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Original Research Paper

Gynaecology

BERNARD SOULIER SYNDROME IN PREGNANCY

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ABSTRACT **B**ernard-Soulier syndrome is an inherited platelet disorder, transmitted in an autosomal recessive pattern. Thrombocytopenia and large defective platelets are characteristics, often presents early with bleeding symptoms, such as epistaxis, ecchymosis, menometrorrhagia, and gingival or gastrointestinal bleeding. Diagnosis can be confirmed by platelet aggregation studies and flow cytometry. Differential diagnosis includes other inherited giant platelet disorders, as well as von Willebrand disease and immune thrombocytopenic purpura. During pregnancy, it can present as recurrent first trimester miscarriages, antepartum, intrapartum and postpartum haemorrhage. Treatment remains generally supportive with platelet transfusions and recombinant factor VII has also been described in literature.

KEYWORDS : Pregnancy, Bernard-Soulier syndrome, thrombocytopenia.

INTRODUCTION

Bernard–Soulier syndrome (BSS) is a rare inherited bleeding disorder of platelet dysfunction (1). First described in 1948 by Jean Bernard and Jean Pierre Soulier, BSS is characterized by thrombocytopenia and abnormally large platelets (macro thrombocytopenia). Majority of cases are inherited in an autosomal-recessive pattern (1). The GPIb- IX-V receptor complex, is composed of 4 transmembrane polypeptide subunits—disulfide-linked alpha and beta subunits of GPIb, and noncovalently bound subunits GPIX and GPV.The platelets of BSS lack or have a dysfunctional GPIb-IX-V receptor resulting in defective adhesion to the subendothelium. The dysfunctional platelets found can result from one of several different glycoprotein mutations such as missense, non- sense, or deletion mutations of the *GPIb-*, *GPIb-*, or *GPIX* genes. The heterogeneity of BSS may be a result of the variety of these mutations (2).

Bernard-Soulier syndrome presents in the early life with bleeding symptoms. The severity of bleeding varies among patients and may range from mild to life-threatening, depending on the degree of thrombocytopenia and functional abnormality of platelets (3). Severity of symptoms may be quite variable in patients who have the same mutations (1).

Laboratory findings include a prolonged bleeding time, abnormal consumption of prothrombin and a normal to decreased number of unusually large platelets, a prolonged closure time using a Platelet Function Analyser (PFA) and decreased glycoprotein Ib-IX-V complex density by flow cytometry (4,5). Clotting factor levels are normal, but platelets fail to aggregate with ristocetin or normal serum this distinguishing it from von Willebrand disease (6).

From obstetric point of view, these patients are at risk of bleeding, mostly intrapartum and postpartum, because of the platelet dysfunction. Fetus also has a risk of Fetal neonatal alloimmune thrombocytopenia (NAIT) due to the passive transfer of antiplatelet antibodies (7)

There is paucity of consensus on the best way to approach pregnancy in these patients. We report a case of a successful pregnancy outcome in a woman with Bernard -Soulier syndrome who was closely monitored during the pregnancy and intrapartum period with judicious use of platelet transfusions and antifibrinolytics.

CASES

There were three mothers with 4 pregnancies with Bernard Soulier syndrome between January 2006 to December 2020.

Patient1 (2008) had a midtrimester loss at 24 weeks, did not require platelet transfusion. Her platelet count at the time of delivery was 74000.

Patient 2 had two deliveries both LSCS in 2010 and 2012, received SDP transfusions in the perioperative period.

Patient 3 is the mother in this case report. None of them had complications in the puerperal period.

Mrs.R, 31 yr. old, known case of BSS, registered for antenatal care at 19 weeks of pregnancy. She was diagnosed to have BSS at 10 years of age when she presented with uncontrolled bleeding from the gums at the time of tooth extraction and required transfusion of six RDP and packed cells to control the bleeding. She also had three episodes of haemoperitoneum at the time of ovulation which required transfusion of blood and platelets. She did not have any history of menorrhagia or developing significant hematoma after accidental bruises There was no history of bleeding diathesis in the family. This pregnancy was a spontaneous conception, after 3 failed intrauterine insemination cycles.

Booking BMI was 29.95 with a total weight gain of 15 kg. She had uneventful first and second trimester. Fetal anomaly screening ultrasound was normal. Detected to have gestational diabetes at 25 weeks of gestation managed initially with medical nutrition therapy and later required Insulin for glycaemic control. Serial fetal growth monitoring was done in view of the GDM. She was under multidisciplinary team management consisting of haematologist, physician, obstetrician and critical care team. Throughout her antenatal period she had been monitored with platelet count, prothrombin time and activated partial thromboplastin time. Platelet count was always less than one lakh and coagulation profile was normal. A birth plan was made after discussion with the multidisciplinary team and the couple. The couple

were counselled regarding the risk of intrapartum and postpartum haemorrhage, need for transfusion of blood and blood products, advised to identify single donor platelet (SDP) donors and also counselled regarding Recombinant Factor VIIA (rFVIIA) and its cost. It has been decided to induce labour at 39 weeks of gestation in view of well controlled gestational diabetes on insulin. At 35 weeks fetus was large for the gestational age with adequate liquor.

She was readmitted at 39+1 weeks of gestation with prelabour rupture of membranes. At admission platelet count was 40,000, coagulation profile was normal. In view of gestational hypertension, she was started on Tab. Labetalol 200 mg thrice a day. Labour was accelerated with oxytocin and an emergency Caesarean section was performed under general anaesthesia in view of non-progress of labour. rFVII A ,2mg given IV before shifting into the operation theatre. She received one unit of single donor platelets. She delivered a healthy baby boy weighing 3.79 kg, 99th centile. Inj. Oxytocin 10 mg IM given immediately after delivery of the baby and 20 units was added to the drip at 125 ml/ hr, drip continued for 6 hrs post operatively. Inj.Carboprost 250 mg IM given for prophylaxis against PPH. Intra op blood loss was 900 ml. Skin was closed with matters sutures with intraperitoneal drain in situ. She also received injection tranexamic acid 500mg IV 8 hourly, for 24 hrs. Haematuria cleared within 24 hrs of delivery. Her vaginal bleeding was with in normal limits and intraperitoneal drain in the first 24 hrs following surgery was 125 ml and clear. Drain was removed on second postoperative day. Oral tranexamic acid 500 mg thrice a day was continued for 1 week. Mattress sutures were removed on 8th post-operative day. Her postpartum period was uneventful.

Neonate was investigated for thrombocytopenia and found to have normal platelet count. Mother was reviewed in postnatal clinic at 6 weeks and combined oral contraception advised

POG (weeks)	5	10	18	22	31	35	37	39
Hb%(gm%)	12.3	11.5	10.6	10.8	10.3	10.3		
Platelet count(mm^3)	65000	78000	57000	65000	50000	50000	52000	40000

POG: Period of gestation

DISCUSSION:

Bernard-Soulier syndrome is an inherited bleeding disorder due to platelet dysfunction that can have serious maternal and fetal/neonatal implications.

A systematic review published in 2010 describes the clinical course and pregnancy outcomes in 30 pregnancies among 18 women with BSS. This review highlights the significant risk of postpartum haemorrhage (PPH) sometimes culminating in emergency obstetric hysterectomy. The foetus/neonate is also at risk of fetal alloimmune thrombocytopenia (2). This study reported primary postpartum haemorrhage in 10 (33%) and secondary in 12 (40%) of pregnancies, requiring blood transfusion in 50% of pregnancies. Out of 30 pregnancies, 2 women had an emergency obstetric hysterectomy. In 6 neonates, alloimmune thrombocytopenia was reported with one intrauterine death and one neonatal death. (8).

Most cases of BSS were diagnosed prior to pregnancy, mostly during childhood or adolescence with spontaneous bruising, epistaxis, or bleeding after minor trauma. Because of its extreme rarity of the condition, a high index of clinical suspicion is a must when a woman presents with unexplained obstetric bleeding and has a family history of bleeding disorder and/or consanguinity. In such woman additional testing is warranted for confirmation of diagnosis to optimize maternal and fetal outcomes. Where the diagnosis is known prior to pregnancy, women with BSS should undergo prepregnancy counselling. They should be counselled in detail regarding the risks of intrapartum and postpartum bleeding, need for transfusion of blood and blood products and also risk to the neonate. Pregnancy should be managed at tertiary care centre with ready access to blood and blood products by multidisciplinary team including obstetrician and haematologist. Prenatal diagnosis should be offered when there is history of consanguinity, both parents are carriers or there is a previous affected child.

Fetus is at risk for NAIT from the transplacental transmission of antiplatelet antibodies, not only due to alloimmunization of the mother as a result of multiple platelet transfusions but also from the fetal platelets carrying the specific paternal IB/IX antigens that are not present on the maternal platelets (7). Intracranial haemorrhage (ICH) and/or visceral bleeding, the most severe complications of NAIT occurs antenatally in up to 50% of cases, and may lead to death or severe neurological sequelae.

Where available, HLA-matched platelet transfusions are preferred to reduce the risk of maternal alloimmunization and NAIT in the fetus . Screening for antiplatelet antibodies in early pregnancy , where facilities are available, and monitoring the fetus for ICH is warranted. One should be cautious about performing any type of invasive procedure as uncontrollable haemorrhage may result.

There is no consensus in the literature regarding the safest mode of delivery in a woman with BSS (3,8,9). Caesarean section does not seem to eliminate the risk of haemorrhage. Hence, it should be reserved for obstetric indications. In our case we gave a trial for vaginal delivery with arrangement for platelet transfusion and rFVII A to be given in case of operative delivery. (10,11)

Appropriate haemostatic cover, arrangement of blood products, and where available, rFVIIa 90 μg/kg (early pregnancy weight) combined with tranexamic acid and active management of third stage of labour are essential to minimize risk of PPH (12). Regional analgesia /anaesthesia is contraindicated. Instrumental deliveries should be avoided. As postpartum (primary and secondary) haemorrhage is common, patients should be educated to contact the hospital immediately if any symptoms of bleeding present. Management of each case should be individualized taking into consideration maternal and fetal risks and couple should be involved in making the plan of management.

CONCLUSION:

It has been our experience that, for a successful pregnancy outcome, patient education, close supervision, multi disciplinary team approach and judicious and timely use of platelet transfusions and antifibrinolytics is needed. Recombinant Factor VII a is an effective treatment option. Continuation of care in the postpartum period and also advise regarding contraception is essential to prevent future morbidity in the women. Obstetrician must consider the risk of NAIT in the fetus and plan for appropriate management should the problem arise.

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