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Thrombocytopenia in pregnancy; prevalence, causes and fetomaternal outcome

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Summary

Background: Thrombocytopenia is seen in up to 12% of pregnancies. Most cases are due to benign gestational thrombocytopenia and have no adverse effects. It can, however, be due to underlying serious causes and can lead to adverse maternal and perinatal consequences. *Objective:* To discover the prevalence and causes of thrombocytopenia and the impact of its severity on feto-maternal outcome. *Materials and Methods:* This is a retrospective comparative study. Thrombocytopenia was defined as platelet count less than 150 x10^9/L detected any time after 24 weeks gestation and averaged during prenatal visits. All thrombocytopenic pregnant patients who completed 24 weeks of gestation were included. Cases were then divided into mild (group 1, platelet count between 70 and 150×10^9/L) and moderate to severe (group 2, platelet count less than 70×10^9/L) thrombocytopenia. *Results:* The prevalence of thrombocytopenia in pregnant women was 7.20%. Benign gestational thrombocytopenia (BGT) accounted for 78.53%, with idiopathic (immune) thrombocytopenic purpura (ITP) accounting for 1.93%, pre-eclamptic toxaemia (PET)/HELLP syndrome accounting for 7.41%, drugs 7.23%, systemic lupus erythematosus (SLE) with or without antiphospholipid antibodies (APA) 0.84%, and various maternal diseases 4.04%. Compared with mild thrombocytopenic pregnant women (group 1), moderate to severe thrombocytopenic women (group 2) were at a significantly greater risk of caesarean section, antepartum hemorrhage (APH), postpartum hemorrhage (PPH), wound haematoma, intrauterine fetal death (IUFD), preterm delivery, and intrauterine growth restriction (IUGR). *Conclusion:* Thrombocytopenia is prevalent in this obstetric population with various obstetric and nonobstetric causes. The consequences of thrombocytopenia in pregnancy are mostly benign, but moderate to severe thrombocytopenia was associated with adverse obstetric and perinatal outcomes. This was due to the nature and severity of the underling maternal diseases and their medication. The authors recommend studying prospectively each of these thrombocytopenia-induced diseases in pregnancy.

Key words: Maternal; Perinatal outcome; Pregnancy; Thrombocytopenia; Postpartum; Antepartum; Hemorrhage.

Introduction

Thrombocytopenia is seen in up to 12% of all pregnancies [1]. Up to 75% of cases are due to a benign gestational thrombocytopenia (BGT), 20% are due to hypertensive disorders, 3-4% are accounted for by an immune process, and 1-2% are caused by rare entities [2]. While most cases are mild and have no adverse consequences, thrombocytopenia can also be part of a complex disease with profound and even life-threatening consequences for both mother and baby with major impact on personal and social levels. In some cases, the etiology is unique to pregnancy and the puerperium. Cases thought to be due to immune thrombocytopenic purpura or microangiopathic processes should be managed in a specialist centre [3]. It was found that the mean platelet counts were significantly higher in healthy nonpregnant women than in pregnant women and the authors also found that in healthy pregnant women, a platelet count over 115×10^9/L late in pregnancy does not require further investigation during pregnancy and may be considered a safe threshold [4, 5].

In a surveillance study by Susanna S *et al.* [6], there was no association between maternal and fetal platelet counts: of the infants born to thrombocytopenic mothers, 2.1% had thrombocytopenia in the cord blood, which did not differ significantly from the 2.0% of thrombocytopenic infants born to non-thrombocytopenic mothers. The authors concluded that women with gestational thrombocytopenia do not require alteration of their treatment and fetal blood sampling is not considered necessary when thrombocytopenia is discovered unexpectedly at term [6]. Moderate to severe maternal thrombocytopenia indicates severe primary disease and is associated with perinatal complications including preterm delivery, placental abruption, higher rates of low Apgar scores, intrauterine growth restriction (IUGR), and stillbirths [7]. The adverse outcome is specifically attributed to preeclampsia, HELLP syndrome and rare causes. Special attention should be given to patients with thrombocytopenia due to preeclampsia, HELLP syndrome, and rarer causes during pregnancy [7].

The authors conducted this study to discover the prevalence of thrombocytopenia in pregnant patients at a tertiary university hospital, its causes, and the consequences on several obstetric and perinatal outcomes.

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Materials and Methods

All deliveries at Jordan University Hospital (JUH) during the period January 1, 2012 to December 31, 2016 were reviewed. The authors identified platelet counts of less than 150×10^9/L [1] detected any time after 24 weeks gestation and averaged during prenatal visits (the average platelet count was considered among all platelet counts performed during the patient's antenatal care). Pregnancies which continued beyond 24 completed weeks were included. The platelet counts and all other clinical data were collected from the hospital electronic database and the medical files of the patients. The present hospital uses both electronic and paper-based database. The clinical notes were written and entered by the specialists and residents. The authors selected a five-year period to be a true representation of the obstetric population and to have a reasonably large number of cases. They did not include early pregnancy (including miscarriage) complications in this study, in order to focus on late (beyond 24 weeks gestation) and perinatal complications. In addition, most of the causes of thrombocytopenia present late in pregnancy. They then divided those cases into two groups: group 1– cases of mild thrombocytopenia, (platelet counts between 70×10^9/L and 150×10^9/L) and group 2– cases of moderate to severe thrombocytopenia, (platelet counts less than 70×10^9/L) [7]. The authors performed a retrospective comparative study between the two groups. An independent *t*-test was used as a statistical tool with calculation of the *p* value to discover the statistical significance between the variables. Informed consent was not required because the authors did not use any personal information. The study was approved by the institutional review board of JUH (No. 67/2017/364, decision 39/2017).

The authors identified the prevalence and various causes of thrombocytopenia in this obstetric population. The impact of the severity of thrombocytopenia was then investigated by studying the following primary parameters: caesarean section rates, types of anesthetics used, rates of antepartum haemorrhage (APH), postpartum haemorrhage (PPH), peripartum hysterectomy, wound haematoma, intrauterine fetal death (IUFD), intrauterine growth restriction (IUGR), preterm deliveries, and termination of pregnancy (TOP). The prevalence of hypothyroidism and diabetes mellitus (DM) were seen as secondary outcomes, because of the known association between hypothyroidism and thrombocytopenia and most of the hypothyroid patients are diabetics

Results

JUH is a busy tertiary referral hospital in Amman, the capital of Jordan. It is affiliated with the University of Jordan. In this five-year period, the total number of deliveries was 23,021, of which 8,976 were caesarean sections, accounting for a rate of 38.99%. There were 211 stillbirths – a rate of 0.92%. The authors found 943 (4.10%) pregnancies with premature rupture of membranes (PROM). We identified 1,658 patients with a platelet count below 150×10^9/L who continued their pregnancies beyond 24 completed weeks. Medical notes for these patients were reviewed. The demographic characteristics in both groups 1 and 2 are shown in Table 1.

Table 1. — *Maternal age, parity, and gestational age at diagnosis in groups 1 and 2.*

Characteristics	Group 1 1,302	Group 2 356	*t* value	*p*
Maternal age (±SD)	25.3 (4.1)	30 (6.5)	8.024	<0.001
Parity mean (±SD)	2 (0.9)	4 (1.6)	1.581	<0.017
Gestational age in weeks (±SD)	30 (3)	28 (1.3)	22.923	<0.001

The different etiologies of thrombocytopenia in these cases along with the numbers and percentages of cases are shown in Table 2. Most cases were due to benign gestational thrombocytopenia (BGT). In fact, all cases of group 1 (mild) were due to BGT. The second most common cause was pre-eclamptic toxaemia (PET)/HELLP syndrome. Despite systemic lupus erythematosus and antiphospholipid antibody syndrome (SLE/APA) were responsible for only 0.24% of cases, they were associated with dismal outcomes. The overall prevalence of thrombocytopenia was 7.20%. There were 1,302 cases (78.53%) in group 1 and 356 cases (21.47%) in group 2.

The 'drugs' subgroup included those cases where the only possible causes of their thrombocytopenia were the use of acetylsalicylic acid in combination with high doses of low molecular weight heparin or unfractionated heparin and several other drugs, including multiple antibiotics mostly of cephalosporin category, for different indications. Most of these cases were diagnosed to have one form or another of thrombophilia. A small proportion of these patients had either previous or current venous thrombo-embolism (VTE). The 'others' category includes those patients with different coexisting medical conditions that could be related to their thrombocytopenia. However, the numbers of each individual condition is too small to find a correlation (Table 3).

The overall cesarean section rate in thrombocytopenic patients (both groups 1 and 2) was 40.17% (666 patients). Of these, 66.82% (445 patients) were performed under spinal anaesthetic (SA), 26.88% (179 patients) were performed under general anaesthetic (GA), and 6.3% (42 patients) were under epidural anaesthetic (EA). PROM complicated 2.29% (38) patients. The spinal or epidural anaesthetic were only offered to patients with mild thrombocytopenia.

Thrombocytopenic patients were generally found to be at a significantly increased risk of caesarean section and at

Table 2. — *Different etiologies of thrombocytopenia.*

BGT n (%)	ITP, n (%)	SLE, n (%)	SLE and APA, n (%)	PET/HELLP, n (%)	DRUGS, n (%)	OTHERS, n (%)
1,302 (78.53%)	32 (1.93%)	10 (0.60%)	4 (0.24%)	123 (7.41%)	120 (7.23%)	67 (4.04%)

BGT: benign gestational thrombocytopenia, ITP: immune (idiopathic) thrombocytopenic purpura, SLE: systemic lupus erythematosus, APA: antiphospholipid antibody, PET: pre-eclamptic toxaemia, HELLP: haemolysis, elevated liver enzymes, low platelets, n = number, % = percentage.

Table 3. — *Category 'others' with different possible etiologies.*

Maternal condition or disease	Number of patients (67)
Aplastic anaemia	1
G6PD deficiency	1
Psoriasis	1
Rheumatoid arthritis	3
FMF	2
Infections	3
Hodgkin's lymphoma	3
Heart diseases	7
AIHA and splenectomy	1
Chronic myeloid leukaemia (CML)	1
Von Willebrand disease	1
Evan's syndrome	1
Kidney transplant on Tacrolimus	4
Bronchial asthma	11
HBs Ag positivity	6
Idiopathic pleural effusion	1
Obstetric cholestasis	4
Brain tumors	1
Lymphoedema (right leg)	1
Sickle cell and thalassemia trait	1
Thalassemia trait	3
Generalized urticaria	1
Glanzmann thrombasthenia	2
Ulcerative colitis (UC)	3
Epilepsy	4

G6PD: glucose 6-phosphate dehydrogenase, FMF: familial mediterranean fever, AIHA: autoimmune haemolytic anemia, HBsAg: hepatitis B surface antigen.

Table 4. — *Prevalence of hypothyroidism and DM, mode of delivery, and type of anaesthetic in groups 1 and 2.*

	Group 1 1,302	Group 2 356	*p* value
Hypothyroidism, n (%)	79 (6.07%)	3 (0.84%)	0.083
DM, n (%)	42 (3.22%)	13 (3.65%)	<0.001
Vaginal delivery, n (%)	812 (62.36)	180 (50.56%)	<0.001
C-sections No. (%)	490 (37.63%)	176 (49.44%)	<0.001
GA, n (%)	7 (1.43%)	172 (97.72%)	<0.001
SA, n (%)	445 (90.82%)	0.00	
EA, n (%)	38 (7.75%)	4 (2.27%)	0.083
Total, n (%)	1302 (78.53%)	356 (21.47%)	<0.001

a significantly lower risk of PROM than the general obstetric population (40.17% *vs*. 38.99%, *t* value 360.467, $p < 0.5$ and 2.29% *vs*. 4.10%, *t*-value 318.178, $p < 0.5$).

The authors compared groups 1 and 2 with regards to caesarean section rate, type of anaesthetic, and the prevalence of hypothyroidism and DM (Table 4). Next, they compared rates of postpartum haemorrhage (PPH), antepartum haemorrhage (APH), peripartum hysterectomy because of bleeding, wound haematoma, gastrointestinal (GI) bleeding, IUFD, preterm deliveries, IUGR and TOP between groups 1 and 2 (Table 5). There were two cases of GI bleeding in group 1 in known cases of peptic ulcer disease.

Table 5. — *Feto-maternal outcome in groups 1 and 2.*

Complication (fetomaternal)	Group 1	Group 2	*p* value
APH, n (%)	1 (0.077%)	14 (3.93)	<0.001
PPH, n (%)	2 (0.077%)	15 (4.21%)	0.163
Peripartum hysterectomy, n. (%)	0 (0.0%)	11 (3.09%)	
GI bleeding, n (%)	2 (0.15%)	0 (0.0%)	
Wound haematoma, n (%)	3 (0.23%)	11 (3.09%)	<0.001
IUFD	3 (0.23%)	18 (5.06%)	<0.001
Preterm deliveries	12 (0.92%)	56 (15.73%)	<0.001
IUGR	7 (0.54%)	4 (1.12%)	<0.001
TOP	0 (0.0%)	3 (0.84%)	

There was a case of DIC, ARDS, acute renal failure, haemodialysis, pulmonary oedema, and haemolytic uremic syndrome (HUS) in an SLE patient (group 2). The risk of wound haematoma was over 13-fold higher in group 2. There were no maternal mortalities.

Regarding fetal outcome, group 2 was associated with a 20-fold increase in the risk of intrauterine fetal deaths (IUFD), around a 15-fold increase in the risk of preterm delivery, and a twofold increase in the risk of IUGR. TOP was seen only in group 2. There were three (0.84%) cases of TOP due to severe PET/HELLP at a very early gestational ages (less than 26 weeks). All these cases underwent induction termination and vaginal delivery. There was one stillbirth at 570 gm (thalassaemia) in group 2. Also in group 2 the authors found four cases of IUGR (two at term and two preterm) with a rate of 1.12%. In group 1 with preterm deliveries, there were no NICU admissions, while in group 2 there were 18, of which two were IUGR cases.

Discussion

The present study showed clearly that all cases of mild thrombocytopenia (group 1) were due to BGT with no significant adverse obstetric or perinatal consequences. It was also found that thrombocytopenia in pregnancy was associated with higher rates of caesarean section than normal pregnancies (40.17% *vs*. 38.99%, $p < 0.5$), and a lower rate of PROM (2.29% *vs*. 4.1%, $p < 0.5$). These findings are statistically significant. In one study [8], 51.7% of patients with chronic ITP delivered by caesarean section and 48.3% delivered vaginally. The caesarean section and type of anaesthesia were also largely influenced by the choice of the patient, the anaesthetist, the obstetrician, and other obstetric factors rather than by only the thrombocytopenia itself.

With regards to PROM, platelets are one of the inflammatory markers, and a high platelet count can be associated with PROM [9, 10]. This could be inferred by the lower rates in thrombocytopenic pregnancies in this study.

The authors found 120 (7.23%) cases of thrombocytopenia caused by the use of different medications, and 67 (4.04%) cases caused by various underlying medical, car-

diovascular, haematological, malignant, and auto-immunological conditions. These two subgroups had moderate to severe thrombocytopenia. These patients also had chronic medical disorders or pregnancy-induced conditions that require further evaluation and therapy. The challenge to the clinician is to weigh the risks of maternal and fetal bleeding complications against the benefits of diagnostic tests and interventions [11].

The maternal age in group 2 was found to be significantly higher than in group 1 (30 years vs. 25.3, $p < 0.001$). This was explained by the fact that most maternal disorders are associated with older age. Parity is significantly higher in group 2 than in Group 1 (4 *vs.* 2, *t*-value 1.581; $p = 0.175$), while gestational age at diagnosis was significantly greater in group 1 than in group 2 (30 *vs*. 28, $p < 0.001$). These are most likely because group 1 comprised patients with mild or benign gestational thrombocytopenia. In a study by Varghese *et al.* [12], the researchers found that maternal age is significantly higher in patients with ITP; parity is higher in patients with BGT, and most patients with pre-eclampsia, eclampsia, and HELLP syndrome were diagnosed before 37 weeks' gestation.

Between groups 1 and 2 the authors found very interesting significant differences. Hypothyroidism was more common in group 1 than in group 2. The association between ITP and hypothyroidism is well-known [13-16]. Diabetes type 2 was found more frequently in group 2 than in group 1. Higher parity and old maternal age were significantly associated with an increased risk of type 2 diabetes [17]. This explains the higher prevalence of parity and diabetes in group 2, which indicates that diabetes type 2 and severe thrombocytopenia are not directly associated but rather indirectly through age and parity and prevalence of other medical diseases.

Also group 2 had a higher rate of caesarean section than group 1 (49.44% *vs* 37.63%, $p = 0.00$). This could be accounted for by the various underlying causes of thrombocytopenia in group 2. As expected, 90.82% of caesarean sections in group 1 were conducted under SA, while none was performed under SA in group 2. Instead, 97.72% of caesarean sections in group 2 were conducted under GA.

The British Committee for standards in Haematology General Haematology Task Force requires a platelet count more than 80×10^9/L for regional anesthesia [18]. Four caesarean sections were performed under EA in group 2. Beilin *et al.* [19] indicated safe epidural analgesia in 30 parturients with platelet counts between 69×10^9/L and 98×10^9/L, and Moeller-Bertram *et al.* [20] reported epidural catheter insertion in a patient with platelet count of 26×10^9/L. Neither study reported any complications with epidural catheters in patients with moderate to severe thrombocytopenia.

In the present study, APH, PPH, and wound haematoma were significantly more associated with moderate to severe thrombocytopenia (group 2) than with mild thrombocytopenia (group 1). In addition, all cases of peripartum hysterectomy were found in group 2. There were two cases of upper GI bleeding which were not related to thrombocytopenia., but associated with peptic ulcers. The association of bleeding with thrombocytopenia, particularly in moderate to severe cases, was highlighted in many studies. Webert *et al.* [21] found that women with thrombocytopenia had moderate to severe bleeding in 21.5% of cases, and 31.1% of their patients required treatment to increase platelet counts. In a prospective study on patients with HELLP syndrome by Sibai *et al.* [22], 21% of patients developed DIC, 16% placental abruption, 55% of their patients required transfusion with blood or blood products, and 2% required laparotomies for major intra-abdominal bleeding. Blood disorders are well-known risk factors for postpartum haemorrhage [23]. Group 2 was also associated with more adverse perinatal outcomes (preterm birth, NICU admissions, IUFD, and IUGR) than in group 1. TOP was only found in group 2. The clinical outcomes in cases of group 2 were a reflection of the underlying maternal diseases, mainly SLE with or without APA, HELLP syndrome, drug use, and various other medical diseases. Secondary ITP can be due to medications or to a concurrent disease such as an autoimmune condition, a lymphoproliferative disease, chronic infection, response to infection, and splenic sequestration of platelets secondary to portal hypertension [24].

The present study indicated a 15-fold rise in the risk of preterm delivery in group 2. Clowse *et al.* [25] found that in lupus patients, the odds ratio for preterm birth was 2:4.

The present study indicated a clear increase in the risk of IUGR, NICU admissions, IUFD, stillbirth, and TOP in moderate to severe thrombocytopenia. In a multicentric study of SLE in pregnancy [26], 8.4% of pregnancies resulted in foetal loss, 28.2% of pregnancies ended pre-term, 12 newborns (16.4%) were small for their gestational age, and active lupus nephritis increased the probability of preterm delivery. Odds for preterm delivery increased by 60% for each quarterly unit increase in SLEDAI, and by 15% for each quarterly increase in proteinuria by 1 gram per day. The probability of having a small baby relative to gestational age was reduced by 85% in women who received hydroxychloroquine therapy.

In a prospective study of 91 pregnancies (84 women) with SLE [27], the incidence of abortion was (15%), IUGR (32%), prematurity (13%), pre-eclampsia (12%), IUFD (8%), NICU (15%), and low birth weight (22%).

In a study by Khan *et al.* [28], the overall pregnancy loss was 14% with no maternal mortality, both SLE and pregnancy tended to influence each other due to complex interaction. However, with multidisciplinary involvement, SLE activity in their series was not an independent predictor of a poor pregnancy outcome.

In a retrospective analysis of 150 pregnancies in 64 patients with lupus [29], an adverse fetal event was observed in 48 (32%) pregnancies. Induced abortions were seen in

4%. Two (1%) died in utero and there was one (1%) neonatal death. Forty-four (29%) babies were born below 2,500 grams, 4 (3%) were premature (less than 37 weeks), and IUGR was observed in 19 (12.6%).

In a prospective study of feto-maternal outcome in severe preeclampsia and eclampsia with and without HELLP syndrome [30], 11.6% maternal mortality was observed in the HELLP syndrome group. Up to 54.5% babies in the HELLP group had an abnormal perinatal outcome as opposed to 24.6% in the non-HELLP group.

Eclampsia is still one of the important and common obstetric emergencies and it has a significant role in maternal and fetal outcomes. The early identification of risk factors and timely intervention is needed to improve maternal and perinatal outcome [31]. In the present study, there were 123 cases with PET/HELLP and they contributed to the adverse perinatal outcome. There were no maternal mortalities.

The results of a study by Lin *et al.* [32] indicate that women who suffered from incidental thrombocytopenia at delivery, but did not have other diseases during pregnancy, were not at any increased risk for adverse pregnancy outcomes. These are consistent with the present results. Unfortunately, we do not have local epidemiological data on thrombocytopenia in pregnancy to compare with.

Conclusion

Thrombocytopenia was prevalent in this obstetric population with various obstetric and nonobstetric causes. The consequences of thrombocytopenia in pregnancy are mostly benign but moderate to severe thrombocytopenia was associated with adverse obstetric and perinatal outcomes. This was due to the nature and severity of the underling maternal diseases and their medication. The authors recommend studying prospectively each of these thrombocytopenia-induced diseases in pregnancy..

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