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5 Years' Experience of a Tertiary Center with Thrombocytopenic Pregnancies: Gestational Thrombocytopenia, Idiopathic Thrombocytopenic Purpura and Hypertensive Disorders of Pregnancy

Fünfjährige Erfahrung eines Krankenhauses der Schwerpunktversorgung mit thrombozytopenischen Schwangerschaften: schwangerschaftsassoziierte Thrombozytopenie, idiopathische thrombozytopenische Purpura und hypertensive Schwangerschaftserkrankungen

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ABSTRACT

Aim To evaluate thrombocytopenic pregnancies including gestational thrombocytopenia (GT), idiopathic thrombocytopenic purpura (ITP), and hypertensive disorders of pregnancy (HDP).

Materials and Methods We evaluated the pregnancy outcomes and laboratory findings of 385 patients diagnosed with GT, ITP, or HDP whose thrombocyte levels were < 150 000/µL.

Results GT, ITP, and HDP were the final diagnoses in 315 (81.8%), 35 (9.1%), and 35 (9.1%) cases, respectively. Patients diagnosed during the 1st trimester and diagnosed with ITP had significantly lower minimal platelet counts during the antenatal period and prior to delivery ($p < 0.001$; $p < 0.001$; $p < 0.001$; $p < 0.001$). Transfusion of any kind of blood product was given in 9.9% (n = 38) of all cases. Twelve patients had methylprednisolone and/or intravenous immunoglobulin treatments during the antenatal period. All patients who had undergone medical treatment were also found to have ITP. Four out of 385 patients underwent hysterectomy post partum due to refractory hemorrhage. Analysis of newborn platelet levels showed no statistical differences between any of the groups. Despite the lack of statistical significance, the rate of thrombocytopenia in newborns was 50% in patients with severe thrombocytopenia, while rates were 25.6 and 18.1% in patients with moderate and mild thrombocytopenia, respectively.

Conclusion Thrombocytopenic pregnancies must be carefully evaluated with regard to the severity of thrombocytopenia, gestational period at initial diagnosis, and etiology. In particular, patients with ITP must be evaluated carefully as these patients are more likely to require transfusions and have platelet counts $< 50 \times 10^3$/µl.

ZUSAMMENFASSUNG

Zielsetzung Ziel war es, thrombozytopenische Erkrankungen in der Schwangerschaft wie beispielsweise die schwangerschaftsassoziierte Thrombozytopenie (GT), idiopathische thrombozytopenische Purpura (ITP) sowie hypertensive Schwangerschaftserkrankungen (HDP) zu untersuchen.

Material und Methoden Das Schwangerschafts-Outcome und die Laborbefunde von 385 Patientinnen mit GT, ITP oder HDP und einem Thrombozytenwert von < 150 000/µL wurden evaluiert.

Ergebnisse GT, ITP bzw. HDP wurde jeweils bei 315 (81,8 %), 35 (9,1 %) bzw. 35 (9.1 %) Patientinnen diagnostiziert. Patientinnen, die bereits im 1. Trimenon mit ITP diagnostiziert wurden, hatten pränatal sowie unmittelbar vor der Entbindung einen signifikant niedrigeren minimalen Thrombozytenspiegel ($p < 0{,}001$; $p < 0{,}001$; $p < 0{,}001$; $p < 0{,}001$). 9,9 % (n = 38) aller Fälle benötigten eine Transfusion von Blutprodukten. Zwölf Patientinnen erhielten Methylprednisolon in der pränatalen Phase und/oder eine intravenöse Behandlung mit Immunoglobulin. Alle Patientinnen, die medikamentös behandelt wurden, wurden mit ITP diagnostiziert. Vier von 385 Patientinnen mussten sich wegen hartnäckiger Blutungen postpartal einer Hysterektomie unterziehen. Eine Analyse der neonatalen Thromobzytenwerte ergab statistisch keine signifikanten Unterschiede zwischen den Gruppen. Obwohl die Grenze zur statistischen Signifikanz nicht erreicht wurde, hatten 50 % der Kinder, deren Mütter an schwerer Thrombozytopenie litten, eine Thrombozytopenie. Dagegen litten 25,6 bzw 18,1 % der Neugeborenen von Müttern mit mittlerer bzw. milder Thrombozytopenie an einer Thrombozytopenie.

Schlussfolgerung Thrombozytopenische Schwangerschaften müssen im Hinblick auf die Schwere der Thrombozytopenie, das Gestationsalter bei der Erstdiagnose und die Ätiologie sorgfältig evaluiert werden. Patientinnen mit ITP bedürfen einer besonders sorgfältigen Evaluierung, da die Wahrscheinlichkeit höher ist, dass sie eine Transfusion benötigen werden und dass ihre Thrombozytenwerte $< 50 \times 10^3$/µl betragen.

Introduction

Pregnancy triggers various biological mechanisms that affect hematopoietic and related systems [1]. Thrombocytopenia is the second most common hematologic disorder after anemia [2]. The incidence of thrombocytopenia during pregnancy has been shown to be between 6 and 10 % and is defined as a platelet count $< 150 \times 10^3$/µl [3]. Gradual decreases in thrombocyte counts are observed during pregnancy, but most of these changes are within physiological levels [4]. Despite the lack of consensus, this mild, physiological decrease has been mostly explained by dilution, decreased production, pooling at placental and splenic circulation, or increased turnover of platelets [5, 6]. These pathophysiological pathways mostly end in mild thrombocytopenia, which is not related to maternal or neonatal complications. Differential diagnosis is critical in the management of patients with idiopathic thrombocytopenic purpura (ITP) or hypertensive disorders of pregnancy (HDP) since they are managed differently and have different outcomes; these conditions are the most common etiological factors in clinically important thrombocytopenia during pregnancy [7].

Gestational thrombocytopenia (GT) is a self-limiting benign condition, which mostly is not related to adverse outcomes and requires no additional evaluation or intervention [8, 9]. GT comprises up to 75 % of all cases of thrombocytopenia in pregnancy [10]. The incidence of GT in moderate and severe thrombocytopenia is mostly decreased since GT is primarily associated with mild thrombocytopenia, which is most commonly diagnosed in the 3rd trimester [11]. Diagnosis of GT is usually incidental, presenting with no clinical signs or symptoms [12]. The diagnosis of GT is one of exclusion, which has no additional findings and resolves quickly in the postpartum period without any prior history of thrombocytopenia before pregnancy [13]. Severe thrombocytopenia, mostly below 100×10^3/µl or 70×10^3/µl are mostly not related with GT [14, 15]. In cases where platelet counts are below these thresholds, other diagnoses must be carefully considered.

ITP is also relatively uncommon with an incidence of 1 in 1000 to 10 000 pregnancies [16]. The rate of ITP is nearly 10-fold greater than the rate in the nonpregnant population which is mostly related to increased turnover of platelets in pregnancy [17]. ITP occurs due to the destruction of circulating platelets via antiplatelet antibodies and may worsen during pregnancy, which can result in the development of severe thrombocytopenia [18, 19]. The maternal immunoglobulins that cause ITP are of the IgG type, which may cross the placenta and may also lead to neonatal thrombocytopenia. Previous studies have found that newborns born to mothers with ITP may have platelet counts $< 50 \times 10^3$/µl with a 3 % rate of major bleeding complication and 1 % rate of intracranial hemorrhage [20]. The differential diagnosis between GT and ITP is challenging primarily due to the lack of specific symptoms. Cases of thrombocytopenia before pregnancy or moderate and severe thrombocytopenia are commonly diagnosed as ITP [21]. Under certain circumstances, such as nonpregnant patients, ITP is also treated with corticosteroids and/or intravenous immunoglobulin (IVIG) [22]. Although corticosteroids are considered to be the first-line therapies in the management of severe ITP, their efficacy is similar to that of IVIG [23, 24]. Treatments such as vasopressin type 2 receptor agonists are also recommended in cases of thrombocytopenia during labor [25].

Thrombocytopenia is also a characteristic feature of hypertensive disorders of pregnancy, including preeclampsia and HELLP syndrome, which comprise 5–21 % of all thrombocytopenia cases [26]. Thrombocytopenia occurs as a result of complex pathophysiological pathways resulting in microangiopathy [27]. Despite sharing similar clinical features and results, the pathophysiology of HELLP syndrome has also some unique characteristics [28]. Thrombocytopenia is found to occur in 50 % of patients with preeclampsia [15]. A platelet count $< 100 \times 10^3$/µl is considered to be a criterion for severe preeclampsia and a diagnostic tool for the

management of preeclampsia [29]. In order to reduce maternal and fetal complications, delivery is the treatment option for severe preeclampsia and HELLP for reducing maternal and fetal complications [30].

In this study, we evaluated the most common etiological factors for thrombocytopenia in pregnancy. We aimed to show the differences between the progression of the diseases and obstetric and neonatal outcomes in terms of etiological factors.

Materials and Methods

Study design

We retrospectively evaluated patients with a thrombocyte level < 150 000/µl, who were hospitalized at the delivery room of our institution, between 2013 and 2018. Patient names and file numbers were obtained from our electronic database; in total, 1474 patients, with a thrombocyte level < 150 000 during hospitalization at the delivery room, were included.

Patients with a complete blood count conducted 7 days before delivery were evaluated. The final laboratory findings taken prior to delivery including hemoglobin (Hb) levels, platelet count, plateletcrit (PCT), Mean Platelet Volume (MPV), and Platelet Distribution Width (PDW) were also recorded as the laboratory findings prior to delivery. ALT, AST, BUN, and serum creatinine levels were also recorded if the related blood samples were collected prior to delivery. We have also recorded the Hb levels on the morning of the first postpartum or postoperative day as the postpartum Hb levels.

Inclusion and exclusion criteria

Etiological factors were evaluated according to follow-up of patients in our department and the hematology department. Patients with gestational thrombocytopenia, ITP, and hypertensive disorders of pregnancy were included in this study. Patients with any other chronic systemic disease or any pathology that may cause thrombocytopenia such as *HUS*, thrombotic thrombocytopenic purpura (TTP), and also lupus erythematosus, APL-Syndrome, von-Willebrand disease type 2b were also excluded. Patients who were diagnosed with pseudothrombocytopenia including pseudo immune thrombocytopenia according to their peripheral blood smear and repeat blood counts were excluded. Patients without adequate information or delivered at other institutions were also excluded. Patients with a thrombocyte level > 150 000/µl prior to delivery were excluded from the study. Pregnancies reaching the 22nd gestational week or a fetal weight of 550 g were included in order to see the delivery outcomes. The lowest platelet count during the pregnancy was also recorded. Patients without adequate laboratory findings were also excluded from the study. Patients with a prior diagnosis of bleeding diathesis, placental invasion anomalies, or those undergoing anticoagulant therapies for any purposes were excluded from the study to prevent any bias related to postpartum results.

After the application of these inclusion and exclusion criteria, 385 patients met all criteria for inclusion. The gestational week at birth, birthweight, route of delivery, and Apgar scores at the 1st and 5th minutes were also recorded as obstetric outcomes.

Procedures

All of the laboratory findings during the whole pregnancy were retrospectively screened. The timing of the initial thrombocytopenia diagnosis was recorded according to trimesters. Platelet counts prior to delivery were classified as < 50 000; 50 000–100 000; and > 100 000, which are defined as mild, moderate, and severe thrombocytopenia, respectively [11]. Any medical intervention during the antenatal period to improve platelet counts was also recorded. Oral prednisolone and intravenous immunoglobulin therapies were applied with initial doses of 1 mg/kg and 1 g/kg, respectively according to practice guidelines of the American Society of Hematology [31]. Treatment indications were similar to the non-pregnant population as recommended in recent literature.

All transfusions of blood products and cellular blood components were recorded and evaluated. Pregnancies that were complicated with postpartum hysterectomies were also recorded. The platelet count of the newborns within the 24 hours after delivery was also recorded if data was available. Fetuses that were diagnosed as thrombocytopenic (< 150 000/µl) were also evaluated for any complications related to thrombocytopenia.

Further comparisons were performed between the groups according to etiology (gestational thrombocytopenia, ITP, or hypertensive disorders of pregnancy), time of initial diagnosis (1st, 2nd, or 3rd trimester), and platelet count prior to delivery (mild, moderate, and severe) in terms of maternal age, rate of nulliparous cases, minimal platelet count during pregnancy, laboratory findings prior to delivery (platelet count, PCT, MPV, PDW, ALT, AST, BUN, and serum creatinine levels), Hb reduction at delivery, any blood product transfusion, and newborn platelet counts.

Diagnostic criteria

Gestational thrombocytopenia was considered to be a diagnosis by exclusion with symptoms initially diagnosed at gestation, no prior history of thrombocytopenia, and no related diseases according to examinations performed by obstetricians and hematologists. Gestational thrombocytopenia diagnosis was excluded in cases in which thrombocytopenia persisted for 6 weeks after delivery or between other pregnancies of patients. A diagnosis of ITP was made by the hematology department relying on the previous history of patients and peripheral blood smears according to international guidelines [31]. Antiplatelet antibodies were not used for the diagnosis of ITP due to low sensitivity and specificity [31]. Hypertensive disorders of pregnancy were also diagnosed according to international guidelines [32].

Statistical analysis

The acquired data was used for descriptive analysis. The data are presented as median (range) or frequencies. Further comparisons between groups were performed by Kruskal-Wallis test or χ^2 test according to variable characteristics. Statistical analyses were performed using SPSS v23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp.). Further pair-wise comparisons were performed between groups by Mann-Whitney U and Chi-Square test in case of significant difference between groups. A p-value < 0.05 was considered to be statistically significant.

This retrospective study was approved by Hacettepe University Ethics Committee (GO: 18/884)

Results

Descriptive statistics

We evaluated the pregnancy outcomes and laboratory findings of 385 patients diagnosed with gestational thrombocytopenia, ITP, or hypertensive disorders of pregnancy (▶ **Table 1**). Median values of minimal platelet counts during pregnancy and platelet counts prior to delivery were determined as 130 (7–149) and 131 (36–149), respectively. Median values of Hb before and after delivery were 12.2 (8.2–16) and 10.6 (2–15), respectively. Median gestational week at birth and birthweight were also determined as 38 (22–41) and 3180 (550–5050), respectively. The majority of patients were found to have been initially diagnosed during the 3rd trimester (77.2%). Gestational thrombocytopenia, ITP, and preeclampsia were the final diagnosis for 315 (81.8%), 35 (9.1%) and 35 (9.1%) cases, respectively. Any kind of blood product transfusion was performed in 38 (9.9%) cases. The most commonly used blood product was packed red blood cells which were used in 23 cases.

A total of 12 patients had undergone medical treatments during the antenatal period including methylprednisolone and/or IVIG at different doses. All of the patients that had undergone medical treatment were also found to have ITP. None of the patients required further medical treatment or a splenectomy during the pregnancy. Median platelet counts prior to treatment and one week after the treatment were determined as 38.5 (7–66) and 68 (37–150), respectively.

Four patients underwent a postpartum hysterectomy due to refractory hemorrhage. None of these 4 patients had been diagnosed with having severe thrombocytopenia prior to delivery. The route of delivery was vaginal in 1 case and cesarean in the remaining 3 cases; all cases required a transfusion. Etiological factors were determined as GT in 3 of the cases and as hypertensive disorders in the remaining case.

The platelet count of the newborn was acquired in 179 cases. The median platelet count was 212.5 (33–376). A total of 38 (21.2%) newborns were evaluated as thrombocytopenic.

Comparison of groups

Patients were compared according to etiology of thrombocytopenia, gestational week at diagnosis, and platelet counts prior to delivery. Analysis of etiological factors revealed that patients with hypertensive disorders were significantly older than patients of the other groups ($p < 0.001$). Distribution of etiological factors according to initial time of diagnosis revealed that ITP was diagnosed at 1st trimester significantly more common than other diseases, while the others were more commonly diagnosed at 3rd trimester compared to ITP ($p < 0.001$). It was also demonstrated that the minimal platelet count during the antenatal period and the platelet count prior to delivery were significantly lower in patients with ITP ($p < 0.001$; $p < 0.001$). PCT values were lower and MPV and PDW values were significantly higher which were compatible with platelet count in patients with ITP compared to other groups ($p < 0.001$; $p = 0.002$; $p = 0.006$; respectively). ITP was also found to be significantly associated with moderate and severe thrombocytopenia compared to other groups, while gestational thrombocytopenia and hypertensive disorders of pregnancy were significantly associated with mild thrombocytopenia ($p < 0.001$). Further analysis regarding serum ALT, AST, BUN, and creatinine levels revealed significantly higher values in patients with hyper-

▶ **Table 1** Characteristics, obstetric outcomes and thrombocytopenia related information about the cases.

	Median (Range)
Maternal age	31 (19–45)
Gravida	2 (1–14)
Parity	1 (0–4)
Abortus	0 (0–12)
Minimal platelet count during pregnancy	130 (7–149)
Laboratory findings prior to delivery	
▪ Platelet count (× 10^3/µl)	131 (36–149)
▪ PCT (%)	0.127 (0.006–0.219)
▪ MPV (femtoliters)	10 (7.1–14.8)
▪ PDW (%)	18.1 (8.1–20.4)
Hemoglobin levels (mg/dL)	
▪ Predelivery	12.2 (8.2–16)
▪ Postdelivery	10.6 (2–15)
Route of delivery*	
▪ Vaginal	37 (9.6%)
▪ Cesarean section	348 (90.4%)
Birthweight	3180 (550–5050)
Gestational week at delivery	38 (22–41)
Apgar scores	
▪ 1st minute	9 (0–10)
▪ 5th minute	10 (0–10)
Initial diagnosis of thrombocytopenia*	
▪ 1st trimester	33 (8.6%)
▪ 2nd trimester	55 (14.2%)
▪ 3rd trimester	297 (77.2%)
Diagnosis*	
▪ Gestational thrombocytopenia	315 (81.8%)
▪ Hypertensive disorders of pregnancy	35 (9.1%)
▪ ITP	35 (9.1%)
Transfusion*	38 (9.9%)
Amount of transfusion (units)	
▪ Erythrocyte suspension (n = 23)	4 (2–13)
▪ Thrombocyte suspension (n = 13)	11 (6–32)
▪ Thrombocyte apheresis (n = 9)	2 (1–5)
▪ Fresh frozen plasma (n = 18)	6 (3–35)
Postpartum hysterectomy*	4 (1%)
Newborn platelet count (n = 179)	212.5 (33–376)

* Rate of event has been given.

▶ **Table 2** Evaluation of laboratory findings, transfusion, hemoglobin level decrement in delivery and newborn platelet counts in terms of etiological factors.

	Gestational thrombocytopenia (GT) (n = 315)	ITP (n = 35)	Hypertensive disorders of pregnancy (HDP) (n = 35)	p value
Maternal age	30 (19–45)	29 (21–40)	34 (19–42)	**0.001**[a]
Nulliparous	120 (38%)	11 (31.4%)	17 (48.5%)	0.323
Initial diagnosis of thrombocytopenia				
▪ 1st trimester	5 (1.5%)	28 (80%)	0 (0%)	**< 0.001**[b]
▪ 2nd trimester	46 (14.6%)	1 (2.8%)	8 (22.8%)	
▪ 3rd trimester	264 (83.8%)	6 (17.1%)	27 (77.2.%)	
Minimal platelet count during pregnancy	133 (62–149)	56 (7–112)	113 (48–149)	**< 0.001**[c]
Laboratory findings prior to delivery				
▪ Platelet count (× 10^3/µl)	133 (62–149)	69 (36–120)	117 (51–149)	**< 0.001**[c]
▪ PCT (%)	0.13 (0.057–0.219)	0.073 (0.006–0.135)	0.118 (0.009–0.145)	**< 0.001**[c]
▪ MPV (femtoliters)	9.9 (7.1–14.8)	10.9 (7.3–14.1)	10.3 (7.2–13.7)	**0.002**[c]
▪ PDW (%)	18.2 (8.1–20.2)	17.8 (15.6–20.4)	17.9 (15.9–19.3)	**0.006**[d]
Severity of thrombocytopenia prior to delivery				
▪ Mild	296 (94%)	5 (14.2%)	27 (77.2%)	**< 0.001**[e]
▪ Moderate	19 (6%)	22 (62.8%)	8 (22.8%)	
▪ Severe	0	8 (22.8%)	0	
Other laboratory findings prior to delivery‡				
▪ ALT	12 (5–42)	15 (9–18)	24 (7–182)	**< 0.001** [a]
▪ AST	20.5 (9–72)	23 (21–32)	31 (12–325)	**< 0.001** [a]
▪ BUN	6.74 (3.2–14.4)	8.18 (4.82–14.4)	11.7 (5.15–21.3)	**< 0.001** [a]
▪ Creatinine	0.47 (0.24–0.99)	0.53 (0.44–0.82)	0.63 (0.34–1.89)	**< 0.001**[a]
Hb decrement during delivery (mg/dL)	1.6 (− 1.4–8.5)	1.5 (− 0.7–6.0)	1.3 (− 1.9–3.9)	0.985
Transfusion	16 (5.0%)	16 (45.7%)	6 (17.1%)	**< 0.001**[c]
Newborn platelet count (× 10^3/µl)[γ]	220 (58–354)	190 (41–345)	207 (33–376)	0.566
Newborn thrombcytopenia	21/119 (17.6%)	10/35 (28.5%)	7/25 (28%)	0.256

Pair-wise comparisons by Mann-Whitney U and χ^2 test resulted in a p value of < 0.05
[a] HDP compared to GT and ITP
[b] ITP compared to GT and HDP in first trimester and third trimester
[c] ITP compared to GT and HDP
[d] GT compared to ITP and HDP
[e] GT compared to ITP and HDP in mild thrombocytopenia and ITP compared to GT and HDP in moderate and severe thrombocytopenia
‡ Given for 112 cases and [γ] given for 179 cases where data was eligible

tensive disorders of pregnancy (p < 0.001). Despite the lack of statistical significance in the reduction of Hb levels at delivery between groups, any kind of transfusion was significantly more common in patients with ITP (p < 0.001) (▶ **Table 2**).

Patients were compared in terms of the timing of the initial diagnosis. Patients diagnosed during the 1st trimester had significantly lower minimal platelet counts during the antenatal period and prior to delivery (p < 0.001; p < 0.001). The transfusion rate was also significantly higher in patients diagnosed during the 1st trimester than the others, despite the lack of statistical significance between groups in terms of reduction of Hb levels (p < 0.001; p = 0.647).

Further analysis was performed to compare patients in terms of severity of the disease. The transfusion rate was found to be significantly higher in patients with severe thrombocytopenia compared to mild and moderate thrombocytopenia, despite the lack of significance in the reduction of Hb levels (p < 0.001; p = 0.647) (▶ **Table 3**).

Analysis regarding newborn platelet levels showed no statistical difference between any groups. None of the 38 thromboyto-

▶ **Table 3** Evaluation of laboratory findings, transfusion, hemoglobin level decrement in delivery and newborn platelet counts gestational trimester at diagnosis and platelet levels prior to pregnancy.

Gestational week at diagnosis	**1st trimester (n = 33)**	**2nd trimester (n = 55)**	**3rd trimester (n = 297)**	
Maternal age	28 (21–40)	31 (22–42)	31 (19–45)	0.100
Nulliparous	11 (33.3%)	22 (44.4%)	115 (38.7%)	0.806
Minimal platelet count during pregnancy	58 (7–125)	119 (35–149)	133 (43–149)	**< 0.001**[a]
Laboratory findings prior to delivery				
▪ Platelet count (× 10^3/µl)	72 (36–126)	123 (37–149)	133 (45–149)	**< 0.001**[a]
▪ PCT (%)	0.085 (0.034–0.155)	0.122 (0.009–0.175)	0.130 (0.006–0.219)	**< 0.001**[a]
▪ MPV (femtoliters)	11.2 (7.3–14.1)	10 (7.1–13.7)	9.9 (7.2–14.8)	**< 0.001**[a]
▪ PDW (%)	17.9 (10.2–20.4)	18.2 (16.3–19.4)	18.1 (8.1–20.2)	0.480
Hb decrement during delivery (mg/dL)	1.6 (− 0.7–4.6)	1.5 (− 1.9–4.6)	1.6 (− 1.0–6.0)	0.647
Transfusion	13 (39.3%)	5 (9.0%)	20 (6.7%)	**< 0.001**[a]
Newborn platelet count[γ]	192 (41–345)	210 (64–376)	219.5 (33–354)	0.907
Newborn thrombcytopenia	7/29 (24.1%)	7/26 (26.9%)	24/124 (19.3%)	0.634
Platelet levels prior to delivery	**Severe thrombocytopenia (n = 8)**	**Moderate thrombocytopenia (n = 49)**	**Mild thrombocytopenia (n = 328)**	
Maternal age	33 (24–40)	30 (19–39)	31 (19–45)	0.515
Nulliparous	1 (12.5%)	18 (36.7%)	129 (39.3%)	0.295
Hb decrement during delivery (mg/dL)	2.35 (0.3–6.0)	1.5 (− 1.0–4.6)	1.65 (− 1.9–5.6)	0.647
Transfusion	6 (75%)	14 (28.5%)	18 (5.4%)	**< 0.001**[b]
Newborn platelet count (× 10^3/µl)[γ]	181 (115–278)	181.5 (58–345)	221.5 (33–376)	0.907
Newborn thrombcytopenia	4/8 (50%)	10/39 (25.6%)	24/132 (18.1%)	0.076

[γ] Given for 179 patients where data is available

Pair-wise comparisons by Mann-Whitney U and χ^2 test resulted in a p value of < 0.05

[a] 1st trimester compared to 2nd trimester and 3rd trimester

[b] Severe thrombocytopenia compared to mild and moderate; moderate thrombocytopenia compared to mild thrombocytopenia

penic newborns required medical therapy to improve platelet counts or had any complications related to hemorrhage, including intracranial hemorrhages. Three out of 38 newborns died due to extreme prematurity, and 3 required transfusions due to increased hematocrit levels (partial Exchange transfusion), Rh incompatibility and fetal anemia. Analysis regarding etiological factors, time of initial diagnosis, and severity of thrombocytopenia did not show any statistical significance in terms of the rate of thrombocytopenia in newborns (p = 0.256; p = 0.634; p = 0.076; respectively). Despite the lack of statistical significance, the rate of thrombocytopenia in newborns was 50% in the patients with severe thrombocytopenia, while rates were 25.6 and 18.1% in patients with moderate and mild thrombocytopenia, respectively (p = 0.076).

Discussion

Thrombocytopenia in pregnancy is usually benign and is not related to obstetric and neonatal complications. The most important determinant of the outcome has been shown to be the etiologic factor. In this study, we compared the 3 most common etiological factors for thrombocytopenia in pregnancy; GT, ITP, and HDP. The rate of moderate thrombocytopenia in patients with GT was found to be 6%. Despite the fact that platelet counts < 70 × 10^3/µl are less likely to be due to GT, previous studies have also shown relatively high rates of GT diagnosis in patients with moderate and severe thrombocytopenia [33]. This study has also shown that all thrombocytopenia cases with a platelet count < 50 × 10^3/µl were found in patients with ITP. This is consistent with the accepted parameters for a differential diagnosis of GT and ITP. The timing of the initial diagnosis was found to be compatible with the etiological factors as most of the patients with ITP and GT were diagnosed during the 1st and 3rd trimester, respectively. The rate of diagnosis during the 1st trimester in GT patients was found to be 1.5%, while previous studies have shown rates as high as 23.1% [21].

The reduction of Hb levels according to etiological factors showed no statistical significance between groups. Four out of 385 (1%) underwent a hysterectomy due to postpartum hemorrhage with moderate and mild thrombocytopenia. Thrombocytopenia in pregnancy is not normally related to postpartum hemorrhage or increased rates of hysterectomy in comparison to normal women [34]. In this study, hysterectomies were performed in patients with a diagnosis other than ITP. This could be explained by the number of cases in each group and the relatively small sample size in the ITP group. However, the rate of blood product transfusions was significantly different between the groups in favor of an increased transfusion rate in the ITP group (p < 0.001). This

may also be explained by the platelet concentrate transfusion requirements of these patients and the ongoing low platelet counts, occurring even after delivery. In addition, the overall rate of administration of any kind of blood product was found to be 9.9% which is slightly lower than that reported in previous studies [35].

Analysis regarding the initial time of diagnosis revealed significantly lower platelet counts in patients diagnosed during the 1st trimester compared with those diagnosed during the 2nd and 3rd trimesters. This is consistent with the fact that most of the patients with ITP were diagnosed during the 1st trimester which was the group with the lowest platelet counts. Reduction of Hb levels was shown to be unrelated to the initial diagnosis time. However, as with the etiological factors, a statistically significant difference in Hb reduction was not observed between groups (0.985). Patients initially diagnosed during their 1st trimester were found to require more transfusions compared with those diagnosed during the 2nd and 3rd trimesters. This is most likely due to different onsets of the disease with the different etiological factors. Similarly, the transfusion requirements were significantly higher in patients with severe thrombocytopenia which consisted only of patients with ITP in this study. Conflicting results on the relationship between the severity of thrombocytopenia and adverse outcomes have been reported. Despite the findings of this study, it has been reported that the severity of GT is not associated with adverse outcomes [36]. Conversely, severe thrombocytopenia was found to be related to adverse outcomes in previous studies that were similar to the present study [37, 38].

Analysis regarding the rate of thrombocytopenia in newborns and the median values of newborn platelet counts showed no significant difference between groups regarding etiological factors, gestational week at diagnosis, and severity of the disease. Despite the lack of statistical significance, neonatal thrombocytopenia occurred in 50% of the cases with severe thrombocytopenia which consisted of patients with ITP. These findings are also consistent with previous studies showing that patients with ITP were the most likely to have a newborn with thrombocytopenia at a rate between 15 and 25%; however, women with ITP should not be discouraged from having babies [39, 40]. Furthermore, in our cohort none of the newborns with thrombocytopenia had a severe bleeding complication or intracranial hemorrhage. The low risk of complications related to newborns is also consistent with previous studies showing low rates of newborn complications [41]. The study has also concluded that predicting thrombocytopenia in newborns is challenging, as there is a lack of significant differences regarding analysis including etiological factors, time of initial diagnosis, and severity of the disease.

Limitations of this study include the retrospective study design and an imbalance between the case numbers of each group. Although we aimed to obtain a complete dataset for all the patients included in the study, some data were not available for certain parameters. However, prepregnancy and postpartum follow-ups of the patients were carefully evaluated to effectively define etiological factors. The evaluation of several factors, including neonatal factors, is a strength of this study.

In conclusion, thrombocytopenic pregnancies must be carefully evaluated in terms of the severity of thrombocytopenia, gestational period of the initial diagnosis, and etiological reasons. In particular, patients with ITP must be carefully evaluated since these pregnancies are more likely to require transfusions and have platelet counts $< 50 \times 10^3/\mu l$. The lack of any relationship between neonatal platelets and etiological factors must also be kept in mind and all neonates born to thrombocytopenic mothers must be carefully evaluated despite the fact that outcomes of neonatal thrombocytopenia are found to be favorable.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Costantine M. Physiologic and pharmacokinetic changes in pregnancy. Front Pharmacology 2014; 5: 65. doi:10.3389/fphar.2014.00065

[2] Pandey A, Singh R. Thrombocytopenia during pregnancy: an institutional based prospective study of one year. International Journal of Research in Medical Sciences 2017; 5: 3502–3505

[3] McCrae KR. Thrombocytopenia in pregnancy. ASH Education Program Book 2010; 2010: 397–402

[4] Reese JA, Peck JD, Deschamps DR et al. Platelet Counts during Pregnancy. N Engl J Med 2018; 379: 32–43. doi:10.1056/NEJMoa1802897

[5] Provan D, Stasi R, Newland AC et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010; 115: 168–186

[6] McCrae KR. Thrombocytopenia in pregnancy: differential diagnosis, pathogenesis, and management. Blood Rev 2003; 17: 7–14

[7] Bergmann F, Rath W. The Differential Diagnosis of Thrombocytopenia in Pregnancy. Dtsch Arztebl Int 2015; 112: 795–802. doi:10.3238/arztebl.2015.0795

[8] Levy JA, Murphy LD. Thrombocytopenia in pregnancy. J Am Board Fam Pract 2002; 15: 290–297

[9] Aster RH. Gestational thrombocytopenia: a plea for conservative management. N Engl J Med 1990; 323: 264–266

[10] Verdy E, Bessous V, Dreyfus M et al. Longitudinal analysis of platelet count and volume in normal pregnancy. Thromb Haemost 1997; 77: 806–807

[11] Parnas M, Sheiner E, Shoham-Vardi I et al. Moderate to severe thrombocytopenia during pregnancy. Eur J Obstet Gynecol Reprod Biol 2006; 128: 163–168. doi:10.1016/j.ejogrb.2005.12.031

[12] Burrows RF, Kelton JG. Thrombocytopenia at delivery: a prospective survey of 6715 deliveries. Am J Obstet Gynecol 1990; 162: 731–734

[13] George JN, Woolf SH, Raskob GE et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996; 88: 3–40

[14] Reese JA, Peck JD, McIntosh JJ et al. Platelet counts in women with normal pregnancies: A systematic review. Am J Hematol 2017; 92: 1224–1232. doi:10.1002/ajh.24829

[15] McCrae KR. Thrombocytopenia in pregnancy. Hematology Am Soc Hematol Educ Program 2010; 2010: 397–402. doi:10.1182/asheducation-2010.1.397

[16] Gill KK, Kelton JG. Management of idiopathic thrombocytopenic Purpura in Pregnancy. Seminars in Hematology 2000; 37: 275–289

[17] Terrell DR, Beebe LA, Vesely SK et al. The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports. Am J Hematol 2010; 85: 174–180. doi:10.1002/ajh.21616

[18] Zufferey A, Kapur R, Semple JW. Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP). J Clin Med 2017; 6: 16

[19] Stavrou E, McCrae KR. Immune thrombocytopenia in pregnancy. Hematol Oncol Clin North Am 2009; 23: 1299–1316

[20] Practice Bulletin No. 166: Thrombocytopenia in Pregnancy. Obstet Gynecol 2016; 128: e43–e53. doi:10.1097/aog.0000000000001641

[21] Kasai J, Aoki S, Kamiya N et al. Clinical features of gestational thrombocytopenia difficult to differentiate from immune thrombocytopenia diagnosed during pregnancy. J Obstet Gynaecol Res 2015; 41: 44–49. doi:10.1111/jog.12496

[22] Sun D, Shehata N, Ye XY et al. Corticosteroids compared with intravenous immunoglobulin for the treatment of immune thrombocytopenia in pregnancy. Blood 2016; 128: 1329–1335. doi:10.1182/blood-2016-04-710285

[23] Xu X, Liang MY, Dou S et al. Evaluation of glucocorticoid compared with immunoglobulin therapy of severe immune thrombocytopenia during pregnancy: Response rate and complication. Am J Reprod Immunol 2018; 80: e13000. doi:10.1111/aji.13000

[24] Sun D, Shehata N, Ye XY et al. Corticosteroids compared with intravenous immunoglobulin for the treatment of immune thrombocytopenia in pregnancy. Blood 2016; 128: 1329–1335

[25] Schlembach D, Helmer H, Henrich W et al. Peripartum Haemorrhage, Diagnosis and Therapy. Guideline of the DGGG, OEGGG and SGGG (S2 k Level, AWMF Registry No. 015/063, March 2016). Geburtsh Frauenheilk 2018; 78: 382–399

[26] Sainio S, Kekomaki R, Riikonen S et al. Maternal thrombocytopenia at term: a population-based study. Acta Obstet Gynecol Scand 2000; 79: 744–749

[27] Sircar M, Thadhani R, Karumanchi SA. Pathogenesis of preeclampsia. Curr Opin Nephrol Hypertens 2015; 24: 131–138

[28] Abildgaard U, Heimdal K. Pathogenesis of the syndrome of hemolysis, elevated liver enzymes, and low platelet count (HELLP): a review. Eur J Obstet Gynecol Reprod Biol 2013; 166: 117–123. doi:10.1016/j.ejogrb.2012.09.026

[29] ACOG. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013; 122: 1122–1131. doi:10.1097/01.aog.0000437382.03963.88

[30] Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol 2003; 102: 181–192

[31] Neunert C, Lim W, Crowther M et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011; 117: 4190–4207. doi:10.1182/blood-2010-08-302984

[32] Gillon TE, Pels A, von Dadelszen P et al. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. PloS One 2014; 9: e113715

[33] Kim BJ, Kim HS, Kim JH et al. Moderate to Severe Thrombocytopenia During Pregnancy: A Single Institutional Experience. Indian J Hematol Blood Transfus 2017; 33: 581–585. doi:10.1007/s12288-017-0784-1

[34] Lin YH, Lo LM, Hsieh CC et al. Perinatal outcome in normal pregnant women with incidental thrombocytopenia at delivery. Taiwan J Obstet Gynecol 2013; 52: 347–350. doi:10.1016/j.tjog.2013.01.025

[35] Parnas M, Sheiner E, Shoham-Vardi I et al. Moderate to severe thrombocytopenia during pregnancy. Eur J Obstet Gynecol Reprod Biol 2006; 128: 163–168. doi:10.1016/j.ejogrb.2005.12.031

[36] Elveđi-Gašparović V, Beljan P, Gverić-Ahmetašević S et al. Fetal-maternal complications and their association with gestational thrombocytopenia. Ginekol Pol 2016; 87: 454–459

[37] Li J, Pan Z, Liu H et al. Retrospective analysis of the risk of hemorrhage associated with moderate and severe thrombocytopenia of 173 patients with systemic lupus erythematosus. Medicine 2018; 97: e11356. doi:10.1097/md.0000000000011356

[38] Mun S, Horasan Çelimli F et al. Pregnancies with Platelet Count Lower Than 70000 Platelets/µl. Gynecol Obstet Reprod Med 2006; 12: 92–95

[39] Loustau V, Debouverie O, Canoui-Poitrine F et al. Effect of pregnancy on the course of immune thrombocytopenia: a retrospective study of 118 pregnancies in 82 women. Br J Haematol 2014; 166: 929–935. doi:10.1111/bjh.12976

[40] Webert KE, Mittal R, Sigouin C et al. A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura. Blood 2003; 102: 4306–4311. doi:10.1182/blood-2002-10-3317

[41] Fujimura K, Harada Y, Fujimoto T et al. Nationwide study of idiopathic thrombocytopenic purpura in pregnant women and the clinical influence on neonates. Int J Hematol 2002; 75: 426–433