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Immune (Idiopathic) thrombocytopenic purpura diagnosed in pregnancy: A case report

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Abstract
Immune (idiopathic) thrombocytopenic purpura (ITP) is an uncommon, but important cause of thrombocytopenia in pregnancy. It is a diagnosis of exclusion, and management should be based on a multidisciplinary care approach. ITP is characterized by moderate to severe thrombocytopenia commonly diagnosed in the first or early second trimester of pregnancy. The severity of thrombocytopenia has adverse implications on both maternal and fetal wellbeing. This paper is based on a case seen and managed in our institution and aims to discuss the various causes of thrombocytopenia and its implications in pregnancy as well as management of ITP in pregnancy based on current evidence and guidelines.

Keywords: Immune thrombocytopenic purpura, Idiopathic thrombocytopenic purpura, ITP, pregnancy management

Introduction
Immune thrombocytopenia (ITP) presents unique challenges in the peripartum setting. The diagnosis of ITP is similar to the non-pregnant patient except pregnancy related causes of thrombocytopenia must be considered. Management of ITP will change over the course of pregnancy and closer monitoring is critical as delivery approaches. The mode of delivery is based on obstetrical indications. First line therapies are glucocorticoids or intravenous immunoglobulin (IVIG). Many second line therapies may be safe in pregnancy. While the majority of neonates are unaffected, neonatal platelet counts can decline in the first days after delivery and may require therapy. Maternal treatment and platelet count do not appear to predict the risk of neonatal thrombocytopenia. The strongest predictor is the previous sibling's history. ITP is not a contraindication for pregnancy; women with a history of ITP should not be discouraged from conceiving as their ITP can be safely managed with close monitoring and multidisciplinary coordination with obstetrics and pediatrics.

ITP is an acquired autoimmune disease characterized by an antibody and cell-mediated destruction of platelets and impairment of megakaryocytic maturation, which leads to transient or permanent decrease in platelet count. It is caused by clusters of IgG antibodies directed against one or more platelet glycoproteins. Antibody coated platelets are destroyed prematurely in the reticuloendothelial system, especially the spleen. ITP can develop at any time point during pregnancy and can be difficult to distinguish from other causes of thrombocytopenia in pregnancy. Pregnancy does not raise the risk of relapse nor it worsens the active disease. The estimated incidence of ITP complicating pregnancy approximates 1 case in 10,000 births. Women with pre-existing ITP may have worsening disease during pregnancy, nearly half requiring treatment. Treatment of peripartum ITP is indicated depending on the signs of bleeding, the degree of thrombocytopenia and clinical course of the pregnancy. Higher platelet count treatment thresholds are required as the mother approaches delivery and is at higher risk for bleeding. Careful monitoring of the mother throughout pregnancy is critical to avoid risk to both the mother and neonate. In this case report, diagnosis and care of women with peripartum ITP will be discussed.

Thrombocytopenia should first be confirmed by reviewing the peripheral smear to exclude pseudothrombocytopenia or platelet clumping. ITP is diagnosed after other causes of acquired thrombocytopenia are excluded such as drug induced thrombocytopenia, cirrhosis and splenic sequestration. Inherited thrombocytopenia should be considered in patients with long standing thrombocytopenia and inadequate platelet count responses to glucocorticoids and/or intravenous

immunoglobulin (IVIG). An absence of a family history of thrombocytopenia does not definitely rule out inherited thrombocytopenia as some have autosomal recessive inheritance pattern and *denovo* mutations can occur.
Obtaining pre-pregnancy platelet counts and an extensive family and bleeding history is critical for diagnosis.

Case Report
We report a case of ITP diagnosed in pregnancy. The patient was a 21 year old primigravida who was transferred at
32 weeks of gestation from a private healthcare institution for thrombocytopenia detected on routine clinical testing. Collaboration between the obstetrician and hematologist in our case was important to provide a smooth antenatal journey to ensure a good maternal and fetal outcome.
Our patient had no past medical history, and her antenatal follow-up was uneventful prior to the transfer. A complete blood count was performed, and the hemoglobin value was 8.6 gm%, leucocyte count was 9400 cells/cumm, platelet value was 30 x 10^9/L. Peripheral blood film showed microcytic hypochromic anemia with thrombocytopenia, polychromasia +, mild anisopoikilocytosis, tear drop cells +, few target cells and elliptocytes. The Sickling test was negative and lactate dehydrogenase (LDH) level was normal. Her blood pressure was normal and there was no evidence of proteinuria. Her baseline liver function, renal function, thyroid function, coagulation screening and uric acid levels were within normal limits. Screening tests for infectious diseases such as hepatitis B, hepatitis C, HIV, dengue were all negative. Autoimmune markers such as antinuclear antibody, anti-dsDNA antibody and anticardiolipin antibodies were also negative.
In view of the acute presentation and with no other obvious causes of thrombocytopenia, a working diagnosis of ITP was made and she was started on intravenous (IV) immunoglobulin and oral prednisolone. Her platelet counts increased to 70 x 10^9/L before discharge from the hospital. She was subsequently followed up at our hospital. Throughout the antenatal period, she had multiple hospital admissions due to low platelet counts. Infusions of IV immunoglobulin and adjustment of her steroid doses had achieved an acceptable platelet count during these admissions. At 37 weeks of gestation, she presented with false labour pain with no cervical dilatation or uterine contractions. An ultrasound scan showed a normal growing fetus in a cephalic presentation with no abnormal placental location, and normal doppler study. She was observed over 24 hours and her symptoms were resolved subsequently.
At 38 weeks, she was again admitted for follow up with platelet counts of 90 x 10^9/L. Inj Leucovorin 500 mg was given 12 hourly followed by Inj Dexona 4 mg over 12 hourly. A repeat ultrasound scan showed a normal fetus with normal Doppler study and an estimated fetal weight of 3.3 kg. In view of increasing resistance to conventional ITP treatment and good fetal weight, plan for delivery was discussed at 39 weeks with the patient and her relatives with opinions from the hematologist after weighing the risks and benefits of worsening thrombocytopenia that could potentially cause maternal morbidity and fetal thrombocytopenia due to transfer of antiplatelet antibodies transplacentally. The patient was offered a trial for normal labor using dinoprostone gel. However due to failure of induction and unfavorable cervical scores, the decision was made to deliver the baby by elective cesarean section at 40 weeks with platelet cover. Her platelet count was 1 lakh/cumm preoperatively and 1 pint platelet concentrate was given prior surgery. Risk of postpartum hemorrhage and possible need for medical treatment, uterine compression sutures, radiological intervention and cesarean hysterectomy were discussed with the patient and the relatives.
The cesarean section was uneventful, the uterus was well contracted and various oxytocics were administered. The patient was post-operatively stable and was managed with 1-pint erythrocyte transfusion and 2-pint FFP transfusion. She delivered a healthy female child who was admitted under NICU for platelet concentrate transfusion and IV IG. The patient was administered oral prednisolone 1 mg/kg from post-op day 2 and dosage was tapered over the next 5 days. She was discharged on day 7 with a platelet value of 120 x 10^9/L.

Discussion
ITP occurs in 0.1-0.2% of all pregnancies and is responsible for 5% of all cases of thrombocytopenia diagnosed in pregnancy [1].
Gestational thrombocytopenia is the most common cause, and it accounts for 65-80% of cases [2]. Due to physiological changes in pregnancy, such as increased blood volume, platelet activation and clearance [3], mild thrombocytopenia occurs during late pregnancy, especially during the third trimester. Most importantly, patients remain asymptomatic, and the platelet counts are usually more than 70 × 10^9/L, with about two-thirds being 130 150 × 10^9/L. Gestational thrombocytopenia is not associated with fetal thrombocytopenia, and it spontaneously resolves after delivery.
Preeclampsia has to be considered in a patient with thrombocytopenia in the third trimester associated with raised blood pressure (≥140/90 mm Hg) and significant proteinuria >0.3 g/day. The triad of microangiopathic hemolytic anemia, abnormal liver function (AST ≥70 IU/L), and thrombocytopenia with a platelet count less than 100 × 10^9/L constitutes the diagnosis of hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome [4]. Other markers include an elevated LDH ≥ 600 IU/L and raised bilirubin levels ≥17.1 μmol/L [5]. Both conditions require medical stabilization followed by delivery.
Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are both manifestations of a similar mechanism of microvascular platelet aggregation. Although rare, these two conditions should be considered in pregnant women with thrombocytopenia. TTP is characterized by a pentad of microangiopathic hemolytic anemia, thrombocytopenia, neurological abnormalities, fever and renal dysfunction, and can occur in any trimester. HUS is predominated by renal abnormalities rather than neurological abnormalities and occurs most commonly in the postpartum period (>90%). The manifestations of TTP and HUS may be confused with preeclampsia or HELLP syndrome, but hypertension is not common in TTP and HUS, and there is no coagulopathy.
Autoimmune conditions such as systemic lupus erythematosus (SLE) and antiphospholipid antibody syndrome may first appear or increase in severity during pregnancy and thrombocytopenia occurs in 10-30% of cases. Other causes of thrombocytopenia in pregnancy include:

Gestational thrombocytopenia	Antiphospholipid antibody syndrome
Preeclampsia/HELLP syndrome	Disseminated intravascular coagulation
Acute fatty liver of pregnancy	Viral infection
TTP	Nutritional deficiency
HUS	Drug use
SLE	Primary bone marrow disorder

1. Disseminated intravascular coagulation, especially in the context of placental abruption, massive hemorrhage secondary to uterine rupture, retention of an intrauterine stillbirth and amniotic fluid embolism.
2. Acute fatty liver of pregnancy, with typical presentations of malaise, anorexia, nausea, vomiting, epigastric or right upper quadrant pain, mental state changes and cholestasis.
3. Viral infections such as HIV and hepatitis C-induced thrombocytopenia.
4. Drug causes, such as heparin-induced thrombocytopenia or use of recreational drugs such as cocaine which has been associated with a syndrome resembling HELLP, and may be accompanied by a transient development of profound thrombocytopenia.
5. Primary bone marrow disorder, usually associated with other blood cell dyscrasias. A bone marrow examination will be necessary to make a diagnosis of the type of bone marrow disorder.

In our case, all the common causes had been excluded by performing initial blood investigations and in the context of the history, physical findings and early presentation, a diagnosis of ITP was made and appropriate treatment was rendered. Generally speaking, thrombocytopenia that occurs in the first or early second trimester or in cases with moderate to severe low platelet counts, the patient should be investigated for secondary causes. ITP can only be diagnosed if all the above-mentioned causes are excluded.

The management of ITP in pregnancy requires close collaboration between the obstetrician, hematologist, anesthetist and neonatologist. Upon diagnosis, the severity of thrombocytopenia should be ascertained, and platelet counts should be increased and stabilized to a safe level in pregnancy, especially during delivery. Patients will require close monitoring, with routine blood pressure and weight measurements, urine dipstick for protein and serial platelet counts at every visit [3]. Treatment should be instituted, if platelets fall to an unsafe low level or if the patient is symptomatic for bleeding. The American Society of Hematology (ASH) and the British Committee for Standards in Hematology (BCSH) - General Hematology Task Force guidelines provide guidance to what is considered a safe platelet level for delivery, antenatal procedures as well as when to institute treatment. The ASH suggests a safe platelet count of at least 50×10^9/L for both vaginal delivery and cesarean section. Platelets less than 10×10^9/L or platelets $10 - 30 \times 10^9$/L in the second/third trimester or symptomatic bleeding are indications for treatment [6]. The BCSH suggests a safe platelet count of at least 50×10^9/L and 80×10^9/L for vaginal delivery and cesarean section respectively. A minimum platelet count of 80×10^9/L is considered safe for epidural analgesia. Platelets less than 20×10^9/L in any trimester is an indication for treatment under the BCSH guidelines [7].

The standard treatment for ITP is corticosteroids, with a starting dose of 1 mg/kg/day (weight based on pre-pregnancy weight), after which the dose should be titrated to the lowest effective dose to achieve remission [5]. If rapid rise of the platelet count is necessary, then IV immunoglobulin would be the treatment of choice. IV immunoglobulin is less likely to cause adverse side effects associated with corticosteroids like diabetes, hypertension, excessive weight gain and osteoporosis. However, the use of IV immunoglobulin is limited by its high cost and transient response. For patients who do not respond to single therapy, a combination of corticosteroids and IV immunoglobulin may be considered. IV steroids such as pulse dexamethasone and methylprednisolone may be used in lieu of oral steroids in such cases.

The use of other medical treatments has also been tested. These treatments are still controversial due to lack of safety data and true efficacy. If these agents are to be used, it has been recommended not to use them in the first trimester when organogenesis occurs. Examples of such treatments include as follows.

1. IV anti-D has been used in women in their second and third trimesters. One study reported that six out of eight women had successful responses, with no maternal or fetal effects and no evidence of fetal hydrops [8].
2. Immunomodulating drugs such as azathioprine have been shown to work and found to be safe in pregnant women with renal transplants. Cytotoxic drugs such as cyclophosphamide cannot be used due to its teratogenic potential.
3. Monoclonal antibodies such as rituximab have been used to treat B-cell lymphoma and recently found to be able to treat ITP. It has been found not to be associated with fetal malformations, although there are a few case reports which documented infants with abnormal B-cell development in the first year of life.
4. Use of thrombopoietic agents such as eltrombopag or romiplostim have been studied, but there is still little experience in their use in pregnancy.

For cases refractory to conventional treatment or if treatment toxicities are unacceptable, splenectomy can be performed in the second trimester when fetal and anesthetic risks are minimal [9]. The BCSH has recommended the laparoscopic approach for splenectomy.

With regards to peripartum management in patients with ITP, the risk of maternal hemorrhage is minimized by ensuring minimum platelet counts required for vaginal delivery, cesarean

section and epidural analgesia as stipulated by the ASH or BCSH guidelines [6, 7]. The transplacental passage of maternal antiplatelet antibodies in pregnancy can cause fetal thrombocytopenia, and the most feared consequence of this is fetal intracranial hemorrhage during vaginal delivery. The risk of fetal thrombocytopenia has been reviewed in a meta-analysis by Burrows *et al*., which showed that 10.1% of infants born to mothers with ITP had platelet counts below 50×10^9/L and 4.2% below 20×10^9/L. Fujimura *et al*. noted that the risk of intracranial hemorrhage in the offspring of patients with ITP is very low (< 1%) [10]. Various studies have also shown no correlation between maternal ITP status, platelet counts and the development of intracranial hemorrhage. There is no role of fetal blood sampling or cordocentesis to predict fetal thrombocytopenia [5]. Evidence so far has suggested that the most reliable predictor of fetal thrombocytopenia is a prior history of thrombocytopenia in an older sibling at delivery.

It was previously believed that cesarean section reduced the risk of fetal intracranial hemorrhage associated with trauma during vaginal birth. Cook *et al*. reappraised the peripartum management of patients with ITP and found no association between the mode of delivery and the risk of intracranial hemorrhage [11]. As evidence has suggested poor correlation between maternal ITP and development of intracranial hemorrhage, it is recommended that cesarean section be performed for obstetric indications only.

The newborn should be assessed for thrombocytopenia with serial platelet counts for 1 week postpartum, as well as assessment for intracranial hemorrhage should be done. Brain imaging should be performed if neonatal platelet count is below 50×10^9/L. It has been shown that neonatal platelet counts fall to a nadir by day 2. By day 7, the platelet counts should have begun to rise or stabilized. ASH has recommended that infants with platelet counts below 20×10^9/L or symptomatic for bleeding receive IV immunoglobulin [6]. The use of steroids is controversial due to predisposition to neonatal sepsis [12].

Conclusion

Thrombocytopenia complicates 10% of all pregnancies and fortunately, the majority of cases are benign and gestation-related. There are, however, other causes which can potentially increase both maternal and fetal morbidity and mortality. When thrombocytopenia is diagnosed, a systematic approach is required to ascertain the cause. Gestational thrombocytopenia or ITP can only be diagnosed if other causes are excluded. Gestational thrombocytopenia is mild and does not have adverse effects on the mother or fetus, does not require treatment and usually resolves after delivery. On the other hand, ITP is associated with moderate to severe thrombocytopenia which increases the risks of maternal hemorrhage as well as fetal thrombocytopenia and potentially, fetal intracranial hemorrhage. Treatment is needed in ITP and is no different from non-pregnant individuals, except for non-conventional drugs such as cytotoxics or thrombopoietic agents. Peripartum management involves optimizing platelet counts for delivery and procedures such as epidural analgesia. Well-controlled ITP with adequate platelet counts is not a contraindication to vaginal delivery, and cesarean section should only be performed based on obstetric indications only. There is also no strong association between maternal ITP and the development of intracranial hemorrhage in the newborn, making difficult predictability of hemorrhage. It is thus recommended to monitor the infant with serial platelet counts and to assess for intracranial bleeding postpartum. Treatment should be instituted if the platelet counts are low, or if the infant is symptomatic.

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