Olgu Sunumu
Case Report

Severe Immune Thrombocytopenia in Pregnancy Treated with Eltrombopag. A Case Report.

ELTROMBOPAG TEDAVİSİ ALTINDA OLAN GEBEDE CİDDİ İMMÜN TROMBOSİTOPENİ. BİR VAKA RAPORU.

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ABSTRACT

Immune Thrombocytopenia (ITP) which is a common, acquired and autoimmune disease is defined as low platelet count secondary to increased platelet destruction or impaired thrombopoiesis by anti-thromboycte antibodies. Pregnancy-associated thrombocytopenia accounts for 5% of all the cases. Thrombopoietin (TPO) mimetic drugs, such as Eltrombopag, have been used successfully in many patients with ITP; however data on its use in pregnancy is limited. In this report, a case who was followed up with ITP and given Eltrombopag during her pregnancy, cause it could not have been controlled by any other treatment is presented. Enoxaparin therapy was iniatiated for thromboprophylaxis after the patient's platelet count responded to Eltrombopag treatment. Delivery was carried out by cesarean section. Baby was born with low birth weight and there was not any malformation. Nevertheless, further research is needed to find out whether there is a relationship between Eltrombopag use in pregnancy and low birth weight.

Keywords: Immune Thrombocytopenia (ITP), eltrombopag, pregnancy, low birth weight

ÖZ

İmmün trombositopeni (ITP), hızlanmış trombosit yıkımına ikincil düşük trombosit sayısı veya anti-trombosit antikorları tarafından bozulmuş trombopoez ile tanımlanan yaygın kazanılmış otoimmün bir hastalıktır. Eltrombopag gibi trombopoietin (TPO) -mimetik ilaçlar, ITP si olan birçok bireyde başarıyla kullanılmıştır, ancak gebelikteki kullanımı ile ilgili veriler kısıtlıdır. Bu sunumumuz da ITP tanısı ile takip edilen ve gebeliği esnasında diğer tedavi yöntemleri ile kontrol altına alınamaması nedeniyle eltrombopag verilen bir olgu sunulmuştur. Eltrombopag tedavisine yanıt alınan hastaya tromboproflaksi amacı ile enoxaparin başlanmıştır. Doğum 38. hafta da sectio ile gerçekleştirilmiştir. Düşük doğum ağırlıklı doğan bebekte herhangi bir malformasyon mevcut değildi. Düşük doğum ağırlıklı doğumlar ve eltrombopag kullanımı arasındaki ilişki hakkında daha fazla araştırma yapılması gerekir.

Anahtar Kelimeler: Immün trombositopeni (ITP), eltrombopag, gebelik, düşük doğum ağırlığı

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Immune thrombocytopenia (ITP) is an autoimmune disease that is chararacterized by antibody-mediated platelet destruction and diminished platelet production (1). Immune thrombocytopenia occurs in about 1 in 10,000 in the general population (1). Thrombocytopenia can be frequently seen during pregnancy, but ITP is responsible for only 4%-5% of thrombocytopenias seen during pregnancy (2).

Glucocorticoids and intravenous immunoglobulin (IVIG) are used in the treatment of ITP during pregnancy (3). Other treatment options come to the fore in the cases resistant to these conventional treatments, but there are safety problems regarding the use of these treatments during pregnancy. Eltrombopag is an orally used, small molecule, non-peptide TpoR agonist that increases the platelet count. Administration of thrombopoietin receptor (TpoR) agonists is an effective treatment option for non-pregnant patients with ITP. However, studies on its use during pregnancy are limited. Available data from published case reports and postmarketing experience with use in pregnant women are insufficient to assess any drug-associated risks for adverse maternal or fetal outcomes. In animal reproduction and developmental toxicity studies, oral administration of eltrombopag to pregnant rats during organogenesis resulted in embryolethality and reduced fetal weights at maternally toxic doses (4-5). Here, we will present a patient who used eltrombopag during the third trimester of her pregnancy and gave birth to a newborn without malformation.

CASE REPORT

A 29-year-old and 16-weeks pregnant woman, who is multigravida, was admitted to our emergency department with epistaxis and petechial rash in her body. In the examinations of the patient, the platelet count was found to be 3,000 u/l. Leukocyte and hemoglobin values were normal. Liver enzymes were not elevated. The coagulation tests of the patient without hemolysis were also evaluated as normal.Therefore, immune thrombocytopenia was considered in the patient. Due to the low platelet count and the high risk of bleeding, methylprednisolone and IVIG treatment at 1 mg/kg equivalent to prednisolone was started urgently. The patient's platelet count increased to 192,000/µl and she was discharged with 32 mg/day oral methylprednisolone and followed up. Two weeks later, while the patient was receiving 32 mg/day oral methylprednisolone, the platelet count was found to be 15,000/µl in the control CBC and the patient was re-interned and IVIG treatment was applied. The patient's platelet count increased to 88,000/µl and she was discharged with 32 mg/day oral methylprednisolone. Three weeks later, while the patient was receiving 16 mg/day oral methylprednisolone, platelet count in the CBC was found to be 1,000/µl and she was re-interned again. The patient was given IVIG and discharged while her platelet count was 36,000/µl. After one week, the patients's platelet count was 8,000/µl and the patient was interned for the fourth time. IVIG treatment was applied again. Her platelet count inclined up to 35,000/µl and the patient was discharged but the patient's platelet count dropped back to 1,000/µl after one week. Despite the initiation of dexamethasone and IVIG treatment, her platelet count remained between 1000 and 5000/µl. Since IVIG and steroid treatment during pregnancy was safer than other drugs used in ITP, IVIG and steroid treatment was repeated. It was not considered in the treatment because the patient was Rh - and had difficulty accessing Anti-D. Splenectomy was planned because there was no response to IVIG and steroid treatment. The patient was consulted to the general surgery and anesthesia departments for splenectomy. It was stated that the operation might have a high risk in terms of surgery and the patient did not give consent to splenectomy. Due to the low platelet count and the need for early response, it was decided to use eltrombopag instead of immunosuppressive drugs such as azathioprine and rituximab by sharing the safety profiles of the drugs with the patient. The patient was informed about eltrombopag treatment. After obtaining informed consent from the patient, eltrombopag was started at 25 mg/day at the 25th week of her pregnancy. Eltrombopag dose was increased up to 50mg/day on the third day of the treatment due to the failure to achieve the desired response. On the fourth day of eltrombopag treatment, the platelet count was observed to exceed 20,000/µl. When the platelet count reached 62.000/µl, the patient was discharged and followed up on a weekly basis. Eltrombopag is a drug with a high risk of thrombosis, and this risk is higher when the platelet count

is above 100,000 u/l. Therefore, when the platelet value increased above 100,000/µl, 60 mg subcutaneous Enoxaparin treatment was started at 28 weeks of gestation for venous thromboembolism prophylaxis. Complete blood count, liver and kidney function tests were followed regularly in clinical follow-ups. She was followed up in the obstetrics and gynecology department in terms of fetal toxicity. The delivery was performed by cesarean section at the 38th week of pregnancy. A healthy baby weighing 2470 grams was born. There was no malformation and the newborn's platelet count were 230,000/µl at birth. No complications were observed in the patient or the baby after delivery. Eltrombopag and enoxaparin treatment, which was started for the mother, was continued after delivery.

DISCUSSION

ITP during pregnancy is a clinical condition that should be managed well. Glucocorticoids are often used as initial treatment. IVIG is also a common treatment option (3). Treatment with TpoR agonists is effective, but there is not enough knowledge acquired from studies to clarify the issues with its use during pregnancy. Therefore, it is not recommended for use in pregnancy unless certain conditions develop. Due to possible teratogenicity, to form an international consensus report on the use of TpoR agonists during pregnancy should be studied. Based on our current knowledge, when a woman wishes to get pregnant, she should stop using TpoR agonist and conceive by controlling her platelet count with corticosteroid treatment (5). We do not have a consensus regarding the use of TpoR agonists in patients who do not respond to the treatments used during pregnancy. From this viewpoint, our case has an important place in terms of showing that it can be used in this patient group and guiding clinical observations.

In the case report by Ferreira et al. (6), a case involving eltrombopag administered in the last period of pregnancy, the birth of a baby with low birth weight was reported. In 25 weeks pregnant morbidly obese patient who was diagnosed with pulmonary sarcoidosis, 50mg/day eltrombopag treatment was initiated at the 27th gestational week and corticosteroid treatment was initiated by 120 mg/day to be reduced gradually during the clinical follow-up, due to the ineffectiveness of the treatments applied before. Enoxaparin was administered to prevent thrombotic events, when the platelet count exceeded 70,000/µl in the case. Since the platelet count was 119,000/µl on the 15th day of the eltrombopag treatment, the dose of eltrombopag was reduced by 25 mg/day together with 90 mg/day methylprednisolone at 29 weeks of pregnancy. Eltrombopag treatment was stopped due to the platelet count of 346,000/µl at the 30th week of gestation. The patient who developed preeclampsia at the 37th week of gestation, gave birth to a 2400 grams baby girl, without any malformation and bleeding disorder. The newborn's platelet count on postpartum day 3 was found to be 282,000/µl (6).

In the case of Suzuki N et al., low birth weight was found in the baby of the patient who received eltrombopag treatment before pregnancy and continued to use eltrombopag throughout her pregnancy with her consent. The patient, who received 12.5 mg/day eltrombopag treatment throughout her pregnancy, was admitted with preeclampsia at the 37th week of her gestation. The patient delivered a baby weighing 1670 grams without any malformation by cesarean section. The platelet count of the baby after birth was found to be 418,000/µl in the complete blood count (7).

In the case report of Purushothaman et al. (8), 27 years old multigravida woman with known ITP diagnosis was admitted with mucosal bleeding. During the 2-week hospitalization, She did not respond to steroid and immunosuppressive therapy by her 26th week of gestation, Due to the high costs, short duration of action and other potential maternal and fetal side effects of IVIG and anti-D immunoglobulin, it was decided to give TPO-mimetic drug, eltrombopag. After initiating treatment with eltrombopag, the patient's platelet count changed between 30,000/µl and 50,000/µl. A baby without malformation was born at the 36th weeks of gestation with a weight of 1860 grams, by preterm vaginal delivery (8).

In this study, our priority was to obtain a rapid response to prevent intracranial hemorrhages that may develop. Additionally, we tried selecting the most appropriate treatment by evaluating the risk together with

the patient, considering the patient's wishes, considering the complications that other treatments may cause both on the mother and newborn. Our case had resisted all the treatments used in the previous month and had been hospitalized 4 times. At her last hospitalization, despite conventional treatments her platelet count remained between 1,000-3,000/µl. Thus, Eltrombopag was initiated as 25mg/day when the patient's platelet count was 3,000/µl, and her platelet count increased to 8,000/µl on the third day of treatment. At once, eltrombopag treatment was increased to 50 mg/day. The next day, the platelet count was 62,000/µl in complete blood count.

In this study, there was a resistant and profound thrombocytopenia. The patient and baby were in danger of life. Finally, we gave eltrombopag to our patient and we got a rapid response to the treatment. A baby was born without malformation after delivery without any bleeding complications. The baby was born with a low birth weight of 2470 g. Low birth weight was also found in other cases reported concerning eltrombopag use in pregnancy.

In pregnant women with ITP, the preterm birth rate was reported as 8.5% and low birth weight by 1.4% (9). The possibility that preterm birth and low birth weight may accompany should also be considered in pregnant patients with ITP.

It is not known exactly why eltrombopag treatment causes low birth weight. However, it is thought that the passage of blood clot products or eltrombopag through the placenta may be the cause. Eltrombopag treatment in pregnancy has not been sufficiently studied yet, and current cases suggest a relationship between eltrombopag and low birth weight babies. We need a more clinical experience to find evidence of the relationship between low birth weight baby and eltrombopag.

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