon signed-rank test was used for dependent variables. Statistical significance was defined as a two-tailed p-value of 0.05.

Results

Demographic parameters were similar between groups, except for the history of abortions, which were found to be higher in the factor deficiency group with a p-value of 0.037. The rate of bleeding history before pregnancy was 22.2% in the factor deficiency group.

Hemoglobin and hematocrit levels were statistically lower in the factor deficiency group than the control group, in the first trimester, with p-values of 0.002 and 0.023, respectively. Postpartum-24-48 hours hemoglobin and hematocrit counts were lower in the factor deficiency group than in the control group, with p-values of 0.028 and 0.013, respectively. Hemoglobin and hematocrit counts were similar in both the postpartum first week and the first 48 hours.

The delta hemoglobin and hematocrit values, the hemoglobin and hematocrit % changes were found to be increased in the factor deficiency group (p-values of 0.019, <0.001, <0.001, 0.010, respectively) (Table 1).

Gestational age at birth, APGAR scores at 1 minute and 5 minutes were found statistically significant and lower in the factor deficiency group, with p-values of 0.016, <0.001, and <0.001, respectively (Table 2). There was only one stillbirth.

Table 1. Demographic and laboratory parameters of factor deficiency and control groups

	Factor deficiency group (n=18)	Control group (n=80)	p-value
Age	29 (11)	27 (13)	0.390
Gravida	2 (2)	1 (1)	0.116
Parity	1 (1)	0 (1)	0.669
Abortion	0 (1)	0 (0)	**0.037**
Living child	1 (1)	0 (1)	0.598
First trimester			
Hemoglobin (g/dL)	12.35 (1.75)	13.15 (1.07)	**0.002**
Hematocrit (%)	37.10 (4.70)	39.00 (3.08)	**0.023**
Platelet (10^9/L)	268.50 (97.75)	267.00 (66.50)	0.670
Second trimester			
Hemoglobin (g/dL)	11.00 (1.55)	11.50 (1.97)	**0.049**
Hematocrit (%)	32.20 (4.92)	34.35 (6.30)	0.219

Table 1. Continued

	Factor deficiency group (n=18)	Control group (n=80)	p-value
Platelet (10^9/L)	266.00 (99.50)	227.00 (97.50)	0.214
Third trimester			
Hemoglobin (g/dL)	11.90 (1.73)	11.70 (2.07)	0.579
Hematocrit (%)	36.55 (6.85)	35.10 (6.23)	0.480
Platelet (10^9/L)	238.50 (104.00)	240.00 (106.25)	0.491
Postpartum 24-48 hours			
Hemoglobin (g/dL)	9.85 (2.48)	11.10 (1.82)	**0.028**
Hematocrit (%)	31.00 (7.45)	34.25 (5.45)	**0.013**
Platelet (10^9/L)	250.50 (93.50)	235.50 (112.00)	0.909
Indices			
Delta hemoglobin	1.05 (1.58)	0.65 (0.95)	**0.019**
Hemoglobin % change	0.11 (0.14)	0.03 (0.10)	**<0.001**
Delta hematocrit	3.85 (5.23)	1.10 (3.75)	**<0.001**
Hematocrit % change	0.09 (0.12)	0.06 (0.07)	**0.010**
Factor deficiency group postpartum parameters	**Postpartum first 48 hours**	**Postpartum first week**	
Hemoglobin (g/dL)	9.85 (2.48)	10.30 (2.40)	0.689
Hematocrit (%)	31.00 (7.45)	32.80 (10.08)	0.556
Platelet (10^9/L)	250.50 (93.50)	282.00 (90.50)	0.206

*Due to the inconsistency with a normal distribution, descriptive statistics were presented as the median and interquartile range. The Mann-Whitney U test was used to compare the parameters between the groups. The chi-square test was used to compare independent variables between groups. Wilcoxon analysis was used for dependent variables

Table 2. Neonatal and obstetric outcomes of factor deficiency and control groups

	Factor deficiency group (n=18)	Control group (n=80)	p-value
Gestational age at birth	38 (1)	39 (2)	**0.016**
Birth weight	3160 (795)	3210 (438)	0.769
APGAR 1st. minute	7 (1)	8 (1)	**<0.001**
APGAR 5th. minute	9 (1)	9 (0)	**<0.001**
NICU (%)	2 (11.8)	2 (2.5)	0.081
Method of delivery (%)			
-Vaginal	7 (38.9)	52 (65)	**0.041**
-Cesarean	11 (61.1)	28 (35)	
Cesarean indications (%)			
-Previous cesarean	6 (54.5)	18 (64.3)	**0.001**
-Fetal distress	2 (18.2)	4 (14.3)	
-Non-vertex presentation	0 (0)	6 (21.4)	
-Hematology suggestion	3 (27.3)	0 (0)	

Table 2. Continued

	Factor deficiency group (n=18)	Control group (n=80)	p-value
Antepartum bleeding (%)	3 (16.7)		
Antepartum treatment (%)	4 (22.2)		
Postpartum bleeding complication (%)	3 (16.7)		
Prepartum treatment (%)	10 (55.6)		
- VWF/fVIII concentrate	2 (20)		
-Tranexamic acid	3 (30)		
-FFP	1 (10)		
-VWF/fVIII concentrate + tranexamic acid	3 (30)		
-VWF/fVIII concentrate + FFP	1 (10)		
Postpartum treatment (%)	15 (83.3)		
-Tranexamic acid	9 (60)		
-VWF/fVIII concentrate + tranexamic acid	4 (26.8)		
-FFP+VWF/fVIII concentrate + tranexamic acid	1 (6.6)		
-Tranexamic acid + desmopressin	1 (6.6)		

*Continuous variables without a normal distribution were presented as medians and interquartile ranges. Categorical variables were presented as numbers (percentages). VWF: Von Willebrand factor, FFP: Fresh frozen plasma, NICU: Neonatal intensive care unit

Three patients (16.7%) had antepartum bleeding, and four patients (22.2%) needed treatment in the antenatal period. Two of them received tranexamic acid treatment in the third trimester, one patient received factor VIII replacement, and another one received factor VIII with VWF replacement in all three trimesters.

Three of the patients (16.7%) had postpartum bleeding complications; one had a postpartum incisional hematoma, one had placental abruption, and the other one had late postpartum bleeding two months postpartum. Prepartum treatment necessities and detailed treatments of patients were given in Table 2. Three patients (16.7%) did well and did not need treatment in the peripartum period.

The factor deficiency subgroups' patient numbers and their hemostatic laboratory parameters are shown in Table 3.

Discussion

Delta hemoglobin/hematocrit and hemoglobin/hematocrit change rate indices increased in the factor deficiency group compared to the control group; however, none of the patients had early PPH or needed transfusion. Although obstetric bleeding complications and the need for transfusion can be reduced by close follow-up of pregnant patients with factor deficiency, there is still an increased bleeding tendency.

Third-trimester hemoglobin and hematocrit results of pregnant women with factor deficiency and the control group were similar, in line with the literature[21]. Postpartum hemoglobin and hematocrit values were lower in the factor deficiency group than in the control group, although major PPH was not reported as a consequence of factor deficiency. Decreased postpartum hemoglobin and hematocrit values in the factor deficiency group did not require a blood transfusion, and none of the patients were clinically symptomatic.

In the literature, PPH was mostly evaluated subjectively, and rates changed between 32-58% in factor deficiency studies[22]. A recent cohort study reported increased PPH and antepartum hemorrhage rates associated with factor levels that were considered safe in the third trimester[23]. In recent literature, new indices were used for the objective evaluation of bleeding in obstetric groups with an increased risk of PPH. In a new study conducted on pregnancies with immune thrombocytopenia, the level of PPH in well-managed cases was similar to that of average pregnant women[24]. In the evaluation of objective bleeding degree in various conditions such as estimated blood loss in c/s, induction of labor, PPH evaluation in intrahepatic cholestasis of pregnancy; delta hemoglobin/hematocrit and hemoglobin/hematocrit change rate indices were used and shown to be more reliable than only postpartum hemoglobin or hematocrit values[14-16].

All patients in the factor deficiency group were followed closely for 4-6 weeks postpartum due to the decrease in factor levels and high bleeding risk. In the literature, late PPH rates, up to 12 weeks postpartum, were reported in the range of 2-66%[22]. In the presented study, there was one patient with late postpartum bleeding and one incisional hematoma. In the first postpartum week, the hemoglobin and hematocrit values for the factor

Table 3. Hemostatic laboratory parameters of factor deficiency subgroups

	Platelet count ($x10^9$)	VWF:RCo (%)	VWF:Ag (%)	Factor VIII (%)	Factor VII (%)	Factor V (%)	Factor XI (%)
Baseline (n)							
VWF (7)	263 (127-326)	46 (3-122)	52 (2-129)	66 (1-170)			
VWF+f8 (4)	255 (220-273)	15.0 (10-19)	28.0 (15-36)	30.0 (2-54)			
f7 (2)	335 (305-365)				30.0 (12-48)		
f8 (2)	365 (360-370)			50.0 (44-56)			
VWF+f8+f5 (1)	300	101.2	98.0	6.0		3.0	
f5+f7 (1)	316				57.0	25.0	
f11 (1)	184						32.0
Third trimester (n)							
VWF (7)	186 (95-321)	71.50 (3-144)	73 (2-150)	81 (2-211)			
VWF+f8 (4)	247 (190-272)	18 (15-75)	45.5 (15-78)	33.50 (3-80)			
f7 (2)	284 (250-312)				52.5 (18-87)		
f8 (2)	268 (256-280)			77.5 (30-125)			
VWF+f8+f5 (1)	227	148.9	129.0	8.0		3.0	
f5+f7 (1)	205				124.0	26.0	
f11 (1)	150						10.5

*Continuous variables without a normal distribution were presented as medians and interquartile ranges. VWF: Von Willebrand factor, VWF:RCo: Von Willebrand factor ristocetin cofactor, VWF:Ag: Von Willebrand factor antigen

deficiency group were similar to the early postpartum values of other patients. Although there is a high bleeding risk due to the decrease in factor levels, the similarity of the parameters might be explained by the close follow-up of patients and their receipt of necessary prophylactic and therapeutic treatments.

In the presented study, VWF and factor VIII levels were increased, and platelet counts decreased in the third-trimester evaluation compared to the baseline levels. A recent review of VWD studies also reported similar results in line with physiological pregnancy changes in factor levels[1]. The Factor VII levels were found to increase, Factor V levels were unchanged, and XI levels were found to be decreased, which is in line with the literature[22].

Most of the patients received peripartum medical treatment: Few received prepartum tranexamic acid treatment, and all received postpartum treatment, with factor derivatives and desmopressin in required cases. In the literature, the administration of the antifibrinolytic tranexamic acid as an adjunctive treatment is recommended to reduce the risk of late PPH[25]. In a study, the PPH ratio was significantly increased in the group not using tranexamic acid compared with the group that received it[26]. Desmopressin and factor derivatives were also used in a limited number of studies, mostly in addition to tranexamic acid. In a study, the use of tranexamic acid for an extended period postpartum was recommended as VWF and factor VIII levels fall to baseline after delivery. Tranexamic acid could be used for prophylactic cases, and factor concentrates or desmopressin could be preserved for severe bleeding cases[27]. In our study, tranexamic acid was used primarily for prophylaxis, factor concentrate was preserved for patients with low factor levels, and bleeding histories, and FFP was used for moderate coagulation parameters in accordance with the literature.

In this study, gestational weeks and APGARs were significantly lower in the factor deficiency group, but this difference was not clinically significant. There was only one stillbirth in the factor deficiency group. In the literature, c/s indications, c/s ratios, APGAR, and birth weights were reported similarly to this study[1,21].

Study Limitations

The strengths of our study were: the bleeding degrees of the patients were evaluated through objective indices; the patients were followed up for all three trimesters and postpartum for four to six weeks in a multidisciplinary manner in the tertiary center; and both obstetric and neonatal results were available. Possible limitations of the study were the relatively small number of patients since factor deficiency is a very rare disease group, and the retrospective design of the study.

Conclusion

The inherited factor deficiency group requires careful follow-up in pregnancy to avoid and manage undesired obstetric and neonatal complications. Delta and change rate indices are

promising for objectively identifying patients at high risk of bleeding and regulating treatment in obstetrics practice.

Ethics

Ethics Committee Approval: The study was approved by the Ankara Bilkent City Hospital Ethics Committee (approval number: E2-23-5850, date: 06.12.2023).

Informed Consent: Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Footnotes

Authorship Contributions

Concept: G.İ., G.P., D.Ş., Design: G.İ., A.T., F.D.Y.Y., Data Collection or Processing: A.A.B., F.D.Y.Y., İ.D., E.B., Analysis or Interpretation: A.T., Literature Search: G.İ., A.A.B., F.D.Y.Y., İ.D., E.B., G.P., Writing: G.İ., A.T., G.P., D.Ş.

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