ORIGINAL RESEARCH

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Maternal-Fetal Outcomes of Pregnancies with Thrombocytopenia-One Center Experience

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ABSTRACT Objective: To investigate the etiology, obstetric risk factors, complications, and outcomes of pregnancies affected by thrombocytopenia. **Material and Methods:** A retrospective surveillance study was conducted based on the hospital records of 1286 women that gave birth during the period between 1st January 2017 and 31st December 2018 at the Department of Gynecology and Obstetrics of the Trakya University's School of Medicine. Clinical data including basic history, physical examination, and investigations of women with thrombocytopenia were evaluated. We randomly selected 154 patients without thrombocytopenia that delivered in our clinic during the same period, as the control group, and compared the maternal and fetal outcomes with the thrombocytopenic patient group. **Results:** A total of 154 out of 1286 women (11.9%) had thrombocytopenia of varying severity. Gestational thrombocytopenia (GT) was the most common cause, being identified in 76.2% of the cases with thrombocytopenia. This was followed by preeclampsia (15.5%). About 4.5% of pregnant women with thrombocytopenia were accounted for by idiopathic thrombocytopenic purpura (ITP), 2.5% of the patients by eclampsia, while HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome was observed in 1.3% of the pregnant women with thrombocytopenia. An increased rate of IUGR (Intrauterine growth restriction), fetal distress, and adverse neonatal outcomes were recorded among patients that had thrombocytopenia with preeclampsia, eclampsia, and HELLP syndrome. Furthermore, we observed higher rates of fetal distress and adverse neonatal outcomes in patients with thrombocytopenia compared to the control group. **Conclusion:** GT was the most common cause of thrombocytopenia in pregnancy, followed by preeclampsia. Eclampsia, HELLP syndrome, and ITP were rare causes of this disorder during pregnancy. Early detection and treatment of expected complications are critical for the effective management of such cases.

Keywords: Gestational thrombocytopenia; HELLP; preeclampsia; pregnancy; thrombocytopenia

Ütrombocytopenia is the most common hematological complication following anemia during pregnancy, and is observed in 6-10% of all pregnancies.[1,2] It is categorized into mild, moderate, and severe thrombocytopenia, based on thrombocyte counts between 100,000-150,000/mm^3, 50,000-100,000/mm^3, and <50,000/mm^3, respectively.[3] Gestational thrombocytopenia (GT) is the most common cause and is observed in approximately 75% of the cases. Preeclampsia, eclampsia, and HELLP cases are among the other pregnancy-specific etiologic factors. The causes of thrombocytopenia that are not specific to pregnancy include primary immune thrombocytopenia; viral infections such as hepatitis B virus (HBV), cytomegalovirus (CMV), Epstein-Barr virus (EBV); secondary immune thrombocytopenia related to autoimmune diseases such as systemic lupus erythematosus (SLE) and antiphospholipid antibodies; thrombotic micro-angiopathies such as thrombotic thrombocytopenic purpura and hemolytic ure-

mic syndrome; disseminated intravascular coagulation (DIC); bone marrow diseases such as myelofibrosis; nutrition and use of drugs such as aspirin; hypersplenism and inherited thrombocytopenia; or very rare diseases such as Evans Syndrome.[4]

GT usually occurs during the last trimester and the platelet count is typically above 70,000/mm^3. The thrombocyte number usually returns to normal levels within 12 weeks after delivery. There is no risk of fetal or maternal bleeding. Although the exact cause is not known, the relative hemodilution during pregnancy is associated with increased placental destruction.[5]

Idiopathic thrombocytopenic purpura (ITP) is caused by the formation of autoantibodies against thrombocyte membrane glycoproteins. It constitutes approximately 5% of all the cases of thrombocytopenia observed during pregnancy. In contrast to GT, the platelet count is moderate or severely low and is associated with a risk of maternal bleeding.[6,7] Therefore, treatment and follow-up are required. The newborn carries a slight risk of thrombocytopenia.

Approximately 2% of the cases of thrombocytopenia during pregnancy comprises patients with preeclampsia and HELLP syndrome.[8] Preeclampsia is a multisystem continuous disease that is defined by newly occurring hypertension and proteinuria, or hypertension and significant end-organ dysfunction with or without proteinuria, during the last half of pregnancy or postpartum. Eclampsia involves the development of new-onset, generalized, tonic-clonic seizures or coma in women with preeclampsia. HELLP is a syndrome that is identified by hemolysis using a microangiopathic blood smear, elevated liver enzymes, and a low platelet count. It apparently depicts a severe form of preeclampsia. These conditions are concomitant with increased risk of mortality, perinatal morbidity-mortality, and increased risk of maternal mortality due to both prematurity and association with ablation placenta.

In this study, we aimed to investigate the determinants of obstetric risk, complications, and maternal-fetal outcomes of pregnancies with thrombocytopenia during labor and delivery, and to analyze the outcomes of various etiologies.

MATERIAL AND METHODS

The medical histories of all pregnant women with thrombocytopenia that had given birth at the Department of Gynecology and Obstetrics Clinic of the Trakya University's School of Medicine from 1st January 2017 to 31st December 2018, and their neonatal outcomes were reviewed retrospectively with the approval of the Trakya University's Human Ethics Committee (2019/45) in accordance with the Declaration of Helsinki. We also randomly selected 154 patients without thrombocytopenia, which had given birth at our hospital during this period, as the control group. The study involved pregnant women with thrombocytopenia (platelet count <150,000/mm^3) as determined by the hematology laboratory report. We excluded thrombocytopenic patients with a disease apart from GT, preeclampsia, eclampsia, HELLP, and ITP as the causative factor for thrombocytopenia. All clinical and pathological results were recorded. Clinical characteristics that were assessed included maternal age, parity, gestational age, past obstetric history, and etiology of thrombocytopenia. After excluding all the diseases causing thrombocytopenia, we diagnosed patients as cases of GT. Patients without the high blood pressure and/or proteinuria consulted to the hematology department for differential diagnosis of thrombocytopenia. Furthermore, we also evaluated the prevalence of thrombocytopenia.

The clinical features and obstetric risk factors were assessed. Immediate antepartum and postpartum complications involving hemorrhage during or after delivery, blood transfusions, and method of delivery which is vaginal delivery or cesarean section were documented. The instant neonatal outcome was also reviewed. The same investigations were performed for the control group and the results were compared.

Statistical analysis was performed using the software SPSS Statics v25. Mean±standard deviation and percentile values were calculated. A *p*-value ≤0.05 was considered to be statistically significant.

RESULTS

A total of 1286 women gave birth during the study. Among them, 154 had thrombocytopenia. The mean age of the patients in the control group was 27±6.4 years, whereas that of patients with thrombocytopenia was 29±5.8 years. The prevalence of thrombocytopenia was evaluated to be 11.9%. The most common cause was GT (76.2%), followed by preeclampsia, ITP, eclampsia, and HELLP syndrome, (15.5%, 4.5%, 2.5%, and 1.3%, respectively) (Table 1). The majority of the women in the thrombocytopenia group (54%) were multiparous, while multiparity in the control group was 49%. Eighty-seven (75%) patients with GT had mild thrombocytopenia, while 30 (25%) had moderate thrombocytopenia. The mean platelet count in patients with GT was 104,000/mm^3. In patients with ITP, the mean platelet count was 66,000/mm^3 and two patients had severe thrombocytopenia. The extent of thrombocytopenia in preeclamptic and eclamptic patients was not as severe (Table 2).

A higher prevalence of deliveries before 34 weeks was seen in pre-eclamptic patients (25%), compared to gestational thrombocytopenia (2.5%) and control group (5.5%) ($p<0.05$). Gestational diabetes mellitus was recorded in 20.8% of the preeclamptic patients, which was higher than that in patients with GT (8.5%) and control group (11%). Also, the prevalence of maternal anemia was significantly higher in the preeclamptic group (29.1%) compared to the GT group (10.7%) ($p<0.05$). The results of the control group were similar to those in patients with GT. Higher rates of oligohydramnios and IUGR were observed among thrombocytopenic patients with preeclampsia (25% and 37.5%, respectively) than in patients with GT (6.8% and 9.4%, respectively) and control group (9.7% and 11%, respectively) ($p<0.05$) (Table 3).

TABLE 1: The distribution of patients according to etiology.

Etiology	n=154	%
Gestational thrombocytopenia	117	76.2%
Preeclampsia	24	15.5%
ITP	7	4.5%
Eclampsia	4	2.5%
HELLP	2	1.3%

n: Number; ITP: Immune thrombocytopenic purpura; HELLP: Hemolysis, elevated liver enzymes, low platelet.

TABLE 2: Number of patients according to platelet count with different etiologies.

	≤50.000/mm^3 (n)	50.000-100.000/mm^3 (n)	100.000-150.000/mm^3 (n)
Gestational thrombocytopenia	-	30	87
Preeclampsia	2	8	14
Eclampsia	1	2	1
HELLP	2	-	-
ITP	2	4	1

n: Number; ITP: Immune thrombocytopenic purpura; HELLP: Hemolysis, elevated liver enzymes, low platelet.

TABLE 3: Obstetric risk factors in pregnant women according to the etiology of thrombocytopenia and in the control group.

Characteristics	Gestational thrombocytopenia (n=117)	Preeclampsia (n=24)	Eclampsia (n=4)	HELLP (n=2)	ITP (n=7)	Control group (n=154)
Gestational DM	10 (8.5%)	5 (20.8%)	-	-	1 (14%)	17 (11%)
Pregestational DM	2 (1.7%)	-	–	-	-	5 (3.1%)
Maternal anemia	12 (10.7%)	7 (29.1%)	2 (50%)	2 (100%)	-	19 (12%)
Polyhydramnios	7 (5.9%)	-	-	-	-	11 (7.1%)
Oligohydramnios	8 (6.8%)	6 (25%)	-	1 (50%)	-	15 (9.7%)
IUGR	11 (9.4%)	9 (37.5%)	2 (50%)	1 (50%)	1 (14%)	17 (11%)

n: Number; DM: Diabetes mellitus; IUGR: In utero mort fetus; HELLP: Hemolysis, elevated liver enzymes, low platelet; ITP: Immune thrombocytopenic purpura.

Higher frequency of cesarean section (CS) and increased requirement for blood transfusion was observed in preeclamptic and eclamptic patients compared to GT patients as well as the control group ($p<0.05$). Six preeclamptic patients were subjected to CS (33%), of which four (75%) showed fetal distress. Among patients with GT, 21 were subjected to CS (24%), and the frequency of fetal distress was lower (28%) than the preeclamptic group patients. In the control group, 112 (73%) patients gave birth by CS and. The most common reason for CS was the failure to progress (17%). Fetal distress was observed in 14% of the patients, which was significantly lower than patients with thrombocytopenia ($p<0.05$). Patients with ITP did not require blood transfusion and had the highest vaginal delivery rate (57%) among all patients (Table 4). Maternal hemorrhagic complications such as postpartum hemorrhage, bleeding from an episiotomy, or the formation of hematoma were not encountered in our study. In six patients with GT (5%), we used blood transfusion because of severe anemia. In group including patients with GT, a total of six units of fresh frozen plasma (FFP) were used while in group including patients with preeclampsia, eclampsia and HELLP overall 16 units of FFP were used. In patients with GT and ITP, no platelet apheresis was required whereas in group including patients with preeclampsia, eclampsia and HELLP totally five units of platelet apheresis were used.

In our study, a higher rate of preterm delivery (<37 weeks) was observed in pregnancies with thrombocytopenia that was caused by preeclampsia, eclampsia, and HELLP syndrome. All the patients with ITP, 72% of the patients with GT, and 74.5% of the control group gave birth after 37 weeks. Our study showed a higher incidence of premature and LBW (low birth weight) infants in the preeclampsia, eclampsia, and HELLP groups (Table 5) ($p<0.05$). IUMF was observed in two pa-

TABLE 4: Mode of delivery and number of patients needed a transfusion after delivery.

Characteristics	Gestational thrombocytopenia (n=117)	Preeclampsia (n=24)	Eclampsia (n=4)	HELLP (n=2)	ITP (n=7)	Control group (n=154)
Mode of delivery						
Vaginal	32 (27%)	6 (25%)	0	0	4 (57%)	42 (27%)
CS	85 (73%)	18 (75%)	4 (100%)	2 (100%)	3 (43%)	112 (73%)
Blood transfusion	6 (5%)	4 (16%)	2 (50%)	2 (100%)	0	14 (9%)

n: Number; CS: Cesarean section; HELLP: Hemolysis, elevated liver enzymes, low platelet; ITP: Immune thrombocytopenic purpura.

TABLE 5: Neonatal outcomes in different patients groups.

Characteristics	Gestational thrombocytopenia (n=117)	Preeclampsia (n=24)	Eclampsia (n=4)	HELLP (n=2)	ITP (n=7)	Control group (n=154)
Before ≤34 weeks of delivery	3 (2.5%)	6 (25%)	2 (50%)	1 (50%)	0	8 (5.5%)
Between 34-37 weeks delivery	21 (17%)	8 (33%)	2 (50%)	1 (50%)	0	32 (20%)
Between 37-40 delivery	70 (59%)	10 (41%)	0	0	5 (71%)	98 (64%)
≥40 weeks delivery	16 (13%)	0	0	0	2 (29%)	16 (10.5%)
≤1.500 g	3 (2.5%)	3 (12.5%)	3 (75%)	1 (50%)	0	7 (4.5%)
1.500-2.500 g	8 (6.8%)	3 (12.5%)	1 (25%)	1 (50%)	0	35 (22.5%)
2.500-4.000 g	84 (71.7%)	18 (15.3%)	0	0	7 (100%)	104 (67.5%)
≥4.000 g	12 (10.2%)	0	0	0	0	8 (5.5%)
IUMF	2 (1.7%)	2 (8.3%)	0	0	0	3 (1.9%)
Apgar score at 1 and 5 min <7	4 (3.4%)	2 (8.3%)	2 (50%)	0	0	2 (1.2%)

n: Number; IUMF: In utero mort fetus; HELLP: Hemolysis, elevated liver enzymes, low platelet; ITP: Immune thrombocytopenic purpura.

tients with GT (1.7%) and the reason was idiopathic, while two patients in the preeclamptic group (8.3%) showed IUMF and the reason was *abruptio placentae*.

DISCUSSION

Normal pregnancy is represented by a physiological reduction in platelet number with a left shift in platelet distribution. Decreased platelet production or dilution explains the physiological decrease in platelet count during pregnancy. However, platelet counts at pathological limits may be encountered during pregnancy. The most common cause of thrombocytopenia during gestation is GT. In our study, the incidence of thrombocytopenia during pregnancy was 11.9%. Burrows et al. found thrombocytopenia in 6% patients, while Sainio et al. reported a 7.3% prevalence of thrombocytopenia in their studies.[9,10] In our study group, a higher prevalence of thrombocytopenia was observed.

It can be difficult to differentiate between GT and ITP until after delivery, as they are diagnosed by exclusion. The presence of thrombocytopenia before pregnancy excludes GT, while thrombocytopenia detected during pregnancy indicates GT.[11] Until the late trimester, a considerably reduced platelet count is more likely to be due to an immune process, and less likely due to insufficient platelet production. In GT, no history of thrombocytopenia is observed, and women are usually asymptomatic during the first and second trimesters of pregnancy. In most of the cases with GT, the disorder remains benign, although sometimes it can pose a risk for significant morbidity and mortality. In contrast, in the pathophysiology of ITP, it involves the destruction of platelets in the reticuloendothelial system because of auto-antibodies against various platelet membrane glycoprotein complexes.[12] In our study, seven patients had ITP disease, majority of which had moderate platelet counts (mean=66,000/mm^3). They did not require platelet transfusion or steroid administration. After delivery, no vaginal hematoma or CS incision bleeding was observed. In contrast to a study by Belkin et al. that reported higher rates of preterm delivery in patients with ITP, we did not observe any cases of preterm delivery among ITP patients.[13] The reason for this could be the close monitoring of the patients, as well as the relative mildness of ITP in our patients.

Ante- or post-partum bleeding is a major problem in mothers with thrombocytopenia. If the platelet count remains deficient (<50,000/mm^3) during the peripartum period, platelets should be made available for replacement.[14] However, as platelets are prone to be destroyed rapidly after transfusion because of immune mechanisms, their administration should be scheduled carefully and should be given in well-established rather than early labor, in case of increased bleeding complications. In our study group, a total of seven patients had severe thrombocytopenia, among which the least platelet count was 38,000/mm^3. Two of these patients were diagnosed with ITP. We did not need to supplement platelets in ITP patients, possibly because of close observation and careful treatment.

The actual cause of thrombocytopenia from preeclampsia, eclampsia, and HELLP syndrome is not yet clear, although it may be related to abnormal vascular tone with resultant accelerated platelet destruction, platelet activation, and coagulation defects.[15] In our study, a higher rate of preterm delivery (<37 weeks) was observed in pregnancies with moderate to severe thrombocytopenia that was influenced by preeclampsia, eclampsia, and HELLP syndrome. A study by Saxena et al. showed that about 48% of such patients had to be subjected to CS.[16] The most common indication for operative intervention in our study was fetal distress, unlike the study by Saxena et al., in which the most common indication for CS was failed induction or non-progress.

Our study reported higher rates of maternal anemia, oligohydramnios, and IUGR in patients with moderate thrombocytopenia in the preeclamptic group. A higher incidence of CS because of fetal distress (75%) was observed in preeclamptic patients with moderate to severe platelet insufficiency. Onisai et al. reported excessive risks related to moderate and severe thrombocytopenia (over twice than reported be-

fore) and suggested that preeclampsia and HELLP syndrome were strongly linked with these adverse neonatal outcomes.[17] Furthermore, in this study, a higher incidence of premature and LBW infants was observed when there was moderate to severe thrombocytopenia with preeclampsia, eclampsia, and HELLP syndrome, but none with GT and ITP. The results of the control group were similar to those from the GT group. Thrombocytopenic pregnant women with preeclampsia and eclampsia delivered significantly more infants with lower Apgar scores (8.3% and 50%, respectively). Patients with ITP did not deliver newborn with low Apgar score.

CONCLUSION

Thrombocytopenia in pregnancy is the most common hematological complication after anemia. When thrombocytopenia is detected, preeclampsia and HELLP syndrome should be considered in the differential diagnosis, as they are associated with negative perinatal outcomes.

The most common cause of thrombocytopenia during gestation was GT, and patients with GT had good maternal-fetal outcomes. Close observation is needed in pregnancies with thrombocytopenia, and they should be followed-up in tertiary centers for the early detection and treatment of possible complications. Thus, maternal and neonatal morbidities can be reduced.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Cenk Sayın;* ***Design:*** *Cenk Sayın;* ***Control/Supervision:*** *Füsun Varol;* ***Data Collection and/or Processing:*** *Sinan Ateş* ***Analysis and/or Interpretation:*** *Cem Yener* ***Literature Review:*** *Havva Sütcü;* ***Writing the Article:*** *Cem Yener;* ***Critical Review:*** *Cenk Sayın;* ***References and Fundings:*** *Füsun Varol;* ***Materials:*** *Sinan Ateş.*

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