CASE REPORT

Management of Hermansky-Pudlak syndrome in pregnancy and review of literature

Freya Van Avermaete,[1] Joke Muys,[2] Yves Jacquemyn[3]

[1]Universiteit Antwerpen Faculteit geneeskunde en gezondheidswetenschappen, Wilrijk, Belgium
[2]University Hospital Antwerp, Antwerp, Belgium
[3]Department of Obstetrics, UZA, Edegem, Belgium

Correspondence to
Professor Yves Jacquemyn, yves.jacquemyn@uza.be

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SUMMARY

We report on the obstetric outcome of a woman aged 27 years with Hermansky-Pudlak syndrome (HPS). She underwent a caesarean section after failed induction of labour. Platelet transfusion was administered in a set schedule for 36 hours, starting 2 hours before delivery. The child had good Apgar scores and there were no significant problems of prolonged bleeding during the procedure. 72 hours postpartum, a haematoma developed at the site of the wound, subsequently complicated by a secondary infection for which she received antibiotics. Wound care was provided in an outpatient setting during 2 weeks, in which the infection stabilised and responded to the treatment. Mother and child could leave the hospital after 6 days.

BACKGROUND

Hermansky-Pudlak syndrome (HPS) belongs to a heterogeneous group of autosomal recessive disorders characterised by the triad of partial oculocutaneous albinism, a disorder of ceroid metabolism and a platelet storage pool deficiency. The variability of HPS is high and dependent to the subtype, as there are nine gene loci described. In some of these subtypes, pulmonary fibrosis, granulomatous colitis or neutropenia can develop. The largest group of patients with HPS originates from the northwestern region of Puerto Rico where its frequency is estimated to be 1:1800, and central Puerto Rico. Patients with HPS of non-Puerto Rican descent have been identified in many other parts of the world, though the overall frequency in the human population is not known.[1]

In pregnant women, bleeding complications during delivery are an important concern. As this syndrome is so rare, we aim to describe the management of HPS at the time of delivery and summarise the recommendations made in the literature.

CASE PRESENTATION

We report on a pregnant woman aged 27 years who is known with HPS and is admitted at the hospital for induction of labour at 40 weeks gestation.

In this case, the medical history is exceptional. As a child, she easily bruised with the formation of multiple haematomas, sometimes by merely touching the skin. At the age of 6, there were suspicions of child abuse by school teachers and an investigation was set out. As she frequently suffered from serious bilateral epistaxis and gingival bleeding, a medical cause was suspected and the thrombocytopathy was eventually discovered. In combination with the spontaneous horizontal nystagmus and signs of ocular albinism, the definite diagnosis of HPS was made a couple of years later by genetic testing.

This woman is of Turkish origin. She is the oldest of six children, of which two brothers are diagnosed with the same syndrome. Neither of the parents or grandparents suffer from the disease, illustrating the autosomal recessive mode of inheritance. In her medical history, she had a tonsillectomy at the age of 17, for which she was readmitted at the hospital because of heavy bleeding and needed platelet transfusion. At the age of 25, she had her wisdom teeth removed without any significant bleeding problems, again by applying the right preventive measures and securing primary haemostasis by administering platelet transfusion. Otherwise, this woman has no history of pulmonary or gastrointestinal problems, as this syndrome can be associated with pulmonary fibrosis or gastrointestinal disorders. In daily life, she mostly suffers from the constant formation of haematomas, but otherwise the syndrome does not affect her quality of life. As follow-up, she has a yearly consult with the ophthalmologist for progressive visual impairment and every 6 months, she visits the general practitioner for a blood sample. In the case of low haemoglobin, she is referred to the haematologist.

In this case, we describe her third pregnancy. The first pregnancy was lost at 8 weeks gestation because of a spontaneous miscarriage. Her second pregnancy was carried out until term and resulted in a secondary caesarean section after insufficient progression of cervical dilation. At the time of the procedure, 2 units of thrombocytes were given postoperatively. There were no problems of prolonged bleeding during nor after surgery. The neonate had good Apgar scores. In the current pregnancy, our patient was admitted for induction at 40 weeks of gestation, considering the risk of bleeding complications that the syndrome holds. Earlier in the pregnancy, a haematological consult had been carried out, in anticipation of the risk of major blood loss at the time of delivery. As expected for the thrombocytopathy, laboratory tests showed normal APTT, PT and platelet count, but a significant prolonged bleeding time using the Ivy method of more than 15 min. There was a disturbed platelet aggregation using the platelet function assay and aggregation tests on whole blood. After administering desmopressin (DDAVP) in vitro, a significant improvement of platelet function

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was noted, though the administration of DDAVP did not correct the bleeding time. The conclusion was made that in the case of serious bleeding and major surgery, transfusion of platelets would be preferable and that in the case of minor bleeding or surgery, DDAVP could be a valid option. In view of the impending delivery, it was advised that primary haemostasis needed to be ensured during 36 hours, consisting of a transfusion of 2 units of platelets on three set moments, respectively, 2 hours before delivery, followed by a transfusion 12 and 24 hours after the administration of the first unit. In addition, epidural anaesthesia should be avoided due to the risk of spinal haematoma, thus a caesarean section must be carried out under general anaesthesia. Otherwise, non-steroidal anti-inflammatory drugs (NSAIDs) must be avoided to prevent disturbance of the remaining platelet function. Laboratory tests before delivery showed a haemoglobin of 12.6 g/dL and 148×10^9/L thrombocytes.

In the evening, an endocervical balloon was placed and a prostaglandin analogue was applied vaginally. The next morning, amniotomy was performed and oxytocin was started. Owing to failed progression and arrest of cervical dilation at 4 cm, it was decided to perform a repeat caesarean section under general anaesthesia in agreement with the patient. The procedure was performed without significant bleeding problems, with an estimated blood loss of 600 cc. Haemostasis by coagulation was achieved successfully while closing the surgical wound. The patient was haemodynamically stable without problems of prolonged bleeding. Laboratory results postoperatively showed a mild decrease in haemoglobin of 10.6 g/dL and 146×10^9/L thrombocytes. Considering the limited loss of blood and reassuring laboratory results, there was no need for transfusion of packed cells.

However, 72 hours after the procedure, a haematoma developed at the site of the wound, which was subsequently complicated by a secondary infection. A regimen of 14 days of amoxicillin/clavulanic acid 875 mg given three times a day was started and transfusion of platelets was repeated prophylactically, though the thrombocyte count remained normal. Mother and child could leave the hospital 6 days after delivery. Wound care was provided in an outpatient setting during 2 weeks, in which the infection stabilised and responded to the antibiotics.

DIFFERENTIAL DIAGNOSIS

Other rare genetic conditions can resemble HPS and are initially often only recognised by their phenotypes. Chediak-Higashi syndrome (CHS), Griscelli syndrome (GS), Elejalde syndrome and Cross syndrome are characterised by silvery hair, which can be found in patients with HPS. Otherwise, patients with CHS or GS may have a syndrome of haemophagocytosis and show the absence of platelet dense bodies as well. Choroideraemia patients share visual defects with HPS patients and individuals with the Gray Platelet syndrome (GPS) have abnormalities in platelet vesicles called alpha granules rather than delta or dense granules. The Wiskott-Aldrich syndrome is another form of a platelet storage pool disorder, while giant platelet disorders, Glanzmann thrombasthenia, platelet release disorders and glycoprotein VI defects are other inherited disorders of platelet function.

TREATMENT

Primary haemostasis was secured for 36 hours by platelet transfusion in a set schedule. The first transfusion was given 2 hours before delivery, the next transfusion 12 hours later and finally a platelet transfusion 24 hours later.

OUTCOME AND FOLLOW-UP

Caesarean section was performed without problems of prolonged bleeding during the procedure. Blood loss was estimated at 600 cc. Postoperatively, the patient was haemodynamically stable and laboratory results showed no significant decrease in haemoglobin or platelets. Seventy-two hours after the procedure, a haematoma developed at the site of the wound, which was subsequently complicated by a secondary infection. A regimen of 14 days of amoxicillin/clavulanic acid 875 mg three times a day was started and mother and child could leave the hospital 6 days after delivery. Wound care was provided in an outpatient setting during 2 weeks in which the wound infection stabilised and responded to the antibiotics.

As follow-up, a postpartum gynaecological consult was planned after 6 weeks.

DISCUSSION

HPS signifies a risk of prolonged bleeding at the time of delivery because of the platelet storage pool deficiency and bleeding diathesis. Different approaches have been described in the literature (table 1). Ten papers describe the effects of HPS at the time of delivery. Of the 14 deliveries that are reported, severe maternal haemorrhage with blood loss of more than 1000 mL has been described in four cases (28.6%),[2–4] with the requirement for red blood cell transfusion in three (21.4%) cases. Women with HPS must therefore be considered at risk of serious bleeding with childbirth.

A possible approach is to optimise coagulation parameters by prophylactic administration of desmopressin acetate (DDAVP).[2 4–6] Prophylactic DDAVP was administered in six (6/14, 42.9%) cases, of which three patients (50%) experienced severe maternal blood loss. Other cases however have proved that DDAVP alone can be effective.[2 5] One case report showed that a good response to DDAVP prophylaxis on one occasion remarkably may not mean a similar reaction to DDAVP at a subsequent event. In the same patient, DDAVP did not prevent severe haemorrhage at the first delivery, while it proved to be successful at the second childbirth. Response to prophylactic DDAVP administration thus can vary between, as well as within patients with HPS. The study concluded that every HPS patient should be tested with DDAVP prior to interventions associated with high risk of haemorrhage.[2] In our patient, laboratory tests had shown in advance that DDAVP, though improving platelet function, did not correct bleeding time. This confirms that not all HPS patients respond to DDAVP.

Another approach is the transfusion of platelets before delivery.[7–11] Of the five (5/14, 35.7%) patients in the literature who received platelets, there were no bleeding complications observed. It should be mentioned that one patient presented with a transfusion reaction after administering platelets, which was treated with diphenhydramine and hydrocortisone. There were no bleeding complications during delivery.[7] Important in our case is the observation that during her first delivery, platelet transfusion was successful with no bleeding complications, while with the current caesarean section, there was a significant problem of haematoma formation despite transfusion of platelets. This could suggest that as is the case with DDAVP, a good outcome with platelet transfusion in one occasion may not predict a similar result at a subsequent event. The prophylactic

Table 1 Treatment of Hermansky-Pudlak syndrome at the time of delivery

Article	Year	Article type	Treatment	Type of delivery	Result
Reiss *et al*[7]	1985	Case report	1. Prophylactic platelet transfusion 2. None	1. Spontaneous labour at 40 weeks. Vaginal delivery 2. Spontaneous labour at 39 weeks. Vaginal delivery	1. Transfusion reaction after platelet administration, treated with diphenhydramine and hydrocortisone. No abnormal intrapartum or postpartum bleeding 2. Epistaxis during second stage of labour. Uncomplicated delivery with an estimated blood loss of 400 mL
Wax *et al*[8]	2001	Case report	Prophylactic platelet transfusion	Vaginal delivery at term	Uneventful delivery
Zatik *et al*[2]	2002	Case report	1. Prophylactic DDAVP (0.3 μg/kg) on induction 2. Prophylactic DDAVP (0.3 μg/kg); 4 units of packed cells and 2 units of platelets standby	1. Induction at 41 weeks resulting in an emergency caesarean section for fetal distress 2. SROM at 39 weeks, resulting in repeat caesarean section for fetal distress	1. Estimated blood loss of 1600 mL, for which 4 units of packed cells and 2 units of platelets were administered. Normal postpartum lochia 2. Uneventful delivery, no need for blood replacement or platelet transfusion
Poddar *et al*[3]	2004	Case report	None	SROM at 40 weeks. Vaginal delivery	Initial estimated blood loss of 250 mL due to second-degree tear, forming a vulval haematoma. Small but continuing blood loss postpartum: re-exploration of the tear revealed no active bleeding, but continuous ooze from raw areas. The vagina was packed with swabs. Systolic blood pressure was 60–70 mm Hg and estimated blood loss was 1800 mL. Two units of blood and 1 L of gelofusine were administered. The surgical pack was removed under DDAVP 0.3 μg/kg in 50 mL of saline intravenous over 20 min with minimal blood loss
Beesley *et al*[4]	2008	Case report	1. DDAVP during second stage of labour with repeat dosing every 8 hours 2. DDAVP infused over 30 min in late second stage of labour	1. Induction at term. Vaginal delivery 2. Induction at term. Vaginal delivery	1. Uncomplicated delivery, estimated blood loss of 1500 mL resulting from second-degree perineal laceration; patient received 2 units of packed cells and 2 units of pooled platelets 2. Episode of brisk bleeding after placental separation, controlled with bimanual massage, 1 unit of platelets and 60 units of oxytocin diluted in 1 L of saline solution. Total blood loss estimated 1000 mL. Normal postpartum lochia
Spencer and Rosengren[11]	2009	Case report	4 units of platelets 2.5 hours prior to delivery	Induction at 39 weeks. Vaginal delivery	Estimated blood loss of 700 mL, causing a drop of haematocrit from 32.6% to 27.9%. Platelet count went from 210 000 before delivery to 326 000 after platelet transfusion. A second-degree laceration was repaired. Discharge after 2 days without complications
Nisal *et al*[9]	2012	Case report	▶ Transfusion of platelets before surgery ▶ Infusion of tranexamic acid postoperatively ▶ 5-day course of oral tranexamic acid postpartum	Elective caesarean section of DCDA twins with general anaesthesia	Uneventful postoperative recovery
Harris-Glocker *et al*[6]	2013	Case report	▶ DDAVP immediately prior to caesarean delivery ▶ Units of packed cells crossed and typed in anticipation of severe bleeding	Urgent caesarean section of spontaneous DCTA triplets at $31^{3/7}$ weeks for oligohydramnios and fetal distress	Severe uterine atony responsive to oxytocin, uterine massage and methylergonovine, with a total blood loss of 800 mL. Preoperative haematocrit value of 26 dropped to a postoperative value of 19 and remained stable. Discharge after 4 days without complications
Bachmann *et al*[5]	2014	Case report	▶ Prophylactic DDAVP ▶ Postpartum DDAVP	Vacuum delivery due to birth arrest	No bleeding complications. Estimated blood loss 300 mL
Civaschi *et al*[10]	2015	Clinical trial Multicentre study	▶ None ▶ Prophylactic platelet transfusion	1. Vaginal delivery 2. Caesarean section with general anaesthesia	No bleeding complications
Van Avermaete	2016	Case report	Prophylactic platelet transfusion in 3 doses over 36 hours	Caesarean section with general anaesthesia	No bleeding complications during the procedure. Estimated blood loss of 600 mL. Haematoma formation at the site of the wound after 72 hours with secondary infection

transfusion of platelets does not guarantee a delivery without complications, even if there were no problems in a previous pregnancy.

In the literature, three patients (3/14, 21.4%) did not receive any kind of prophylactic treatment at the time of delivery, in which diagnosis of HPS was not known in advance.[3 7 10] One of these patients presented with severe maternal haemorrhage at the time of delivery, requiring red blood cell transfusion.

One case report describes the management of the delivery of dichorionic diamniotic twins. Elective caesarean section under general anaesthesia was performed, with transfusion of platelets immediately before surgery and administration of tranexamic acid postoperatively. The operation was uncomplicated with no problems of prolonged bleeding.[9] Similarly, a case of dichorionic triamniotic triplets has been described, in which DDAVP was administered prior to an urgent caesarean section under general anaesthesia at $31^{3/7}$ weeks. In this case, severe uterine atony was reported, which was responsive to oxytocin, uterine massage and methylergonovine. There was a blood loss of only 800 cc. The mother could be discharged after 4 days without complications.[6]

Of the four (4/14, 28.6%) cases with severe maternal haemorrhage, three were treated with prophylactic DDAVP and one case received no prophylactic treatment at the time of delivery. Of these four cases, three were vaginal deliveries and in one case, prolonged bleeding occurred after caesarean section. After vaginal delivery, perineal laceration can lead to prolonged oozing with the formation of vulval haematoma.[3 4] In one patient, vaginal packing was required, next to transfusion of fluids and packed cells. In another case, placental separation resulted in an episode of brisk bleeding, which was controlled with bimanual massage, 1 unit of platelets and 60 units of oxytocin diluted in 1 L of saline solution.[4] Except for the case of dichorionic triamniotic twins,[6] neonates had good Apgar scores in all described cases. Maternal mortality has not been described.

In conclusion, it is crucial to optimise primary haemostasis at the time of delivery in the case of a known diagnosis of HPS by administering platelets, or DDAVP if proven effective. Otherwise, it is important to keep HPS in mind, in the case of prolonged postpartum bleeding in combination with normal platelet counts and normal coagulation factor activity. Thrombocytopathy combined with signs of oculocutaneous albinism are significant clinical factors leading to diagnosis. Specific obstetric recommendations in the case of delivery of a pregnant woman with HPS consist of the avoidance of regional anaesthesia, because of the possible bleeding complications. In the case of caesarean section, general anaesthesia should be carried out. The mode of delivery must be decided individually since there are no contraindications for a vaginal delivery; moreover, there is no contraindication for the use of vacuum or forceps either. NSAIDs should be avoided at all time.

Learning points

- In view of possible bleeding complications during delivery, a haematological consult should be initiated once pregnancy is confirmed.
- The patient should be seen by an anaesthesiologist early in pregnancy, as caesarean section must be under general anaesthesia if needed and non-steroidal anti-inflammatory drugs are contraindicated.
- The available options to minimise blood loss in the case of thrombocytopathy consist of prophylactic administration of DDAVP or platelet transfusion. In this case, laboratory tests showed that DDAVP would not correct bleeding time and would be insufficient.
- Response to prophylactic DDAVP administration can vary between, as well as within patients with Hermansky-Pudlak syndrome.
- Prophylactic transfusion of platelets does not guarantee a delivery without complications, even if there were no problems in a previous pregnancy.

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