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Eltrombopag use for refractory immune thrombocytopenia in pregnancy: A case report

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ABSTRACT

Background: Immune thrombocytopenic purpura (ITP) is a rare autoimmune disorder that involves platelet destruction in the spleen. Eltrombopag (Promacta®), a thrombopoietin agonist, has been used in non-pregnant patients to manage ITP, but few cases of its use in pregnancy have been reported.
Case Presentation: We present a case of a pregnant patient at 26 weeks of gestation with severe refractory ITP. After first-line therapies failed, the patient was treated with the drug eltrombopag. The patient had no response to initial therapy, and the fetus developed supraventricular tachycardia (SVT). This resolved with maternal digoxin but the patient elected to stop the eltrombopag. The patient refused further experimental and second-line treatments, and after a multidisciplinary meeting a decision was made to deliver by cesarean section at 30 weeks of gestation due to severe refractory ITP and allow other therapies to be tried postpartum. Preeclampsia and neonatal atrial flutter were encountered in the postpartum period but both mother and baby had good outcomes.
Conclusion: Refractory ITP in pregnancy is not well studied. Eltrombobag could have maternal and fetal side-effects but a multidisciplinary approach to management leads to favorable maternal and fetal outcomes.

1. Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder that involves anti-platelet glycoprotein antibodies that stimulate platelet destruction in the spleen. It is a rare complication in pregnancy that accounts for about 3–4% of cases of thrombocytopenia in pregnancy [1]. Maternal complications of ITP in pregnancy include mild to severe bleeding [2,3].

Current consensus supports the use of corticosteroids and intravenous immune globulin (IVIG) for ITP in pregnancy [4]. Anti-D immune globulin and platelet transfusions are also therapeutic options for patients with severe ITP. However, platelet transfusions have limited utility in ITP due to rapid platelet destruction. Splenectomies are about 90% effective in refractory ITP [5]; however, in pregnancy they may have associated maternal and fetal risks. The two most commonly used medications in the non-pregnant population are rituximab and thrombopoietin receptor agonists (eltrombopag and romiplostim), but neither is well studied in this population.

Eltrombopag (Promacta®) is a thrombopoietin receptor agonist that interacts with the transmembrane domain of the thrombopoietin receptor, leading to increased platelet production [6]. Reported side-effects include headaches, upper respiratory tract infections, nasopharyngitis, fatigue, back and bone pain, anemia, cataracts, pneumonia, liver enzyme and bilirubin elevation, and thrombotic events [7–9]. Based on limited data in pregnant women, eltrombopag is designated pregnancy category C [10]. We present a report of maternal eltrombopag use with possible side-effects of preeclampsia and fetal supraventricular tachycardia (SVT). We also offer a perspective on the multidisciplinary approach to ITP in pregnancy.

2. Case Presentation

A 35-year-old patient, G2P1001, with a history of ITP, presented at 26 weeks of gestation to a local emergency room with unremitting epistaxis and was found to have platelets of 12×10^9/L and hemoglobin of 6.2 g/dL. She received blood products and intravenous dexamethasone, and was transferred to a tertiary care center. Her history was significant for unprovoked nosebleeds throughout childhood and postpartum hemorrhage in a prior pregnancy requiring blood transfusion. She reported no significant family history of bleeding disorders. A hematologist had seen her two weeks earlier, when her platelets were 77×10^9/L and hemoglobin 6.3 g/dL, and recommended B12 injections and prednisone but the patient did not take them due to concern about potential fetal side-effects.

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On hospital day 2, the patient's platelet count was 9×10^9/L and epistaxis stopped with a nasal tamponade device. A low-lying placenta was noted on ultrasound with an estimated fetal weight in the 39th percentile. A multidisciplinary approach was taken, with the involvement of maternal fetal medicine (MFM), obstetrics, anesthesia, neonatology and hematology, in order to work up the case and plan management. Testing included a bone marrow biopsy, preeclampsia, anemia and infectious workups. The workup still led to the diagnosis of ITP by exclusion.

The patient received multiple rounds of IVIG and high-dose steroids, along with platelet transfusions, but with minimal response. Platelets remained less than 10×10^9/L, and epistaxis continued. The patient was counseled by MFM and hematology on the options of splenectomy and eltrombopag. The patient elected to proceed with eltrombopag; she received 25 mg daily for 5 days with minimal response, with platelets less than 10×10^9/L. The eltrombopag dose was increased to 50 mg daily. On the second day of increased dose therapy, at 28 weeks of gestation, fetal SVT was noted, with a fetal heart rate of 210–220 beats per minute. Pediatric cardiology was consulted and a fetal echocardiogram showed no structural malformations or hydrops fetalis. Maternal oral digoxin was prescribed and the fetal heart rate returned to normal (as shown in Fig. 1).

The patient was counseled by MFM and hematology but she elected to discontinue the eltrombopag. She was concerned about the potential effects on the fetus, even with no further fetal SVT while taking the digoxin and with no confirmation that the SVT was from the eltrombopag. She also did not wish to undergo splenectomy or consider rituximab during pregnancy due to possible risks to the fetus.

A multidisciplinary meeting was held and options were reviewed. Due to the patient having declined other treatment options and concerns for serious adverse events, such as intracranial or vaginal hemorrhage, she was offered elective preterm delivery or expectant management. The patient decided on elective preterm delivery to avoid further adverse outcomes and to allow for further treatment postpartum. She understood the risks of preterm delivery and elected to proceed. The decision was thus made for delivery in a planned setting due to severe refractory ITP.

Cesarean delivery, due to low-lying placenta, was performed at 30 weeks of gestation. The patient's platelets were 11×10^9/L. Surgery was performed under general anesthesia and she received 4 superpacks of platelets, 3 units packed red blood cells, 2 units fresh frozen plasma, 1 L albumin and 120 mL cell saver. She received carboprost tromethamine, methylergonovine and tranexamic acid intraoperatively due to uterine atony. The quantitative blood loss was 1500 mL. A live vertex female neonate was born with Apgar scores of 4 and 7 at 1 and 5 min respectively, with weight 1370 g (44th percentile). The cord blood gases did not show acidosis. The neonate was transferred to the neonatal intensive care unit (NICU) on a continuous positive airway pressure device. The patient was extubated after surgery and transferred to the recovery room.

On the first postoperative day, maternal platelets were 10×10^9/L. The patient was started on rituximab, eltrombopag and intravenous steroids. She developed mild-range blood pressures (defined as systolic 140–159 and diastolic 90–109) and severe, unrelenting headache,and was diagnosed with preeclampsia with severe features. She received magnesium sulfate for 24 h for seizure prophylaxis. The patient was discharged home on post-operative day 10 with a platelet count 18×10^9/L after 2 cycles of rituximab. The patient was advised not to breastfeed while using eltrombopag (rat pup exposure via lactation was noted in animal studies) [11]. One month postoperatively her platelets were 45×10^9/L and at two months 78×10^9/L.

On day of life 1, the neonate's platelets were 274×10^9/L. At 2.5 h of life, atrial flutter was noted with 2:1 conduction, as shown in Fig. 2. Adenosine was given with continued atrial flutter and decreased atrioventricular conduction, thus the neonate was cardioverted to normal sinus rhythm. Echocardiography was performed and no structural abnormalities were noted. The neonate remained in sinus rhythm until day of life 10, when atrial flutter returned and cardioversion was performed again. The neonate was started on sotalol and switched to propranolol prior to discharge. The neonate was discharged on day of life 71, when platelets were 511×10^9/L.

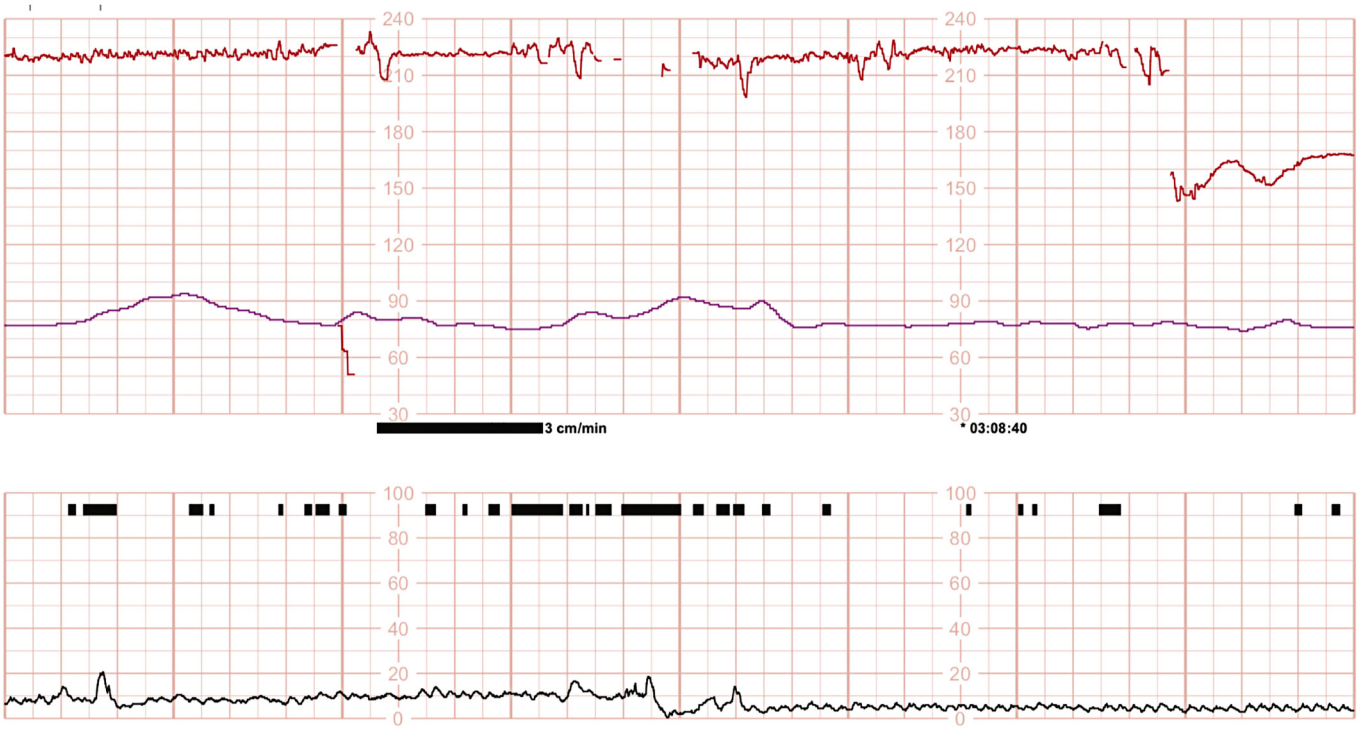

Fig. 1. Fetal heart tracing with the transition point from fetal SVT to normal fetal heart rate with a baseline of 160 beats per minute.

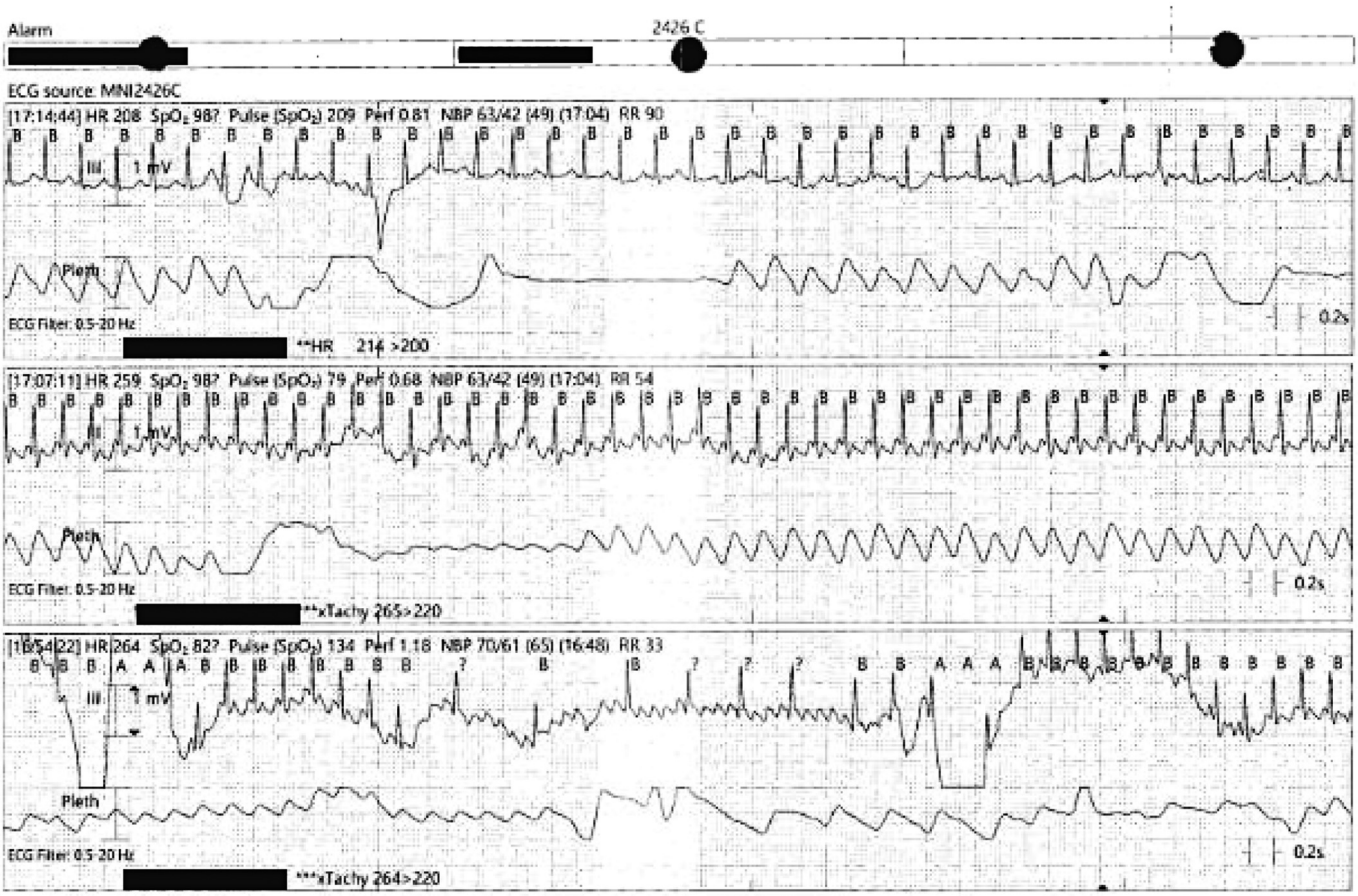

Fig. 2. Neonatal electrocardiogram from telemetry strip demonstrating atrial flutter on day of life 1. The second line demonstrates atrial flutter with 2:1 atrioventricular conduction and the third line shows a higher degree of block.

3. Discussion

Refractory ITP is diagnosed when first-line therapies fail. Only splenectomy, romiplostim, rituximab and eltrombopag have been considered and studied in pregnancy, with limited data available. In animal studies of eltrombopag, there was evidence of embryo lethality and fetal growth restriction at maternally toxic doses [12]. Case reports of maternal use during pregnancy have demonstrated development of antepartum preeclampsia, growth restriction and preterm birth [13–15]. There are no reports of fetal or maternal SVT in patients treated with eltrombopag or romiplostim.

In our case, eltrombopag was ineffective during pregnancy. Postpartum combination therapy helped achieve response, thus we cannot make conclusions that the eltrombopag alone was beneficial. In our case, the patient declined treatment options and thus patient counseling and planning by multiple providers helped to achieve good maternal and fetal outcomes.

Fetal SVT and postpartum preeclampsia were noted during treatment with eltrombopag. The timing of the events and lack of cardiac structural abnormalities originally led us to believe the fetal SVT might be a side-effect of eltrombopag. Fetal SVT, including atrial flutter, is an uncommon arrhythmia, sometimes associated with fetal accessory pathways, structural anomalies, or hereditary channelopathies [16]. After birth, the neonate had sustained atrial flutter even without further exposure to eltrombopag. In retrospect and upon discussion with the neonatologists, we believe the drug could have triggered the arrhythmia in a fetus with an underlying predisposition, but the sustained atrial flutter was likely unrelated to the medication. Decision for delivery in patients with refractory ITP is crucial and usually needs a multidisciplinary approach, especially when preterm delivery is being considered.

4. Conclusion

This is the fourth known report of eltrombopag use in pregnancy. In the other cases, it had a positive impact with minimal side-effects on pregnant women with refractory ITP [10,13–15]. Our case is the first report known to us of minimal response and fetal SVT. Although we cannot prove causation, this is the first report in the literature and we believe it is important for others to be aware of when considering eltrombopag use in pregnancy. We again noted the finding of preeclampsia in a patient treated with eltrombopag. More research needs to be done to determine association and causation with these side-effects, and efficacy of the drug. We still believe this medication has potential for benefit in pregnant women. We agree that we would trial the medication in the future with close observation for side-effects in both mother and fetus, and updated counseling on risks and benefits. In addition, further research would be extremely valuable in assessing the use and risks of this drug in pregnancy. Our case highlights the importance of a multidisciplinary approach in the management of refractory ITP to achieve optimal outcomes.

Contributors

All authors contributed equally to the preparation of this case report.

Conflict of Interest

Dr. Friedman reports personal fees from AstraZeneca, which is outside the scope of the submitted work. The other authors declare that they have no conflict of interest.

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Patient Consent

The patient gave signed consent and authorized a case report to be written on behalf of advancing medical knowledge. She understands that the case report is fully de-identified. She was given the opportunity to write a section for the paper from her perspective but declined.

Provenance and Peer Review

This case report was peer reviewed.

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