Prevalence and etiological classification of thrombocytopenia among a group of pregnant women in Erbil City, Iraq

Irak‘ın Erbil şehrindeki bir grup gebe kadında trombositopeni prevalansı ve etiyolojik sınıflandırması

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Abstract

**Objective:** To determine the prevalence and define the causes of pregnancy-associated thrombocytopenia.

**Materials and Methods:** A total of 850 pregnant women at different ages of gestation were screened for thrombocytopenia. A control group of 150 age-matched non-pregnant women were tested for platelet count. Newborns of thrombocytopenic women were tested within 24 hours of delivery and reassessment of the women’s platelets was done within 7-10 days post-delivery.

**Results:** The mean platelet count in pregnant women was significantly lower than in non-pregnant women (221±59.9/mm³ vs. 273±66.9/mm³). Thrombocytopenia affected 8% of cases, with peak incidence during the third trimester. Gestational thrombocytopenia was found to be the principal cause (73.8%); hypertensive disorders caused thrombocytopenia in 23% of cases and two cases (4%) were due to immune thrombocytopenic purpura. No maternal or fetal complications were noted. The mean platelet count of 51 newborns of thrombocytopenic women was 240±7.1. Two newborns (4%) had low platelet counts.

**Conclusion:** The majority of thrombocytopenias were mild gestational and occurred in late pregnancy. No maternal or neonatal bleeding complications were observed. (Turk J Hematol 2009; 26: 123-8)

**Key words:** Thrombocytopenia, pregnancy, preeclampsia, HELLP, gestational thrombocytopenia

Özet

*Amaç:* Gebelik ile ilişkili trombositopeni prevalansını saptamak ve nedenlerini tanımlamak.

**Yöntem:** Farklı gebelik haftalarındaki 850 gebe kadının trombositopeni yönünden tanılandı. Gebe olmayan ve yaşlanışa uğramış 150 kadının kontrol grubu, trombosit sayısı yönünden değerlendirildi. Trombositopenik kadınların yeni doğan bebekleri doğumdan 24 saat içinde test edildi ve kadınların trombositleri doğumdan sonra 7-10 gün içinde tekrar değerlendirildi.

**Bulgular:** Gebe kadınlarında ortalama trombosit sayısı gebe olmayan kadınlara göre anlamlı derecede düşük bulundu (221±59,9/mm³ ve 273±66,9/mm³). Trombositopeni, 3. trimesterde en yüksek insidans ile olguların %8’i etkiledi. Gestasyonel trombositopeninin (%73,8) ana neden olduğu bulundu, trombositopeniye olguların %23’ünde hipertansif bozuk-
Thrombocytopenia during pregnancy is defined as a platelet count of less than 150 ×10⁹/L as classically defined in normal individuals [1]. Thrombocytopenia is fairly common in pregnancy; it is the second most common hematological abnormality during pregnancy, affecting up to 10% of all pregnancies [2,3]. The increased recognition of the condition is mainly attributable to the increased use of automated blood counters in routine prenatal screening [2].

Thrombocytopenia is caused by accelerated platelet consumption or decreased production. It is classified as mild with a platelet count of 100-150 ×10⁹/L, moderate with 50-100 ×10⁹/L, and severe with less than 50 × 10⁹/L [4]. Gestational thrombocytopenia (GT) is the most prevalent cause, and accounts for about 75% of cases of thrombocytopenia during pregnancy [4]. It is defined by a platelet count of no less than 70 ×10⁹/L, especially during the third trimester, [5] and the count returns to normal within 12 weeks of delivery [6]. The etiology is unknown, but is considered to be due to the relative hemodilution in pregnancy, amplified by the capture or destruction of platelets in the placenta [6]. GT does not carry risk of hemorrhage to the mother or infant.

Immune thrombocytopenic purpura (ITP) is caused by platelet destruction in the reticulendothelial 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 [5,7].

Preeclampsia (PE) 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 [8,9]. The maternal platelet count returns to normal within 3–5 days of delivery [5].

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), and anti-phospholipid antibodies syndrome, or it may be induced by drugs (such as heparin) [4].

Studies of platelet count variation during pregnancy have generally been performed on a limited number of pregnancies and reported variable prevalence rates [10-14]. Two separate studies that assessed a large number of pregnant women reported prevalences of 6.6% [9] and 11.6% [3]. In most pregnant women, platelet counts remain within normal range; however, the mean platelet count may be slightly lower than in healthy non-pregnant women [15]. Recent studies have reported a 10% drop in platelets in pregnant women, with the platelet count distribution histogram at term being normally distributed but shifted to the left [3,16]. In most cases, this physiologic decrease in platelets occurs in the third trimester.

Thrombocytopenia in pregnancy has become a cause for unnecessary, often invasive, additional testing as well as cesarean deliveries [16]. The evaluation and treatment of this condition can be expensive and distressing to the patient and can result in an adverse outcome [17]. Obstetricians in our locality have no comprehensible guide for managing pregnant women with thrombocytopenia due to a lack of data about the frequency, severity and causes of this condition. Moreover, no relevant data is available from the other parts of Iraq. Therefore, we deemed it necessary to carry out this study in order to provide a principle guide for approaching women with thrombocytopenia. This study was aimed at determining the prevalence of thrombocytopenia among pregnant women in Erbil City, and at defining and estimating the proportions of the underlying causes.

Materials and Methods

Subjects

This prospective study was carried out from mid November 2007 to end of September 2008. A total of 850 pregnant women at different ages of gestation attending the antenatal care unit at Nazdar Bamarni Health Center and the outpatient clinic and delivery room of the Maternity Teaching Hospital in Erbil City were screened for the presence of thrombocytopenia. Normal and complicated pregnant women were conveniently included into the study sample; however, mothers who received blood within 10 days of the interview date were not considered. Pregnant women were interviewed and examined after obtaining their verbal consent; clinical data as well as obstetrical history were registered in a detailed questionnaire form.

Laboratory tests were performed at the Maternity Teaching Hospital’s laboratories. Venous blood (2.5 ml) was collected from each subject into an EDTA anticoagulated tube; a complete blood count was done using automated blood counter (Beckman Coulter® model AC.T-diff™ Analyzer; calibration done regularly every 2 weeks). Peripheral blood smear examination was performed for cases with platelet count below 150×10⁹/L to rule out pseudo-thrombocytopenia and to possibly detect features of microangiopathy and TTP. Complementary laboratory tests including blood urea level, serum creatinine, protein in urine, total serum bilirubin (TSB), serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) were done according to the standard methods.
Coagulation screening represented by prothrombin time (PT) and activated partial thromboplastin time (APPT) was done for thrombocytopenic mothers who had PE or HELLP syndrome according to the standard manual methods [18], using BIO kits of Biolabo, France.

Three cases with thrombocytopenia of no obvious cause were screened by enzyme-linked immunosorbent assay (ELISA) technique for presence of antibodies and viral antigens. Tests were done for antinuclear antibody (ANA), anti-double stranded DNA antibody, anticardiolipin antibody (aCL), lupus anticoagulant (LA), cytomegalovirus (CMV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV).

**Controls**

A control group of 150 apparently healthy non-pregnant women aged between 15 to 46 years was taken during the period of this study. Control subjects were mostly in-patients and out-patients who agreed to a complete blood test. The main purposes for having a control group were: 1) to compare the mean platelet count of the pregnant group with that of a control group, and 2) to confirm that the usual threshold of 150×10⁹/L is appropriate for non-pregnant women.

**Follow-up**

Clear instructions were given to 68 thrombocytopenic pregnant women through a specially prepared follow-up card to contact the hospital soon after delivery in order to arrange for subsequent tests for both the neonate and the mother. Sixty-one women completed the follow-up process, while 7 refused follow-up. Fifty-one neonates of thrombocytopenic pregnant group were clinically examined for apparent purpura and petechiae, and neonatal platelet count was checked. Cord blood sample was collected when applicable; ordinary venous sample was taken within 24 hours post-delivery after obtaining the mother’s consent. Maternal platelet count was rechecked within 8-10 days. Serum samples of 61 mothers were collected and kept in deep freezing (-20°C) for further serological testing if required.

**Statistical Analysis and Data Management**

Statistical analysis was performed using the Microsoft® Excel, Professional Edition 2003. Descriptive statistics (means, percentiles, and proportions) are mostly presented. Confidence intervals on percentile were computed using a binomial method [19]. Statistical significance was calculated using the X²-test for categorical variables and Student t-test for continuous variables. A p-value of <0.05 was considered statistically significant.

**Results**

**Characteristics of the Pregnant and Control Women**

A total of 850 pregnant women were included in this study; 68 were in the first trimester of pregnancy, 329 in the second and 453 in the last. Their ages ranged between 15 to 45 years (mean: 28.2±5.9 years). The control group included 150 apparently healthy non-pregnant women, and their ages ranged between 15 and 49 years (mean: 25.1±6.6 years).

The mean platelet count of pregnant women (221±59.9) was significantly lower compared with controls (mean: 273±66.9) (Table 1). Platelet counts of 150×10⁹/L represented the first percentile in the control group and the 8th percentile in the pregnant women. The 2.5 percentile for the platelet count during pregnancy (120×10⁹/L) was significantly lower than the value usually accepted in a general population. Figure 1 reveals a significant left sequence of platelet count histogram in pregnant compared with non-pregnant women.

The 2.5 percentile for the platelet count of the control non-pregnant women was 162×10⁹/L with confidence interval (CI =10.7) including 150×10⁹/L, thus confirming that the usual threshold of 150×10⁹/L is appropriate for non-pregnant women of childbearing age in the general population.

**Prevalence and Causes of Thrombocytopenia Among the Pregnant Group**

Out of 850 pregnant women, 68 had platelet count <150×10⁹/L (prevalence 8%); of them, 60 (88.2%) had mild thrombocytopenia (counts of 100-149×10⁹/L) and 8 (11.8%) had moderate thrombocytopenia (counts of 50-99×10⁹/L); no case was found to have severe thrombocytopenia (counts <50×10⁹/L).

Sixty-one women of the thrombocytopenic pregnant group completed follow-up. Causes of maternal thrombocytopenia are shown in Figure 2.

More than two-thirds of the thrombocytopenic pregnant group (70.6%) had platelet count above the 2.5 percentile for the platelet count during pregnancy (counts between 120 and 149×10⁹/L). The remaining 29.4% had platelet count below the 2.5 percentile (<120×10⁹/L). Severity of thrombocytopenia in relation to the causes is shown in Table 2.

**Clinical Characteristics of Thrombocytopenic and Non-thrombocytopenic Pregnant Women**

The clinical characteristics among the thrombocytopenic and non-thrombocytopenic pregnant women are shown in Table 3.

<table>
<thead>
<tr>
<th>Platelet count (&lt;10⁹/L)</th>
<th>Pregnant women</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>221±59.9</td>
<td>273±66.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>215</td>
<td>273</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Range</td>
<td>71-471</td>
<td>136-527</td>
<td></td>
</tr>
<tr>
<td>2.5 percentile</td>
<td>120</td>
<td>162</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>97.5 percentile</td>
<td>356</td>
<td>442</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>4</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;150×10⁹/L)</td>
<td>8%</td>
<td>0.7%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
More than 70% of the thrombocytopenic pregnant women were in the third trimester of pregnancy and none was in the first trimester. Figures 3 reveals an increasing frequency of thrombocytopenia with progression of pregnancy. The difference in gestational age was highly significant (p<0.001), though parity difference was not statistically significant.

**Women with GT**

Pregnant women with GT (45 cases) constituted 73.8% of thrombocytopenic pregnant cases and 5% of the whole pregnant sample under the study. Their mean platelet count was 125×10^9/L. Forty women had mild and 5 had moderate thrombocytopenia; none of the latter group had platelet count < 75×10^9/L. The majority (78%) were in the third trimester of pregnancy and 22% were in the second trimester, of which 2 cases were at < 20 weeks of gestation. The difference in gestational age between women with GT and the rest of the pregnant cases was highly significant (p<0.001).

**Women with Thrombocytopenia due to Hypertensive Disorders of Pregnancy**

The total number of women who had hypertensive disorders of pregnancy was 88 (10% of all women): PE: 63 cases (40 severe), gestational hypertension: 16 cases, chronic hypertension: 10 cases (5 proceeded to PE and one to partial HELLP syndrome), and HELLP syndrome: 3 cases. The relative frequency of thrombocytopenia among this group was 16% (11 PE and 3 HELLP cases). Hypertensive disorders were present in 23% of all thrombocytopenic women. Seven mild and 2 moderate thrombocytopenias were recorded among 40 women with severe PE; only 2 mild thrombocytopenias were recorded among 23 mild PE. This indicates that the frequency and severity of thrombocytopenia were proportional to the severity of the disease; however, this difference was not significant.

**Newborns of Thrombocytopenic Mothers**

Sixty-one thrombocytopenic pregnant women gave birth to 57 (89%) viable and 7 (11%) dead babies (58 single and 3 twin pregnancies). All deaths were intrauterine deaths (IUD). Of the 57 viable newborns, 51 (89%) were tested for platelet count within the first 24 hours post-delivery. Only 2 (4%) had a platelet count below 150×10^9/L with no bleeding complications (Table 4). The mean platelet count among tested newborn babies was 240 (±7.1) (range: 79-355×10^9/L).

**Table 3. Clinical characteristics of pregnant women with and without thrombocytopenia**

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Thrombocytopenia</th>
<th>No thrombocytopenia</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age (Year±S.D.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>28.4±5.52</td>
<td>28.2±5.97</td>
<td>0.88</td>
</tr>
<tr>
<td>Median</td>
<td>28</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>19-41</td>
<td>15-45</td>
<td></td>
</tr>
<tr>
<td>Gestational age (week)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-13 wk (68)</td>
<td>0 (0%)</td>
<td>68 (100%)</td>
<td></td>
</tr>
<tr>
<td>1-26 wk (329)</td>
<td>20 (6%)</td>
<td>309 (94%)</td>
<td></td>
</tr>
<tr>
<td>≥ 27 wk (453)</td>
<td>48 (10.6%)</td>
<td>405 (89.4%)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>P0 (311)</td>
<td>26 (8%)</td>
<td>285 (92%)</td>
<td></td>
</tr>
<tr>
<td>P1 (202)</td>
<td>23 (11%)</td>
<td>179 (89%)</td>
<td></td>
</tr>
<tr>
<td>P2-4 (259)</td>
<td>12 (4.5%)</td>
<td>247 (95.5%)</td>
<td></td>
</tr>
<tr>
<td>P5+ (78)</td>
<td>7 (9%)</td>
<td>71 (91%)</td>
<td></td>
</tr>
</tbody>
</table>

GT: Gestational thrombocytopenia; PE: Preeclampsia; HELLP: Hemolysis, elevated liver enzymes, low platelet count; ITP: Immune thrombocytopenic purpura.
Discussion

There are several causes of thrombocytopenia in pregnancy; however, in practice, few are common. The prevalence of thrombocytopenia in this study was 8%, which is quite close to the result of a relevant study by Burrows and Kelton [9]. Boehlen et al. [3] reported a higher prevalence rate (11.5%) among near-term pregnant women because of the higher incidence of GT and pregnancy-induced hypertension in late pregnancy [20,21]. The prevalence rate of our study would have risen to 10% if pregnant women of <20 weeks of gestation were excluded.

In our study, no maternal and/or fetal complications due to thrombocytopenia were noted. None of the thrombocytopenic pregnant women had severe thrombocytopenia (<50 \times 10^9/L). The majority (88%) had mild thrombocytopenia, and only 12% had moderate thrombocytopenia. These results are close to what have been reported by Boehlen et al. and Burrows and Kelton [3,9]. GT and thrombocytopenias caused by hypertensive disorders of pregnancy together made up 96.7% of all cases. GT formed the majority of cases (73.8%), which in turn made up the bulk of the mild thrombocytopenic group. Five cases with GT (11%) had moderate thrombocytopenia, and the latter constituted 62.5% of all moderate thrombocytopenic women, which is comparable to results of Parnas et al. [22], who reported 59.3% GT among a group of moderate and severe thrombocytopenic pregnant women in Be’er-Sheva, Israel.

Thus, it does not seem reasonable to perform detailed investigations in all cases of mild maternal thrombocytopenia during the third trimester, as a specific diagnosis is rarely found. This may be due to lack of some investigations to identify ITP, and because mild maternal thrombocytopenia is usually not associated with maternal or neonatal morbidity. For these reasons, in the absence of an underlying disease, it would be prudent to refrain from detailed investigations in the presence of a platelet count above 120 \times 10^9/L late in pregnancy. This is quite consistent with the directions given by Boehlen et al. [3]. This attitude does not imply that thrombocytopenia late in pregnancy should be neglected.

In our study, two women had ITP, with relative frequency equalling 0.2% (1:425), while Boehlen et al. [3] reported 1:1700 pregnancies, McCrae et al. [23] reported 1:1000 pregnancies, and Burrows and Kelton [9] reported 1:500 pregnancies [3,23,9]. Hypertensive disorders of pregnancy affected 10% of women; 21% of them had thrombocytopenia, who in turn accounted for 23% of all thrombocytopenic cases. Very similar rates were reported by Parnas et al. [22] and Burrows and Kelton [9] (22%, 21%, respectively). The frequency of thrombocytopenia was greater among severe hypertensive cases (systolic blood pressure of ≥160 and/or diastolic of ≥110 mm Hg), but not to a significant level. None of the thrombocytopenic cases was identified to be attributed to drugs, SLE, DIC, TTP or HUS.

Our study does not allow us to define a clear protocol for pregnant women with platelet counts between 75 and 119 \times 10^9/L. It seems reasonable, however, to follow the directions of Boehlen et al. [3] and to consider limited investigations when clinical history and examination are normal. On the other hand, thrombocytopenia below 70 \times 10^9/L, a threshold beneath which the diagnosis of GT is generally not considered, requires investigation.

The frequency of thrombocytopenia was increasing with progression of gestation with a peak in the last four weeks of gestation. These results were expected because both PE and GT (>96% of thrombocytopenic cases) occur in the late second and third trimesters. The placental size enlarges with progression of gestation, and consequently more capturing and destruction of platelets ensue [1]. Maternal parity was found to be influential but not to a statistically significant degree (p=0.08). Multiparous women will have larger placental size [21]. Similar results were observed by Burrows and Kelton [12].

Two newborns of thrombocytopenic mothers had thrombocytopenia. The first had moderate thrombocytopenia, born to an ITP mother, while the second had mild thrombocytopenia and was born to a mother with GT. Both were full-term and had no bleeding complications. Mothers with GT might give birth to thrombocytopenic fetuses who may stay thrombocytopenic for two to four weeks. Song and Kim [24] reported 10% of newborns born to a group of GT mothers as having mild to moderate thrombocytopenia. Kaplan et al. [25] reported 12% of newborns of GT mothers as thrombocytopenic, and all were mild. Seven cases of fetal deaths (intrauterine) occurred, and all were due to obstetrical problems, and three were immature.

Table 4. Characteristics of newborns of thrombocytopenic pregnant women

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GT</th>
<th>PE</th>
<th>HELLP</th>
<th>ITP</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2 of 51</td>
</tr>
<tr>
<td>Twins</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>6 of 61</td>
</tr>
<tr>
<td>IUDs</td>
<td>2</td>
<td>2</td>
<td>2*</td>
<td>0</td>
<td>6 of 61</td>
</tr>
<tr>
<td>Pre-term</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>5 of 61</td>
</tr>
<tr>
<td>Cesarian deliveries</td>
<td>17</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>25 of 61</td>
</tr>
<tr>
<td>Viable newborns</td>
<td>45</td>
<td>9</td>
<td>1</td>
<td>2</td>
<td>57 of 64</td>
</tr>
<tr>
<td>Dead newborns</td>
<td>2</td>
<td>2</td>
<td>3**</td>
<td>0</td>
<td>7 of 64</td>
</tr>
</tbody>
</table>

* 1 was twin ** 1 was premature twin

GT: Gestational thrombocytopenia; PE: Preeclampsia; HELLP: Hemolysis, elevated liver enzymes, low platelet count; ITP: Immune thrombocytopenic purpura; IUD: Intrauterine death.

References