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# Moderate to severe thrombocytopenia during pregnancy

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**Abstract**

*Objective:* The objective was to investigate obstetric risk factors, complications, and outcomes of pregnancies complicated by moderate to severe thrombocytopenia.
*Materials and methods:* A retrospective case-control study comparing 199 pregnant women with moderate to severe thrombocytopenia (platelet count below $100 \times 10^9$/l) with 201 pregnant women without thrombocytopenia, who delivered between January 2003 to April 2004. Stratified analysis, using the Mantel–Haenszel procedure was performed in order to control for confounders.
*Results:* The main causes of thrombocytopenia were gestational thrombocytopenia (GT) (59.3%), immune thrombocytopenic purpura (ITP) (11.05%), preeclampsia (10.05%), and HELLP (Hemolysis, elevated liver enzymes and low platelet count) syndrome (12.06%). Women with thrombocytopenia were significantly older ($30.7 \pm 5.9$ versus $28.7 \pm 5.7$; $p = 0.001$) compared with patients without thrombocytopenia, and had higher rates of labor induction (OR = 4.0, 95% CI = 2.2–7.6, $p < 0.001$) and preterm deliveries (OR = 3.5, 95% CI = 1.9–6.5, $p < 0.001$). Even after controlling for labor induction, using the Mantel–Haenszel technique, thrombocytopenia was significantly associated with preterm delivery (weighted OR = 3.14, 95% CI = 1.7–6.0, $p < 0.001$). Higher rates of placental abruption were found in pregnant women with thrombocytopenia (OR = 6.2, 95% CI = 1.7–33.2, $p = 0.001$). In a comparison of perinatal outcomes, higher rates of Apgar scores <7 at 5 min were noted in infants of mothers with thrombocytopenia (OR = 6.3, 95% CI = 1.8–33.8, $p = 0.001$), intrauterine growth restriction (IUGR; OR = 4.6, 95% CI = 1.5–19.1, $p = 0.003$), and stillbirth (65/1000 versus 0 $p < 0.001$). These adverse perinatal outcomes were found in rare causes of thrombocytopenia such as disseminated intravascular coagulation (DIC), familial thrombotic thrombocytopenic purpura (TTP), anti-phospholipid antibodies (APLA) syndrome, and myeloproliferative disease, and not among patients with GT.
*Conclusions:* Moderate to severe maternal thrombocytopenia points to a higher degree of severity of the primary disease, which increases perinatal complications. However, the adverse outcome is specifically attributed to preeclampsia, HELLP syndrome, and rare causes, while the perinatal outcome of GT and ITP is basically favorable. Special attention should be given to patients with thrombocytopenia due to preeclampsia, HELLP syndrome, and rarer causes during pregnancy.


*Keywords:* Moderate to severe thrombocytopenia; Pregnancy; Preeclampsia; HELLP; Gestational thrombocytopenia

## 1. Introduction

Thrombocytopenia is defined as a platelet count below $150 \times 10^9$/l, caused by accelerated platelet destruction or decreased production. It is classified as mild with a platelet count of 100–150 $\times 10^9$/l, moderate at 50–100 $\times 10^9$/l, and severe with less than $50 \times 10^9$/l [1].

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Thrombocytopenia occurs in approximately 10% of pregnant women [2] and is caused by the conditions described below.

Gestational thrombocytopenia (GT) is considered the most prevalent cause of thrombocytopenia in pregnancy and accounts for about 75% of cases of thrombocytopenia during pregnancy [1]. It is defined by a platelet count of no less than $70 \times 10^9$/l, especially during the third trimester, [3] and the count returns to normal within 12 weeks of delivery [1]. The etiology is unknown, but is considered to be the due to the relative hemodilution in pregnancy, amplified by the capture or destruction of platelets in the placenta [4]. GT is considered a minor form of thrombocytopenia in the fetus or newborn, with no risk of hemorrhage to the mother or infant.

Immune thrombocytopenic purpura (ITP) is caused by platelet destruction in the reticular endothelial system, due to platelet auto-antibodies against several platelet membrane glycoprotein complexes. ITP is characterized by a moderate to severe decrease in the platelet count, and constitutes approximately 5% of cases of thrombocytopenia in pregnancy [3,5]. ITP requires monitoring during pregnancy and after delivery, and may require treatment, due to the higher risk of maternal hemorrhage when the platelet count is low. There is a minor risk of thrombocytopenia in the newborn.

Preeclampsia and HELLP (Hemolysis, elevated liver enzymes and low platelet count) syndrome are considered to be the cause of thrombocytopenia in pregnancy in about 21% of cases [6,7]. The maternal platelet count returns to normal within 3–5 days of delivery [3]. HELLP syndrome is a variant of preeclampsia, and is characterized by hemolytic anemia, elevated liver enzymes, and a low platelet count (usually below $100 \times 10^9$/l) [1]. It is responsible for maternal deaths (up to 3.0% of HELLP cases may end in maternal mortality) and stillbirth (in up to 20% of cases), especially as a result of placental abruption and preterm delivery [1].

There are additional, rarer causes of thrombocytopenia during pregnancy, including thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC), systemic lupus erythematosus (SLE), anti-phospholipid antibodies syndrome (APLA), or it may be induced by drugs (such as heparin) [1].

Most existing studies [8–12] have addressed a specific etiology of thrombocytopenia in pregnant women, but only a few have compared different etiologies, all using a platelet count of $150 \times 10^9$/l as the reference value. Since it is acceptable that the prognosis of mild thrombocytopenia (platelet count above 100,000, generally caused by GT) is good with no major complications, we decided to focus on moderate to severe thrombocytopenia.

The present study was aimed at investigating obstetric risk factors, complications, and outcomes of pregnancies complicated by moderate to severe thrombocytopenia, compared with pregnant women with a normal pregnancy, and to compare the outcomes of different etiologies.

## 2. Materials and methods

A retrospective case-control study comparing all ($n = 199$) pregnant women with moderate to severe thrombocytopenia with 201 pregnant women without thrombocytopenia, delivered during the same study period, was conducted. Deliveries occurred between 1 January 2003 and 1 April 2004 at the Soroka University Medical Center, which is the sole hospital of the Negev, the southern part of Israel. Out of 17,499 deliveries at the time of the research, moderate to severe thrombocytopenia was observed in 1.14%.

The study population included all pregnant women with moderate to severe thrombocytopenia (platelet count below $100 \times 10^9$/l) identified by the computerized hematology laboratory report of the hospital. The control group consisted of consecutive patients without thrombocytopenia and hypertensive disorders delivered during the same period. The clinical details of all women were collected by reviewing their hospital as well as their prenatal records.

The following clinical characteristics were evaluated: maternal age, previous gestations, parity, gestational age, birth weight, and the cause of thrombocytopenia. The following obstetrical risk factors were examined: previous cesarean section (CS), gestational diabetes mellitus, pre-gestational diabetes mellitus, maternal anemia, hydramnios, oligohydramnios, multiple pregnancies (twins/triplets), and intrauterine growth restriction (IUGR). The following pregnancy and labor complications were assessed: blood and platelet transfusions, placental abruption, placenta previa, labor induction, mode of delivery including spontaneous, CS or vacuum delivery (no forceps deliveries occurred during the study period), Apgar scores at 1 and 5 min of less than 7, umbilical cord artery pH less than 7.2, DIC, meconium-stained amniotic fluid, stillbirth, intra-partum fetal death (IPD), and post-partum neonatal death (PPD). The local ethics institutional review broad approved the study.

Statistical analysis was performed using the SPSS package (SPSS, Chicago, IL, USA). Statistical significance was calculated using the $\chi^2$-test, or Fisher's exact test for categorical variables. Student's $t$-test was used for continuous variables. Stratified analysis, using the Mantel–Haenszel procedure, was performed in order to control for confounders. Odds ratios (OR) and their 95% confidence intervals (CI) were computed. $p < 0.05$ was considered statistically significant.

## 3. Results

Out of 199 pregnant women with a platelet count below $100 \times 10^9$/l, the diagnosis included: 118 women with GT, 22 with ITP, 20 with severe preeclampsia, 24 with HELLP syndrome, 10 with DIC, one with familial TTP, one with APLA syndrome, two due to dilution caused by massive blood transfusions, and one with myeloproliferative disease

Table 1
Etiology of thrombocytopenia in the study group (i.e., patients with moderate to severe thrombocytopenia)

| Characteristics | $n = 199$ (%) |
|---|---|
| Gestational thrombocytopenia | 118 (59.3) |
| ITP | 22 (11.05) |
| Preeclampsia | 20 (10.05) |
| HELLP syndrome | 24 (12.06) |
| DIC | 10 (5.02) |
| Familial TTP | 1 (0.5) |
| APLA syndrome | 1 (0.5) |
| Dilutional | 2 (1.0) |
| Myeloproliferative disease | 1 (0.5) |

ITP: immune thrombocytopenic purpura, DIC: disseminated intravascular coagulation, TTP: thrombotic thrombocytopenic purpura, APLA: anti-phospholipid antibodies.

Table 2
Clinical characteristics of pregnant women with and without thrombocytopenia

| Characteristics | Thrombocytopenia ($n = 199$) | No thrombocytopenia ($n = 201$) | $p$ |
|---|---|---|---|
| Maternal age (mean years ± S.D.) | 30.7 ± 5.9 | 28.7 ± 5.7 | 0.001 |
| Previous gestations | | | |
| 1 | 18.5% | 21.3% | |
| 2–4 | 45.1% | 50.3% | |
| 5+ | 36.4% | 28.4% | 0.310 |
| Parity | | | |
| 1 | 21.9% | 31.1% | |
| 2–4 | 49.0% | 45.7% | |
| 5+ | 29.1% | 23.2% | 0.161 |
| Gestational age | | | |
| <37 weeks | 25.6% | 9.0% | |
| 37–39 weeks | 46.2% | 44.8% | |
| 40+ weeks | 28.1% | 46.3% | <0.001 |
| Birth weight | | | |
| <2500 g | 7.1% | 5.0% | |
| 2500–4000 g | 84.3% | 89.1% | |
| >4000 g | 8.6% | 6.0% | 0.382 |

(Table 1). During the study period these 199 women delivered 214 infants, there were 13 deliveries of twins and one set of triplets. Treatment included mostly blood products. The ITP patients were treated with steroids, immunoglobulin and one patient was treated with tranexamic acid.

Women with thrombocytopenia were more likely to deliver preterm (<37 weeks) compared with women without thrombocytopenia (Table 2, data are shown per pregnancy). The higher rates of preterm deliveries found among patients with thrombocytopenia (OR = 3.5, 95% CI = 1.9–6.52, $p < 0.001$) were not explained by labor induction. Using the Mantel–Haenszel procedure to control for labor induction, thrombocytopenia was significantly associated with preterm deliveries (weighted OR = 3.14, 95% CI = 1.7–6.03, $p < 0.001$).

Obstetric risk factors are presented in Table 3. Higher rates of IUGR were found among patients with moderate to severe thrombocytopenia compared with the control group. Previous CS, gestational and pre-gestational diabetes mellitus, maternal anemia, delivery of twins/triplets, and hydramnios were more prevalent in the study group, but the differences were not statistically significant.

Labor complications and birth outcomes are presented in Table 4. Higher rates of placental abruption, labor induction, CS, and low Apgar scores (<7) at 1 and 5 min and the need for blood transfusions were found among patients with moderate to severe thrombocytopenia compared with the control group. In addition, there were significantly more stillbirths in this group. Controlling for advanced maternal age (≥35 years), using the Mantel–Haenszel procedure, did not change the significant association between thrombocytopenia and adverse perinatal outcome (IUGR, low 5-min Apgar scores, and perinatal mortality; weighted OR = 5.5, 95% CI = 2.22–13.92). A significant linear association was noted between the severity of thrombocytopenia and adverse perinatal outcome. The rate of adverse perinatal outcome (IUGR, low 5-min Apgar scores, and perinatal mortality) among patients with severe thrombocytopenia (<50,000 platelets) was 23.1%, versus 16.2% among the moderate thrombocytopenia, and 3.5% in the controls ($p < 0.001$).

Table 3
Obstetric risk factors in women with or without thrombocytopenia

| Characteristics | Thrombocytopenia ($n = 199$, %) | No thrombocytopenia ($n = 201$) | OR | 95% CI | $p$ |
|---|---|---|---|---|---|
| Previous CS | 21.1 | 13.9 | 1.6 | 0.95–2.9 | 0.059 |
| Gestational DM | 8.0 | 4.0 | 2.1 | 0.8–5.5 | 0.107 |
| Pre-gestational DM | 1.0 | 0.0 | Undefined | | 0.249 |
| Maternal anemia | 3.0 | 0.5 | 6.2 | 0.7–287.4 | 0.067 |
| Hydramnios | 3.5 | 0.5 | 7.3 | 0.9–330.2 | 0.072 |
| Oligohydramnios | 3.0 | 2.0 | 1.5 | 0.4–7.5 | 0.542 |
| Twins/triplets | 7.0 | 3.0 | 2.5 | 0.9–8.0 | 0.077 |
| IUGR | 8.5 | 2.0 | 4.6 | 1.5–19.1 | 0.003 |

CS: cesarean section, DM: diabetes mellitus, IUGR: intra-uterine growth restriction, OR: odds ratio, CI: confidence interval.

Table 4
Labor complications and birth outcomes in women with or without thrombocytopenia

| Characteristics | Thrombocytopenia ($n = 199$, %) | No thrombocytopenia ($n = 201$) | OR | 95% CI | $p$ |
|---|---|---|---|---|---|
| Placental abruption | 8.5 | 1.5 | 6.2 | 1.7–33.2 | 0.001 |
| Placenta previa | 2.5 | 1.0 | 2.6 | 0.4–27.2 | 0.283 |
| Labor induction | 27.1 | 8.5 | 4.0 | 2.2–7.6 | <0.001 |
| Mode of delivery | | | | | |
| CS | 36.2 | 20.9 | 1.7 | 1.1–2.7 | 0.011 |
| Vacuum | 2.5 | 4.5 | 0.6 | 0.2–1.9 | 0.302 |
| Apgar at 1 min <7 | 16.8 | 6.0 | 3.2 | 1.5–6.7 | 0.001 |
| Apgar at 5 min <7 | 8.7 | 1.5 | 6.3 | 1.8–33.8 | 0.001 |
| [a]pH <7.2 | 16.8 | 9.8 | 1.9 | 0.95–3.65 | 0.073 |
| DIC | 2.0 | 0.0 | | | 0.062 |
| Meconium-stained amniotic fluid | 12.1 | 9.0 | 1.4 | 0.7–2.8 | 0.361 |
| Stillbirth | 6.5 | 0.0 | Undefined | | <0.001 |
| IPD | 1.0 | 0.0 | Undefined | | 0.247 |
| PPD | 1.5 | 0.5 | 3.1 | 0.2–161.5 | 0.311 |
| Blood transfusions | 16.6 | 2 | 9.8 | 3.4–38.6 | <0.001 |

CS: cesarean section, DIC: disseminated intravascular coagulation, IPD: intra-partum fetal death, PPD: post-partum neonatal death, OR: odds ratio, CI: confidence interval.
[a] There were missing data in the thrombocytopenia group ($n = 161$) and in the no thrombocytopenia group ($n = 194$).

Table 5
Characteristics of women receiving blood transfusion

| Characteristics | Thrombocytopenia ($n$) | Controls ($n$) |
|---|---|---|
| GT | 9 | |
| ITP | 1 | |
| Preeclampsia + HELLP syndrome | 11 | |
| DIC | 9 | |
| Familial TTP | 1 | |
| Dilutional | 2 | |
| Uterine atony | | 4 |
| Total | 33 | 4 |

GT: gestational thrombocytopenia, ITP: immune thrombocytopenic purpura, DIC: disseminated intravascular coagulation, TTP: thrombotic thrombocytopenic purpura.

Six women needed platelet transfusions for major bleeding, four with DIC and two with HELLP syndrome. A total of 33 women received blood in the thrombocytopenic group versus four in the non-thrombocytopenic group. Their characteristics are described in Table 5.

A total of seven infants were thrombocytopenic, two born to mothers with ITP, four to mothers with preeclampsia and HELLP syndrome, and one to a mother with familial TTP. Their platelet counts were 50–100 $\times$ $10^9$/l in five cases and 20–50 $\times$ $10^9$/l in two cases. There was no major bleeding although one infant received platelet transfusion.

Adverse pregnancy outcomes according to the etiology of thrombocytopenia are presented in Table 6. IUGR was more common in the preeclampsia and HELLP syndrome group compared with the other etiologies. However, placental abruption, stillbirths, and low Apgar scores (<7) at 1 min and 5 min were more common in DIC, familial TTP, APLA syndrome, and myeloproliferative disease, as a group.

## 4. Discussion

The present study was aimed at investigating obstetric risk factors and outcomes of pregnancies complicated by moderate to severe thrombocytopenia. Most cases of thrombocytopenia were caused by GT (58.2%), even though our reference

Table 6
Adverse pregnancy outcomes according to the etiology of thrombocytopenia

| Characteristics | GT ($n = 118$) | ITP ($n = 22$) | Preeclampsia/HELLP syndrome ($n = 44$) | [a]Others ($n = 15$) |
|---|---|---|---|---|
| IUGR | 5.1% (6) | 4.5% (1) | 20.5% (9) | 0% |
| Placental abruption | 1.7% (2) | 0% | 15.9% (7) | 46.7% (7) |
| Still birth | 0.85% (1) | 0% | 4.5% (2) | 53.3% (8) |
| Apgar at 1 min <7 | 10.17% (12) | 9.09% (2) | 18.6% (8) | 60% (9) |
| Apgar at 5 min <7 | 2.54% (3) | 4.54% (1) | 6.98% (3) | 53.33% (8) |

GT: gestational thrombocytopenia, ITP: immune thrombocytopenic purpura, IUGR: intra-uterine growth restriction.
[a] Others-MPD: myeloproliferative disease ($n = 1$), DIC: disseminated intravascular coagulation ($n = 10$), TTP: thrombotic thrombocytopenic purpura ($n = 1$), APLA: anti-phospholipid antibodies ($n = 1$), dilutional ($n = 2$).

platelet count was below $100 \times 10^9$/l. GT is known to be the most common cause of thrombocytopenia in pregnancy, and although the platelet count of these women is usually above $110 \times 10^9$/l, there are several cases in healthy pregnant women with no history of ITP who have platelet counts as low as $70 \times 10^9$/l [8,13,14]. The rarer causes included DIC, dilutional state (caused by blood transfusion), familial TTP, APLA syndrome, and myeloproliferative disease.

The major findings of our study were that thrombocytopenia points to a higher degree of severity of the primary disease (APLA, HELLP, etc.), which is known to increase perinatal complications, both maternal and neonatal. Such complications include placental abruption, preterm deliveries, low Apgar scores, IUGR, and stillbirths.

Higher rates of preterm deliveries (<37 weeks) were observed among parturients with moderate to severe thrombocytopenia. Since the management of preeclampsia and HELLP syndrome includes early delivery of fetus, [6,8] labor induction could be a confounder for this association. However, the relationship between thrombocytopenia and preterm delivery remained significant even after controlling for labor induction.

It is interesting that even while dealing with moderate to severe thrombocytopenia, major bleeding requiring blood and platelet transfusion was rare, and occurred in only six patients. These patients had either DIC or HELLP syndrome. It is probably the result of careful surveillance and treatment. Indeed, since there were very few occurrences of massive bleeding, it seems that severe thrombocytopenia is a marker of a grave medical condition, more than the cause.

Adverse perinatal outcome was mostly associated with preeclampsia, HELLP syndrome, and the group of rarer causes, including DIC, familial TTP, APLA syndrome, and myeloproliferative disease. McCrae concluded that hypertensive disorders are associated with more severe cases of IUGR [8,15]. Likewise, Aslan et al. [16] found a significant difference in the incidence of IUGR in pregnant women with HELLP syndrome compared with women without HELLP syndrome. Placental abruption, low Apgar scores (<7) at 1 and 5 min, and stillbirth were found in the group of rarer causes. Similarly, Shamseddine et al., [9] investigating the pregnancy outcome of patients with TTP, found that TTP was complicated by IUGR and death, and McCrae [8,17] suggested that APLA syndrome may be associated with recurrent neonatal losses.

In general, the GT and ITP groups had a favorable pregnancy outcome in our analysis. It is known that GT is not associated with an increased incidence of pregnancy-related complications or with the delivery of a thrombocytopenic offspring [8,13,14]. Women with ITP and severe thrombocytopenia may have bleeding complications, which were not observed in our study population, probably due to strict surveillance and treatment. Thrombocytopenia in the neonate, as reported by McCrae [8] and Cook et al., [10] was rare and treated promptly without any bleeding complications.

Patients with moderate to severe thrombocytopenia were significantly older than women without thrombocytopenia ($30.7 \pm 5.9$ versus $28.7 \pm 5.7$; $p = 0.001$). This finding, although statistically significant, does not seem to have clear clinical implications. Lee [11] investigated the pregnancies of women with ITP and concluded that ITP tends to occur in younger women. Hence, it commonly affects women in the childbearing age group [11]. Likewise, Webert et al. [12] found that the median age of women with ITP at the time of delivery was 29 years. Indeed, the mean maternal age in our whole population was very similar to that in the above studies.

In conclusion, the common cause of moderate to severe thrombocytopenia in pregnancy is mainly GT, while ITP, preeclampsia, and HELLP syndrome are less common. Patients with GT and ITP have favorable maternal and perinatal outcomes. On the other hand, preeclampsia and HELLP syndrome are associated with IUGR. The rarer and more serious group of causes of thrombocytopenia, including DIC, familial TTP, APLA syndrome, and myeloproliferative disease, are associated with placental abruption, low Apgar scores (<7) at 1 and 5 min, and stillbirths. Careful surveillance is required for these pregnancies in high-risk units for early detection and treatment of possible complications, in order to try to reduce maternal and neonatal morbidities. Further prospective studies among these high-risk populations with moderate to severe thrombocytopenia should investigate the efficacy of possible surveillance programs.

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