



Prevalence of Thrombocytopenia and Platelet Dysfunction in Women Delivering at a Tertiary Care Hospital and Prevalence of Platelet Abnormalities in their Neonates with Perinatal Outcomes: A Retrospective Study

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Abstract

Objective: To study the etiology and severity of platelet disorders, clinical manifestations, mode of delivery and neonatal outcome in pregnant women with thrombocytopenia and platelet dysfunction delivering in a tertiary care center in the Middle east. **Methods:** A retrospective cohort study was done on pregnant women admitted to Sultan Qaboos University Hospital (SQUH) from January 2011 to December 2020 with platelet abnormalities as per the registry were included. Thrombocytopenia associated with drugs, viral infection, pre-eclampsia, and HELLP syndrome were excluded. **Results:** Total number of deliveries were 39,522 during the study period. Of these 220 patients had thrombocytopenia and platelet abnormalities according to our inclusion criteria. The incidence of platelet abnormalities was 0.56% The mean gestational age at delivery was age 37.53 weeks. The mean platelet count was 90.41 cells/dl. The highest two etiologies in this study were gestational thrombocytopenia (GT) (24.6%) and immune thrombocytopenic purpura (ITP) (22.6%). Out of 220, 9.5% were treated with prednisolone. There was a significant correlation between maternal platelet counts and medical treatment was received. No significant correlation between maternal platelet counts and mode of delivery was obtained. Nine neonates had platelet abnormalities, of which 44.4% were born to mothers with immune thrombocytopenic purpura (ITP). Mild to moderate neonatal thrombocytopenia was present in 66.6% of the neonates. 33.3% of the thrombocytopenic neonates had experienced hemorrhagic manifestations with good clinical outcome. **Conclusion:** The incidence of platelet abnormalities was 0.56% according to our study. ITP was more associated with severe thrombocytopenia and premature delivery.

Keywords: Gestational Thrombocytopenia, Immune Thrombocytopenic Purpura, Platelet abnormalities, prednisolone, vaginal delivery, Caesarean Section.

Introduction

The platelets are found in the blood with a normal count range from 150,000 to 400,000 cells/ μ l, and spleen¹. Thrombocytes' function is to limit or stop the bleeding when there is damage to blood vessels in a process called hemostasis in which the thrombocytes are activated by the damaged tissues to form a localized clot that plugs the injury, and it is the first step in the wound healing process^[1].

Platelet disorders include thrombocythemia, thrombocytosis, thrombocytopenia, and platelet dysfunction¹. Thrombocythemia and thrombocytosis are characterized by high platelet count (primary and secondary causes respectively) while thrombocytopenia is characterized by low platelet count^[1]. An abnormal function of the platelet is called platelet dysfunction.

Thrombocytopenia is commonly found in neonates admitted to the neonatal intensive care unit (NICU) with a prevalence of 22-35% as many studies have reported, depending on the population studied^[2]. However, the incidence of thrombocytopenia in the

overall neonates are less than 1-5%^[2]. Neonatal thrombocytopenia could be congenital or acquired, due to low platelet production, high platelet destruction, or a combination of these two mechanisms^[3]. Mild to moderate neonatal thrombocytopenia usually returns to normal without any intervention after the first seven days of life^[4]. Though, severe neonatal thrombocytopenia must be treated appropriately due to the high risk of developing intracranial, intraventricular, and pulmonary hemorrhages^[4,5]. The treatments involved are the transfusion of platelets and intravenous immunoglobulins (IV Ig)^[2].

Thrombocytopenia in neonates can be due to low maternal platelet count, prematurity, and low fetal weight, and/or the presence of neonatal thrombocytopenia history in previous pregnancies^[6,4]. Platelets' dysfunction in neonates also could be congenital or acquired, however, congenital dysfunction is rare, and acquired is more common^[3]. Acquired platelet dysfunction is related to the medications given to the neonate, or to the mother during the

gestational period, however, many cases of platelets' dysfunction are unexplained [3].

This study was done to find the incidence, etiology severity and treatment of thrombocytopenia and platelet dysfunction among mothers delivering in SQUH from 2011 and 2020. The severity of platelet disorders in these neonates, their clinical features, and the treatments received were also studied. Although the etiology of thrombocytopenia and platelet disorders was looked into, maternal outcome like postpartum hemorrhage, need for platelet transfusion and blood transfusion was not studied.

Aim of the study

This study aims to identify the prevalence of thrombocytopenia among pregnant women delivering at SQUH and their neonatal outcomes.

Specific Objectives

1. To look at the etiology of thrombocytopenia and platelet dysfunction in pregnant women delivering in SQUH from 2011 to 2020 as per the inclusion criteria
2. To find the association of platelet abnormalities in the pregnant women and its effects on the neonates.
3. To analyze the severity of thrombocytopenia in the neonates, their clinical features, and the treatments given to the neonates with low platelets.

Materials and Methods

Study design & study population

This is a retrospective study over a period of 10 years from January 2011 to December 2020, which assess the prevalence of thrombocytopenia in mothers and neonates of mothers with platelet abnormalities and their perinatal outcomes delivered at SQUH. The inclusion criteria include all neonates of women with platelet abnormalities (a low platelet count or abnormal platelet function) delivered at SQUH. The exclusion criteria include neonates of women with a low platelet count due to pre-eclampsia, HELLP syndrome, viral infection, or drug induced.

Data collection

The data were collected using the Hospital Information System (HIS) (TrakCare) and maternity registers. Collected data are divided into mothers' data and their neonates' data. Mothers' data included parity, gestational age, platelet count, etiology of the platelet abnormality, and the severity of the abnormality. Neonates' data included any bleeding manifestation, platelet count, birth weight, gender, APGAR score, and the treatment received.

Data analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 27 to calculate the prevalence and appropriate percentages. Chi-square was used to measure the significance of association between the variables, and the P-value of less than 0.05 was considered significant. Frequency tables, pie and bar charts, and box plot also were used to describe the variables.

Ethical consideration

The ethical approval was obtained from the Medical Research Ethics Committee (MREC), College of Medicine and Health Sciences (COMHS), Sultan Qaboos University (SQU) (MREC#2529 and 2316).

Definition of terms

Thrombocytopenia was defined as platelet count of less than $150 \times 10^9/L$, divided according to severity into mild (from $100 \times 10^9/L$ to $149 \times 10^9/L$), moderate (from 50×10^9 to 99×10^9), and severe (less than 50×10^9).

According to the gestational age the neonates were divided into pre-term/premature (a gestational age of less than 37 weeks), full-term (a gestational age from 37 weeks to 42 weeks), and post-term (a gestational age of more than 42 weeks).

Low birth weight was defined as birth weight of less than 2.5 kilograms (Kg), normal birth weight is a birth weight ranges from 2.5 Kg to 4.0 Kg, while high birth weight (macrosomia) was defined as birth weight of more than 4.0 Kg.

According to the APGAR score in 5 minutes the neonates were classified into normal neonates (a score from 9 to 10), neonates needing resuscitation (a score from 7 to 8), and neonates with asphyxia (a score of less than 7).

Results

There were 39 522 deliveries in SQUH between 2011 and 2020. In our retrospective study, we identified 220 pregnant women with platelet abnormalities.

In the studied population, the mean age was found to be 30.55, with a range of (17-44) and average gestational age (GA) of 37.53 weeks (28-41). The incidence of platelet abnormalities was 220 (0.56%) among the total number of deliveries. The mean platelet count was 90.41 cells/dL (1 cells/dL-253 cells/dL). Most women had moderate thrombocytopenia, 40.7% (90). 37.7% (83) had mild thrombocytopenia, and 17.3% (38) had severe thrombocytopenia. Of the 220 women 19% were nulliparous and the rest were parous. Most of them delivered at term (80%).

The highest three etiologies were Gestational Thrombocytopenia with 24.6% (62), Immune Thrombocytopenic Purpura 22.6% (57), Systemic Lupus Erythematosus with 19.4%. The other etiologies are shown in figure 1.

The mean platelet count was 92.84 cells/dL in GT and 53.49 cells/dL in ITP. In addition, the mean gestational age was 38.15 weeks in GT and 36 weeks in ITP.

A total of 21 (9.5%) patients required treatment with corticosteroids during the study period. Our results show a significant association between the severity of thrombocytopenia and the requirement of prednisolone tablets [P value = 0.003398]. As figure 2 illustrates, there was an inverse relationship between platelet count and the dose prednisolone.

Most women had spontaneous vaginal delivery (75.0%), while (15.9%) had an emergency lower Segment Cesarean Section, and 5.5% had elective lower segment cesarean Section. vacuum delivery was in 1.4% and forceps delivery in 2.3%.

However, there was no significant correlation between maternal platelet counts (cells/dL) and mode of delivery (p-value = 0.056556).

Association between maternal thrombocytopenia and different perinatal outcomes

In this study there were 219 live neonates and 1 intrauterine fetal death, 220 product of conceptus of 217 pregnancies in total.

Table 1 shows that 210 (95.9%) live neonates were having normal platelet count, only 9 (4.1%) were thrombocytopenic. Out of the thrombocytopenic neonates, 7 (77.8%) were males, and 2 (22.2%) were females. It shows also that 175 (79.9%) live neonates were full term, and 44 (20.1%) were preterm in which males (23) and females (21) were representing 52.3% and 47.7% respectively. 35 (16.0%) live neonates were having low birth weight, divided into 14 (40.0%) males and 21 (60.0%) females as shown in table 1.

The study showed a statically significant association between severe thrombocytopenia in mothers and the following: thrombocytopenia in neonates, prematurity, the presence of bleeding manifestations and neonates receiving treatment with P-values of 0.009, <0.001, 0.009 and 0.001 respectively. While severe maternal thrombocytopenia was insignificantly associated with low birth weight in neonates (P-value = 0.095). Among the 220 neonates whose mothers had platelet abnormalities in pregnancy, 38 mothers

had severe thrombocytopenia (<50,000), and 182 mothers had mild or moderate platelet abnormalities.

Although table 2 shows that there was no significant association between severe maternal thrombocytopenia and low birth weight in neonates, mothers with severe thrombocytopenia had relatively smaller babies with a median birth weight of 2.84 Kg although not less than 2.5 Kg. The mean birthweight of the neonate was 2980 grams in women with normal platelets, 2950grams in women with platelets range 100-149 x10⁹/L, 3030grams in women with a platelet count of 50-99x10⁹/L and 2840 grams in the group with platelets less than 50x 10⁹ /L.

The largest percentage (44.4%) of the thrombocytopenic neonates were born to mothers with immune thrombocytopenic purpura (ITP), 33.3% were born to mothers with gestational thrombocytopenia (GT), and 22.2% were born to mothers with systemic lupus erythematosus (SLE).

Clinical features, the severity of thrombocytopenia in neonates, and the treatment received

Table 3 shows that only three neonates were severely thrombocytopenic, all of them born to mothers with ITP. five thrombocytopenic neonates had received treatment for thrombocytopenia, four of them were born to mothers with ITP. The thrombocytopenic neonates born to mothers with ITP were the only neonates received treatment with IV Ig and/or platelet transfusion. In addition, all mothers with ITP were severely thrombocytopenic.

The majority (96.3%) of the neonates were having a normal APGAR score in 5 minutes. 2.7% were having APGAR score indicates a need for resuscitation, and only 0.9% were having APGAR score indicates asphyxia in neonate.

The largest percentage (44.4%) of the thrombocytopenic neonates were mildly thrombocytopenic, one third (33.3%) were severely thrombocytopenic, and 22.2% were having moderate thrombocytopenia.

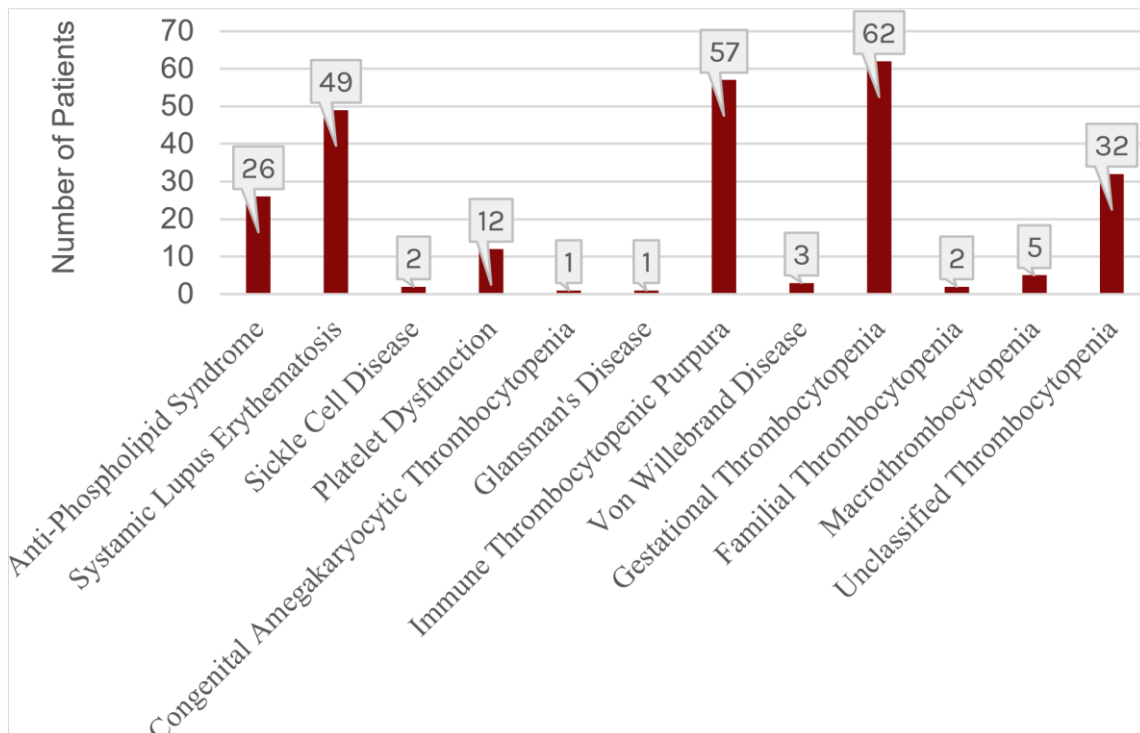


Figure 1: Etiology of Platelets Abnormalities in Patients

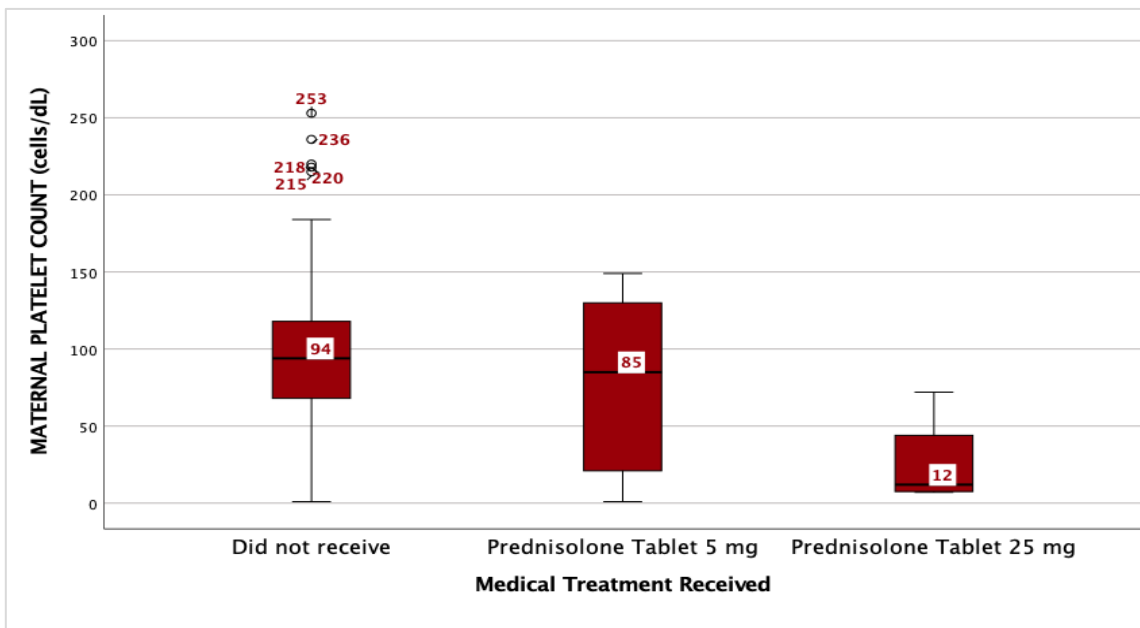


Figure 2: Association between platelet count and steroid dose requirement

Table 1: Distribution of the live neonates according to their sex differences and different perinatal outcomes.

Groups		Neonatal platelet count status			Total
		Normal		Thrombocytopenic	
Neonates' sex n (%)	Male	96 (45.7%)		7 (77.8%)	103 (47.0%)
	Female	114 (54.3%)		2 (22.2%)	116 (53.0%)
Total n (%)		210 (95.9%)		9 (4.1%)	219 (100%)
		Gestational age			Total
		Preterm		Full term	
Neonates' sex n (%)	Male	23 (52.3%)		80 (45.7%)	103 (47.0%)
	Female	21 (47.7%)		95 (54.3%)	116 (53.0%)
Total n (%)		44 (20.1%)		175 (79.9%)	219 (100%)
		Neonate's birth weight			Total
		Low	Normal	High	
Neonate's sex n (%)	Male	14 (40.0%)	88 (48.6%)	1 (33.3%)	103 (47.0%)
	Female	21 (60.0%)	93 (51.4%)	2 (66.7%)	116 (53.0%)
Total n (%)		35 (16.0%)	181 (82.6%)	3 (1.4%)	219 (100%)

n = Number of cases

Table 2: Association between severe maternal thrombocytopenia and different perinatal outcomes.

Variables	Maternal platelet count		P-Value
	$\geq 50 \times 10^9/L$	$< 50 \times 10^9/L$	
Thrombocytopenic neonate n (%)	4 (2.2%)	5 (13.2%)	0.009
Premature neonate n (%)	28 (15.4%)	16 (42.1%)	<0.001
Neonate with low-birth-weight n (%)	25 (13.8%)	10 (26.3%)	0.095
Presence of bleeding manifestation n (%)	2 (1.1%)	4 (10.5%)	0.009
Neonate had received treatment n (%)	1 (0.5%)	5 (13.2%)	0.001

n = Number of cases

Table 3: Clinical profiles of neonates with thrombocytopenia.

n	Sex	GP (weeks)	BW (Kg)	Maternal plt count (*10 ⁹ /L)	etiology of plt abnormality	Neonatal plt count (*10 ⁹ /L)	APGAR 1 min	APGAR 5 min	Bleeding manifestation	Neonatal treatment	IV Ig	Plt transfusion
1	M	38	2.965	13	ITP	47	9	10	Yes	Yes	+	-
2	M	38	2.985	16	ITP	23	9	10	Yes	Yes	+	+
3	M	36	3.14	3	ITP	82	9	10	Yes	Yes	+	-
4	M	35	1.875	1	ITP	25	5	9	No	Yes	+	+
5	M	35	1.755	98	SLE	131	5	8	No	Yes	-	-
6	M	39	2.695	80	GT	83	7	10	No	No	-	-
7	M	38	2.885	147	SLE	127	9	10	No	No	-	-
8	F	38	2.835	141	GT	141	9	10	No	No	-	-
9	F	37	3.75	40	GT	139	9	10	No	No	-	-

BW: Birth Weight, F: Female, GP: Gestational Period, M: Male, n: case number, Plt: Platelet.

Discussion

Maternal outcome

The mean age of the women with thrombocytopenia and platelet disorder was 30.55 years in the studied population, with (17-44) and the average gestational age was 37.53 weeks [7,8]. The average GA was 37.53 weeks (28-41) but other studies reported lower GA, 36.5 weeks and 36.2 weeks [9,10].

In our study, the incidence of platelet abnormalities was 0.56%. However, our findings are still significantly lower than most other studies. The lowest reported incidences were 1.90% [11,12]. All mentioned incidences were studies conducted in Asian countries. While the other studies reported a higher incidence of 8.4% in Chauhan study [13], 8.2% in Misra [14], 7.60% in Burrows et al [15,16], 8.80% in Nisha's study [17], the highest incidences were reported by Ajibola et al (13.50%), [18] These differences could be because of varying inclusion and exclusion criteria.

This study reported gestational thrombocytopenia as the highest platelet abnormalities (24.6%). GT. It was found to be the

most common aetiology in all other cases. However, our findings were lower than other studies, as Nisha et al [17] reported 64.21% While 22.6% of our study group had ITP, Tasneem et al [19] had only 1 case of ITP.

Treatment with prednisolone is considered the first line of treatment in many studies. Both Yassae et al and Karanth et al recorded that prednisolone was the most used corticosteroid in their studies, 61.5% and 75.4%, respectively [20,10]. Women in pregnancies treated for thrombocytopenia had significantly lower platelet counts at delivery than those who did not require treatment.

There was no significant difference in platelet counts between the modes of delivery (p = 0.057) in our study. We found that the median platelet count is 87 for pregnant women delivered via a caesarean section (CS) and 95cells/dL for pregnant women who delivered vaginally. A study conducted in India reported no significant difference in platelet counts between the modes of delivery (p = 0.58). The median was 92 cells/dL for those delivered via a caesarean section and vaginally [21].

Neonatal outcome

The present study also aimed at identifying the prevalence of thrombocytopenia in neonates of mothers with platelet abnormalities and their perinatal outcomes. Out of 1848 thrombocytopenic neonates born during the period from January 2011 to December 2020 only 9 neonates were born to mothers with platelet abnormalities. The most thrombocytopenic neonates were born to mothers with ITP (44.4%), while others were born to mothers with GT or SLE (33.3% and 22.2% respectively). A retrospective study reported seven thrombocytopenic neonates born to mothers with moderate to severe thrombocytopenia, four born to mothers with preeclampsia and hemolysis, elevated-liver-enzymes, low-platelet (HELLP) syndrome, two to mothers with ITP, and one to a mother with familial thrombotic thrombocytopenic purpura (TTP) [22]. Thus, ITP in pregnant women is always constituting a significant percentage in the cases of thrombocytopenia in neonates, as neonatal thrombocytopenia is a major problem associated with maternal ITP [23]. In addition, other studies reported that the incidences of thrombocytopenia in neonates born to women with ITP are about 50% to 67% [4].

The major finding of our study was that severe thrombocytopenia in mothers is significantly associated with a low platelet count in their neonates (P-value = 0.009). Although our study was not aimed at the relationship between the maternal characteristics (such as age, parity, history of complicated pregnancy or abortion, etc) and the perinatal outcomes in neonates, a prospective study conducted in Saudi Arabia showed no statistically significant differences between the maternal characteristics and the baseline platelet count of their thrombocytopenic neonates [4].

A retrospective study reported a statistically significant association between moderate to severe thrombocytopenia in mothers and preterm babies (< 37 weeks) (P-value < 0.001), and a higher rate of preterm deliveries among mothers with moderate to severe thrombocytopenia as their study included preeclampsia and HELLP syndrome which require early delivery of fetus for management [22]. In our study, although preeclampsia and HELLP syndrome were excluded, a statistically significant association between severe maternal thrombocytopenia and prematurity in neonates was still found (P-value < 0.001).

Although preeclampsia and HELLP syndrome are associated with intrauterine growth restriction (IUGR) [22], a retrospective study reported a statistically insignificant association between moderate to severe thrombocytopenia in mothers and low birth weight (< 2.5 Kg) in neonates (P-value = 0.382) [22]. Correspondingly, our study found no significant association between severe maternal thrombocytopenia and low birth weight in neonates (P-value = 0.095). However, mothers with severe thrombocytopenia had relatively small babies with a median birth weight of 2.84 Kg although not less than 2.5 Kg.

As the neonatal thrombocytopenia incidences are inversely proportional to gestational age and birth weight [24], a Turkish retrospective study reported that IUGR is the most common cause of early-onset thrombocytopenia in neonates [6]. In addition, the low fetal weight is considered as a risk factor for thrombocytopenia in neonates [4]. However, our study showed a statistically insignificant association between low birth weight and low platelet counts in neonates. The Turkish study also showed a statistically significant association between prematurity and thrombocytopenia in neonates (P-value < 0.001) [6]. While, in our study there was an insignificant association between preterm babies and neonatal thrombocytopenia (P-value = 0.389), and this could be explained due to the exclusion of preeclampsia and HELLP syndrome which are known to cause preterm deliveries, low birth weight and thrombocytopenia especially in preterm low-birth-weight babies [25].

This present study corresponds to previous studies in that neonatal thrombocytopenia is higher in males than females (7:2 respectively), although there was no statistically significant

association between male gender and thrombocytopenia in neonates (P-value = 0.087). Male gender is known to be a risk factor for neonatal thrombocytopenia [26,6].

In our study, the majority (96.3%) of neonates born to mothers with platelet abnormalities were having a normal APGAR score at 5 minutes (>8), while in other study, moderate to severe maternal thrombocytopenia is significantly associated to low APGAR score at 5 minutes (<7) (P-value < 0.001) which indicates asphyxia in neonates [22]. The difference in the findings could be explained by preeclampsia and HELLP syndrome which are primary diseases that increase the perinatal complications in neonates such as prematurity, low APGAR scores and IUGR [22].

The risk of bleeding manifestations appears to be higher in neonates with neonatal alloimmune thrombocytopenia (NAIT) or sepsis, especially those who were very preterm [27]. Adverse bleeding manifestations include intracranial hemorrhage, pulmonary hemorrhage, intraventricular hemorrhage, and gastrointestinal hemorrhage [28,6]. Severe maternal thrombocytopenia was significantly associated with the presence of bleeding manifestation in neonates. Another study stated that intraventricular bleeding is more often in thrombocytopenic neonates, however, this relationship is independent of the severity of neonatal thrombocytopenia [29]. In our study, the bleeding manifestations were either oozing, petechia, bruise, or subconjunctival hemorrhage.

Neonatal thrombocytopenia is usually mild to moderate (66.6%). In contrast, other studies also have reported that the most neonatal thrombocytopenia incidents were mild to moderate, however, the severe cases were representing 2.5%-26% [24,30,31,6]. While, in our study the prevalence of severe neonatal thrombocytopenia was 33.3%. Another study showed that the thrombocytopenic neonates born to mothers with ITP were 60% severely thrombocytopenic, which is relatively high percentage [23].

In our study 6 neonates had received treatment, 5 were thrombocytopenic and one was not. Types of treatment received include IV Ig, platelet transfusion with IV Ig, a whole blood transfusion, and romiplostim. While romiplostim was given to a non-thrombocytopenic neonate who had no bleeding manifestations, however, she was preterm with low birth weight, and born to severely thrombocytopenic mother having SLE and ITP. Therefore, the type of treatment received was according to the severity of neonatal thrombocytopenia and the presence or absence of bleeding manifestations. Such finding is in good agreement with other similar studies [23,4]. As one retrospective study reported 10 thrombocytopenic neonates born to mothers with ITP had received treatment, all of them received IV Ig, and only one received platelet transfusion [23], this finding is in good agreement with our study which showed that all thrombocytopenic neonates born to mothers with ITP had received IV Ig and only 2 had received platelet transfusion. The need for platelet transfusion is associated with increased [28,30,31,32]. In addition, 5 neonates who had received treatment for thrombocytopenia were born to severely thrombocytopenic mothers, thus this study showed a statistically significant association between severe maternal thrombocytopenia and neonates having treatment for thrombocytopenia (P-value = 0.001).

Conclusion

The incidence of platelet abnormalities was 0.56% among the total number of deliveries in SQUH from 2011 - to 2020. The mean platelet count was 90.41 cells/dL (mild: 37.7%, moderate: 40.7% and Severe: 17.3%). The highest two etiologies in this study were Gestational Thrombocytopenia (24.6%,62) and Immune Thrombocytopenic Purpura (22.6%, 57). There was a significant correlation between maternal platelet counts and whether medical treatment was received (P-value < 0.05). There was no significant correlation between maternal platelet counts and mode of delivery (P-value > 0.05).

In conclusion, only 9 neonates were born with thrombocytopenia, which was usually mild to moderate. Most of them were born to mothers with ITP. Severe maternal thrombocytopenia was considered as risk factor for low platelet count, prematurity, and the presence of bleeding manifestations in neonates. The most thrombocytopenic neonates were males.

Ethics approval and consent to participate

Approval was obtained from the Medical and Research Ethics Committee at the College of Medicine and Health Sciences (MERC #2316).

Data Availability

Raw Data is available on request

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.”

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Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section.

MG- conceptualized the research and guided the students on data collection, analysis and writing up

MSA- collected the data and did statistical analysis and drafted the manuscript

LSH- collected data and did part of the analysis on maternal outcome and also drafted the manuscript

VG- revised the manuscript and edited the tables and bibliography

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