The presentation and outcomes of Hermansky-Pudlak syndrome in obstetrics and gynecological settings: A systematic review

Deborah Obeng-Tuudah¹,²,³ | Brwa A. Hussein¹ | Amir Hakim⁴,⁵ | Keith Gomez¹ | Rezan Abdul Kadir¹,²,³

¹Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Hospital NHS Trust, London, UK
²Department of Obstetrics and Gynaecology, Royal Free Hospital NHS Trust, London, UK
³EGA Institute for Women's Health, University College London, London, UK
⁴Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
⁵National Heart and Lung Institute, Imperial College London, London, UK

Correspondence
Rezan Abdul Kadir, Department of Obstetrics and Gynecology, Royal Free Hospital NHS Trust, Pond Street, London, NW3 2QG, UK.
Email: rezan.abdul-kadir@nhs.net

Abstract
Background: Hermansky-Pudlak syndrome (HPS) is a rare autosomal-recessive disorder with clinical manifestations of bleeding diathesis, multi-organ disease and variable oculocutaneous albinism (OCA). In women, it can cause life-threatening obstetric and gynecological (OB/GYN) bleeding.

Objective: To summarize OB/GYN presentations, outcomes, and management strategies in women with HPS.

Search strategy: Main databases (MEDLINE, EMBASE, Cochrane, PubMed, Web of Science Core Collection and Google Scholar) were searched from inception until June 30, 2020.

Selection criteria: Case reports/series of women with confirmed HPS.

Data collection and analysis: A systematic review using PRISMA guidelines. Methodological quality assessment performed using adapted Newcastle Ottawa scale.

Main results: A total 29 pregnancies in 15 women and 2 gynecological patients were identified. Heavy menstrual bleeding (HMB), the most common bleeding symptom, was reported in 8/15 (53%) of women. HMB and post-partum hemorrhage (PPH) led to diagnosis of HPS in 5/17 (29%) women. Primary PPH was reported in 12/27 (44%) of viable pregnancies; half were major PPH. In 17 pregnancies with known HPS diagnosis, 9 had hemostatic cover with desmopressin and 8 with platelet transfusion. Major PPH occurred in 3/9 (33%) pregnancies covered with desmopressin compared with none in the platelet group.

Conclusion: Diagnosis of HPS should be considered in women with OCA presenting with HMB or PPH. Hemostatic management options include desmopressin and platelet transfusion. Management should be multidisciplinary with close collaboration between OB/GYN and hematology teams.

KEYWORDS
delta storage pool disorder, heavy menstrual bleeding, Hermansky-Pudlak syndrome, HPS, labor, obstetrics and gynecology, OB/GYN, oculocutaneous albinism, postpartum hemorrhage, pregnancy
Hermansky-Pudlak syndrome (HPS) was first described in 1959. It is characterized by dense granule deficient platelets (delta storage pool disorder), oculocutaneous albinism (OCA) with present tyrosinase activity and intracellular accumulation of ceroid lipofuscin. Clinically, it manifests as variable degrees of bleeding diathesis, skin hypopigmentation, visual impairment, nystagmus, pulmonary fibrosis, granulomatous colitis and renal impairment. It is heterogeneous in its presentation, clinical course and prognosis.

Early diagnosis in childhood is common due to OCA, which encompasses skin/eye hypopigmentation, visual impairment and nystagmus. Skin and hair color ranges from pale white to light brown/tan and iris color tends to be blue, green or brown. Cases of iris heterochromia are also reported. OCA is only apparent after comparison to unaffected close relatives. HPS patients are prone to ultra-violet light mediated skin damage.

Bleeding symptoms of HPS, typical of platelet storage pool disorders, include excessive bruising, epistaxis, bleeding from other mucosal membranes, excessive bleeding after surgical or dental procedures, heavy menstrual bleeding (HMB) and postpartum hemorrhage (PPH). This is due to reduced platelet aggregation function resulting from the deficient dense granules/bodies.

Pulmonary fibrosis, inflammatory granulomatous colitis and renal failure are thought to be complications from multiple organ accumulation of an amorphous lipid-protein complex called ceroid lipofuscin. The lung pathology is a restrictive type with variable life expectancy, often presenting between the ages of 30–50 years.

Hermansky-Pudlak syndrome is a heterogeneous, autosomal recessive disorder and it is commonly found in Northwest Puerto Rico and the Swiss Valois region populations with an approximate prevalence of 1 in 1800 and a carrier frequency of 1 in 20. Outside these populations it is rare, with a prevalence of about 1 in 100 000 to 1 000 000 worldwide. Variants in at least 10 different genes are known to cause HPS (subtyped HPS1 to HSP10) of which variants in HPS1 are the most frequently reported. The resultant intracellular defect is the disruption of the synthesis and trafficking of lysosome-related organelles, which include platelet dense bodies and melanosomes, thus impairing their relative functions.

The diagnosis of a delta storage pool disorder is indicated by low platelet nucleotides with decreased ADP:ATP ratio, reduced ATP secretion and characteristic impaired platelet aggregometry. A definitive diagnostic feature seen under electron microscopy is the significant decrease in platelet dense granules/bodies. Molecular genetic analysis enables classifications into the different subtypes of HPS and aids in management and prognosis.

Due to its rare nature, most of our knowledge on HPS is through case reports and mouse-model laboratory experiments. HPS presentation in obstetrics and gynecology (OB/GYN) settings can pose significant risks to the patient and challenges for the clinicians involved. This review collates and summarizes the presentations, different management strategies and their effects available in clinical case reports with the main focus on obstetrics and gynecological aspects of care.

2 | MATERIALS AND METHODS

A systematic literature search according to PRISMA guidelines was performed to identify all eligible clinical cases and studies without language or time restriction. Electronic databases of MEDLINE, EMBASE, Cochrane, PubMed, Web of Science Core Collection and Google Scholar were searched from inception until June 30, 2020, using the following keywords: HPS, platelet storage pool disorders, OCA, women, females, pregnancy, labor, delivery, postpartum hemorrhage, obstetrics, HMB, menorrhagia, ovulation bleeding, ovarian bleeding and gynecology. The bibliographic references of the retrieved articles were also screened for additional cases/studies of relevance. We identified 220 articles altogether.

Abstracts of the articles in the literature searches were reviewed independently by two authors (DO-T and BH) for their relevance to OB/GYN outcomes in HPS patients. Sixteen articles were relevant and included in the review. The full articles were retrieved and the information extracted. One article was written in Spanish, so we obtained its translation into English. The other 15 articles were published in English.

Quality assessment of case reports and case studies were evaluated using the adapted Newcastle-Ottawa Scale recommended by Murad and colleagues. Each study was assessed against four major domains: selection, ascertainment, causality and reporting.

Demographic, medical, obstetrical and/or gynecological history of the women were collected from the included articles. Information retrieved included: author and year of publication; ethnicity; age at diagnosis of HPS; age at presentation to OB/GYN; family history of HPS and parental consanguinity; bleeding symptoms and results of investigations (platelet count, clotting screen, bleeding time, platelet function tests, presence of antiplatelet antibodies, and the causative genetic variant if stated). Detailed gynecological (menstrual history; hemostatic prophylactic cover for menstruation; treatment for HMB and other gynecological problems and treatment) and obstetric (gravidity and parity; antenatal complications; hemostatic prophylactic cover for labor, delivery and puerperium; gestational age at delivery; mode of delivery (MOD); type of anesthesia employed; estimated blood loss (EBL) at delivery; postpartum complications and treatments received; any neonatal complications) data were also collected.

3 | RESULTS

Of the 16 articles included in this review, 14 articles addressed pregnancies and two reported gynecological cases. There were 29 pregnancies described in 15 women and 2 gynecological cases in two women, making a total of 17 patients with HPS to evaluate. The data extracted from the cases are represented in Tables 1 and 2.
In all the studies, diagnosis of HPS was confirmed by a hematologist; of which nine (56%) studies fully described the diagnostic criteria met by subject(s). Further subgroup analysis revealed a high percentage of studies \( n = 15; 94\% \) adequately described and reported study outcome(s) and ensured adequate subject follow-up. Whereas a lesser number of studies fully described patient baseline characteristics \( n = 5; 31\% \) or adequately described the case(s) \( n = 8; 50\% \). Consequently, reporting of patient baseline characteristics and adequate description of case(s) posed the greatest risk of publication bias.

In terms of ethnicity, six (35%) out of the 17 women described were Puerto Rican, two (12%) Indian, one (6%) Hungarian, one (6%) Spanish, one (6%) Hispanic and one (6%) Turkish. The ethnicities of the remaining five (29%) women were not stated. Parental consanguinity was stated in only two (12%) women. Affected siblings and family members were reported in six (35%) women.

The diagnosis of HPS in cases included in this review were made based on clinical and laboratory findings. Only two (12%) women had their diagnosis confirmed by genetic analysis but mutational information was not given. The ages at diagnosis were mentioned for 11/17 (65%) women and ranged from 6–42 years with a median age of 14 years.

In obstetrics, HPS diagnosis was known prior to first pregnancy in 9/15 (60%) women. Two (13%) women were diagnosed antenatally on clinical suspicion due to their OCA and bleeding diathesis history. PPH led to the diagnosis of HPS in three (20%) women. One (7%) woman presented after her fourth child with shortness of breath secondary to pulmonary disease, which led to her diagnosis. In gynecology, severe HMB necessitating packed red cells transfusion was the presenting symptom in both women that led to HPS diagnosis.

Previous bleeding history was reported in 15/17 (88%) women. In two (12%) women, no information was given. The frequency of bleeding symptoms and other HPS associated signs/symptoms reported are described in Table 3. HMB was the most common bleeding symptom reported in 8/15 (53%) women. As part of OCA, nystagmus and significant visual impairment including blindness were reported in 11/15 (73%), 7/15 (47%) and 7/15 (47%) women, respectively.

### 3.1 Gynecological presentation

The two gynecological cases were aged 13 and 42 years at presentation. They were both nulligravida and presented with HMB, which led to the diagnosis of HPS.

A 13-year-old girl with OCA presented with 14 days history of HMB at menarche. Her hemoglobin level and hematocrit were 55 g/L and 0.15, respectively. She was transfused eight units of packed red cells and one pool of fresh frozen plasma. Norethisterone was started at presentation with little effect. Her OCA roused a high suspicion for a platelet function disorder, so five doses of intravenous desmopressin (0.3 µg/kg every 8–12 h) and intravenous tranexamic acid (TXA, 12 mg/kg 3 times a day) were tried. However, desmopressin was not effective despite laboratory normalization of prolonged collagen/epinephrine PFA-100 closure times by it. Her HMB was resolved after 4 days with a single injection of recombinant factor VIIa (rFVIIa; NovoSeven® at 100 µg/kg). Symptoms were managed with a progesterone derivative and TXA to prevent further HMB during periods. TXA was taken 2 days before her periods and continued 2 days after period cessation. She had a family history of parental consanguinity. Her younger sister was subsequently diagnosed with HPS due to OCA and skin bruising tendency.

The second case was in a 42-year-old woman of Indian ethnicity presenting with a 7-month history of HMB. She had skin hypopigmentation, easy bruising, nystagmus and poor visual acuity. Her hemoglobin level was 74 g/L and she was transfused packed red cells (number of units transfused not reported). She had a normal pelvic ultrasound. She was commenced on oral contraception, TXA and desmopressin, which controlled her heavy bleeding. She was continued on maintenance therapy of TXA and desmopressin during her periods. A chest X-ray and chest CT scan both showed mild pulmonary fibrosis. Her lung function was normal. An echocardiogram showed normal heart function. She had two siblings with similar phenotype and consanguineous parents.

### 3.2 Pregnancy and obstetric outcomes

A total of 29 pregnancies were reported in 15 women; eight women had one pregnancy, three women had two pregnancies, two women had three pregnancies, one woman had four pregnancies and one woman had five pregnancies described. Twenty-seven pregnancies were singletons, one dichorionic diamniotic twin pregnancy and one dichorionic, triamniotic (DCTA) triplet pregnancy.

Two (7%) of the 29 pregnancies resulted in miscarriage. There was no further information regarding the management and bleeding outcomes of these miscarriages. Twenty-seven (27) viable pregnancies and deliveries were thus reported in 15 women.

The median age of the women during pregnancy was 22 years (age range 18–40 years). No antenatal bleeding was reported. None of the cases reported development of antiplatelet antibodies. One woman required bronchodilators in her pregnancy to relieve shortness of breath secondary to HPS-related pulmonary fibrosis.

The gestational age at delivery was mentioned in 23/27 (85%) cases. Twenty (87%) pregnancies delivered at term (i.e. ≥37 weeks gestation). The three preterm deliveries were in the same woman—the gestational ages at delivery for the first two pregnancies were not mentioned, but the third was the DCTA triplet pregnancy delivered at 31 weeks and 3 days by emergency cesarean section because one of the fetuses had intrauterine growth restriction with abnormal Dopplers (absent end-diastolic flow), non-stressed cardiotocography and biophysical profiles.
| Author Year of publication | Pregnancy number if same woman | Maternal age/age at diagnosis (years) | Gravidity/parity F.N. | Parental consanguinity | FHx Ethnicity | Bleeding history prior to pregnancy | Other signs and symptoms | Clotting screen BT and other investigations |
|----------------------------|--------------------------------|--------------------------------------|-----------------------|------------------------|--------------|-----------------------------------|------------------------|---------------------------------------------|
| Reiss et al. 1985<sup>22</sup> | 16/NS Dx several years before pregnancy | G1P0 Singleton | NS | NS | Puerto Rican | Prolonged bleed after tooth extraction, epistaxis, menorrhagia, OCA (blonde hair, nystagmus, poor visual acuity) | Pot count x10<sup>5</sup>/L | PT 11.5 s (normal 10.5 s), PTT 35 s (normal 35 s) BT 15 min (normal <10 min) |
| Reiss et al. 1985<sup>22</sup> | 1<sup>st</sup> | NS/undiagnosed | G1P0 Singleton | NS | NS | Puerto Rican | Heavy bleed at time of a tooth extraction, prolonged bleeding from minor cuts, occasional epistaxis, single episode of menorrhagia, OCA (including nystagmus), interstitial pulmonary fibrosis No Hx of PPH Skin BCC | Pot count x10<sup>5</sup>/L | BT 6–15 min during antenatal period |
| Reiss et al. 1985<sup>22</sup> | 2<sup>nd</sup> | NS/undiagnosed | G2P1 Singleton | NS | As above | NS | NS |
| Reiss et al. 1985<sup>22</sup> | 3<sup>rd</sup> | NS/undiagnosed | G3P2 Singleton | NS | As above | NS | NS |
| Reiss et al. 1985<sup>22</sup> | 4<sup>th</sup> | NS/undiagnosed | G4P3 Singleton | NS | As above | NS | NS |
| Reiss et al. 1985<sup>22</sup> | 5<sup>th</sup> | 40/NS but dx after 4<sup>th</sup> baby above. Presented with SOB. HPS dx due to restrictive lung disease, OCA and bleeding diathesis | G5P4 Singleton | NS | As above | NS | NS |
| Wax et al. 2001<sup>18</sup> | 18/18 Dx at 32 weeks of this pregnancy on clinical suspicion due to OCA and ethnicity | G1P0 Singleton | NS | None | Puerto Rican | Prolonged bleed after tooth extraction, epistaxis, menorrhagia, OCA (blonde hair, nystagmus, poor visual acuity) | Pot count x10<sup>5</sup>/L | Normal PT, APTT Normal PT and APTT BT 6–15 min during antenatal period |
| Zatik et al. 2002<sup>16</sup> | 1<sup>st</sup> | 18/8 | G1P0 Singleton | NS | NS | Hungarian | Severe bleeding after tooth extraction | Pot count x10<sup>5</sup>/L | Normal PT/APTT/TT Prolonged BT >20 min (ref <10 min) |
| Zatik et al. 2002<sup>16</sup> | 2<sup>nd</sup> | 22/8 | G2P1 Singleton | NS | NS | Hungarian | Severe bleeding after tooth extraction | Pot count x10<sup>5</sup>/L | Normal PT/APTT/TT Prolonged BT >20 min (ref <10 min) |
| Poddar et al 2004<sup>15</sup> | 1<sup>st</sup> | 21/21 Dx after major PPH complicated this incident pregnancy | G1P0 Singleton | NS | Sister | Asian/Indian | Epistaxis, menorrhagia, easy bruising, OCA (including nystagmus, visual impairment) | Pot count x10<sup>5</sup>/L | INR 1, APTT 1.1 Hb 113 g/L Prolonged BT >20 min (2–9 min) |

**TABLE 1** Main characteristics of the reported pregnancies with HPS
| Prophylactic treatment prior to delivery | GA (weeks) at delivery | MOD/labor complication | Mode of analgesia/anesthesia | Blood loss (ml) | Treatment and maternal outcome | Neonatal outcome/birth weight/Apgar/HPS status if known |
|----------------------------------------|------------------------|------------------------|-------------------------------|-----------------|-------------------------------|--------------------------------------------------|
| Platelet transfusion                    | 40 SOL                 | NVD                    | NS                            | Normal EBL      | Sustained 1st degree tear sutured under local anesthesia | Male 3500 g Apgar 8¹, 9⁵                     |
| Had a transfusion reaction              |                        |                        |                               | Postpartum Hct 0.40 |                               |                                                   |
| None                                    | NS                     | NS                     | NS                            | No PPH          | None needed                   | NS                                               |
| Dx unknown                              |                        |                        |                               |                 |                               |                                                   |
| None                                    | NS                     | NS                     | NS                            | No PPH          | None needed                   | NS                                               |
| Dx unknown                              |                        |                        |                               |                 |                               |                                                   |
| None                                    | NS                     | NS                     | NS                            | No PPH          | None needed                   | NS                                               |
| Dx unknown                              |                        |                        |                               |                 |                               |                                                   |
| None                                    | NS                     | NS                     | NS                            | No PPH          | None needed                   | NS                                               |
| Dx unknown                              |                        |                        |                               |                 |                               |                                                   |
| None                                    | 39 NS                  | NVD                    | Intact perineum               | 400 ml          | None needed                   | Female 3420 g Apgars 8¹, 9⁵                      |
| Bloods in labor: Plt 321                |                        |                        |                               |                 |                               |                                                   |
| Hct 0.33                                |                        |                        |                               |                 |                               |                                                   |
| BT 6 (normal)                           |                        |                        |                               |                 |                               |                                                   |
| 5 units of platelets transfused in labor| 40 SOL                 | NVD                    | Analgesia by iv butorphanol   | Normal          | None needed                   | Male 3374 g                                      |
|                                        |                        |                        |                               | Uneventful      |                               |                                                   |
|                                        |                        |                        |                               | postpartum      |                               |                                                   |
|                                        |                        |                        |                               | period          |                               |                                                   |
| Desmopressin                            | 41 IOL due to non-reactive nonstress testing and meconium liquor | EmCS due to fetal distress Major PPH 1.6 L | NS | 1600 Hb fall from 129 to 77 g/L, Hct 0.37 to 0.23 Plts from 134 to 65 | 4 units packed red cells and 2 units plts transfusion | NS |
|                                        |                        |                        |                               |                 |                               |                                                   |
| Desmopressin                            | 39 SOL                 | EmCS due to fetal distress | NS | Normal Hb fall from 107 to 93, Hct from 0.29 to 0.27 | No need for blood or platelet transfusion | NS |
|                                        |                        |                        |                               |                 |                               |                                                   |
| None                                    | 40 SOL                 | NVD with initial EBL 250 ml Extended 2nd degree tear upto right fornix, vulval hematoma | Epidural analgesia/anesthesia | 1800 | Return to theatre for vaginal tear exploration Vaginal pack inserted, hypotensive, 1 L gelofusine, 2 units RBC Tx, Desmopressin | NS |
| Dx unknown                              |                        |                        |                               |                 |                               |                                                   |

(Continues)
| Author Year of publication | Pregnancy number if same woman | Maternal age/age at diagnosis (years) | Gravidity/parity F.N. | Parental consanguinity | FHx Ethnicity | Bleeding history prior to pregnancy | Other signs and symptoms | Plt count ×10^9/L | Clotting screen BT and other investigations | GA (weeks) at delivery | Onset of labor (SOL/IOL) | MOD/labor complication | Mode of analgesia/anesthesia | Blood loss (ml) | Postdelivery blood results | Treatment and maternal outcome | Neonatal outcome/birth weight/Apgar/HPS status if known |
|---------------------------|-------------------------------|--------------------------------------|-----------------------|------------------------|---------------|-----------------------------------|--------------------------|----------------|--------------------------------|---------------------|-------------------|-----------------------------|---------------------|----------------|--------------------------|--------------------------------|-----------------------------------|
| Nisal et al. 2012^17       | 2nd First pregnancy described by Poddar et al. 2004^14 | 26/21 | G2P1 Twins DCDA Unknown if spontaneous or assisted conception | NS | As above | As above | NS but same patient as above | 9/10 |  | | NS |  | | | | | | |
| Beesley et al. 2008^20     | 1st 17/17 Dx after major PPH complicated this incident pregnancy | G1P0 Singleton | NS | NS Puerto Rican | NS | NS | NS | | | | | | | | | | | | |
|                           | 2nd 19/17 | G2P1 Singleton | NS | | | | | | | | | | | | | | | |
|                           | 3rd 22/17 | G3P2 Singleton | NS | | | | | | | | | | | | | | | |
| Tong et al. 2008^25        | 20/7 | G1P0 | NS | FhX NS Puerto Rican | Bleeding diathesis OCA | | | | | | | | | | | | |
|                           | | | | | | | | | | | | | | | | | | |
| Spencer et al. 2009^19     | 19/14 | G1P0 Singleton | NS | NS Puerto Rican | OCA (including blindness), recurrent epistaxis, easy bruising, menorrhagia. | | | | | | | | | | | | |
|                           | | | | | | | | | | | | | | | | | | |
| Harris-Glocker et al. 2013^23 | 1st NS/NS Dx Unknown | G1P0 | NS | Brother Hispanic | Occasional prolonged bleeding, PPH at first delivery led to diagnosis. Confirmed by genetic testing. PMHx of Asthma and fibromyalgia | | | | | | | | | | | | |
|                           | 2nd NS/NS but dx after first delivery complicated with PPH | G2P1 | NS | | | | | | | | | | | | | | | |
|                           | 3rd NS/As above | G3P2 | NS | | | | | | | | | | | | | | | |
| Prophylactic treatment prior to delivery | GA (weeks) at delivery | Onset of labor (SOL/IOL) | MOD/labor complication | Mode of analgesia/ anesthesia | Blood loss (ml) | Postdelivery blood results | Treatment and maternal outcome | Neonatal outcome/birth weight/Apgar/HPS status if known |
|----------------------------------------|------------------------|--------------------------|------------------------|-------------------------------|----------------|-----------------------------|-------------------------------|--------------------------------------------------|
| Platelet transfusion before ELCS       | NS                     | NS                       | ELCS                   | History of traumatic delivery – maternal request for cesarean section | NS but uncomplicated delivery reported | Prophylactic iv TXA after C/S then 5 days oral TXA | Maternal outcome uneventful | NS                                                |
| None                                   | 39                     | NS                       | EmCS for FTP           | NS                            | Severe hemorrhage | 8 units of packed red cells transfused | Not stated if FFP or platelets given | NS                                                |
| Desmopressin                           | Term ≥37 weeks IOL     | NVD                      | PCA with remifentanil  | 1500                          | From second degree perineal tear | 2 units packed red cells and 2 units of pooled platelets | Male 3032 g Apgar 8<sup>1</sup> 9<sup>5</sup> | |
| Desmopressin                           | 39                     | NVD                      | PCA with ramifentanil  | 1000                          | Uterine atony also reported requiring uterine massage | 1 unit pooled platelets and 60 units of oxytocin infusion used | Female | |
| Desmopressin                           | 37                     | SOL Booked for ELCS (maternal request) at 38 weeks but presented in labor with SROM at 37 weeks | NVD Sustained 2nd degree perineal tear Active management of third stage with oxytocin Regional analgesia/ anesthesia avoided | Moderate major bleeding (about 1500 ml as Hb dropped from 127 to 97 g/L) from perineal area Plts 173 | 2 units platelet transfusion Discharged day 4 | Male 3000 g Apgar 5<sup>1</sup> and 9<sup>5</sup> Negative HPS testing | |
| 4 units of platelets transfused prophylactically in labor | 39                     | IOL                      | NVD                    | NS                            | 700             | Hct fall from 0.33 to 0.28 | 2nd degree tear sutured with no problems | Declined fetal or partner testing Female 3130 g Apgar 9<sup>1</sup> 9<sup>5</sup> |
| None – diagnosis unknown               | Preterm                | NVD                      | NS                     | Severe PPH                    | NS              | No information on treatment given for PPH | NS | |
| Desmopressin                           | Preterm                | NVD                      | NS                     | No PPH                        | None needed     | NS | |
| NS                                     | Pregnancy miscarried/ aborted. | NVD | No further information given | NS | NS | N/A | |
| (Continues) |
| Author Year of publication | Pregnancy number if same woman | Maternal age/age at diagnosis (years) | Gravidity/parity F.N. | Parental consanguinity | FHx | Ethnicity | Bleeding history prior to pregnancy | Other signs and symptoms | Plt count \( \times 10^9/L \) | Clotting screen BT and other investigations |
|---------------------------|-------------------------------|--------------------------------------|----------------------|------------------------|-----|----------|-----------------------------------|-------------------------|-----------------|-----------------------------------|
| Tudela SV et al. 2013\(^{13}\) | 30/NS but dx before pregnancy | G1P0 Singleton | NS | Sister Paternal aunt Spanish | OCA (including minor visual deficit), menorrhagia | Plts 171 |
|                           |                              |                                      |                      |                        |     |          | Hb 120 g/L                         | Hct 0.36                     |                 | Normal clotting Prolonged BT >20 min |
|                           |                              |                                      |                      |                        |     |          |                                    |                          |                 |                                    |
| Bachmann et al. 2014\(^{24}\) | 30/NS but dx before pregnancy | G7P0 Singleton | NS | NS | OCA (including visual impairment, nystagmus) Heavy surgical bleeding, prolonged menstrual period | Plts 237 |
|                           |                              |                                      |                      |                        |     |          | Normal Hb                          |                           |                 | Normal clotting screen Prolonged BT 6 min (Duke normal 3–5 min) |
| Civaschi et al. 2015\(^{21}\) | 20/6                          | NS                                   | NS                   | NS                     | Petechiae | Plts 281 |
|                           |                              |                                      |                      |                        |     |          |                                    |                          |                 |                                    |
| Civaschi et al. 2015\(^{21}\) | 36/34                         | NS                                   | NS                   | NS                     | Mild blood loss—site not stated | Plts 301 |
| Van Avermaete et al 2016\(^{26}\) | 1st 27/8                      | NS                                   | NS                   | NS                     |                            |                            |
|                           |                              |                                      |                      |                        |     |          |                                    |                          |                 |                                    |
|                           | 2nd 27/8                      | G2P0M1                               | NS                   |                        |                            |                            |
|                           | 3rd 27/8                      | G3P1 M1                               | NS                   |                        |                            |                            |
| Prophylactic treatment prior to delivery | GA (weeks) at delivery | MOD/labor complication | Mode of analgesia/ anesthesia | Blood loss (ml) | Postdelivery blood results | Treatment and maternal outcome | Neonatal outcome/birth weight/Apgar/HPS status if known |
|----------------------------------------|------------------------|------------------------|-------------------------------|----------------|---------------------------|-------------------------------|---------------------------------------------------|
| 2 doses of Desmopressin prior to emergency C/S due to delays | 31 + 3 | Semi-planned as hospitalized | Preterm triplets delivered due to baby B having IUGR with abnormal dopplers, BPP and CTG. Also had Grade1 IVH | General Anesthesia | 800 | Uterine atony also reported | None needed Discharged day 4 | Apgars and gases Baby A: 5\(^1\), 9\(^5\) Baby B (compromised fetus): 1\(^1\), 4\(^4\), 8\(^10\). Art pH 7.27 BE ~4, Ven pH 7.30 BE ~3 Baby C: 4\(^4\), 7\(^5\) All babies growing well and meeting milestones |
| TXA 1 g 12 hourly Desmopressin | 38 + 2 | SOL IOL was planned but presented in labor 3 h before admission | NVD with episiotomy under local anesthesia | Acupuncture, Entonox, homeopathy, PCA | No PPH reported Post-delivery Hb 101 g/L Hct 0.296 | Continued prophylactic TXA postpartum Discharged day 2 | Female 3190 g Apgar 9\(^1\) 10\(^5\) 10\(^10\) Art pH 7.29 |
| Desmopressin | 39 | SOL | Vacuum delivery Due to failure to progress in second stage of labor | Regional anesthia avoided | 300 | Post-delivery Plts 236 Normal clotting | One more prophylactic dose of desmopressin postpartum Discharged day 3 | Female 3100 g Apgar 9\(^1\) 10\(^5\) 10\(^10\) Art pH 7.25 |
| None | Term | NVD | None | Normal EBL | No further treatment | NS |
| Platelets transfusion | Term | CS Reason unknown | General Anesthesia | Normal EBL | No further treatment | NS |
| NS | None | Spontaneous miscarriage at 8 weeks | N/A | NS | No information on amount of bleeding during miscarriage | N/A |
| 2 units platelet transfusion during and immediately post-delivery (cesarean section) | Term \(\geq37\) weeks | NS | EmC/S for FTP in first stage | NS | Normal EBL | None | Baby weight not stated. Good Apgar scores reported |
| 4 units prophylactic platelet transfusion within 24 h postdelivery | 40 | IOL | EmC/S for FTP in first stage Wound hematoma developed 72 h after C/S and subsequent secondary infection | No regional anesthesia or analgesia General anesthesia for cesarean section | 600 Hb 106 g/L Plt 146 | 14 days antibiotics regime (Co-amoxiclav 875 mg tds) Plus prophylactic platelet transfusion Discharged day 6 | NS |

(Continues)
TABLE 1 (Continued)

| Author Year of publication | Pregnancy number if same woman | Maternal age/age at diagnosis (years) | Gravidity/ parity F.N. | Parental consanguinity | FHx Ethnicity | Bleeding history prior to pregnancy | Other signs and symptoms | Clotting screen BT and other investigations |
|-----------------------------|--------------------------------|--------------------------------------|-----------------------|------------------------|--------------|------------------------------------|--------------------------|-------------------------------------------|
| Yusuf et al 2016            | 1st                            | NS/NS but diagnosis suspected during this pregnancy | G1P0                  | NS                     | NS           | OCA (including nystagmus), easy bruising, bleeding after tooth extraction | Normal platelets | Hb 115 g/L predelivery | No HLA or Human platelet antigen antibodies |
|                             | 2nd                            | 31/As above                          | G2P1                  | NS                     |              |                                    |                          |                                           |

Abbreviations: APA, antiplatelet antibody; APTT, activated partial thromboplastin time; BT, bleeding time; DCDA, dichorionic, diamniotic twins; DCTA, dichorionic, triamniotic triplets; Dx, diagnosed or diagnosis; EBL, estimated blood loss; ELCS, elective cesarean section; EmCS, emergency cesarean section; F.N., number of fetuses; FHx, family history; FTP, failure to progress in labor; G, gravida; GA, gestational age; Hb, hemoglobin; Hct, hematocrit; HPS, Hermansky-Pudlak syndrome; INR, international normalized ration; IOL, Induction of labor; IVH, intraventricular hemorrhage; M, miscarriages; MOD, mode of delivery; NS, not stated; NVD, normal vaginal delivery; OCA, oculocutaneous albinism; P, parity; PCA, patient controlled analgesia; Plt, platelets; PND, prenatal diagnosis; PPH, postpartum hemorrhage; PT, prothrombin time; SOL, spontaneous onset of labor; TT, thrombin time; TXA, tranexamic acid.

3.3 | Labor and delivery

Mode of delivery was mentioned in 23/27 (85%) pregnancies, of which 13/23 (57%) delivered by normal vaginal delivery, 2/23 (9%) by instrumental delivery (vacuum or forceps), 7/23 (30%) by emergency cesarean section and 1/23 (4%) by maternal request elective cesarean section due to previous traumatic delivery. This woman had heavy bleeding from continuous oozing raw areas of adequately repaired vaginal and perineal tears (second degree). A return to theatre for re-exploration confirmed this and ruled out actively bleeding areas. She required vaginal pack insertion, blood transfusion and desmopressin administration. She was subsequently diagnosed with HPS postnatally. Three (43%) of the seven emergency cesarean sections were due to fetal distress (includes the DCTA triplets mentioned above), 3 (43%) for failure to progress in first stage of labor and no reason stated in 1 (15%).

The type of analgesia and/or anesthesia was stated in 12/27 (44%) cases. Regional analgesia and anesthesia were avoided in 11/12 (92%) cases because of HPS. Epidural anesthesia was used in one case where the diagnosis of HPS was unknown at the time with no report of spinal hematoma. General anesthesia was employed in four cases for cesarean sections. The women used a variety of methods for analgesia ranging from patient-controlled analgesia with remifentanil or butorphanol, entonox, acupuncture, homeopathy to no analgesia.

At the time of labor, HPS diagnosis was known in 20/27 (74%) and unknown in 7/27 (26%) pregnancies. Three women diagnosed postnatally after PPH in their first pregnancies, subsequently had pregnancies described where HPS status was known and one woman had four deliveries before HPS was diagnosed.15,20,22,23

3.4 | Postpartum hemorrhage

Quantitative value for EBL was reported in 10/27 (37%) pregnancies (mean 950 ml, range 300–1800 ml). Descriptive EBL using words such as normal blood loss, no PPH and severe hemorrhage were reported in the remaining 17 (63%) pregnancies.

Primary PPH was reported in 12 (44%) pregnancies, of which six (50%) were major PPH (defined as EBL >1000 ml).20 Of vaginal deliveries and cesarean sections 8/15 (53%) and 4/8 (50%) had PPH, respectively. One case had a cesarean wound hematoma requiring platelet transfusion.

PPH was the presenting symptom that led to the diagnosis of HPS in 3/15 (20%) women: one case had 1800 ml blood loss requiring a return to theatre for vaginal/perineal tears re-exploration, vaginal pack insertion and transfusion of two units of red blood cells; the second case had severe hemorrhage requiring transfusion of eight units of red blood cells, and the third case reportedly had severe hemorrhage but blood loss or treatment details were not given.

Of the 20 pregnancies with known HPS diagnosis at labor, hematostatic cover for labor and delivery was administered in 17/20 (85%); 9/17 (53%) received desmopressin and 8/17 (47%) received platelet transfusion. TXA was used in conjunction with desmopressin and platelets in two cases. In 3/20 (15%) no hemostatic prophylaxis was given in labor and delivery (Table 4).

Pregnancies managed with hemostatic platelet transfusion had lower EBL (8 cases, highest EBL 800 ml) compared to those managed with desmopressin (9 cases, highest EBL 1600 ml).13,16–27 Major PPH occurred in 3/9 (33%) cases in the desmopressin group compared to none when platelets were used. Platelets and packed red cells transfusion were required to treat PPH in 4/9 (44%) and 2/9 (22%) cases in the desmopressin group respectively.16,20,25 Among women
receiving desmopressin prophylaxis, there were 6/9 (67%) vaginal and 3/9 (33%) cesarean deliveries compared to 4/8 (50%) vaginal and 4/8 (50%) cesarean deliveries among those with platelet prophylaxis.

The two cases, where there was no PPH despite no hemostatic cover in pregnancies with known HPS diagnosis, were noted to be in women with mild bleeding phenotype (one had only petechiae as her pre-pregnancy bleeding history and the other had occasional bleeding history with a normal bleeding time documented during labor.21,22 One of these women also had no PPH in four previous deliveries where HPS diagnosis was unknown, and thus no hemostatic cover instituted.

Hemostatic cover immediately after delivery and the puerperium were only reported in 6/27 (22%) cases. TXA was continued as prophylaxis in three cases.13,17,27 In the immediate postpartum period, one pregnancy received an additional dose of desmopressin and two pregnancies received further units of platelets.24,26

3.5 Neonatal outcome

Altogether, there were 30 neonates in 27 pregnancies—25/30 (83%) neonates were born at term (≥37 weeks) and 5/30 (17%) were born preterm. The preterm deliveries were all in one woman and included the DCTA triplet pregnancy.23 Information on neonatal outcome were given in 9/30 (30%) neonates. Where stated, babies had good birth weight (range 3–3.5 kg) and Apgar >8 at 5 min.

4 DISCUSSION

This is the first extensive systematic review into the obstetric and gynecological problems and their management in women with HPS. It highlights the bleeding diathesis during menstruation, labor and delivery associated with HPS, making affected women a high-risk population in obstetrics and gynecology setting.

The diagnostic age of HPS was wide, ranging from 6 to 42 years with a median age of 14, interestingly near the general age of menarche.21 Thus, presentations may occur in a variety of medical specialties including pediatrics, OB/GYN, adult general medicine and surgery. HMB was commonly the bleeding symptom reported, affecting 8 (53%) of women. Both gynecological cases initially presented with acute HMB and severe anemia. Therefore, platelet function disorders should be considered in the differential diagnosis of acute HMB. The treatment options include a combination of hormonal therapy and hemostatic therapy with TXA and/or desmopressin. Platelet transfusion and rFVIIa should be considered in cases of intractable bleeding.

Primary PPH occurred in 12 (44%) out of 27 deliveries, with half progressing into major PPH (EBL > 1000 ml). In three (20%) women, major PPH was the presenting symptom leading to diagnosis and they had the highest blood loss necessitating the use of high volumes of packed red cells, return to theatre and/or hemostatic products.15,20,23 There were no reports of antenatal bleeding.

Desmopressin, platelet transfusion and/or TXA, were the main products used for both hemostatic prophylaxis and treatment in these patients, with platelet transfusion generally being preferred in high-risk hemorrhagic situations e.g. major surgery.21,10 rFVIIa has been used to treat acute bleeding in patients with various platelet function defects with variable success.28,32

In this review, we observed that platelet transfusion provided a better hemostatic cover in labor and delivery than desmopressin despite more cesarean sections in the platelet group. Comparing prophylaxis with desmopressin to platelet transfusion, the highest EBL was 1600 ml versus 800 ml and major PPH occurred in 3 (33%) versus none, respectively. In the prophylactic desmopressin
group, 4 (44%) and 2 (22%) subsequently received platelets and red blood cells transfusion respectively to control PPH. The majority of studies featured in this systemic review were case reports, which only permit narrative descriptions or descriptive statistics. Observational studies, especially case reports or case studies, have well known limitations such as heterogeneity between subjects, care settings and methodologies between case reports that need careful consideration when undertaking statistical analyses. Although, randomized controlled trials are difficult to perform for rare diseases such as HPS, future studies should consider other types of observational studies that permit estimations of effect size to test for statistical significance between different prophylactic hemostatic covers of HPS during labor and delivery.

Women with HPS, like other platelet storage pool disorders, have variable response to desmopressin. A particular patient’s response may also differ on separate occasions to desmopressin, and a confirmed laboratory response to desmopressin does not necessarily lead to clinical effectiveness. On the other hand,
TABLE 2 Main characteristics of the reported gynecological cases with HPS

| Year of publication | Presenting complaint | Age/age at menarche | Menorrhagia | Consanguinity | Ethnicity | Other signs and symptoms |
|---------------------|----------------------|---------------------|-------------|--------------|----------|-------------------------|
| Ray et al. 2013      | Heavy menstrual bleeding | 28 months          | Yes          | Yes          | Indian   | 7 months menorrhagia, Easy bruising |
| Lohse et al. 2011    | Menorrhagia           | 13/13              | NS (Sister)  | NS           | NS       | Parental consanguinity, Other signs and symptoms |

Platelet transfusion carries risks of transfusion reactions, the development of antibodies against human leucocyte antigen (anti-HLA) and transfusion-transmitted infections. Platelet alloimmunization could render future platelet transfusion ineffective due to immune-mediated destruction. Thus, it is best practice to reduce patients’ exposure to platelets.

Desmopressin is safe in pregnancy and can therefore be used initially. However, HLA-matched platelets or pre-stored and leucodepleted platelet concentrates should be ready for transfusion if needed. Platelet transfusion should be instituted where there is a high hemorrhagic emergency with or without desmopressin; random platelets may be required in such instances. In intractable hemorrhagic cases, rFVIIa can be considered.

An epidural block was used in a case where HPS diagnosis was unknown with no adverse outcome. However, the Royal College of Obstetricians and Gynaecologists recommend that women with severe platelet function disorders should avoid regional analgesia or anesthesia, to prevent spinal hematoma and
its devastating neurological consequences.\textsuperscript{37} Individual case assessment for suitability of regional block should involve a senior anesthetist and hematologist. Non-invasive analgesia options including Entonox, transcutaneous electrical nerve stimulation, and/or intravenous patient-controlled analgesia, are safe to use. Where regional anesthesia is contraindicated, a general anesthesia is recommended.\textsuperscript{15,37}

As HPS is an autosomal recessive condition, the fetus of a woman with HPS can be affected if the father is a carrier (50% chance) or has HPS (100% chance). Heterozygous carriers are asymptomatic and do not have a bleeding phenotype. Unless the fetus has the potential to be affected, there are no restrictions on invasive obstetric procedures such as fetal blood sampling, fetal scalp electrode and instrumental deliveries. However, difficult instrumental delivery in such women requires delicate care as deep perineal/vaginal trauma could lead to significant hemorrhage and the development of hematomas.\textsuperscript{15,25}

Non-bleeding complications of HPS requires consideration in managing these women. This review highlighted significant visual impairment and nystagmus in almost half the women (Table 3). Most patients with HPS have horizontal nystagmus and poor vision with acuity of 20/50 or worse.\textsuperscript{2} Pulmonary fibrosis and skin basal cell carcinoma were reported in 2/15 (13%) and 1/15 (7%) of women respectively in this review.

Limitations of this review include a small number of cases due to the rarity of HPS, risk of publication bias and heterogeneity in data obtained from case reports as authors focused on one aspect of care or another. The risk of publication bias, overall, was moderate with more than 90% of the studies, clearly ascertained study outcome(s) and had appropriate subject follow-up, ensuring a low level of publication bias but reporting of patient baseline characteristics posed the greatest risk. However, this is the first and largest review possible in OB/GYN presentations of HPS to provide some guidance to clinicians managing pregnancy or gynecological problems in such women.

In conclusion, the care of the woman with HPS should take a holistic approach, considering both hematological and non-hematological aspects. HPS diagnosis should be considered in women with OCA presenting with HMB or PPH. Women with HPS should be managed in a multidisciplinary setting involving OB/GYN team, hematologists with bleeding disorders expertise and anesthetists. Other non-hematological aspects of HPS such as respiratory, gastroenterology or renal problems require attention by their respective specialties.

In pregnancy, a detailed delivery plan should be made in advance of expected date of delivery and communications disseminated to relevant teams. Although anemia is not a direct focus in this review, it is important in HMB, pregnancy and PPH, so it should be investigated and treated accordingly. Anti-HLA antibodies should be checked in previously platelet transfused patients antenatally. Perineal evaluation should be considered in women with granulomatous colitis of HPS, particularly if vaginal delivery is planned, as it can involve the perineum. Ideally, delivery should be in a center with obstetric experience and hemophilia unit with easy access to laboratory and blood products. Planned delivery may be considered to facilitate the availability of resources and experienced clinicians.

The decision on type of hemostatic cover for delivery should take into consideration the woman’s previous bleeding history, response to hemostatic treatment and her obstetric risk factors. Desmopressin is safe in pregnancy and can be used initially; however, HLA-matched platelets should be ready if needed. Platelet transfusion should be used in women with a high risk of bleeding.

Active management of third stage of labor and steps to minimize tissue trauma during delivery in addition to appropriate hemostatic cover are important to minimize risk of PPH. Non-steroidal anti-inflammatory drugs should be avoided to preserve any residual platelet function.

The MOD should depend mainly on obstetric indications. If the fetus is at risk of HPS, invasive procedures such as fetal blood sampling, fetal scalp electrode and instrumental deliveries should be avoided, except for easy lift out forces when the fetal head is deeply engaged in the pelvis. The choice of analgesia/anaesthesia should be individually assessed by the multi-disciplinary team.

Supportive measures like modulated lighting in care areas and increased healthcare workers’ assistance for women with significant visual impairment should be established whilst hospitalized.

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CONFLICTS OF INTEREST
The authors do not have any conflicts of interest.

AUTHOR CONTRIBUTIONS
R.A.K. and K.G. conceptualized and designed the study. D.O-T. and B.A.H. performed literature research and retrieved the data from case reports. A.H. and D.O-T. conducted methodological quality assessment of the studies and reviewed data analysis. D.O-T. wrote the first draft of the manuscript, revised it, performed project administration, and incorporated revisions by R.A.K., K.G., B.A.H. and A.H. All authors approved the final draft.

ORCID
Deborah Obeng-Tuudah https://orcid.org/0000-0002-0334-1121
Rezan Abdul Kadir https://orcid.org/0000-0002-2684-1006

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