Original Article

Management of refractory itp in pregnancy with eltrombopag and neonatal outcomes

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Abstract

Background: Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by accelerated platelet destruction and impaired platelet production. During pregnancy, refractory ITP presents significant clinical challenges because severe thrombocytopenia increases the risk of maternal bleeding and complicates delivery planning. Eltrombopag, a thrombopoietin receptor agonist, may be considered in selected patients with refractory disease; however, evidence regarding its safety during pregnancy and its effects on neonatal outcomes remains limited.

Objective: To evaluate the clinical management of refractory ITP in pregnant women treated with eltrombopag, focusing on maternal platelet response, bleeding complications, delivery outcomes, and neonatal health.

Methods: This study was designed to assess pregnant women diagnosed with refractory ITP who received eltrombopag after inadequate responses to conventional therapies, including corticosteroids and intravenous immunoglobulin. Maternal clinical characteristics, platelet counts, treatment responses, bleeding events, delivery methods, and neonatal outcomes were evaluated. Neonatal assessments included platelet counts, birth weight, Apgar scores, and reported complications. The study design, sample size, treatment duration, and statistical methods should be specified according to the actual research protocol.

Results: The principal outcomes of interest included changes in maternal platelet counts following eltrombopag administration, achievement of platelet levels considered adequate for delivery, and the incidence of maternal hemorrhagic complications. Neonatal evaluation focused on thrombocytopenia, bleeding events, birth outcomes, and the need for specialized neonatal care. Actual numerical findings are required to establish the effectiveness of treatment and determine whether neonatal complications were associated with maternal disease severity or treatment exposure.

Conclusion: Refractory ITP during pregnancy requires individualized management through multidisciplinary collaboration among hematologists, obstetricians, and neonatologists. Eltrombopag may provide a therapeutic option in carefully selected cases when conventional treatments are ineffective, but its use during pregnancy requires cautious risk–benefit assessment because pregnancy-specific safety evidence remains limited. Maternal platelet response and neonatal outcomes should be monitored closely, and larger prospective studies are needed to clarify its safety and effectiveness.

Keywords: Immune thrombocytopenia, pregnancy, eltrombopag, refractory ITP, maternal outcomes, neonatal thrombocytopenia, platelet count.

INTRODUCTION

The autoimmune condition known as primary immune thrombocytopenia (ITP) is typified by a reduction in platelet count (thrombocytopenia) brought on by the body's immune system inadvertently attacking and eliminating its own platelets. Autoantibodies against platelet surface antigens, particularly glycoproteins IIb/IIIa and Ib/IX, are the main cause of this immune-mediated death. Splenic macrophages then recognize and phagocytose these antigens [1]. In certain instances, decreased bone marrow platelet production may also be involved. Depending on the severity of thrombocytopenia, the illness can cause symptoms that range from minor petechiae and bruises to more serious bleeding episodes. With an estimated yearly prevalence of 2–5 per 100,000 individuals, ITP is a very uncommon illness. Although it can happen at any age, young women are most frequently diagnosed with it, especially when they are fertile [2]. Blood testing are the main method used to diagnose ITP in expectant mothers. To determine platelet levels, a full blood count (CBC) is necessary. A peripheral blood smear, on the other hand, can assist in ruling out pseudo thrombocytopenia, where due to clumping, platelet levels appear low. Additionally, coagulation studies are essential for assessing distributed pregnancyrelated intravascular coagulation (DIC), a serious disorder [4]. Furthermore, liver function tests to rule out illnesses such HELLP syndrome or preeclampsia, which can present with comparable symptoms. A bone marrow test could be used in certain situations to rule out other reasons for thrombocytopenia, even if it's not always necessary to diagnose ITP in pregnant women. Imagining studies like abdominal ultrasonography or MRI can be used to check for splenomegaly, which can suggest a haematological disease that is underlying. All things considered, a thorough strategy that incorporates clinical assessment, blood tests, and additional diagnostic procedures as needed are crucial for precisely identifying ITP in expectant mothers[2,5].

It is estimated that there are 1-2 cases of ITP for every 1,000 pregnancies. 4-5% of pregnancyrelated thrombocytopenia are caused by ITP. The most significant fetal or neonatal consequence of ITP during pregnancy is "fetal or neonatal alloimmune thrombocytopenia." Because pharmacological side effects might impair fetal development and the course of pregnancy, the management of ITP during pregnancy is different from that for nonpregnant women. If no life-threatening bleeding signs are present, glucocorticoids are taken into consideration as the first line of treatment. Another therapeutic option is intravenous immunoglobulin (IVIgG), which is safe for the fetus but frequently expensive and linked to negative effects in mothers. There is little experience treating pregnant women with anti-Rh(D) treatment. The treatment of immune thrombocytopenia (ITP) in adults has evolved rapidly over the past decade. The second-generation thrombopoietin receptor agonists (TPO-RAs), romiplostim, eltrombopag, and avatrombopag are approved for the treatment of chronic ITP in adults. However, their use in pregnancy is labeled as category C by the United States Food and Drug Administration (FDA) due to the lack of clinical data on human subjects [6]. Drugs that mimic TPO, such romiplostime and eltrombopag, have been effectively employed. Many nonpregnant people with ITP have found benefit with TPO-mimetic medications such eltrombopag and romiplostime; however, there are few research and tests on how these medications affect pregnant women [3]. Here,

we describe a pregnant case of refractory ITP treated with eltrombopag.

CASE REPORT

25 years old G2P1 @ 32+5 weeks gestation presented to Maternal and Child Healthcare Unit II emergency, PIMS, Islamabad. This patient was a booked patient, had her booking at 16 weeks of gestation. Patient was married for 3 years and known case of ITP for 5 years. She had previous 1 scar 1 year back due to refusing trial of labour and severe thrombocytopenia. There were no other comorbid. This patient presented to emergency department at 32+5 weeks with complain of PV leaking. Upon arrival vitals were taken which came out to be normal, per abdominal examination was done on which abdomen was soft, non-tender with fundal height corresponding to her gestational age, scar tenderness was negative with no other findings. Per speculum examination was done on which there was frank pooling of clear amniotic fluid, amnicator stick came out be positive confirming initial diagnosis of PPROM, HVS was taken and there was no other positive finding. On bedside ultrasound there was single alive fetus with transverse lie, BPD/FL parameters corresponding to gestational age, placenta was anterior upper with adequate liquor and positive gross body movements. CTG was reactive. The patient was given 1 mega platelet transfusion in her current pregnancy and was on tablet Deltacortril 5mg 3tablets twice daily in BD. At the time of admission her platelet count came out to be 4k, with manual platelet count of 14k, all other labs except raised ALT were normal mentioned in Table 1.

Table 1: Blood Investigations

Tests (Normal Range)	**Results**
TLC (4-10x10^9 /L)	17.37
HB (12-15 g/dl)	11.1
Plt (150-410x10^9 /L)	4
ALT (5-42 U/L)	169
AST (5-45 U/L)	94.4
Uric Acid (3.4-8.2 mg/dl)	6.15
PT (13sec)	11.5
APTT (33sec)	28
INR	0.87
Urine Protein Creatinine Ratio ≤0.1	0.289

At first, her platelet count was declining and did not increase to a sufficient level. She didn't react to immunosuppressants and steroids. She needed platelet transfusions. Additional ITP treatment alternatives had to be such as immunoglobulin administered intravenously (IV), anti-D, and medications that mimic TPO. Because of the high expenses, short turnaround times, and Further possible adverse effects of IVIgG and anti-D on mothers, it was determined that the TPO-mimetic medication eltrombopag would be administered at 28 weeks of pregnancy. 25 mg of elthrombopag once daily (OD) was over a period of seven days. After that, the dosage was raised to 50 mg. After

two After receiving eltrombopag for weeks, her platelet count increased to

20,000/µl. Eltrombopag persisted till the baby was born. Her platelet counts never dropped below 10,000/µl after beginning eltrombopag medication. At 31+3 weeks gestation patient presented to emergency with PV spotting due to which 1 mega platelet unit was transfused Table 2.

At 32+5 weeks of gestation, patient presented to emergency with PV leaking. LSCS was planned. Dexamethasone cover was planned but due to 16,000 platelets hematology consultation was done and 40mg intravenous injection Decadron slow infusion was given. 2 mega platelet units, 6 red cell concentrates and 6 FFPs were arranged. Patient developed constant maternal tachycardia and CTG was non-reactive therefore emergency LSCS was planned. Patient was given neuroprotection (I/V MgSO4) and 1 mega platelet unit was transfused pre-op. Emergency LSCS was performed by senior obstetrician due to previous 1 + PPROM+ suspicion of chorioamnionitis + maternal tachycardia. Paediatrician was on board. Male child of 2kg with good APGAR of 7/10 and 8/10 was delivered. Per op estimated blood loss was 300-350cc, uterus was intermittently relaxing therefore classical B-Lynch was applied and haemostasis was secured with drain placed in peritoneal cavity. Per op 1 mega platelet unit was transfused due to anticipated bleeding. Peri partum and post partum periods were uneventful. On 0 post operative day her platelet count was 93,000 which decreased to 39,000 on 1st post operative day. Patient had fall of Hb of 1gm/dl therefore 1 red cell contrate was transfused. Drain was removed on 3rd post operative day as it was empty for 24 hours.

After birth, baby was immediately shifted to NICU. Platelet count of baby on 1st day of life were 82,000 which decreased to 5,000 on 2nd day of life. Suspecting neonatal alloimmune thrombocytopenia (NAIT), 2 FFPs and 2 Platelet units were transfused due to the risk of intracranial haemorrhage. But there was no increase in platelet count rather it decreased to 4000. There fore IVIgG administration was planned. After two doses of IVIgG, the baby's platelet count increased to 95,000/µl. The mother and baby were discharged from the hospital approximately 2 weeks after delivery. At the time of discharge from the hospital, her platelet count was 60,000/µl and that of the baby was 112,000/µl. She was reviewed 6 weeks after delivery. Both the mother and baby were in good health. Her platelet count was 70,000/µl.

Table 2: Platelet Count, Management, And Clinical Conditions of The Patient from The Time of Admission to Discharge from The Hospital

Date	Gestational Age (Weeks)	Danger Signs	Manual Platelet Count	Platelet Transfusion	Ongoing Treatment
25/04/2024	10+3	-	18	-	3 Tab Deltacortril X BD
30/04/2024	11+1	-	12	-	3 Tab Deltacortril X BD
14/05/2024	13+1	-	13	-	3 Tab Deltacortril X BD
25/06/2024	19+1	-	4	-	3 Tab Deltacortril X BD
19/09/2024	31+3	PV Spotting	12	1 Mega Unit Transfused	3 Tab Deltacortril X BD Tab Eltrombopag (Pagatrol) 50mg X OD
20/09/2024	31+4	-	13	-	3 Tab Deltacortril X BD Tab Eltrombopag (Pagatrol) 50mg X OD
28/09/2024	32+5	PV Leaking	16	2 Mega Units Transfused	3 Tab Deltacortril X BD Tab Eltrombopag (Pagatrol) 50mg X OD
29/09/2024	Post Natal	-	93	-	3 Tab Deltacortril X BD
30/09/2024	Post Natal	-	39	-	3 Tab Deltacortril X BD

DISCUSSION

Pregnancy-related thrombocytopenia is somewhat prevalent. The primary causes of thrombocytopenia during pregnancy include immunological disorders of pregnancy (3–4%), due to hypertensive problems (15–20%), and gestational thrombocytopenia (75%). Abnormal clinical and laboratory findings can be used to diagnosis conditions such as haemolytic uremic syndrome, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, acute fatty liver, HELLP syndrome, and preeclampsia. Moreover, thrombocytopenia can also be the main sign of viral infections or severe drug and supplement reactions, which should be carefully distinguished by examining a patient's medical history and performing laboratory tests. However, in clinical practice, GT and ITP that initially manifests during pregnancy are frequently mistaken for one another. Bone marrow aspiration is not usually performed when otherwise asymptomatic thrombocytopenia initially manifests during pregnancy. Bone marrow aspiration is not commonly used when otherwise asymptomatic thrombocytopenia initially manifests during pregnancy. The primary criteria used by haematologists and obstetricians to distinguish ITP from GT are platelet count and onset time. The diagnosis of ITP is most compatible with significant thrombocytopenia in the first or early-second trimester of pregnancy, accompanied by a decreasing platelet count as gestation advances. In contrast, GT is typically characterized as moderate thrombocytopenia that develops late in the third trimester and is not linked to proteinuria or hypertension; in these cases, the platelet count hardly ever falls below 70,000/μL[7]. The use of multiple treatment options, including glucocorticoid medication (prednisolone, prednisone, or dexamethasone), azathioprine, IVIG, rituximab, cyclophosphamide, anti-D, and platelet transfusion, before starting a TPO-RA was a typical strategy reported in the case reports. The case reports emphasized the use of eltrombopag as a final treatment option following patient consent. To further determine the safety profile of TPO-RAs, our review emphasizes their use in pregnant women. Due to the paucity of knowledge regarding their use, TPO-RA use during pregnancy has been considered difficult. The administration of eltrombopag during pregnancy is presented in case reports and cohort studies, considering the advantages and disadvantages. Eltrombopag was used in patients who were not responding to first-line treatments such IVIG, corticotherapy, azathioprine, cyclophosphamide, rituximab, and transfusion, according to all case reports.

The FDA states that it is crucial to advise expectant mothers about the possible negative effects of eltrombopag during pregnancy. The FDA advises using eltrombopag throughout pregnancy and for seven days following the last dose in conjunction with proper contraception (by using contraceptive methods that would result in <1% pregnancy rates) [8]. The approved eltrombopag dosage starts at 50 mg/day, with titration down to 25 mg/kg or up to 75 mg/kg based on platelet response.

Because of concerns regarding fetal toxicity, pregnant individuals with ITP have few therapy options for controlling thrombocytopenia. The most common medications used to treat pregnant patients with ITP are steroids and intravenous immunoglobulin. TPO-RAs may assist pregnant patients with ITP increase their platelet count within two to three weeks, according to our evaluation of the literature. According to the body of research, using TPO-RAs during the second and third trimesters appears to be safe. However, until more

data proving their safety for both the mother and the fetus is known, their usage during the first trimester, when organogenesis is at its height, must be avoided [9, 10].

CONCLUSION

Treating primary immune thrombocytopenia (ITP) during pregnancy involves a complicated web of risks and difficulties that call for a meticulous, customized strategy. Healthcare professionals must strike a balance between fetal health and maternal safety because of the autoimmune nature of ITP and the physiological changes that occur during pregnancy. A thorough grasp of the pathophysiology of the illness, a precise diagnosis, and a customized treatment plan are all necessary for effective care. Therapy choices, including thrombopoietin receptor agonists, intravenous immunoglobulin, and corticosteroids and immunosuppressive medications, need to be chosen according to the stage of pregnancy and degree of thrombocytopenia. For pregnant patients with ITP who are transfusiondependent and have not responded to steroids and immunosuppressants, eltrombopag may be a viable therapy choice. Additionally, we can lower the dangers of receiving platelet transfusions frequently. A multidisciplinary team's participation, comprising obstetricians, hematologists, and pediatricians are essential for improving outcomes for both mothers and newborns. The potential to increase therapy efficacy and safety is increasing as research advances and new treatments are developed. But maintaining a patient-centered approach is still crucial to making sure that management choices are informed based on the greatest available data and tailored to the unique needs of each patient. This thorough review emphasizes the need for more research while highlighting the state of knowledge and practice today to improve our knowledge of and approach to treating ITP during pregnancy.

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