CASE SERIES

Case Series: Maternal and Fetal Outcome in Patients with Immune Thrombocytopenic Purpura Admitted to a Tertiary Care Institution

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Abstract

Thrombocytopenia in pregnancy is defined as platelet counts of <150,000/cu.mm. Most commonly, the fall in platelet counts is due to gestational thrombocytopenia which is usually a self-resolving condition. However, immune thrombocytopenia (ITP) appears to be a relatively rare cause of thrombocytopenia which may complicate certain pregnancies and predispose affected patients to severe hemorrhagic complications. Therefore, it is important that ITP may be identified promptly during pregnancy as it has the potential to affect the mother and the fetus adversely. Here, we have followed the pregnancy outcomes of five women who were diagnosed cases of ITP.

Keywords: Corticosteroids, Pregnancy, Thrombocytopenia.

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Introduction

Thrombocytopenia affects approximately 10% of all pregnancies while platelet counts <100,000/cu.mm are seen in 1% of pregnancies.[1,2] The most common cause of thrombocytopenia in pregnancy is gestational thrombocytopenia (GT) which accounts for approximately 75% of such patients. Other important causes include HELLP syndrome seen in association with preeclampsia, acute fatty liver of pregnancy (AFLP), ITP, thrombotic microangiopathies (TMAs), thrombotic thrombocytopenic purpura (TTP), atypical hemolytic uremic syndrome (aHUS), among others.[3]

Immune thrombocytopenia is an autoimmune disorder that brings about immune-mediated destruction of platelets causing isolated thrombocytopenia. It has an incidence of 1 in 1000 to 1 in 10,000 pregnancies.[4] Patients with ITP are more predisposed to develop life-threatening bleeding especially during delivery. Immune thrombocytopenia is the most common cause for platelets counts falling to less than 50×10^9/L during pregnancy.[5]

Immune thrombocytopenia is primarily a diagnosis of exclusion. There are no specific tests to diagnose ITP in pregnancy and it is advisable to examine a peripheral blood smear to rule out pseudothrombocytopenia and platelet clumping.[5] Antiplatelet antibodies have poor sensitivity and specificity and are not clinically indicated.[6] While thrombopoietin levels are elevated in pregnant women with ITP, such testing is not routinely available or recommended.[7]

Here, we elucidate the clinical course and fetomaternal outcome of five patients who had presented to us with thrombocytopenia at varying gestational ages and were eventually diagnosed with ITP.

Case Description

Case 1

A 32-year-old G6P1IUFD1SA4 woman who is a diagnosed case of chronic ITP had come to the outpatient department for antenatal registration at 8 weeks of gestation. She had a history of four spontaneous miscarriages, all within the 1st trimester. On running a profile for recurrent pregnancy loss, APLA, ANA, and lupus anticoagulant antibodies were all negative. She was diagnosed as a case of ITP when she presented with severe thrombocytopenia during her 3rd miscarriage and was started on corticosteroids. However, she did not respond to steroids and had to be given IVIg prior to a suction and evacuation done in view of missed abortion. After this, she was started on azathioprine along with corticosteroids. However, during follow-up, the patient had persistent thrombocytopenia and a conjoint decision was taken to start her on romiplostim. The patient showed transient improvement in platelet count which did not last. Romiplostim was discontinued as she conceived again. This pregnancy continued till 28 weeks when she had a sudden, unexplained intrauterine fetal death. She had presented to the hospital with a platelet count of 1000/cu.mm at that time. She was given IVIg at a dose of 1 mg/kg/day for 2 days and labor was induced for her. She delivered a fresh stillborn male fetus weighing 880 gm. Peripartum, she had an episode of traumatic postpartum hemorrhage requiring packed cell and platelet transfusion. Post-delivery, the patient was restarted on romiplostim and weekly doses were adjusted which however, did not improve her thrombocytopenia significantly

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with platelets always remaining between 30,000/cu.mm to 40,000/cu.mm. After a joint consensus, a decision of laparoscopic splenectomy was taken for the patient. The procedure was completed uneventfully on a platelet count of 50,000/cu.mm with perioperative platelet transfusion. Post-procedure, the patient was lost to follow-up, conceived spontaneously and reported to the institution with a platelet count of 10,000/cu.mm. She had no complaints of bleeding from anywhere. She was given IVIg at a dose of 1 mg/kg/day for 2 days and her platelet count after 1 week was 100,000/cu.mm. Prednisolone was also continued for her and was planned to be titrated. However, despite best efforts, the patient was lost to follow-up and next reported to us at 35 weeks of gestation with a platelet count of 10,000/cu.mm. As per the patient, she had no complaints whatsoever throughout the pregnancy. She was given pulse dose of methylprednisolone for 3 days along with IVIg at 1 mg/kg/day for 2 days. Platelet counts after 1 week was 120,000/cu.mm. Consequently, labor was induced at 37 weeks of gestation in view of intrauterine growth restriction and she normally delivered a female child weighing 2.234 kg. Post-delivery recovery was rapid and uneventful. The infant showed no evidence of thrombocytopenia at 1 week of life. Repeat platelet counts on the 3rd day after delivery was 100,000/cu.mm and a healthy mother and baby was discharged on the 5th day. On her 2 weekly follow-up, her platelet counts were 100,000/cu.mm and both mother and baby were healthy.

Case 2

A 22-year-old G2P1L1 presented with severe thrombocytopenia with platelet count of 30,000/cu.mm at 33 weeks of gestation. She had no complaints whatsoever. Platelets were reduced on smear while hemoglobin levels were 8 g% suggestive of moderate anemia. WBC counts was normal at 6600/cu.mm. All of her viral markers were negative and there was no apparent cause for her thrombocytopenia. She was started on pulse dose of intravenous methylprednisolone at 20 mg/kg for 3 days followed by oral prednisolone at 1 mg/kg. Her platelet counts increased to 40,000/cu.mm. However, within a week, the platelet counts again dropped to 30,000/cu.mm and continued dropping up to 20,000/cu.mm. However, patient had no complaints of bleeding from any site. After consultation with the hematologist, intravenous immunoglobulin (IVIg) was given at 35 weeks at a dose of 1 mg/kg/day for two consecutive days. Platelet counts repeated on the 3rd and 7th days after giving IVIg were 70,000/cu.mm and 110,000/cu.mm. Patient was also continued on prednisolone. She went into spontaneous labor at 36 weeks of gestation and decision for an emergency cesarean section was taken as patient was not willing for vaginal birth after cesarean section. Procedure was uneventful with no requirement of blood or blood product transfusion intraoperatively. She delivered a healthy female child of birth weight 2.234 kg with a 5-minute APGAR score of 9/10. The baby had normal platelet count as per postnatal evaluation. The mother was continued on prednisolone at 1 mg/kg dose and both mother and baby was discharged uneventfully on the 5th postoperative day. On 1-year follow-up, the patient was started on azathioprine by hematologists when her thrombocytopenia relapsed on corticosteroid.

Case 3

A 33-year-old G2P1L1 with previous lower segment caesarean section (LSCS) done 5 years back came to the outpatient department at 31 weeks of gestation with a platelet count of 70,000/cu.mm. A peripheral smear showed normal morphology with decreased platelets on smear. There were no giant platelets or clumping of platelets on smear. Viral markers for HIV, HBV, HCV, and Dengue virus were negative. A diagnosis of ITP was made on joint consensus with hematologists. An obstetric scan showed the fetus to be having hydrops along with polyhydramnios with an amniotic fluid index (AFI) of 27 cm. The patient was started on prednisolone at a dose of 1 mg/kg to which her platelet counts were gradually increasing. However, the patient had an unexplained IUFD at 32 weeks of gestation and induction of labor was done. She underwent an emergency LSCS in view of a failed induction and received four units of random donor platelets (RDP) transfusion in view of increased intraoperative bleeding. Preoperatively, her platelet count was 80,000/cu.mm. There was no episode of postpartum hemorrhage. She was restarted on prednisolone 1 mg/kg post-delivery with a plan for weekly tapering subject to further platelet counts.

Case 4

A 30-year-old G3P1L1SA1 woman diagnosed with chronic ITP during her last pregnancy 3 years back was referred to our institute at 10 weeks of gestation with a platelet count of 6,000/cu.mm. She was on oral azathioprine for her ITP and had a history of corticosteroid therapy during her previous pregnancy. She was given pulse dose of methylprednisolone for 3 days at 1 mg/kg/day followed by IVIg 1 gm/kg/day for two consecutive days. Following this, her platelet count picked up to 70,000/cu.mm. Azathioprine and prednisolone (with gradual tapering) was started for her and she was maintaining platelet counts between 60,000/cu.mm to 70,000/cu.mm. However, at 24 weeks of gestation, her platelet counts dropped to 20,000/cu.mm. and she was given another dose of IVIg at 1 mg/kg/day for two consecutive days which brought up her platelet count to 80,000/cu.mm. Her pregnancy was uneventful with platelet counts ranging between 60,000/cu.mm and 70,000/cu.mm until the 35th week of gestation when she went into preterm labor. An emergency cesarean section was planned for her as the patient had a history of cesarean section 3 years back and was not willing for a trial of labor. Her platelet count was 20,000/cu.mm and eight units of platelet transfusion were given preoperatively. She also received intravenous methylprednisolone at a dose of 10 mg/kg body weight before the procedure. The procedure was uneventful and she delivered a healthy male baby of birth weight 2.836 kg with APGAR of 9/10 at 5 minutes of life. The postoperative platelet count was 30,000/cu.mm on which she received IVIg at a dose of 1 gm/kg/day for 2 days. Her platelet counts post-IVIg was 120,000/cu.mm. Notably the patient developed hyperglycemia with ketonuria and mild acidosis on blood gas analysis on the second postoperative day. Intravenous steroids were withheld and the hyperglycemia responded to insulin drip and the crisis of a full-blown diabetic keto acidosis could be averted. As of the 4th postoperative day, oral prednisolone had been restarted at minimal dose with strict blood glucose monitoring and the patient was provisionally planned to be started on romiplostim after detailed evaluation and risk and benefit ratio assessment by hematologists. Presently, both mother and baby are doing well.

Case 5

A 26-year-old primigravida presented to us at 35 weeks of gestation with platelet count of 30,000/cu.mm. Her pregnancy was uneventful until the 30th week of gestation wherein a CBC report showed her platelet count to be 80,000/cu.mm which showed progressive decline to 72,000/cu.mm, 50,000/cu.mm and then 30,000/cu.mm. HIV. HBV, HCV, and Dengue virus markers were negative. She had no

complaints of fever or bleeding from any site. There was no history of pregnancy-induced hypertension and her BP was recorded to be normal on current visit. A peripheral blood smear showed reduced platelets while hemoglobin and WBC counts were normal. There was no giant platelets or clumping of platelets on the smear. She had been started on prednisolone by another practitioner elsewhere but there was clearly, no response. On joint consultation with hematology, she was provisionally diagnosed as a case of ITP and IVIg at a dose of 1 gm/kg/day was given for two consecutive days. Platelet counts showed an increasing trend after this with a maximum count of 100,000/cu.mm after 5 days. Induction of labor was done at 37 weeks of gestation in view of intrauterine growth restriction labor progressed and the patient delivered a female child weighing 2.124 kg uneventfully with episiotomy. However, the patient had one episode of atonic postpartum hemorrhage which was controlled with uterotonics. The mother was restarted on oral prednisolone with weekly tapering of doses and the baby showed no evidence of thrombocytopenia on blood count sent on the 5th day of life.

Discussion

Immune thrombocytopenia is primarily a diagnosis of exclusion. It is advisable to have a hematology consultation before finalizing a diagnosis of ITP in pregnancy. ITP may be primary without an underlying disease or secondary to viral infections (HIV, CMV), diseases like SLE, or certain medications.[8] All the five patients mentioned above had primary ITP as no discernible cause could be identified.

In pregnancy, treatment may be undertaken for patients with platelet count less than 20,000/cu.mm to decrease chances of bleeding or during the peripartum period to reduce complications like postpartum hemorrhage. Ideally, platelet count should be more than 50,000/cu.mm for vaginal delivery and more than 70,000/cu.mm for a cesarean section to minimize risk of intrapartum bleeding and postpartum hemorrhage.[9]

The first line of therapy in ITP is corticosteroids which should be limited to the lowest possible dose as it may be associated with gestational diabetes mellitus, hypertension, excessive weight gain and sometimes, cleft lip in the fetus when given during the first trimester.[8,10] Corticosteroids and IVIg form the first line of treatment for ITP in pregnancy with around 70–80% of responders.[12] The dose of IVIg used is usually 1 gm/kg/day following which platelet counts are repeated and a second dose may be repeated if there is no appreciable increase in platelets. Appreciable rise in platelets is documented within 2–3 days while the maximum efficacy of IVIg is seen in 7–9 days.[11,12] However, the response is short-lived with platelets dwindling in 3–4 weeks after therapy and repeat doses of IVIg may be required as is seen with our 3rd and 4th cases.

An International Working Group (IWG) defined refractory ITP as disease that does not remit with splenectomy or relapses after splenectomy.[13] The American Society of Hematology 2019 guidelines recommend thrombopoietin receptor agonists (romiplostim, eltrombopag), immunotherapy with rituximab, antimetabolites (azathioprine, mycophenolate mofetil) and if all else fails, splenectomy as second line therapies.[14] It is however, a category C drug and its safety for use in pregnancy requires further studies.[14] It is given as a weekly subcutaneous injection with doses starting at 2–3 µg/kg which may be increased to 10 µg/kg weekly depending on the response.[15] The initial response occurs within 7–14 days and the remission is varied with studies pointing toward as short as 1 year to 4–5 years.[13,15,16] Romiplostim can cross the placenta and possible adverse effects include fetal thrombocytosis thus warranting caution.[17] Response rates to romiplostim in adults go as high as 95% outside pregnancy.[17]

Antimetabolites like azathioprine which was tried for both our 1st and 4th patients are usually given when corticosteroids and/or IVIg have failed to elicit response. Response rates to the drug in ITP is modest at best and the drug is presently used when first line responses or second line responses like thrombopoietin receptor agonists have failed.[18] Azathioprine is a category D drug in pregnancy.

Splenectomy is usually avoided in the first 12 months of the diagnosis of ITP to allow for spontaneous or therapy-induced remissions.[14]

The role of platelet transfusion in ITP is limited to control episodes of acute bleeding or to raise platelet counts rapidly when an emergent procedure is being planned.

There is evidence of fetal ITP wherein the antiplatelet antibodies crossover via the placenta from the mother as they are IgG type.[5,17] Around 21–28% of neonates may develop thrombocytopenia with less than 1% having intracranial hemorrhage due to severe thrombocytopenia.[5,6] Thus, it is recommended to perform platelet count of the baby and monitor the baby after birth. For those with thrombocytopenia, the ASH recommends therapy with IVIg when there is bleeding or platelet counts are less than 30,000/cu.mm.[6] In the face of an intracranial hemorrhage, the platelet should be above 100,000/cu.mm during the 1st week and then above 50,000/cu.mm during the 2nd week of therapy.[6]

Conclusion

Diagnosing ITP in pregnancy requires a high level of clinical suspicion and a multidisciplinary team approach comprising of an obstetrician, a hematologist, an anesthetist, and a neonatologist is advisable. Treatment for ITP remains highly individualized as each patient responds differently during pregnancy. Proper counseling and due explanation of the risks of her condition to both the patient and her attendant is of extreme importance as it enables the patient to know what is to be expected. While the clinical scenario is certainly challenging for an obstetrician, the maternal and fetal outcomes with a multidisciplinary approach at a tertiary setup are mostly favorable.

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