

# Thrombocytopenia in pregnancy

## Abstract

Thrombocytopenia is a frequent hematological finding in pregnancy. Resulting from diverse etiologies, it may be pregnancy specific; in others instances, it may be unrelated to pregnancy. Although pregnancy is associated with certain physiological changes leading to decrease in platelet count, there are certain pathological conditions that may have a significant impact on both mother and fetus. These conditions may vary from clinically benign to life threatening states, e.g., HELLP syndrome. In this review we will briefly discuss various conditions causing thrombocytopenia in pregnancy and approach to their optimal management.

**Keywords:** HELLP syndrome, platelet count, peripheral blood film, traumatic vaginal, non-pregnant IT

Volume 5 Issue 5 - 2017

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**Received:** December 18, 2016 | **Published:** December 12, 2017

**Abbreviations:** GT, gestational thrombocytopenia; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulins; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; SLE, systemic lupus erythematosus; AFLP, acute fatty liver of pregnancy; PT, prothrombin time; APLS, antiphospholipid syndrome

## Introduction

Thrombocytopenia is second only to anemia as a common hematological abnormality occurring during pregnancy, and is observed in approximately 8-10% of pregnancies.<sup>1</sup> It may result from a number of causes ranging from benign disorders like gestational thrombocytopenia to life threatening illnesses, e.g., HELLP syndrome, that are associated with variable degree of maternal and fetal morbidity and mortality. During pregnancy, there is usually a decrease in platelet count, especially towards the end of pregnancy. This is mainly due to dilutional effect by increased plasma volume and accelerated platelet destruction across the placenta.<sup>2,3</sup> Majority of females have platelet counts within normal range; however, if platelet count was towards the lower limit of normal range in the initial part of pregnancy, there may be a steeper decline and thus thrombocytopenia may set in towards the later part of pregnancy. It is advisable that before labeling the patient as thrombocytopenic, factitious thrombocytopenia should be ruled out first by reviewing peripheral blood film.

About 75% of cases of thrombocytopenia during pregnancy are due to benign process of gestational thrombocytopenia; rests are due immune mechanism, hypertensive disorders, infections or drugs etc. Some of these processes are pregnancy specific, while others are not specific to pregnancy and also occur in non-pregnant settings.<sup>4</sup> In this review we will briefly discuss various pathophysiological mechanisms leading to thrombocytopenia during pregnancy and precise review of their diagnosis and management.

## Gestational thrombocytopenia

Gestational Thrombocytopenia (GT) is a variant of physiological thrombocytopenia observed mostly in second and third trimester. However, there is a minimal risk of bleeding in the mother as well as the fetus. GT is the diagnosis of exclusion. There is no history of thrombocytopenia prior to pregnancy, though there may be history of thrombocytopenia in previous pregnancies only recurring in the

subsequent pregnancies. GT must be differentiated from immune thrombocytopenia. Confirmation of normal platelet count before pregnancy reduces the probability of ITP. Exact cause of GT is not known, dilutional effect due to increased plasma volume; decreased platelet production and increased turnover are presumed as probable mechanisms.<sup>5</sup> Platelet count is usually above  $70 \times 10^9/l$ ; however, there are reports of more severe thrombocytopenia, not responding to steroids and resolving after pregnancy. GT is usually not associated with any adverse effects to the fetus, neonate, or mother, and no management is necessary other than periodic monitoring, usually at 4-6weeks intervals. Anesthetic referral may be required for counts less than  $70 \times 10^9/L$ . As a rule, epidural anesthesia is safe above  $80 \times 10^9/l$  counts.<sup>1</sup> Traumatic vaginal delivery should be avoided; however caesarean section may have to be opted for obstetric reasons. GT is self-limited and resolves within 1-2months after delivery.<sup>4</sup>

## Immune thrombocytopenia

Immune thrombocytopenia (ITP) is occasionally observed in pregnancy, occurring in 1 in 10,000 pregnancies.<sup>6</sup> It can occur as a primary condition or may be secondary to viral infections or autoimmune diseases. Of all cases of primary immune thrombocytopenia, about two third of patients have pre-existing disease and the remaining one third are diagnosed for the first time during pregnancy. It is an immune mediated thrombocytopenia usually occurring in first trimester with moderate to severe reduction in platelet count. Previous history of thrombocytopenia and severity of thrombocytopenia differentiate ITP from GT. However, cases with mild thrombocytopenia and no previous history are difficult to be differentiated.<sup>7-10</sup> Clinical presentation is similar to that in non-pregnant IT, and generally has a correlation with the severity of thrombocytopenia; however, in most cases thrombocytopenia and bleeding tendency worsen with the progress of pregnancy. Patients may present with purpura, bruising or mucosal bleeding or sometimes may be asymptomatic. Though immune thrombocytopenia may occur at any time during pregnancy, it is commonly seen in the first trimester. Primary IT is the diagnosis of exclusion. The goal of treatment is to prevent bleeding. Treatment is required if platelet count falls below  $50 \times 10^9/l$ , especially late in pregnancy or if there is bleeding at any stage. Corticosteroids and intravenous immunoglobulins (IVIg) are the agents of choice. Corticosteroids are as effective in pregnant women as in non-pregnant women with 70-80% response rate.<sup>4</sup> However, keeping in view the

toxic effects of steroids during pregnancy; minimal effective dose should be administered.<sup>11</sup> IVIg may be considered in some cases, especially late in pregnancy. Rituximab has been used for IT in pregnancy but has been observed to cause a delay in lymphocyte maturation. It is thus suggested that advantages and disadvantages of each agent should be considered separately depending upon severity of thrombocytopenia, time and duration of pregnancy and patient's symptoms.

Decision about mode of delivery should be made on obstetric grounds. However, use of forceps, fetal blood sampling and fetal electrodes should be avoided and anesthetic consultation should be sought especially for counts less than  $70 \times 10^9/L$ . In general, it is advisable to avoid epidural, if count is  $<80 \times 10^9/L$ , although anesthetists usually make a decision on a case to case basis. IgG antibodies cross the placenta and may cause fetal thrombocytopenia.<sup>12</sup> There is no definite correlation between degree of fetal and maternal thrombocytopenia. The best predictor is history of thrombocytopenia in prior sibling. Fetal platelet count is closely monitored immediately after delivery and for first 5-6days, especially if initial count is low. Treatment with immunoglobulins may be required if platelet count falls below  $20 \times 10^9/L$ . Fetal platelet count usually returns to normal by one month of age.<sup>4</sup>

### Preeclampsia and HELLP syndrome

Preeclampsia is the commonest cause of maternal mortality and is characterized by hypertension and significant proteinuria ( $>300\text{mg}/24\text{hrs}$ ) after 20weeks of gestation. Thrombocytopenia is seen in 50% cases of Preeclampsia.<sup>13</sup> It is usually observed in the third trimester and is mild to moderate in majority of cases. Severe thrombocytopenia is observed in  $<5\%$  of cases. Sometimes thrombocytopenia is seen before the symptoms of preeclampsia and therefore preeclampsia should be considered in patients of isolated thrombocytopenia seen in late second and during the third trimester. Pathogenesis is unknown, however it is proposed that there is some endothelial cell activation in preeclampsia that leads to platelet activation, coagulation cascade activation and thus platelet consumption. The condition resolves spontaneously after delivery. Since thrombocytopenia is mostly mild to moderate, no treatment is usually required, and conservative management is the priority. However severe cases may require treatment by correction of coagulopathy and expeditious delivery. Fetal thrombocytopenia is usually not observed except in premature and growth retarded fetuses.

HELLP syndrome, characterized by hemolysis, elevated liver enzymes and low platelet count, is observed during the third trimester and in 30% of cases manifests in postpartum period. It has high mortality rate of 3-4%. Thrombocytopenia is mainly due to endothelial damage, leading to platelet aggregation and thus consumption.<sup>14</sup> Micro thrombi also get deposited in liver sinusoids and cause their obstruction and elevation of liver enzymes. Complications include DIC, abruptio placentae and renal failure. Management should aim to deliver the mother as early as possible depending upon maternal and fetal condition.<sup>15,16</sup> Treatment includes maternal support with FFP, cryoprecipitate and platelet transfusion, and for fetal lung maturity, steroids are helpful. Condition improves quickly after delivery, though may worsen sometimes in first 24-48hours.<sup>17</sup>

### Thrombotic microangiopathies

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are referred to as thrombotic microangiopathies and

are not pregnancy specific.<sup>18,19</sup> TTP and HUS share many overlapping features and it is sometimes difficult to differentiate them from each other and sometime there is difficulty even in differentiating them from other disorders like Preeclampsia, HELLP syndrome and acute fatty liver of pregnancy, which may also show the features of microangiopathic hemolytic anemia and thrombocytopenia.<sup>4</sup> TTP is a rare disorder classically characterized by microangiopathic hemolytic anemia, thrombocytopenia and neurological abnormalities, fever and renal disease; however neurological symptoms are more prominent.<sup>20</sup> TTP is usually due to acquired deficiency of ADAMTS-13 observed mostly during mid-second or third trimesters.

Why the incidence of TTP increases in pregnancy is not known but it has been observed that patients with pregnancy associated TTP are at increased risk of TTP in subsequent pregnancies. HUS is usually observed after delivery and is predominated by renal symptoms and minimum neurological symptoms.<sup>4,21</sup> Both conditions require supportive management.<sup>22</sup> Rational Plasma therapy and its use has significantly reduced fetal as well as maternal mortality. Urgent and repeated plasma exchange may be required until platelet count is normal. Renal dialysis may be required in case of marked renal insufficiency (as in HUS). Platelet transfusion is contraindicated in both conditions.

### Miscellaneous causes for thrombocytopenia

**Nutritional deficiency:** In folic acid and vitamin B12 deficiencies, thrombocytopenia is usually observed as a part of pancytopenia. However, folic acid deficiency is not common in pregnancy as most of the women take folic acid supplements. B12 deficiency is rare and is not pregnancy associated. Supplement therapy leads to dramatic improvement in blood counts including platelet count.

**Drug induced thrombocytopenia:** Drug induced thrombocytopenia occurs during pregnancy as it occurs in non-pregnant women. Quinidine, sulfonamides and heparin therapy are among the most common drugs associated with acute thrombocytopenia. Management includes stoppage of the offending drug and use of a suitable alternative.<sup>3</sup>

**Autoimmune disease:** The most common disorder among autoimmune diseases seen in females and associated with thrombocytopenia is Systemic Lupus Erythematosus (SLE). SLE is a multisystem disorder commonly observed among females of child bearing age. Thrombocytopenia is seen in 14-26% patients of SLE and is mainly due to peripheral destruction caused by autoantibodies or immune complexes.<sup>3</sup> Maternal antibodies may cross the placenta and cause fetal thrombocytopenia. The thrombocytopenia is less severe than that seen in patients of ITP. Management should focus on therapeutic measures for primary disorder. IVIGs are indicated in patients presenting with bleeding or marked thrombocytopenia particularly towards the end of the third trimester.

**Acute fatty liver of pregnancy (AFLP):** AFLP typically presents in the first pregnancy usually during the second and third trimesters. There is usually a short history of nausea, vomiting, abdominal pain, altered maternal behavior and laboratory features of cholestasis.<sup>23</sup> Thrombocytopenia is mild and other laboratory features include prolonged Prothrombin time (PT), low fibrinogen and features of low grade DIC.

**Antiphospholipid syndrome (APLS):** APLS is characterized by recurrent thrombosis of placental blood vessels, fetal loss and thrombocytopenia.<sup>24</sup> About 28-40% of SLE patients has

antiphospholipid antibodies or Lupus anticoagulant and has increased risk of thromboembolism as compared to those who lack these antibodies.<sup>3</sup>

**Other obstetric causes:** Other obstetric diseases such as amniotic fluid embolism, abruptio placenta and uterine rupture are associated with DIC and thus thrombocytopenia due to consumption coagulopathy.<sup>25</sup>

## Conclusion

Thrombocytopenia in pregnancy may occur as a physiological phenomenon or may be due to diverse pathological processes. It may range from mild to severe thrombocytopenia and may have high maternal and fetal mortality. It is thus very important to understand various pathophysiological mechanisms leading to thrombocytopenia in pregnancy, and to make a precise diagnosis of the underlying mechanism in every patient so as to ensure a good maternal and fetal outcome.

## Acknowledgements

None.

## Conflict of interest

The author declares no conflict of interest.

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