452

CASE REPORT

DAPSONE, DANAZOL, AND INTRAPARTUM SPLENECTOMY IN REFRACTORY ITP COMPLICATING PREGNANCY

LILLY VARGHESE, AURO VISWABANDYA¹, ARPIT JACOB MATHEW²

ABSTRACT

Currently there is no consensus on the treatment of refractory idiopathic thrombocytopenic purpura (ITP) complicating pregnancy. Our patient with chronic ITP complicating pregnancy, who was refractory to steroids, dapsone, and danazol, was treated successfully with intrapartum splenectomy.

Key words: Cesarean section, dapsone, danazol, intrapartum splenectomy, refractory idiopathic thrombocytopenic purpura

INTRODUCTION

Refractory idiopathic thrombocytopenic purpura (ITP) is uncommon in pregnancy. The British Committee for Standards in Haematology and the American Society of Hematology provide guidelines for the care of these patients but, currently, there is no consensus on the treatment in pregnancy.^[1,2]

To the best of our knowledge, the use of dapsone in pregnancy with refractory ITP has been reported only once.^[3] Danazol is used in chronic refractory ITP when second-line agents fail.^[1,4] Three reports so far document the use of this drug in pregnancy. In this

Obstetrics and Gynecology Unit 1, ¹Department of Clinical Haematology ²Department of General Surgery, Christian Medical College, Ida Scudder Road, Vellore, India

Correspondence:

Dr. Lilly Varghese

Obstetrics and Gynecology Unit 1, Christian Medical College, Ida Scudder Road, Vellore - 632 004, India E-mail: lillyanil@cmcvellore.ac.in, anilthomaslilly@yahoo.com **DOI:** 10.4103/0019-5359.44483 patient, we used these two drugs to improve the platelet number during pregnancy. The patient underwent cesarean delivery for fetal indications. Simultaneous splenectomy was performed during this procedure.

CASE REPORT

A gravida 2, with chronic ITP not on any medication, presented at 8 weeks of gestation. Her platelet count was 59,000/µL. As she was asymptomatic, she was advised a close follow-up with serial platelet counts.

Prednisolone was started 1 mg/kg/day at 14 weeks of gestation when the platelet count dropped to $20,000/\mu$ L although she was asymptomatic. Following an initial rise, there was a subsequent fall in the platelet counts to $32,000/\mu$ L a month later.

The patient did not accept the recommended treatment options (intravenous immunoglobulin [IV IgG], azathioprine, anti-D immune globulin)

due to financial constraints. The risks and benefits of dapsone were discussed with the couple and dapsone was added at 25 mg/day along with folic acid at 20 weeks of gestation and gradually increased to 125 mg/day.

Dexamethasone (40 mg intravenously, once daily) was administered for 4 days at 31 weeks of gestation as the platelet counts remained persistently low at 10,000/µL. A decline of platelets to 7,000/µL necessitated the addition of danazol 200 mg thrice daily at 34 weeks, taking into consideration the decreased likelihood of teratogenicity at this gestational age. The patient rejected the options of IVIgG, anti-D and rituximab once again due to financial reasons.

At 37 weeks of gestation, the patient presented with ecchymosis and platelets of 8000/µL. As she was refractory to all instituted therapy, the delivery was planned with augmentation of platelets by administration of a platelet-rich concentrate (PRC). Splenectomy to increase the platelet count would be considered if patient required cesarean section for an obstetric indication. Within 3 h following intracervical instillation of prostaglandin E2, the cardiotocogram showed features of fetal distress – poor variability, shallow decelerations, and thick meconium-stained amniotic fluid.

Cesarean section with concurrent splenectomy was performed under general anesthesia. Eight PRCs were transfused as bolus before incision for the cesarean. Because of the laxity of the abdominal wall, a lower midline incision extending just above the umbilicus was sufficient for access to the spleen.

There were no intraoperative complications.

The estimated intraoperative blood loss was 600 cc. Other than the eight PRCs, no blood or blood products were transfused. In the immediate post-operative period, activated partial thromboplastin time and prothrombin time were within normal limits. Hemoglobin (Hb%) was 12.3 gm% and platelets were 98,000/µL, which fell to 13,000/µL on the fifth post-operative day. Tranexamic acid was started prophylactically along with the prednisolone 70 mg orally/day.

Her post-operative course was uneventful and the patient was discharged with a platelet count of $2,31,000/\mu$ L on the 12^{th} post-operative day.

The neonate (term female 3.13 kg) was admitted to the neonatal intensive care unit, with a platelet count of 182,000/µL and Hb% 18.8 at birth. On the seventh day of life, the platelet counts dropped to 8000/µL. She was transfused with 1 unit (10 mL/kg) of PRC and was given immunoglobulin (2 gm/kg), after which her counts reached 87,000/µL at discharge on the 17th post-natal day. The neonate's HB and counts remained within normal limits throughout, showing no evidence of hemolysis.

DISCUSSION

Patients who fail to respond to first-line treatment or require unacceptably high doses of steroids to maintain a safe platelet count are said to have refractory ITP.^[1] Corticosteroids and IVIgG are recommended as first-line therapy in pregnancy, with laparoscopic splenectomy if required in the second trimester as second-line therapy.^[1,2]

Treatment of severe refractory ITP in pregnancy is a particularly vexing issue in a developing country due to the lack of access to tertiary health care and high costs of recommended treatment like immunoglobulins (IVIgG). Our patient refused IVIgG due to the cost factor at various stages of her pregnancy.

Azathioprine is the only immunosuppressive drug used in pregnancy. Vinca alkaloids, androgens, and most immunosuppressive drugs are not recommended in pregnancy.^[1] Dapsone, a category C drug, and Danazol, a category X drug, are not recommended in pregnancy.^[1,2]

Dapsone, an immunosuppressive and antibacterial, is not known to cause any major fetotoxicity in patients with Hansen's disease and malaria complicating pregnancy.^[5,6] Our patient received up to 125 mg/day from 20 weeks of gestation until delivery. Neonatal hemolytic anemia and jaundice attributed to dapsone were not seen.^[6] Only one other case has been reported on the successful use of dapsone 100 mg daily from 27 weeks, following a lack of response to splenectomy in pregnancy with refractory ITP. Here, a response after a 2-week period was observed.^[3]

In an analysis of the outcome of 35 children and 55 adults with chronic refractory ITP at our institution, improvement in platelet counts of 65.7% and 61.8% were observed, respectively. Therapy was discontinued in three (2%) patients due to acute hemolysis and erythematous rash. Fever, pruritus, peripheral neuropathy, nephritic syndrome, and iron overload may be seen on long-term treatment. Dapsone was found to be an effective, inexpensive, and well-tolerated drug for chronic ITP when steroids or other immunosuppressants failed.[7]

Danazol, a category X drug, is best avoided in pregnancy due to possible pseudohermaphroditism and virilization.^[1]

In a retrospective review, 129 pregnancies exposed to danazol resulted in 94 live children. Twenty-three of the 57 female children born were virilized. Virilization did not occur when danazol was discontinued before the eighth week of pregnancy.^[8] The use of danazol in two other situations has been reported. One patient was treated with vincristine along with danazol for ITP, which resulted in the birth of a normal male baby.^[9] The other patient with SLE, who was treated in the second half of pregnancy with danazol, had a normal female baby.^[10] Two hundred milligrams for 9 weeks in one case resulted in virilization.^[7] Use of 600 mg in our patient for 3 weeks after 34 weeks of gestation did not cause virilization possibly due to the short duration of exposure. This was consistent with a previous case wherein danazol was used.^[10]

Splenectomy was considered concurrently with cesarean section as medical intervention proved ineffective in raising the platelet counts. It is considered an effective mode of treatment in ITP despite the risk of perioperative complications, sepsis, pulmonary hypertension, and athero sclerotic events . Less than 10% of the patients may be refractory after splenectomy.^[4]

Our report validates that splenectomy is a safe option during cesarean section in refractory ITP if it is not considered during the second trimester as recommended. Although short-term use of danazol in our patient did not cause any morbidity, it is better avoided in early pregnancy in view of its documented teratogenecity. There may be a limited and cautious role for its use in later pregnancy. Dapsone, given from 20 weeks onwards, was not effective in our patient. However, it did not cause any maternal or neonatal morbidity. In countries where other recommended options such as IVIg and ritumaxib may not be affordable, management should be individualized and dapsone should be considered as a treatment option in refractory ITP in pregnancy.

REFERENCES

- British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and Management of ITP in adults, children and pregnancy. Br J Haematol 2003;120:574-96.
- Gernsheimer T, McCrae KR. Immune thrombocytopenic purpura in pregnancy. Curr Opin Hematol 2007;14: 574-80.
- Lush R, Iland H, Peat B, Young G. Successful use of dapsone in refractory pregnancy-associated idiopathic thrombocytopenic purpura. Aust N Z J Med 2000;30:105-7.
- 4. George JN. Management of patients with

refractory immune thrombo cytopenic purpura. J Thromb Haemost 2006;4:1664-72

- Briggs GP, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 7th ed. Lippincott (Philadelphia): Williams and Wilkins; 2005.
- Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: Implications for prevention programmes in Plasmodium falciparum-endemic sub-Saharan Africa. Trop Med Int Health 2003;8: 488-506
- Damodar S, Viswabandya A, George B, Mathews V, Chandy M, Srivastava A. Dapsone for chronic idiopathic thrombocytopenic purpura in children and adults: A report on 90 patients. Eur J Haematol 2005;75:328-31
- Brunskill PJ. The effects of fetal exposure to Danazol. Br J Obstet Gynaecol 1992;99:212-5.
- Gross Z, Rodriguez JJ, Stalnaker BL. Vincristine for refractory autoimmune thrombocytopenic purpura in pregnancy. J Reprod Med 1995;40:739-42.
- Insripong S, Chanchairujira T, Bumpenboon T. Danazol for thrombocytopenia in pregnancy with underlying systemic lupus erythematosus. J Med Assoc Thai 1996;79:330-2.

Source of Support: Nil, Conflict of Interest: None declared.