The Journal of Obstetrics and Gynecology of India (September–October 2023) 73(5):445–450
https://doi.org/10.1007/s13224-023-01745-z

CASE REPORT

Pregnancy Outcome in Bernard–Soulier Syndrome

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Received: 16 July 2022 / Accepted: 26 February 2023 / Published online: 17 March 2023

Introduction

Inherited platelet function disorder (IPFD) or thrombocytopathies are hereditary disorders of platelet that can be classified into platelet adhesion disorders, platelet aggregation disorders, platelet activation disorders, platelet secretion disorders, and platelet procoagulant function disorders. Bernard–Soulier syndrome (BSS) is a platelet adhesion disorder caused by a deficiency of glycoprotein Ib-IX-V complex (Von Willebrand factor receptor). These defects can be quantitative or qualitative. It has a prevalence of 1 in 1 million individuals [1] affecting both males and females. The mutations are a point or a frameshift type resulting in premature stop codon leading to deficiency of the membrane glycoproteins. This defective primary haemostasis can cause bleeding from mucocutaneous sites, menorrhagia, and bleeding in the antepartum, intrapartum, and postpartum period. Pregnant women with these spectra of disorders are considered high risk and should be managed at a tertiary care centre with an availability of a multispecialty team. We report our experience in handling such a pregnant woman.

Case Report

A 26-year-old primigravida, a known case of Bernard–Soulier syndrome conceived by ovulation induction, came to our hospital in labour for the first time at 38 + 6 weeks of gestation. She was born out of non-consanguineous marriage with no family history of bleeding disorders. She had bleeding gums while brushing and irregular cycles once in 3 months after attaining menarche, which was managed with oral contraceptives intermittently without evaluation. At the age of 21, she had heavy menstrual bleeding with severe anaemia managed with blood transfusions, tranexamic acid, and medroxyprogesterone acetate, during which she was found to have Bernard–Soulier syndrome. Investigations at the time of diagnosis are given in Table 1. Antenatally, she did not have any bleeding episodes. Due to her late presentation at term, she had not received any genetic counselling. At admission, her haemoglobin was 12.8 g/dl, platelet count of 1,53,000 per cu. mm with average bleeding time. The routine antenatal investigations were normal. There were no signs of bleeding diathesis on examination, and the uterus corresponded to term gestation with a live foetus in breech presentation. An emergency caesarean under general anaesthesia was done on the same day because of breech in labour and delivered a healthy female baby of 2.5 kg. The intraoperative blood loss was 300 ml. Though uneventful, she received prophylactic random donor platelet transfusions, four preoperatively and four intraoperatively. The neonate platelet count was 1,70,000 per cu. mm with no bleeding manifestations. Her postoperative period was uneventful and was discharged on postoperative day 7 with further follow-up in haematology and postnatal clinics.

Discussion

Bernard–Soulier syndrome was described by Jean Bernard and Jean Pierre Soulier in 1948. Glycoprotein Ib-IX-V complex is a Von Willebrand factor receptor which is deficient in BSS. The genes coding for GpIbα, GpIbβ, GpIX, and

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Table 1 Investigations at the time of diagnosis

Tests	Patient's value	Reference Range
Haemoglobin (g/dl)	6.5	12.1–15.1
Platelet count (per cu. mm)	1,10,000	1,50,000–3,50,000
Platelet morphology	Few giants	Biconvex discoid
Bleeding time (minutes)	11.5	2.0–9.0
Clotting time (minutes)	4.5	2.0–8.0
PT (seconds)	14.4	11.1–14.5
aPTT (seconds)	30.7	28.1–39.7
INR	1.2	0.8–1.1
vWF: RCO assay (IU/dl)	103	50–200
Platelet aggregation studies (%)		
Ristocetin	8	64
ADP	80	54
Epinephrine	67	63
Collagen	60	56
Flow cytometry	67% of CD42b, 70% of CD42a, 94.5% of CD42d	≥ 70.0%

PT prothrombin time, *aPTT* activated partial thromboplastin time, *INR* international normalised ratio, *vWF: RCO* Von Willebrand Ristocetin Cofactor assay, *ADP* adenosine diphosphate

GpV are GP1BA, GP1BB, GP9, and GP5 and are located in chromosomes 17, 22, and 3 respectively, with markers CD42b, CD42a, CD42d respectively.

We performed an electronic search on PubMed, Embase, Cochrane, Scopus, Science Direct, and Google scholar using the word combinations: 'Bernard-Soulier' AND 'pregnancy' OR 'gestation'; the articles published only in English and between 2000 and till date were included. We identified 24 relevant articles which fit into our search criteria. After thoroughly evaluating the abstracts, 15 articles were excluded, and nine were included (Table 2). A total of 12 patients and 19 pregnancies were reviewed. Most women were primigravida (60%), commonly presented in the third trimester. The average platelet count was 49,500 per cu. mm. Caesarean section was the common mode of delivery in 78.6% of individuals. Platelet transfusions were given intrapartum in all the cases. Few received tranexamic acid, but desmopressin (DDAVP: 1-desamino-8-d-arginine vasopressin), recombinant factor VIIa (r-VIIa), and intravenous immunoglobulin (IVIG) were used rarely. Thrombocytopenia was detected in 22.2% of the neonates, the cause being alloimmunisation which required platelet transfusions and immunoglobulins. Cordocentesis was performed on two patients [2].

Being autosomal recessive, only homozygous individuals manifest the disease, and the phenotypic trait may become visible, especially with consanguineous marriages. Although significant consanguinity was present in five reviewed studies, our case did not have a family history of a bleeding disorder, raising the possibility of denovo genetic mutation or carrier parents, which can be further analysed by genetic testing. BSS is usually diagnosed with mucocutaneous bleeding or menorrhagia in early childhood or adolescence. In our review, the mean age at diagnosis is 17.45 years, and epistaxis was the presenting symptom in 58.3%, followed by menorrhagia in 41.6% and skin bruising in 25%.

BSS is diagnosed with increased bleeding time with few giant platelets and low platelet count in the peripheral smear, average coagulation profile, defective platelet aggregation to ristocetin, normal aggregation to all platelet agonists, standard Von Willebrand Ristocetin Cofactor assay (vWF: RCO) and decreased CD42b, CD42a in flow cytometry as in our case.

The obstetric complications occurring in BSS can be either antepartum or postpartum haemorrhage. Primary or secondary postpartum haemorrhage (PPH) was reported in 33% of cases.

Management includes the use of antifibrinolytics, platelet transfusions, or rVIIa. Tranexamic acid is safe and effective in managing bleeding in pregnancy and postpartum. Though studies say that the role of prophylactic platelet transfusions is ineffective in preventing PPH [3], our case was effectively handled with prophylactic platelet transfusions providing functional platelets to the haemostatic system. Surgical intervention for PPH is rarely required. In patients with multiple platelet transfusions, anti-platelet antibody titre plays a role as the transplacental passage of IgG type of anti-platelet antibodies can lead to fatal neonatal alloimmune thrombocytopenia and refractoriness to fresh platelet transfusions. This increases the bleeding risk, necessitating the need for monitoring titre. However, it was not done in our patient due to presentation at term gestation. Alloimmunisation can be prevented by judicious use of leuco-depleted HLA-matched

Table 2 Literature review of pregnant women with Bernard-Soulier syndrome

Author name and year	Age	Obstetric index and Gestational age	Consanguinity	Age at diagnosis (years)	Platelet count at the time of diagnosis (per cu. mm)	Clinical features at the time of diagnosis	Treatment prior to pregnancy	Platelet count during pregnancy (per cu. mm)	Mode of delivery and anaesthesia	Management during pregnancy/ post-partum	Maternal complications	Neonatal outcome
Kriplani, 2005	31	G2A1 37 weeks	First degree cousins consanguineous	15		Menorrhagia Spontaneous bruising	Three units of blood Haemostatic agents Oral contraceptive pills	47,000	Elective caesarean i/v/o borderline mid-pelvis	2 PRBC 1 SDP 6 RDP Tranexamic acid 500 mg IV TDS Uterotonics	Primary PPH	Normal platelet count
		Previous spontaneous abortion, 8 weeks							D and C done		Uneventful	
Rahimi, 2005	22	G1 34 weeks				Menorrhagia		17,000	Elective LSCS	Multiple blood and blood products	Anaemia Secondary PPH	Healthy
Prabhu, 2006	23 17	25 weeks	Consanguineous	23		Bruising	Blood transfusion ten years before for nasal bleed	37,000	Ventouse	10 PRBC 12 ATD of platelet Tranexamic acid 1 g TDS IV DDAVP single dose	Primary PPH Secondary massive PPH	Normal platelet count
		Multigravida 41 weeks	Consanguineous	12	14,000	Bruising Recurrent nasal bleed Menorrhagia			Vaginal	4 PRBC 8 ATD of platelet Oral tranexamic acid 1 g TDS	Secondary PPH	
		Previous pregnancy 40 weeks							Vaginal	4 ATD of platelet Oral tranexamic acid 1 g TDS 4 PRBC	Antepartum haemorrhage Primary PPH	

Table 2 (continued)

Author name and year	Age	Obstetric index and Gestational age	Consanguinity	Age at diagnosis (years)	Platelet count at the time of diagnosis (per cu. mm)	Clinical features at the time of diagnosis	Treatment prior to pregnancy	Platelet count during pregnancy (per cu. mm)	Mode of delivery and anaesthesia	Management during pregnancy/ post-partum	Maternal complications	Neonatal outcome
Zafar, 2007	26	5 weeks of gestation		26		Epistaxis Menorrhagia Intra-peritoneal bleed Haemorrhagic shock	Multiple blood and platelet transfusions	23,000	Elective LSCS i/v/o abnormal doppler, pre-eclampsia at 37 weeks	Prophylactic 1 PRBC and 1 SDP Uterotonics	Minor gum bleed Pre-eclampsia Foetal growth restriction	Platelet count: 2.6 lakh/ cu.mm
Uotila, 2008		P3L3		19		Recurrent epistaxis Excessive bleeding after tonsillectomy	Splenectomy Steroids	19,000 to 1.09 lakh	LSCS i/v/o failed induction	IVIG Platelet transfusion Cordocentesis	Recurrent epistaxis	Normal platelet count
		P3L3		21	10,000	Ecchymosis Recurrent epistaxis	Splenectomy Steroids Azathioprine IVIG Platelet transfusion	10,000 to 1 lakh	Elective LSCS i/v/o foetal thrombocytopenia at 36 weeks	IVIG Platelet transfusion Cordocentesis	Primary and secondary PPH	Platelet count: 8,000–16,000/ cu.mm Platelet transfusion IVIG Prednisolone
Pascual, 2011	33	G2P1L1 32 weeks		1.5		Epistaxis	Multiple platelet transfusions		Emergency LSCS at 32 weeks i/v/o deteriorating maternal condition	4 SDP 2 RDP	Severe anaemia	Normal platelet count
		Previous pregnancy 38 weeks			40,000				Elective LSCS at 38 weeks	4 SDP		Normal platelet count
Macedo, 2015	28	G1 39 + 4 weeks	Consanguineous	18		Epistaxis Gingival bleeding	Prophylactic platelet transfusion	43,000	Elective LSCS under general anaesthesia	10 prophylactic RDP	Minor gingival bleeding	Healthy
Perez, 2019	21	G1 33 + 4 weeks	Consanguineous	5		Gingival bleed		30,000	Elective LSCS under general anaesthesia at 37 + 4 weeks	21 platelet concentrates Tranexamic acid 10 mg/ kg TDS	Minor gingival bleed	Platelet count: 53,000/cu.mm

Table 2 (continued)

Author name and year	Age	Obstetric index and Gestational age	Consanguinity	Age at diagnosis (years)	Platelet count at the time of diagnosis (per cu. mm)	Clinical features at the time of diagnosis	Treatment prior to pregnancy	Platelet count during pregnancy (per cu. mm)	Mode of delivery and anaesthesia	Management during pregnancy/ post-partum	Maternal complications	Neonatal outcome
Demicri, 2021	24	G1 6 weeks				Nasal bleed GIT bleeding		6000	Emergency LSCS under general anaesthesia i/v/o prolonged latent phase of labour	*Antepartum* Multiple platelet transfusions *Intrapartum* 2 platelet transfusions r-VIIa 15mcg/kg *Post-partum* 3 PRBC 1 platelet 1 g carboxymaltose	Epistaxis Gingival bleed Primary PPH	Healthy Normal platelet count
The index case, 2022	26	G1 38 + 6 weeks	Non-consanguineous	21	1,10,000	Heavy menstrual bleeding	Blood transfusion Tranexamic acid Medroxyprogesterone acetate	1,53,000	Emergency LSCS under GA i/v/o breech in labour	Prophylactic, 4 RDP preoperatively 4 RDP intraoperatively	Uneventful	Healthy Platelet count: 1,70,000 per cu. mm

LSCS lower segment caesarean section, *SDP* single-donor platelet, *RDP* random donor platelet, *PRBC* packed red blood cells, *IVIG* intravenous immunoglobulins, *PPH* post-partum haemorrhage, *ATD* adult therapeutic dose, *DDAVP* desamino-d-arginine-vasopressin

platelet transfusions [3]. The r-VIIa increases thrombin production, and fibrin deposition at the sites of vascular injury is an available alternative for patients who are refractory to platelet transfusions [4]. Steroids, intravenous γ globulins, and plasmapheresis can treat alloimmunised individuals. Though invasive prenatal tests can be performed, it is better avoided in patients with BSS as there is an increased risk of bleeding and uncertain foetal benefits with relatively scant data in the literature. Uotila [2] described cordocentesis in two patients to assess the severity of foetal thrombocytopenia and to decide on caesarean delivery for severe foetal thrombocytopenia.

Vaginal delivery is preferred, and care should be taken to avoid neonatal intracranial haemorrhage, mainly instrumental delivery. As in our case, general anaesthesia for caesarean delivery is generally indicated as there is a high risk of intrathecal bleed with regional anaesthesia.

Conclusion

Our patient was diagnosed with BSS in early adulthood during the evaluation of menorrhagia with flow cytometry findings of decreased CD42b and CD42a platelet surface markers. She had an uneventful antenatal period and presented to us at late gestation in labour. She received perioperative platelet transfusions without any adverse maternal or neonatal outcomes. She was managed by a multidisciplinary team involving obstetricians, anaesthesiologists, haematologists, and neonatologists and had a good pregnancy outcome.

Funding Not applicable.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Informed consent A written informed consent was obtained from the patient to publish their clinical details.

Human or Animal Rights Not applicable.

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