

Maternal Thrombocytopenia: Obstetricians Dilemma, to Act or Not?

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Abstract

Pregnancy is an altered physiological state characterized by hemodilution and increased platelet consumption leading to thrombocytopenia. Gestational thrombocytopenia is the most common cause of decreased platelets in pregnancy but the diagnosis is challenging due to lack of specific diagnostic test. The degree of thrombocytopenia in gestational thrombocytopenia is mild with minimal risk of maternal bleeding and fetal complications. It needs to be differentiated from other etiologies like pre-eclampsia, DIC, HELLP syndrome, drug induced, systemic causes and alloimmune maternal ITP as well as fetal neonatal alloimmune thrombocytopenia (FNAIT) as maternal ITP has lower platelet counts and mild risk of fetal hemorrhage whereas FNAIT rarely has platelet count above 20,000/L. The treatment for alloimmune causes includes steroids and or IVIg. None of the causes of maternal thrombocytopenia dictates mode of delivery or forms basis for decision of cesarean delivery, however for surgical procedures maternal platelet counts of > 50,000/L and for epidural anesthesia > 70,000/L are recommended.

The current paper focuses on the etiology, symptom, diagnosis, treatment and implications of maternal thrombocytopenia on mother and fetus in light of currently published literature by The American college of Obstetricians and Gynecologists committee.

Keywords: *Gestational Thrombocytopenia; Alloimmune Maternal ITP; Fetal Neonatal Alloimmune Thrombocytopenia*

Platelets play a pivotal role in primary and secondary homeostasis. Pregnancy is an alters physiological state characterized by hemodilution. In pregnancy thrombocytopenia is partly due to hemodilution and due to increased consumption in peripheral tissue with increased platelet aggregation due to thromboxane A2 levels. However, this physiological thrombocytopenia of pregnancy is mild and has no adverse effect on fetus and mother [1,2].

Thrombocytopenia is defined as blood platelet count less than $150 \times 10^9/L$ the normal range been $150 - 450 \times 10^9/L$. It is arbitrarily categorized as mild ($100 - 150 \times 10^9/L$), moderate ($50 - 100 \times 10^9/L$) and severe ($< 50 \times 10^9/L$) [3].

Gestational thrombocytopenia

It is the most common cause of thrombocytopenia in pregnancy affecting 5 - 11% of pregnant women and responsible for 75% of cases of thrombocytopenia in pregnancy (Table 1). The exact pathophysiology is unknown, but it may be the result of various processes notably haemo dilution will increase platelet consumption across placenta possibly attributed to immune process [4].

Gestational Thrombocytopenia-75%
Immunological basis - Immune ITP Fetal and neonatal alloimmune thrombocytopenia (FNAIT)
Hypertensive disorders of pregnancy- Preeclampsia, HELLP, TTP, HUS- 15 - 20%
Others- APLA, SLE, Infections (HIV, CMV, <i>H. pylori</i> , Hepatitis C)
Drugs- Heparin, Antimicrobials, Analgesics, Anticonvulsants
Systemic disorders- DIC, Splenic sequestration, Bone marrow disorders, Nutritional deficiency

Table 1: *Thrombocytopenia in pregnancy.*

In most of the patients, gestational thrombocytopenia is an incidental finding posing no bleeding risk to mother of fetus with occurrence in third trimester of pregnancy. The platelet counts are typically more than $70 \times 10^9/L$ and usually more than $100 \times 10^9/L$ [5]. The differentiation from immune thrombocytopenic can be difficult as there is lack of specific diagnostic test and the diagnosis is based on exclusion. However, the platelet count in gestational thrombocytopenia is rarely as low as $50 \times 10^9/L$.

The incidence of neonatal thrombocytopenia in women with gestational thrombocytopenia is 0.1 - 2.8% [5] based on the available literature studies. It resolves quickly after delivery, but it is desirable to perform platelet count at 6 weeks post-natal. Gestational thrombocytopenia and does not lead to maternal bleeding risk or fetal thrombocytopenia [6,7]. Therefore, it is not an indication for cesarean delivery. In case of low platelets less than 50000/L fetal scalp electrodes or sampling and high or mid cavity operative delivery should be avoided and cesarean section should be done for only obstetrics indication.

In case of platelet count less than 80000/L epidural anesthesia should be avoided, and cord sample should be taken to ascertain baby’s platelet count. It is also advisable to monitor in neonate for potential thrombocytopenia by sampling on day 1st and 4th. The summary of flash points related to gestational thrombocytopenia are depicted in table 2.

Most common cause occurring in III trimester
No specific test for diagnosis
Perform peripheral blood smear examination for platelet count
Mild thrombocytopenia < 70,000/L
Not associated with maternal bleeding
Spontaneous resolution after pregnancy

Table 2: *Gestational thrombocytopenia.*

Thrombocytopenia within immunological basis

It can be of two types 1) maternal immune (idiopathic) thrombocytopenic purpura ITP and 2) Fetal and neonatal alloimmune thrombocytopenia (FNAIT).

Maternal immune (idiopathic) thrombocytopenic purpura ITP

It is chronic condition characterized by antibody-mediated destruction impaired platelet production [5] with incidence of 0.1/1000 pregnancies [7,8]. It occurs due to specific platelet antibodies against surface glycoproteins that cause immune-mediated platelet destruction in mother and after crossing placenta causing fetal thrombocytopenia. Generally, the platelet count less than $100 \times 10^9/L$ [9].

In primary form there is isolated thrombocytopenia where in second form it is associated with underlying disease or drugs [10]. It can be classified on the basis of duration into newly diagnosed, persistent (3 - 12 months) and chronic (more than 12 months) [9,11]. The diagnosis is by exclusion due to lack of availability of specific test and Bone marrow examination is not indicated unless there are unusual features or lack of response to specific treatment [12].

In studies by Webert., *et al.* [13] and Loustav., *et al.* [14] minimal maternal risk of bleeding was noted and if at all reading was noted it was mild. Care A., *et al.* [15] in their study concluded that in severe ITP with platelet count less than $50 \times 10^9/L$ the incidence of post partum hemorrhage was 21%. The incidence of fetal thrombocytopenia was low, and the fetal platelet count did not correlate with maternal thrombocytopenia with the incidence of fetal hemorrhage been less than 1% [13,14].

The primary concern is maternal hemorrhage and there is a general consensus that 50,000 platelets are safe for vaginal or operative delivery. Epidural anesthesia should not be given in patients with platelet count less than 80000 [9]. The most dreaded complication is neonatal intracranial hemorrhage. Fetal scalp samples do not give reliable counts not do percutaneous umbilical blood sampling owing to risk of hemorrhage. There is lack of evidence that cesarean prevents intracranial hemorrhage and hence isolated maternal ITP is not an indication for surgery. All necessary measures to avoid baby’s head trauma should be employed. Neonatal thrombocytopenia is expected therefore neonatal team should be alerted. Cord sample may be taken for platelet count assessment but capillary sample is preferred. Intramuscular vitamin K should be avoided in neonates without platelet count estimate. Neonates are treated by IV IG and its are given if there is any life threatening hemorrhage. It is always useful to do early pregnancy counseling in women with Maternal immune (idiopathic) thrombocytopenic to make them aware of possible risks like relapse, risk to fetus, treatment required during pregnancy, PPH, restrictions on the use of epidural anesthesia and remote like fetal intracranial hemorrhage and maternal death. The summarized flash points are shown in table 3.

Immune mediated
Platelet count < 1,00,000/L
Risk of post-partum hemorrhage if count < 50,000/L
Increased risk of fetal thrombocytopenia
Prednisone first line treatment
Intra venous immunoglobulins IVIg second line treatment

Table 3: Maternal immune thrombocytopenia.

Fetal and neonatal alloimmune thrombocytopenia (FNAIT)

It occurs due to maternal alloimmunization to fetal platelet antigens with trans placental transfer of platelet specific antibodies leading to platelet destruction in neonate. It is platelet equivalent of hemolytic (Rh) disease of newborn. Its occurrence is 1 per 1000 - 3000 live births [16]. Clinical evidence suggest that it occurs in first live born infants and is potentially life-threatening [17]. Dreadful sequel is intracranial hemorrhage [18].

Fetal intracranial hemorrhage due to fetal and neonatal alloimmune thrombocytopenia can occur in uterus and in half of the patients could be detected by Ultrasonography before labor onset. In contrast, hemorrhage in ITP occurs in neonatal period [19]. There can be intraventricular, periventricular and parenchymal hemorrhage. This alloimmune thrombocytopenia is due to antigens on platelet membrane glycoprotein, the antigens designated as human platelet antigen (HPA) [20] with more than 15 recognized plated specific antigens with most of the severe cases associated with HP A1a [21] which may occur as earliest 20 weeks of gestation [22]. The disease may be worse in subsequent pregnancies [23]. However newer studies do not suggest the same. Maternal anti HPA1a antibody levels may help to identify whether succeeding pregnancy will have thrombocytopenia or not [24] (Table 4).

Rare immune mediated
Platelet equivalent of hemolytic (RH) disease of new born
Life threatening fetal intracranial hemorrhage
Human platelet antigen HPA-1a
Fetal platelet count typically < 20,000/L
First line treatment - IVIg and or Prednisone

Table 4: Fetal and neonatal alloimmune thrombocytopenia (FNAIT).

Other causes

The hypertensive disorders causing maternal thrombocytopenia like preeclampsia HELLP syndrome resolve after delivery. The incidence of DIC might prompt clinician for aggressive treatment like FFP infusion, cryoprecipitate and platelet transfusion if needed.

The microangiopathy is like TTP and HUS have higher propensity to cause placental ischemia making baby’s prognosis poor. Plasma exchange, Rituximab monoclonal antibody against CD 20 are mainstay of treatment with platelet infusion been contraindicated in TTP and HUS. Antiphospholipid syndrome and SLE can cause maternal thrombocytopenia but it is rarely severe. Administration of Aspirin during pregnancy has a good outcome. Infections particularly virus can also cause reduction in platelet count which is usually transient but prolonged HIV and CMV are notorious for it. Heparin induced thrombocytopenia is also not uncommon in mother occurring due to maternal administration of unfractionated heparin.

Flash points

- Rarely hematological malignancies, bone marrow failure syndromes and nutrition deficiency can attribute to maternal thrombocytopenia. The treatment depends on treating the underlying causes. Peripheral blood smear examination to rule out platelet clumping as a cause of pseudo thrombocytopenia [4]. Antiplatelet antibody is not recommended for work up of routine maternal thrombocytopenia [11]. Platelet count between 100000 to 150000 in a symptomatic women is usually gestational thrombocytopenia. Platelet count less than 100000 is suggestive and less than 50000 almost certain due to ITP. Sudden onset of thrombocytopenia during last trimester of postpartum is likely due to pre-eclampsia, TTP, HUS, DIC or ITP. Preeclampsia associated thrombocytopenia resolves after delivery, platelet transfusion are recommended for thrombocytopenia with active bleeding and or cases for major surgery (target maternal platelet count > 50,000/L) [25].
- Gestational thrombocytopenia and does not increase significant risk of maternal bleeding of fetal thrombocytopenia and therefore cesarean delivery and fetal platelet count determination regularly are not indicated [1,3,6,7]. Generally, platelet count decrease for 1 to 2 days after birth followed by rapid recovery within 2 - 6 days [26,27].
- There is no specific platelet threshold which pregnant patient should be treated for ITP initiation of treatment when there is symptomatic bleeding or platelet count below 30000 [28] or to increase platelet count to safe level for procedure (for epidural anesthesia [9] 70,000 and for cesarean delivery 50,000) [28,29].
- Corticosteroids or IVIG or both as first-line treatment for ITP up to 21 days. Prednisone at dose of 0.5 - 2 mg/Kg body weight daily as initial treatment then adjusted to minimum dose, the initial response comes in 4 - 14 days and reaches peak in 1-4 weeks [9,11,28]. IV IG initial dose 1 gram per kg body weight as first-line dose initial response occurs in one two three days with peak response into 2 - 7 days [11]. Those failing for these treatments should go for splenectomy [9]. It should ideally be done in second trimester. Platelet transfusion is reserve for life threatening hemorrhage or those who are in need of urgent surgery [28].
- There is lack of reliable data to suggest that medical therapies reliably prevent fetal thrombocytopenia or improve fetal outcome and that cesarean delivery safer than vaginal delivery for fetus [28]. No maternal test and reliably predict severity of thrombocytopenia and fetus and there is no evidence to support routine use of intrapartum fetal platelet count. Alloimmune thrombocytopenia should be suspected in unexplained fetal and neonatal thrombocytopenia hemorrhage or USG consistent with intracranial bleeding.
- Serological determination of platelet typing HPA using amniocytes or cell free fetal DNA from maternal blood, [30] is a complex test and should be performed by experience laboratory as ambiguous results can occur. Population based screening for platelet antigens incompatibility is not recommended due to doubtful clinical use and cost-effectiveness [31]. Fetal platelet counts are measured by percutaneous umbilical cord blood samples. Early cordocentesis is unnecessary [32,33]. Fetal blood sampling reserved until 32 weeks of gestation in women planning for vaginal delivery.
- Early therapy (IV IG with oral prednisone) based on risk of recurrence of fetal intracranial hemorrhage is instituted [34].
- Labor and vaginal delivery and not contraindication for fetus with platelet count greater than 50000 but a cesarean delivery is recommended below 50,000 /L level.

Treatment

Platelet transfusion is contraindicated in immune thrombocytopenia- maternal and FNAIT and Prednisone and IVIG are the mainstay of treatment. Platelet transfusion is indicated for counts below 50,000/L along with IVIG. Prednisone during first trimester may substantially increase the risk of cleft lip and may worsen gestational diabetes, osteoporosis and maternal hypertension. Splenectomy is the last treatment resort reserved for second trimester.

Conclusion

Thrombocytopenia, defined as blood platelet count below 150,000/ L, is the second commonest bleeding disorder after anemia in pregnancy. Gestational thrombocytopenia explains 70 - 80% of all cases of thrombocytopenia in pregnancy. Hypertensive disorders account for approximately 20% and immune thrombocytopenic purpura for about 3 - 4%. Blind platelet transfusion for immune mediated thrombocytopenia should not be carried out and all risk benefits need to be evaluated, a multidisciplinary approach can be useful in such situation.

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Conflict of Interest

I declare no conflict of interest.

Author Contributions

Concept, search, draft, final approval.

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