

Maternal and Fetal Outcomes of Gestational Thrombocytopenia

Gestasyonel Trombositopeninin Maternal ve Fetal Sonuçları

Bahar TAŞ¹

 0000-0003-4835-9998

Oğuzhan GÜNENC²

 0000-0003-4373-5245

¹Department of Obstetrics and Gynecology, Dr. Ali Kemal Belviranlı Obstetrics and Gynecology Hospital, Konya, Türkiye

²Department of Obstetrics and Gynecology, Konya City Hospital, Konya, Türkiye

ABSTRACT

Aim: The study aimed to evaluate maternal and fetal outcomes of gestational thrombocytopenia according to platelet levels.

Material and Methods: The cases who were followed up in our clinic between January 2017 and December 2018, who had no additional diseases, who had term deliveries, and who had gestational thrombocytopenia, were screened retrospectively. The pregnant women included in the study were divided into two groups according to their platelet values, $\leq 70 \times 10^3/\text{mm}^3$ and $>70 \times 10^3/\text{mm}^3$, and the subgroups were analyzed among themselves. The demographic, clinical, and laboratory data of the patients were also compared between the groups.

Results: Among the patients with gestational thrombocytopenia, it was found that the birth week was significantly earlier in the group with platelet $\leq 70 \times 10^3/\text{mm}^3$ ($p=0.002$). When perinatal characteristics were compared between the groups, the birth weight of the infants in the group with platelet $\leq 70 \times 10^3/\text{mm}^3$ was found to be significantly lower than in the other group ($p=0.033$). APGAR 1st-minute score was found to be significantly decreased in the group with platelet $\leq 70 \times 10^3/\text{mm}^3$ when compared to the other group ($p=0.039$). Single and multiple regression analyzes were performed on pregnant women with gestational thrombocytopenia. No risk factors that were associated with adverse maternal and perinatal outcomes were detected in the group with platelet values $\leq 70 \times 10^3/\text{mm}^3$.

Conclusion: Fetal growth retardation is seen in patients diagnosed with gestational thrombocytopenia and with platelet values below $70 \times 10^3/\text{mm}^3$ and their APGAR scores are lower. The premature birth rate is higher in the same patient group.

Keywords: Gestational thrombocytopenia; pregnancy; maternal outcomes; fetal outcomes.

ÖZ

Amaç: Bu çalışmanın amacı gestasyonel trombositopeninin maternal ve fetal sonuçlarının trombosit seviyelerine göre değerlendirilmesidir.

Gereç ve Yöntemler: Ocak 2017 ve Aralık 2018 tarihleri arasında kliniğimizde takip edilen, ek bir hastalığı olmayan, miad doğum yapmış olan ve gestasyonel trombositopeni saptanmış olan olgular geriye dönük olarak tarandı. Çalışmaya dahil edilen gebeler trombosit değerlerine göre $\leq 70 \times 10^3/\text{mm}^3$ ve $>70 \times 10^3/\text{mm}^3$ şeklinde iki alt gruba ayrıldı ve bu alt gruplar kendi arasında analiz edildi. Ayrıca, hastaların demografik, klinik ve laboratuvar verileri de gruplar arasında karşılaştırıldı.

Bulgular: Gestasyonel trombositopeni tanısı olan hastalardan; trombosit değeri $\leq 70 \times 10^3/\text{mm}^3$ olan grupta doğum haftasının anlamlı olarak daha erken olduğu görüldü ($p=0,002$). Gruplar arasında perinatal özellikler karşılaştırıldığında ise, trombosit değeri $\leq 70 \times 10^3/\text{mm}^3$ olan gruptaki bebeklerin doğum ağırlıklarının diğer grupta olanlara göre anlamlı şekilde daha düşük olduğu bulundu ($p=0,033$). APGAR 1. dakika skoru trombosit değeri $\leq 70 \times 10^3/\text{mm}^3$ olan grupta diğer grup ile karşılaştırıldığında anlamlı şekilde azalmış olarak bulundu ($p=0,039$). Gestasyonel trombositopenisi olan gebelerde tekli ve çoklu regresyon analizi yapıldı. Trombosit değerleri $\leq 70 \times 10^3/\text{mm}^3$ olan grupta olumsuz maternal ve perinatal sonuçlar ile ilişkili olan bir risk faktörü saptanmadı.

Sonuç: Gestasyonel trombositopeni tanısı alan ve trombosit değerleri $70 \times 10^3/\text{mm}^3$ altında olan hastalarda fetal gelişme geriliği görülmekte ve APGAR skorları daha düşük olmaktadır. Aynı hasta grubunda erken doğum oranı daha yüksektir.

Anahtar kelimeler: Gestasyonel trombositopeni; gebelik; maternal sonuçlar; fetal sonuçlar.

Corresponding Author

Sorumlu Yazar

Bahar TAŞ

drbahartas@gmail.com

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INTRODUCTION

Thrombocytopenia is among the most common hematological problems in pregnancy and is defined as a platelet count of less than $150 \times 10^3/\text{mm}^3$ (1). Considering the etiological causes, gestational thrombocytopenia is the most common. Thrombocytopenia can be detected because of many reasons such as immune thrombocytopenia (ITP), pregnancy-specific hypertensive diseases (preeclampsia, eclampsia, hemolysis, elevated liver enzymes, and low platelets, HELLP), connective tissue diseases (systemic lupus erythematosus, SLE, antiphospholipid syndrome), drug interactions, and infections (2). Depending on the severity and cause of thrombocytopenia, the follow-up and treatment protocols of pregnant women might vary (3). Gestational thrombocytopenia accounts for approximately 80% of thrombocytopenia cases during pregnancy (4) and there is no specific test for its diagnosis. It is detected in a routine blood count during pregnancy, diagnosed by excluding other diseases, and the platelet count is typically above $70 \times 10^3/\text{mm}^3$. The platelet count reaches normal values approximately 12 weeks after delivery (5-7). Maternal and fetal prognosis is generally good in cases with thrombocytopenia (8).

Thrombocytopenia is classified as mild, moderate, and severe thrombocytopenia according to platelet values (9). Approximately 8% of pregnant women have mild thrombocytopenia. Moderate and severe thrombocytopenia might accompany other diseases (9,10). Considering the neonatal outcomes of pregnant women with moderate and severe thrombocytopenia, it was detected that the risk of low 5th-minute APGAR score, intrauterine growth restriction (IUGR), and stillbirth is high (11).

In previous studies, thrombocytopenia cases that were detected generally during pregnancy and maternal and fetal complications that might be related to additional diseases in its etiology were evaluated together (9). Studies conducted on whether gestational thrombocytopenia causes an increased risk of maternal and fetal complications according to platelet levels in pregnant women are limited. For this reason, in the present study, the patients diagnosed with gestational thrombocytopenia were divided into subgroups according to their platelet levels. The purpose of the present study was to evaluate maternal and fetal outcomes and investigate their relationship with the degree of thrombocytopenia.

MATERIAL AND METHODS

The present study was a hospital-based case-control study that included pregnant women, who applied to the Health Sciences University Konya Training and Research Hospital, Gynecology and Obstetrics Clinic, and who were followed up with the diagnosis of gestational thrombocytopenia and was conducted between January 2017 and December 2018. The study was approved with the decision of the Konya Training and Research Hospital ethics committee with the numbers 01-13 on 03.01.2019 and 13826 on 29.04.2019.

The information of the pregnant women who applied to our clinic between January 2017 and December 2018 and were followed up because of thrombocytopenia was obtained from the hospital information management system and patient files. The demographic data of the patients, routine

blood test results, prenatal-postnatal follow-ups, and fetal results were examined and recorded.

Term (>37) and late-preterm (34-36 6/7) pregnant women who were aged 20-40 years were included in the study as those with thrombocyte count of $<150 \times 10^3/\text{mm}^3$ as a result of complete blood counts performed 3 times during pregnancy. Platelet counts were divided into two groups as below or above $70 \times 10^3/\text{mm}^3$, and it was planned to analyze whether there were significant differences between the subgroups in terms of maternal and fetal outcomes.

The patients who were not followed up because of thrombocytopenia and patients who did not give birth in our hospital were not included in the study. Those who were under the age of 20 and over the age of 40 were not included in the study. The diagnosis of thrombocytopenia before pregnancy, bleeding profile disorder, ITP, use of acetic salicylic acid and/or low molecular weight heparin or unfractionated heparin, hepatic or renal dysfunction, venous thrombosis, hepatitis, sepsis, viral and/or bacterial infection, gestational diabetes, autoimmune disease, drug use that would affect platelet functions or structure, hereditary factor deficiency such as von Willebrand factor (vWF), patients with bone marrow disease such as leukemia, lymphoma, patients receiving intravenous immune globulin (IVIG) and/or steroids, pregnancy-related preeclampsia, pregnancy cholestasis, HELLP, disseminated intravascular coagulation (DIC), those with diseases affecting liver and kidney functions were not included in the study.

Spontaneous single pregnancies without fetal ultrasonographic and/or cytogenetic fetal anomalies were included in the study and patients who were <34 early preterm and those who had multiple pregnancies with fetal anomalies, intracranial hemorrhage detected on ultrasound and/or fetal MR, and intrauterine fetal interventions were not included in the study.

Statistical Analysis

The IBM SPSS Statistics for Windows, Version 22.0 and PASTE programs were used for data analysis. The Kolmogorov-Smirnov test and Shapiro-Wilk test were used to determine the conformity of the data to normal distribution. A parametric test (independent sample t-test) was used for the analysis of the normally distributed variables, and a non-parametric test (Mann-Whitney U) was used for those that were not. The descriptive statistics for normally distributed variables were expressed as mean±standard deviation, and median, interquartile range, and minimum-maximum were used for non-normally distributed variables. The categorical data were analyzed with Pearson's chi-square test and represented by numbers and percentages. Univariate and multiple logistic regression analysis was used to identify the risk factors that were associated with adverse maternal outcomes and adverse perinatal outcomes in pregnant women. The data were analyzed at a 95% confidence interval and a p-value of <0.050 was accepted as statistically significant.

RESULTS

A total of 200 patients with gestational thrombocytopenia were included in the study. The demographic and clinical characteristics of the cases included in the study and

laboratory data evaluated in routine follow-ups were examined. It was found that the pregnant women included in the study did not have any additional problems other than thrombocytopenia (Table 1).

Since it was reported that especially platelet levels below $70 \times 10^3/\text{mm}^3$ are rarely seen in the definitions for gestational thrombocytopenia, the pregnant women were divided into two subgroups according to their platelet counts as below $70 \times 10^3/\text{mm}^3$ and above, and the groups were compared among themselves. In the comparison made according to demographic characteristics, the week of delivery was statistically significantly earlier in the group with platelet value $\leq 70 \times 10^3/\text{mm}^3$ than in the other group ($p=0.002$). No significant differences were detected in terms of other parameters (Table 2).

When both subgroups were evaluated in terms of laboratory parameters, urea ($p<0.001$), creatinine ($p=0.008$), prothrombin time ($p=0.011$), and activated partial thromboplastin time ($p=0.008$) were statistically significantly higher in the platelet $\leq 70 \times 10^3/\text{mm}^3$ group, and the hemoglobin level was found to be significantly lower ($p<0.001$) compared to the other group (Table 3).

When ultrasonographic and perinatal characteristics were compared between the groups, the birth weights of the infants in the group with platelet $\leq 70 \times 10^3/\text{mm}^3$ were significantly lower than in the other group ($p=0.033$). The 1st-minute APGAR score was found to be significantly lower in the group with platelet $\leq 70 \times 10^3/\text{mm}^3$ when

compared to the other group ($p=0.039$). Neonatal intensive care hospitalization rates of the infants were not found to be different between the groups (Table 4).

After the subgroup analysis, it was planned to analyze whether there was an increased risk of adverse maternal, and fetal outcomes, especially in pregnant women who had platelet count $\leq 70 \times 10^3/\text{mm}^3$, and possible risk factors were evaluated. According to pregnancy results, the presence of any of the postpartum complications, and/or admission to the intensive care unit, and/or any two of the patients who received massive blood transfusion were determined as adverse maternal outcomes. Admission to the neonatal intensive care unit, and/or patients with an APGAR score of <7 and/or any two of those with postnatal complications (postpartum death, intracranial bleeding, fetal growth restriction, FGR, prematurity) were considered adverse perinatal outcomes (11,12).

As a result of the analysis, no relationship was detected between the parameters examined here and negative maternal outcomes and negative perinatal outcomes in pregnant women with gestational thrombocytopenia and platelet counts $\leq 70 \times 10^3/\text{mm}^3$ (Table 5).

Table 1. The demographic and clinical characteristics of pregnant women with gestational thrombocytopenia

| | |
|--|--------------|
| Age (years) | 29.41±5.93 |
| Gravida | 3 (2) [1-10] |
| Living | 2 (1) [0-9] |
| BMI (kg/m^2) | 30.16±4.74 |
| Weight gained during pregnancy (kg) | 12.61±4.57 |
| Gestational week (week) | 38.03±2.44 |
| Platelet ($\times 10^3/\text{mm}^3$) | 101.68±24.81 |
| Hemoglobin (g/dl) | 10.77±1.36 |
| Urea (mg/dl) | 17.57±9.54 |
| Creatinine (mg/dl) | 0.63±0.10 |
| AST (U/L) | 20.65±7.53 |
| ALT (U/L) | 11.01±4.64 |
| INR | 0.92±0.58 |
| PT (s) | 8.28±4.96 |
| aPTT (s) | 24.21±2.77 |

BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio, PT: prothrombin time, aPTT: activated partial thromboplastin time, mean±standard deviation or median (interquartile range) [min-max]

Table 2. Comparison of intragroup demographic and clinical characteristics

| | Platelet ≤ 70 ($\times 10^3/\text{mm}^3$) | Platelet >70 ($\times 10^3/\text{mm}^3$) | p |
|--|--|--|--------------|
| Age (years), mean±SD | 28.85±5.95 | 29.49±5.93 | 0.604 |
| Gravida, median (IQR) [min-max] | 3 (2) [1-10] | 3 (2) [1-8] | 0.854 |
| Living, median (IQR) [min-max] | 1 (1) [0-9] | 1 (1) [0-5] | 0.771 |
| BMI (kg/m^2), mean±SD | 28.85±3.59 | 30.35±4.87 | 0.133 |
| Weight gained during pregnancy (kg), mean±SD | 12.12±3.27 | 12.68±4.74 | 0.556 |
| Gestational week (week), mean±SD | 36.65±2.96 | 38.24±2.29 | 0.002 |

BMI: body mass index, SD: standard deviation, IQR: interquartile range

Table 3. The comparison of intragroup laboratory findings

| | Platelet ≤ 70 ($\times 10^3/\text{mm}^3$) | Platelet >70 ($\times 10^3/\text{mm}^3$) | P |
|--------------------|--|--|------------------|
| Hemoglobin (g/dl) | 9.91±1.29 | 10.90±1.32 | <0.001 |
| Urea (mg/dl) | 24.96±2.46 | 16.46±5.36 | <0.001 |
| Creatinine (mg/dl) | 0.66±0.17 | 0.62±0.08 | 0.008 |
| AST (U/L) | 19.50±4.27 | 26.91±5.65 | 0.058 |
| ALT (U/L) | 16.73±2.40 | 19.63±6.83 | 0.066 |
| INR | 0.87±0.07 | 0.92±0.62 | 0.665 |
| PT (s) | 10.57±3.66 | 7.94±0.75 | 0.011 |
| aPTT (s) | 25.54±3.63 | 24.01±2.57 | 0.008 |

AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio, PT: prothrombin time, aPTT: activated partial thromboplastin time, the results were reported with mean±standard deviation

Table 4. The comparison of perinatal characteristics

| | Platelet ≤ 70 ($\times 10^3/\text{mm}^3$) | Platelet >70 ($\times 10^3/\text{mm}^3$) | P |
|--------------------|--|--|--------------|
| Birth weight (g) | 2820.58±810.06 | 3102.43±594.14 | 0.033 |
| APGAR, n (%) | | | |
| <7 | 4 (15.4) | 7 (4) | 0.039 |
| ≥ 7 | 22 (84.6) | 167 (96) | |
| Newborn ICU, n (%) | | | |
| Yes | 5 (19.2) | 31 (17.8) | 0.521 |
| No | 21 (80.8) | 143 (82.2) | |

ICU: intensive care unit

Table 5. Risk factors associated with adverse maternal and perinatal outcomes in pregnant women with platelet ≤ 70 ($\times 10^3/\text{mm}^3$)

| | Adverse Maternal Outcomes | | Adverse Perinatal Outcomes | |
|--------------------------------|---------------------------|-------|----------------------------|-------|
| | OR (95% CI) | p | OR (95% CI) | p |
| Age | 1.077 (0.937-1.239) | 0.296 | 1.020 (0.865-1.204) | 0.814 |
| Gravida | 1.185 (0.736-1.907) | 0.485 | 1.126 (0.678-1.870) | 0.647 |
| BMI | 1.175 (0.920-1.502) | 0.197 | 1.013 (0.769-1.333) | 0.928 |
| Weight gained during pregnancy | 1.075 (0.841-1.375) | 0.562 | 0.866 (0.623-1.205) | 0.395 |
| Gestational week | 0.714 (0.499-1.021) | 0.065 | 0.256 (0.065-1.019) | 0.053 |
| Birth weight | 0.999 (0.998-1.000) | 0.060 | 0.993 (0.986-1.000) | 0.063 |
| Hemoglobin | 0.499 (0.242-1.028) | 0.059 | 0.741 (0.341-1.613) | 0.450 |
| Urea | 0.990 (0.949-1.033) | 0.639 | 1.016 (0.978-1.056) | 0.413 |
| Creatinine | 2.877 (0.120-6.874) | 0.229 | 13.145 (0.591-29.263) | 0.068 |
| AST | 1.003 (0.997-1.010) | 0.269 | 1.008 (0.999-1.017) | 0.081 |
| ALT | 1.007 (0.997-1.016) | 0.178 | 1.014 (1.001-1.026) | 0.040 |
| INR | 0.037 (0.001-2.684) | 0.563 | 0.010 (0.001-12.439) | 0.263 |
| PT | 1.160 (0.353-3.814) | 0.804 | 0.118 (0.006-2.265) | 0.156 |
| aPTT | 0.886 (0.701-1.121) | 0.315 | 1.372 (0.985-1.912) | 0.061 |

OR: odds ratio, CI: confidence interval, BMI: body mass index, Hgb: hemoglobin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio, PT: prothrombin time, aPTT: activated partial thromboplastin time

DISCUSSION

There might be a physiological tendency to thrombocytopenia in the usual course of pregnancy. Increased destruction, decreased platelet production, or dilutional causes during pregnancy explain the decreased physiological limits (2). Gestational thrombocytopenia is the most common cause of thrombocytopenia during pregnancy (3). It usually occurs in the last trimester and the platelet count is typically above $70 \times 10^3/\text{mm}^3$, maternal and fetal outcomes are milder. It is diagnosed by excluding other diseases causing low platelet values, and there is usually no need for additional treatment (5,6,8). When the etiology of thrombocytopenia in pregnancy is evaluated, gestational hypertensive diseases and ITP, another common group, have a higher risk of fetal and maternal complications (9). For this reason, when pregnancy thrombocytopenia cases are evaluated holistically, the rate of negative results also increases (5). Since the risk of additional disease increases, especially in patients with moderate and severe thrombocytopenia in cases diagnosed with thrombocytopenia during pregnancy, other diagnoses should be excluded (5). In the present study, it was planned to examine the pregnancy outcomes of patients diagnosed with gestational thrombocytopenia by excluding these groups, according to their platelet levels. It was also planned to investigate whether there is a significant difference in terms of maternal and fetal outcomes in gestational thrombocytopenia cases with moderate and severe thrombocytopenia.

In the study conducted by Artunç Ülkümen et al. (13), the rate of low birth weight (<2500 g) and very low birth weight infants (<1500 g) in thrombocytopenic pregnant women were found to be significantly more frequent than in the control group. When newborn results were compared, a decrease was detected in the 5th-minute APGAR score in the group with thrombocytopenia, and the stillbirth and intrauterine growth retardation rates were found to be significantly higher (9). In the present study, birth weight and APGAR scores were found to be lower in the group with severe thrombocytopenia. Unlike the

results of the present study, maternal and fetal adverse outcome rates were found to be higher in previous studies because gestational thrombocytopenia was not evaluated alone.

In the study of Parnas et al. (9), when the newborns with thrombocytopenia were compared with the healthy group, the 5th-minute APGAR scores were found to be lower in the thrombocytopenia group, and the rates of stillbirth and intrauterine growth retardation were found to be significantly higher. Similarly, in the present study, birth weights and weeks were found to be lower in the group that had lower platelet levels. When evaluated in terms of maternal and fetal negative outcomes, the rate of negative outcomes was found to be higher in pregnant women diagnosed with HELLP syndrome and preeclampsia than in other causes of thrombocytopenia. Since hypertensive diseases of pregnancy among the causes of thrombocytopenia are a group with maternal and fetal risks, it is known that premature birth and stillbirth rates increase relatively (6,7). Since conditions complicating pregnancy such as gestational hypertensive diseases were excluded in the present study, no adverse maternal and fetal outcomes were observed.

In the study that was conducted by Wang et al. (14), when evaluating thrombocytopenia in pregnancy, the patients were grouped according to etiology and the groups were compared. Postpartum hemorrhage rate and newborn 5th-minute APGAR scores were found to be similar in the three groups. No adverse maternal and fetal outcomes were detected in the group diagnosed with gestational thrombocytopenia.

In the study conducted by Elvedi-Gašparović et al. (15), gestational thrombocytopenia was analyzed retrospectively against the control group and it was found that thrombocytopenia did not have a significant effect on the mode of delivery, and preterm delivery. The need for neonatal intensive care, low 1st-minute APGAR score, and fetal growth retardation were found to be significantly higher in the thrombocytopenic group than in the control

group. The present study had similar results to the literature in this regard. Fetal weight, week of birth, and APGAR scores were significantly lower during delivery in groups with severe thrombocytopenia. After evaluating the subgroups, univariate and multivariate regression analyzes were made in terms of the parameters considered in terms of negative maternal and fetal outcomes, and as a result, no negative maternal and fetal outcomes were detected.

It was detected that 3% of the cases included in the study were followed up and treated for reasons such as the threat of premature birth or vaginal bleeding during pregnancy. FGR was observed in 4.5% and amniotic fluid anomalies in 4%. After the delivery, 5% of patients required additional intervention because of bleeding. These results obtained with the available data were relatively high in terms of isolated gestational thrombocytopenia results in the literature. Since the patients in the present study were examined retrospectively based on the files and systems, it was not known whether the additional disease was diagnosed in the long-term postpartum results. For this reason, we think that the presence of possible diseases that might cause these outcomes should be evaluated with other studies that include long-term results.

The results of the present study were compatible with general literature data. The study was conducted in a single center with a sufficient number of patients for power analysis. On the other hand, since it was a retrospective study based on the patient files and system, we do not have data on maternal and fetal outcomes other than routine follow-ups. We think that clearer results will be obtained by examining and evaluating long-term maternal and fetal outcomes, especially in the postpartum period.

CONCLUSION

Gestational thrombocytopenia has significant effects on fetal birth weight, APGAR scores, and gestational week, especially in low platelet levels; however, it was found in the present study that it did not cause adverse maternal and fetal outcomes. We think that prospective studies to be conducted with large case series and long-term postpartum follow-ups are needed to elucidate the maternal and fetal effects of gestational thrombocytopenia.

Ethics Committee Approval: The study was approved by the Ethics Committee of Konya Training and Research Hospital (03.01.2019, 01-13, and 29.04.2019, 13826).

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