Update on inherited disorders of haemostasis and pregnancy

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Abstract

Inherited bleeding disorders have the potential to cause bleeding complications during pregnancy, childbirth and the postpartum period as well as effect fetal outcomes. There is an evolving understanding of the need for specialised and individualised care for affected women during these times. The aim for each patient is to estimate the risk to mother, fetus and neonate; to implement measures to minimise these risks; and to anticipate complications and develop contingencies for these scenarios. This includes accurate diagnosis, preconceptional care, prenatal diagnostic options, antenatal care, delivery and postpartum care as well as care of an affected neonate. An understanding of the physiologic haemostatic changes associated with pregnancy as well as the scope of defects, inheritance and management of inherited bleeding disorders is paramount when caring for these women. Collaborative and prospective management in conjunction with haematology services underpins the approach advocated. This review draws on the available literature, and outlines the principles of care for women with inherited bleeding disorders before, during and after pregnancy, as well as their babies, based on both available data and collective clinical experience.

Keywords

Haematology, haemorrhage, high-risk pregnancy, complications

Date received: 6 July 2015; accepted: 30 November 2015

Introduction

Women with inherited bleeding disorders (InBD) are at risk of bleeding complications during pregnancy, childbirth and during the postpartum period. In early pregnancy, they may also be at increased risk of miscarriage.¹ InBD are characterised by the total or partial deficiency of plasma proteins involved in haemostasis and are caused by various inherited genetic defects. Maternal bleeding may affect the mother and/or fetus, and the offspring may inherit the bleeding disorder and suffer bleeding complications. Haemophilia A and B together with von Willebrand's disease (vWD) account for 95–97% of all cases, with the remaining 3–5% representing rare bleeding disorders (RBDs) which include inherited deficiencies of fibrinogen, factors II, V, V + VIII, VII, X, XI and XIII (Table 1).² Inherited disorders of platelet function are a separate clinical entity and may also pose a bleeding risk to women in pregnancy. These include disorders of platelet adhesion, aggregation, secretion and pro-coagulant activity.³ These diseases are not dealt with in this review.

Multidisciplinary care models have evolved with growing recognition that women with InBD require specialised and individualised care. To optimise outcomes prenatally, at delivery and in the neonate, these multidisciplinary teams need to include obstetricians, geneticists, anaesthetists, neonatologists, paediatricians, haematologists and midwives. Worldwide, there is variable access to such services and resources, which needs to be addressed to optimise the care of all women with InBD.

In this article, we review the literature and outline the principles of care for women with InBD before, during and after pregnancy, and their babies, based on both available data and collective clinical experience (Figure 1).

Haemostatic changes in pregnancy

During pregnancy a number of physiological changes in haemostasis occur which alters the haemostatic balance towards a more pro-coagulant state.¹ In InBD, these changes are variable and unpredictable and may lead to a temporary correction of the haemostatic defect.² Those with homozygote or severe deficiencies tend to have persistent haemostatic abnormalities.²

Table 2 outlines the main changes in haemostatic factors during pregnancy. Most factor levels will return to the patient's baseline within days to weeks of delivery.⁴ The increase in factor VIII generally peaks between 29 and 35 weeks of pregnancy, and in most haemophilia A carriers levels will increase to the normal range.⁴ Haemophilia B carriers rarely experience a clinically significant rise in factor levels. In women with type 1 vWD (quantitative defect), increased vWF antigen and activity levels together with increased factor VIII improves haemostasis in the third trimester. However, the rise is unpredictable.⁴ Patients with severe type 1 vWD, type 2 vWD and type 3 vWD usually show no improvement in their haemostatic defect.² In type 2B vWD, thrombocytopenia may develop or be exacerbated by pregnancy due to increased production of abnormal intermediate vWF multimers, which bind to platelets and cause spontaneous platelet aggregation.² Regardless of fluctuating factor levels in pregnant women with InBD, the hereditary risk to the fetus remains.⁴

Diagnosis and preconceptional care

In many cases, bleeding disorders are diagnosed prior to pregnancy, frequently with presentation at menarche with menorrhagia. Clinical features of a possible underlying bleeding disorder are outlined in Table 3.⁵ In women who have a known InBD, *preconception counselling* is important to assess the risk to the mother and the offspring, and to discuss management options, especially in haemophilia carriers and women with a family history of severe InBD. Counselling through a multidisciplinary team consisting of experienced obstetricians, haematologists and clinical geneticists aims to provide the best available information to explain the risk of bleeding, genetic implications of the

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Table 1. Clinical features and management of the common inherited bleeding disorders.

Disorder	Defect	Prevalence	Mode of inheritance	Maternal bleeding risk	Fetal risk of transmission	Target replacement for delivery and procedures	Replacement options	Other considerations
Haemophilia A carrier	Factor VIII deficiency	1 in 5000 male births	X-linked recessive 30% spontaneous mutation	Factor VIII levels increase during pregnancy Carriers usually asymptomatic, unless factor VIII <40%	50% male offspring affected 50% female offspring carriers	Factor VIII ≥ 50 IU/dL	Rarely required Recombinant factor VIII products preferred Biosate and DDAVP second line	Male offspring may be severely affected despite asymptomatic mother Factor VIII levels increase during pregnancy
Haemophilia B carrier	Factor IX deficiency	1 in 30,000 male births	X-linked recessive Spontaneous mutations rare	May be increased if Factor IX <50%	50% male offspring are affected 50% female offspring are carriers	Factor IX ≥ 50 IU/dL	May need haemostatic support during pregnancy Recombinant factor IX products preferred	DDAVP ineffective
vWD Type I	Partial quantitative deficiency of vWF	70% of vWD 0.7% of population	Autosomal dominant	Mild to moderate bleeding	50% offspring with variable penetrance and expression Similar phenotype to mother	vWF:Ag ≥ 50 IU/dL	DDAVP if factor VIII or vWF:Ag <50 IU/dL and previously documented response. Titrate infusions according to daily factor VIII and vWF:Ag Maintain levels ≥ 50 IU/dL during labour, delivery and up to 5 days postpartum If prolonged treatment with DDAVP, consider adding vWF concentrates	Risk of delayed PPH Avoid hypotonic solutions at delivery if using DDAVP to prevent hyponatraemia
vWD Type 2	Qualitative/functional defect of vWF (plasma concentrations vWF near normal) Subtypes: -2A-2B-2M -2N	10–20% of vWD 0.1–0.2% of population	Autosomal dominant	Mild to moderate	50% offspring with variable penetrance and expression Similar phenotype to mother	Follow factor VIII and vWF:AC daily (titrate infusions accordingly) Maintain levels of both ≥ 50 IU/dL during labour, delivery and up to 5 days postpartum	vWF concentrates DDAVP if response previously documented on test dose (mainly 2A)	Regular monitoring of vWF:Ag and vWF:AC together with factor VIII:C is essential Should be performed at presentation, prior to any invasive procedures, and in third trimester In 2B: thrombocytopenia may develop or worsen during pregnancy Platelets (in type 2B vWD)

(continued)

Table 1. Continued

Disorder	Defect	Prevalence	Mode of inheritance	Maternal bleeding risk	Fetal risk of transmission	Target replacement for delivery and procedures	Replacement options	Other considerations
vWD Type 3	Severe quantitative defect of vWF Undetectable levels of vWF:Ag	1–2 cases per 1,000,000	Autosomal recessive	Very high	Obligate heterozygote Risk of homozygosity low	Maintain levels ≥ 50 IU/dL during labour, delivery and up to 5 days postpartum Follow factor VIII and vWF:AC daily (titrate infusions accordingly)	vWF concentrates	
Factor XI deficiency (haemophilia C)	Quantitative defect of factor XI	1 in 100,000	Autosomal recessive	Variable spontaneous bleeding rare Risk of excessive uterine bleeding Variable phenotype inconsistent within a family, not clearly related to factor levels	Obligate heterozygote Risk of homozygosity low	Factor XI 20–70 IU/dL	Factor XI levels < 15 IU/dL should receive prophylactic factor XI concentrate or, FFP at onset of labour; induction, caesarean section Peak levels should not exceed 70 IU/dL	Increased risk of both primary and secondary PPH. Prophylactic treatment with tranexamic acid should be considered post delivery up to two weeks, Concomitant use of tranexamic acid and factor XI concentrates should be avoided.
Disorders of fibrinogen (Afibrinogenaemia, hypofibrinogenaemia,							dysfibrinogenaemia)	Qualitative or quantitative defects of fibrinogen
Afibrinogenaemia: 1:1,000,000	Quantitative deficiencies generally autosomal recessive	Obstetric complications frequent: pregnancy loss, haemorrhage, placental abruption, thrombosis	50% offspring	Fibrinogen 1.5–2 g/L	Cryoprecipitate FFP Fibrinogen concentrates	Risk of postpartum thrombosis and PPH		
Dysfibrinogenaemia: rare (difficult to estimate prevalence)	Qualitative defects generally autosomal dominant							
Factor XIII deficiency	Quantitative defect of factor XIII	XIII (1:2,000,000)	Autosomal recessive	Severe in most patients	Obligate heterozygote	Factor XIII: ≥ 10 –20 IU/L	20–30 IU/d factor XIII concentrates throughout pregnancy, FFP	Recurrent spontaneous abortions common without factor XIII replacement

vWD: von Willebrand disease; DDAVP: desmopressin; FFP: fresh frozen plasma; PPH: postpartum haemorrhage.

Figure 1 Algorithm for Managing Women in Pregnancy with an Inherited Bleeding Disorder.

disorders, suitable reproductive options for affected couples, methods of prenatal testing, antenatal management of mother and affected offspring, limitations of investigations and potential complications.⁶ Other considerations include optimisation of iron status, screening for red cell antibodies, routine antenatal screening and folic acid supplementation.²

Prenatal diagnosis to determine fetal genotype

Current methods of prenatal diagnosis of InBD include both non-invasive and invasive techniques, employed according to the

Table 2. Haemostatic changes in pregnancy.

Fibrinogen, VII, VIII, X, XII, vWF	Increased
II, V, IX, XI	Equal/increased
XIII	Decreased
Antithrombin	Equal
Protein C	Equal/increased
Protein S	Decreased
Platelets	Decreased

^aChanges most pronounced in third trimester.

Table 3. Clinical features of a possible underlying bleeding disorder.

- Menorrhagia since menarche with iron deficiency or failure to respond to conventional management.
  - Family history of a bleeding disorder.
  - Personal history of epistaxis (bilateral for 10 min once in the last year requiring packing or cautery).
  - Notable bruising without injury.
  - Minor wound bleeding from trivial cuts lasting at least 5 min.
  - Bleeding from oral cavity or gastrointestinal tract without obvious anatomical lesion.
  - Prolonged or excessive bleeding after dental extraction. Unexpected post-surgical bleeding.
  - Haemorrhage from ovarian cysts or corpus luteum.
  - Haemorrhage requiring blood transfusion.
- Previous postpartum haemorrhage (especially delayed postpartum haemorrhage).

availability of services, maternal choice, the severity of the bleeding disorder and whether a mutation has been identified. Prenatal diagnosis is an integral part of the care of pregnant women with InBD and is of greatest importance in haemophilia because of the severity of the disorder in male offspring in an asymptomatic mother. Prenatal diagnosis requires the exact genetic mutation to be identified in the mother or suitable markers for linkage analysis. Prenatal diagnosis aims to provide a rapid and accurate diagnosis for any fetus potentially carrying an InBD in order to estimate risk, guide obstetric management and, in some cases, to have the option of termination.⁷ Termination is a vexed decision influenced by ethical and cultural issues, disease severity and personal and family experience with the disorder.⁷ Recent improvements in the management and prognosis of some InBD, such as haemophilia, have changed perceptions regarding quality of life.

Non-invasive testing may be used to confirm fetal gender prior to the use of invasive techniques in X-linked InBD to avoid additional testing if the fetus is a female. *Free fetal DNA* (ffDNA) techniques are increasingly being used for diagnostic purposes in early pregnancy using blood collected from maternal circulation.⁸ Despite technological progress, ffDNA techniques are not yet sufficient to diagnose haemophilia in the male fetus as the maternally inherited fetal allele is not able to be distinguished from the carrier maternal DNA. A recent study identifying mutant and wild-type alleles ffDNA in pregnant carriers of severe haemophilia with a male fetus as early as 11 weeks' gestation has demonstrated promising results using advances in quantitative PCR technology and relative mutation dosage techniques in the common genetic mutations.^{7,9} Imaging with *prenatal ultrasound* to identify gender is available and accurate from 11 to 15 weeks' gestation.²

Invasive prenatal genetic testing on fetal tissue acquired by *chorionic villus sampling* (CVS) or *amniocentesis* allows a definitive diagnosis but carry a 1% procedure-related fetal loss risk.² Third-trimester

amniocentesis has recently been suggested as an option for haemophilia carriers with a male fetus to help manage delivery and circumvent the potential risks of performing the procedure earlier in pregnancy.^{10–13} There is no published data available to support the safety and effectiveness of third-trimester amniocentesis in pregnancies in women with other InBD.

Cordocentesis is more rarely carried out to obtain ultrasound-guided fetal blood samples from the umbilical cord at 18–20 weeks. This technique may be used to assess fetal clotting and factor levels particularly in cases without an identified causative mutation. Procedure-related fetal loss is reported at 1–2%,² which may be higher if the fetus is affected by InBD.⁷ Its utility is uncertain because results for fetal coagulation parameters are difficult to interpret due to poorly defined reference ranges and the potential for maternal contamination.^{6,7} Prior to invasive prenatal testing, the mother's coagulation studies should be checked to arrange prophylactic treatment if required. Invasive testing may cause fetomaternal haemorrhage and anti-D immunoglobulin should be given to Rhesus D-negative mothers.⁷

A further reproduction option for families with severe InBD is *preimplantation genetic diagnosis* in which blastocysts are tested for the presence of the specific mutation, allowing unaffected or carrier embryos to be implanted, thus avoiding the need for prenatal testing and selective termination of pregnancy. It involves *in vitro* fertilisation, is expensive, technically challenging, labour intensive although becoming more readily available.⁶

Antenatal care

Women with InBD should be managed by a multidisciplinary team. The aim for each patient is to estimate the risk to mother, fetus and neonate; to implement measures to minimise these risks; and to anticipate complications and develop contingencies for these scenarios.

During the antenatal period the relevant factor levels should be assessed at presentation to antenatal care, prior to planned invasive procedures and repeated during the third trimester (usually between 32 and 34 weeks) to determine prophylaxis for invasive procedures and treatment of bleeding.

Women with severe factor XIII deficiency, fibrinogen deficiency or functional fibrinogen deficiency require routine prophylactic factor replacement therapy throughout pregnancy.^{14,15} Factor XIII deficiency is associated with spontaneous recurrent miscarriage due to its role in pregnancy maintenance and more specifically, the development of the cytotrophoblastic shell.¹⁶ In the absence of prophylactic replacement therapy, a recent systematic review of the literature documents a 91% miscarriage rate in 136 pregnancies.¹⁷ Dysfibrinogenemia is associated with significant obstetric complications including first-trimester pregnancy loss, haemorrhage, thrombosis and placental abruption.¹⁸ Women with fibrinogen abnormalities should be monitored for thrombotic complications, balanced against haemorrhagic risk. The role of fibrinogen in pregnancy maintenance is well established with fibrinogen knockout mice in which gestation cannot be continued to term.¹⁹ Fibrinogen replacement is required throughout pregnancy often weekly though should be individualised to the patient's needs.

In the third trimester, ensure women are iron, B12 and folate replete. If levels are suboptimal in the third trimester, then replacement should be arranged to optimise haemostasis and ensure reserves are replete in the event of significant haemorrhage.⁴ Synthetic clotting factor or blood product replacement is chosen according to the specific InBD and product availability (Tables 1 and 4). Doses should be calculated by an experienced haematologist, aiming to normalise factor levels and functional assays.⁴

In the event of antenatal bleeding, obstetric assessment should be rapidly expedited to assess the cause and appropriate management. Consult the haematologist early to discuss haemostatic treatment.

Antenatal complications

There is a paucity of literature to estimate the risk of bleeding and miscarriage during the first trimester for women with most bleeding disorders.¹ Factor XIII and fibrinogen abnormalities increase miscarriage risk due to their role in placental implantation.²⁰ In a review of 172 pregnancies in carriers of haemophilia A and B, miscarriage rates of 31% and 17%, respectively, were reported.¹¹ General obstetric literature quotes rates of miscarriage between 8 and 20% in women prior to 20 weeks' gestation.²¹ In vWD, the overall rates of miscarriage in two series were 22%²² and 21%²³ with the later study suggesting a higher rate of early pregnancy bleeding compared to the general population. Reporting bias in women with a known InBD should be considered when evaluating these results.²³

Antepartum haemorrhage (APH) data in women with InBD is conflicting. Factor XIII and fibrinogen deficiencies are associated with placental abruption and hence increased fetal loss or premature delivery.^{24,25} In other bleeding disorders, the associations are not clear.^{1,51} A study based on discharge coding from the United States Nationwide Inpatient Sample found that women with vWD are 10 times more likely to be admitted to hospital with APH²⁶ but without increased risk of placental abruption, premature labour, fetal growth restriction or intrauterine fetal loss. There may be a lower threshold for admitting a woman with an InBD for observation which may not correlate with pregnancy morbidity.¹

Delivery

The mode of delivery should be planned on obstetric indications. These should be discussed, whether spontaneous or induced vaginal delivery or caesarean section, and a written plan should be provided to all clinicians and the mother including details of factor replacement. Importantly, there should be contingencies for possible complications, including bleeding during or after delivery and preterm labour.⁶

Recent literature demonstrates that caesarean section does not eliminate the risk of intracranial haemorrhage in neonates with haemophilia and may in fact increase bleeding risks in the carrier mother.^{7,8,27} This suggests spontaneous vaginal delivery is the preferred option in countries with well-developed healthcare,^{7,15,28–31} and in developing countries albeit higher absolute risk.³⁰ Other studies, however, have demonstrated a reduced rate of intracranial haemorrhage by up to 85% in haemophilic neonates delivered by caesarean section, and this risk is almost eliminated if elective delivery is performed prior to the onset of labour.³² The literature does suggest that bleeding complications for the mother are increased in caesarean deliveries.³³

In all pregnancies, vacuum extraction and use of forceps during labour have all been associated with an increased rate of subdural or cerebral haemorrhage in Towner et al.³⁴ There is clear evidence against the use of ventouse vacuum extraction and the use of high forceps delivery in women with InBD carrying potentially affected neonates.³⁵ Similarly, fetal scalp electrodes and blood sampling should be avoided with a low threshold to convert to caesarean section if indicated to avoid prolonged vaginal labour.^{1,8}

Best practice is therefore determined on an individual basis – weighing maternal and fetal risks and benefits. Deliveries should be consultant-led, and delivery at a tertiary referral centre is not necessary unless the patient has a severe InBD or is known to be carrying an affected offspring,^{4,7,36} provided adequate expertise and a management plan is available. Specialist units have the advantage of on-site, rapid laboratory testing and readily available factor replacement therapy for these women and neonates. Patients who live a distance from appropriate care may be considered for induction of labour; however, spontaneous labour is preferred due to the increased risk of prolonged labour and instrumental deliveries in induced labour. However, these risks have not been corroborated in all recent literature.³⁷

At the onset of labour, intravenous access should be secured with maternal sampling for full blood count and group and hold.⁷

Table 4. Products available in the management of inherited bleeding disorders.

Product	Description	Indications
Advate Recombinate Kogenate Xyntha	• Recombinant factor VIII. • Lyophilised powder in vials for reconstitution and intravenous use. • Glycoprotein synthesised by a genetically engineered Chinese Hamster ovary cell line.	Haemophilia A • Prevention of bleeding if FVIII $\leq$ 50%: at delivery, for spinal anaesthesia, for procedures. • Control of bleeding.
Benefix MonoFIX-VF Rixubis	• Recombinant factor IX. • Lyophilised powder in vials for reconstitution and intravenous use. • Glycoprotein synthesised by a genetically engineered Chinese Hamster Ovary cell line.	Haemophilia B • Prevention of bleeding if FVIII $\leq$ 50%: at delivery, for spinal anaesthesia, for procedures. • Control of bleeding.
Biostate	• Purified human coagulation factor VIII and vWF. • Lyophilised powder prepared from blood donors in packs for reconstitution and intravenous use.	Von Willebrand Disease and Haemophilia A. • Control and prevention of bleeding (see Table 1 for indications).
Prothrombinex	• Coagulation factor concentrate containing factors II, IX, and X and a small amount of factor VII.	Single or multiple congenital deficiencies of factor II or X. • Prophylaxis and treatment of bleeding.
DDAVP	• Synthetic derivative of the antidiuretic hormone, vasopressin (1-deamino-8-D-arginined vasopressin). • Available as intravenous, subcutaneous and intranasal preparations.	Type 1 and Type 2N Von Willebrand Disease (Possible benefit in Types 2A and 2B). • Prophylaxis of bleeding. • Perioperative management. <i>Benefit of effect must be demonstrated prior to therapeutic use</i>
Fresh frozen plasma (FFP)	• Human-derived unit of fresh frozen plasma (FFP) from voluntary donors containing all coagulation factors.	Type 1 and Type 2N Von Willebrand Disease (Possible benefit in Types 2A and 2B). • Prophylaxis of bleeding. • Perioperative management. <i>Benefit of effect must be demonstrated prior to therapeutic use</i>
Antifibrinolytics – Aminocaproic acid – Tranexamic acid	• Agents that inhibit the conversion of plasminogen to plasmin, inhibiting fibrinolysis and thereby helping to stabilise clots that have formed	Variable. Consult with haematologist
Platelets	• Human-derived pooled unit from voluntary donors, leukodepleted and irradiated	May be appropriate in massive transfusion and type 2B vWD
Cryoprecipitate	• Human-derived from whole blood or apheresis prepared by thawing FFP and recovering the precipitate containing Factor VII, fibrinogen, factor XIII, vWF and fibronectin	Fibrinogen replacement in inherited deficiency or massive transfusion
Fibrinogen concentrates – Haemocomplettan – RiaSTAP	• Human-derived freeze-dried concentrate	Inherited fibrinogen deficiency • Control of acute bleeding.

vWF: von Willebrand disease; DDAVP: desmopressin.

Factor levels are not practically measured in the acute setting.⁸ If a woman requires factor replacement, this should be given as close to delivery as possible.⁴

Anaesthesia

There are no specific guidelines available to advise clinicians about the choice of anaesthesia in pregnant women with InBD. Inhalation analgesia and most non-pharmacological measures of pain relief are suitable. Intramuscular opioids may be contraindicated in women because of haematoma risk at the injection site.²

There is a potential risk of epidural or spinal haematoma with insertion and removal of catheters used for regional blocks.^{8,38} With adequate correction of the haemostatic abnormality, it is safe to offer women regional blockade in close consultation with haematology and anaesthetic services.^{4,39} Such procedures should be performed by an experienced anaesthetist with regular assessment of neurological

function. The lowest concentration of local anaesthetic should be used to achieve adequate analgesia while preserving motor function.⁶ These women require factor levels to be maintained in the normal range for 12 h (mild bleeding disorder) to 24 h (moderate-to-severe bleeding disorder) after catheter removal.⁴

Factor replacement and haemostatic agents for prevention and management of bleeding (Tables 1 and 4)

Factor replacement is tailored to the individual defect and arranged by the haematologist with the blood service. Recombinant factor is preferred, because of its superior safety profile but is expensive and not available in all disorders and healthcare settings.

Tranexamic acid has been demonstrated as safe and effective in the management of antenatal bleeding in obstetric patients.⁴⁰ Prolonged use of tranexamic acid in pregnancy is not recommended as the

inhibition of fibrinolysis may increase thrombosis. It is contraindicated in women with a history of thromboembolism.⁴⁰ It may be used safely in lactation because excretion in breast milk is low. The standard adult dose is 1 g orally six hourly.

Desmopressin (DDAVP) increases vWF and factor VIII plasma concentrations and has been used in pregnant women with haemophilia A and type 1 vWD, despite carrying a category B2 safety warning for use in pregnancy in Australia.^{7,41,42} In haemophilia A, response correlates with patient age, baseline factor levels and genotype.⁴³ It is ineffective in type 3 vWD and contraindicated in type 2B vWD.⁴⁴ Important side effects include uterine contraction, premature labour and hyponatraemia.⁴⁵ Both DDAVP and tranexamic acid potentially reduce the need for blood products.

A recent systematic review demonstrated successful use of DDAVP during the first and second trimester in 51 pregnancies for prophylaxis prior to invasive procedures with no reported neonatal complications.⁴⁶ In 172 pregnancies with DDAVP use for postpartum haemorrhage (PPH) prevention, there were no thromboses reported, and bleeding was seen in five deliveries. Maternal side effects were generally mild, including facial flushing and headache.⁴⁶

Postpartum

PPH prevention and management

Women with InBD are at significantly increased risk of both primary and secondary postpartum haemorrhage.^{1,2,15,28,45,47} InBD may increase the incidence and magnitude of bleeds caused by uterine atony, retained placenta and genital tract trauma.^{1,6} In one population-based study, vWD was shown to confer a higher risk of massive PPH (>1.5 L; odds ratio: 3.3).¹ Case series suggest a significantly higher prevalence of perineal bleeding/haematoma: 1–6% vs. 0.2% in the normal population.^{1,15}

Minimising the incidence of PPH involves maintaining factor levels within the normal range for 3–4 days after vaginal delivery and for seven days following caesarean section.⁴ Physiological increases in endogenous factor levels will decline after three days post-delivery and return to normal within 7–21 days of delivery^{1,4} (Table 1). Close monitoring and prophylaxis may be needed for several weeks in women with severe InBDs.

Active management of the third stage of labour including the use of uterotonics, controlled cord traction and fundal massage is essential to reduce the risk of PPH and genital and perineal haematoma.⁴⁸ The need for pharmacological thromboprophylaxis should be determined on a case-by-case basis. It may not be appropriate in the postpartum period in women with InBD.⁸ However, pharmacological thromboprophylaxis should be considered in women with additional risk factors, taking into consideration baseline non-pregnancy levels and anticipated physiological changes immediately postpartum.⁸

Persistent or severe PPH requires aggressive management.⁵² Refractory uterine atony requires second line agents and haemodynamic instability should be promptly managed with crystalloid and blood products administered as necessary. Antifibrinolytics and coagulation factor replacement should be based on ongoing laboratory assessment of coagulation, guided by a haematologist.⁶ PPH can be sudden, massive and catastrophic.

Contraception

There is no contraindication to specific contraceptive methods; however, hormonal agents such as the oral contraceptive pill have the advantage of reducing menstrual blood loss, suppressing ovulation, preventing haemorrhagic ovarian cysts and possibly elevating levels of factor VII and vWF. A hormone-releasing intra-uterine device such as a levonorgestrel – releasing intrauterine system is favoured after pregnancy as it significantly reduces menstrual blood

Approach to the neonate

Management of the neonate is guided by the clinical condition, gestational age and mode of delivery. All neonates who may be affected by a severe InBD should have a careful physical examination to detect signs of bleeding and cranial ultrasound.⁸ Cord blood sample should be collected from neonates at risk of moderate or severe InBD to assess coagulation status and clotting factor levels.² Intramuscular injections and surgical procedures should be avoided. Vitamin K should be given orally and routine immunisations given intradermally or subcutaneously. The interpretation of neonatal clotting factor levels correlates with gestational age, and therefore it may not be reliable to diagnose mild forms of InBD at birth.² Neonatal samples are frequently unsuitable for analysis due to difficulty with venepuncture, under-filling, haemolysis or partially clotted samples. A high haematocrit may interfere with diagnostic tests.² Newer assays, such as thrombelastography or thrombin generation, are under investigation but not part of current clinical practice.^{49,50}

Specialist paediatricians should be involved early if the neonate is known to be severely affected by haemophilia. Factor levels should be repeated if equivocal. In mild to moderate nNBD, factor assays can be delayed until the child is older though some advocate testing to be performed within the first year of life, ideally prior to any invasive procedures and the onset of menarche.

Conclusion

Women with an InBD should be managed collaboratively and prospectively by a multidisciplinary team of experienced clinicians on an individualised basis). Management plans should be comprehensive and documented clearly in order to minimise maternal and neonatal complications. Women with mild to moderate InBD, such as type 1 vWD and haemophilia carriers with a female fetus, may have shared management between their local maternity unit and a tertiary referral unit. However, those who are affected by severe or rare disorders or those women carrying affected infants should be delivered in a tertiary centre with specialist services and an onsite laboratory.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

All literature sourced was based on ethically approved studies where patient consent was obtained.

Guarantor

GKG

Contributorship

OL was responsible for literature review and writing. GKG was the supervisor, provided expert guidance and opinion and edited the article.

References

- Huq FY and Kadir RA. Management of pregnancy, labour and delivery in women with inherited bleeding disorders. *Haemophilia* 2011; 17(Suppl 1): 20–30.
- Chi C and Kadir RA. Inherited bleeding disorders in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2012; 26: 103–117.

3. Lefkou E and Hunt BJ. Bleeding disorders in pregnancy. *Obstet Gynaecol Reprod Med* 2008; 18: 217–223.
4. Dunkley SM, Russell SJ, Rowell JA, et al. A consensus statement on the management of pregnancy and delivery in women who are carriers of or have bleeding disorders. *MJA* 2009; 191: 460–463.
5. James AH, Kouides PA, Kadir RA, et al. Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel. *Am J Obstet Gynaecol* 2009; 12: 1–8.
6. Kadir RA, Davies J, Winikoff R, et al. Pregnancy complications and obstetric care in women with inherited bleeding disorders. *Haemophilia* 2013; 19(Suppl 4): 1–10.
7. Lee CA, Chi C, Pavord SR, Bolton-Maggs PHB, et al. The obstetric and gynaecological management of women with inherited bleeding disorders – review with guidelines produced by a task-force of UK Haemophilia Centre Doctors Organization. *Haemophilia* 2006; 12: 301–336.
8. Peyvandi F, Bidlingmaier C and Garagiola I. Management of pregnancy and delivery in women with inherited bleeding disorders. *Semin Fetal Neonatal Med* 2011; 16: 311–317.
9. Tsui NBY, Kadir RA, Chan KCA, et al. Noninvasive prenatal diagnosis of hemophilia by microfluidics digital PCR analysis of maternal plasma DNA. *Blood* 2011; 117: 3684–3691.
10. Chi C, Lee CA, Shiltag N, et al. Pregnancy in carriers of haemophilia. *Haemophilia* 2008; 14: 56–64.
11. Kadir RA, Economides DL, Braithwaite J, et al. The obstetric experience of carriers of haemophilia. *Br J Obstet Gynaecol* 1997; 104: 803–810.
12. Zalud I and Janas S. Risks of third-trimester amniocentesis. *J Reprod Med* 2008; 53: 45–48.
13. Cutler J, Chappell LC, Kyle P, et al. Third trimester amniocentesis for diagnosis of inherited bleeding disorders prior to delivery. *Haemophilia* 2013; 19: 904–907.
14. Kadir RA, Chi C and Bolton-Maggs P. Pregnancy and rare bleeding disorders. *Haemophilia* 2009; 15: 990–1005.
15. Mumford AD, et al. Guideline for the diagnosis and management of the rare coagulation disorders. A United Kingdom Haemophilia Centre Doctors' Organisation guideline on behalf of the British Committee for Standards in Haematology. *Br J Haematol* 2014; 167: 304–326.
16. Asahina T, et al. Maternal blood coagulation factor XIII is associated with the development of the cytotrophoblastic shell. *Placenta* 2000; 21: 388–393.
17. Sharief LAT and Kadir RA. Congenital factor XIII deficiency in women: a systematic review of the literature. *Haemophilia* 2013; 19: 349–357.
18. Franchini M and Lippi G. Fibrinogen replacement therapy: a critical review of the literature. *Blood Transfus* 2012; 10: 23–27.
19. Casini A, Blondon M, Leebretton, et al. Natural history of patients with congenital dysfibrinogenemia. *Blood* 2015; 125: 553–561.
20. Inbal A and Muzbek L. Coagulation factor levels and pregnancy loss. *Semin Thromb Hemost* 2003; 29: 171–174.
21. Tulandi T. Miscarriage (beyond the basics) Uptodate, www.uptodate.com (accessed 20 May 2015).
22. Foster PA. The reproductive health of women with von Willebrand disease unresponsive to DDAVP: results of an international survey. On behalf of the subcommittee on von Willebrand factor of the Scientific standardization Committee of the ISTH. *Thromb Haemost* 1995; 74: 784–790.
23. Kadir RA, Lee CA, Sabin CA, et al. Pregnancy in women with von Willebrand's disease or factor XI deficiency. *Br J Obstet Gynaecol* 1998; 105: 312.
24. Burrows RF, Ray JG and Burrows EA. Bleeding risk and reproductive capacity among patients with factor XIII deficiency: a case presentation and a review of the literature. *Obstet Gynecol Surv* 2000; 55: 103–108.
25. Kobayashi T, Kanayama N, Tokunaga N, et al. Prenatal and peripartum management of congenital afibrinogenemia. *Br J Haematol* 2000; 109: 364–366.
26. James AH and Jamison MG. Bleeding events and other complications during pregnancy and childbirth in women with von Willebrand disease. *J Thromb Haemost* 2007; 5: 1165–1169.
27. Street AM, Ljung R and Lavery SA. Management of carriers and babies with haemophilia. *Haemophilia* 2008; 14(Suppl 3): 181–187.
28. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung and Blood Institute (NHLBI) expert panel report (USA). *Haemophilia* 2008; 14: 171–232.
29. Ljung RC. Intracranial haemorrhage in haemophilia A and B. *Br J Haematol* 2008; 140: 378–384.
30. Ljung RC. The optimal mode of delivery for the haemophilia carrier expecting an affected infant is vaginal delivery. *Haemophilia* 2010; 16: 415–419.
31. Canadian Hemophilia Society. Women with inherited bleeding disorders, www.hemophilia.ca/en/bleeding-disorders/women-with-inherited-bleeding-disorders/ (accessed 2 September 2009).
32. Kadir R and Lee CA. Obstetrics and gynecology: hemophilia. In: Lee CA, Berntorp EE and Hoots WK (eds) *Textbook of hemophilia*. Oxford: Blackwell, 2005, pp.249–256.
33. James AH and Hoots K. The optimal mode of delivery for the haemophilia carrier expecting an affected infant is caesarean delivery. *Haemophilia* 2010; 16: 420–424.
34. Towner D, Castro MA, Eby-Wilkens E, et al. Effect of mode of delivery in nulliparous women on neonatal intracranial injury. *N Engl J Med* 1999; 341: 1709–1714.
35. Madan B and Street AM. What is the optimal mode of delivery for the haemophilia carrier expecting an affected infant-vaginal delivery or caesarean delivery? *Haemophilia* 2010; 16: 425–426.
36. The British Committee for Standards in Haematology. Guideline on the management of haemophilia in the fetus and neonate. A United Kingdom Haemophilia Centre Doctors' Organisation guideline approved by the British Committee for Standards in Haematology 2011, www.bcsghguidelines.com/documents/NeonatalGuidelineFinalNov2010.pdf (accessed 29 March 2011).
37. Rane SM, Guirgis RR, Higgins B, et al. Models for the prediction of successful induction of labour based on pre-induction sonographic measurement of cervical length. *J Matern Fet Neonatal Med* 2005; 17: 315–322.
38. Horlocker TT, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus conference on neuroaxial anesthesia and anticoagulation). *Reg Anesth Pain Med* 2003; 28: 172–197.
39. Chi C, Lee CA, England A, et al. Obstetric analgesia and anaesthesia in women with inherited bleeding disorders. *Thromb Haemost* 2009; 101: 1104–1111.
40. Peitsidis P and Kadir RK. Antifibrinolytic therapy with tranexamic acid in pregnancy and the postpartum. *Expert Opin Pharmacother* 2011; 12: 503–516.
41. Mannucci PM. Use of desmopressin (DDAVP) during early pregnancy in factor VIII-deficient women. *Blood* 2005; 105: 3382.
42. Australian Drug Evaluation Committee. *Prescribing medicines in pregnancy*, 4th ed. Canberra: Therapeutic Goods Administration, 1999, (this document is being updated), www.tga.gov.au/DOCS/HTML/med-preg.htm (accessed 8 August 2009).
43. Seary ME, Feldman D and Carcao MD. DDAVP responsiveness in children with mild or moderate haemophilia A correlates with age, endogenous FVIII: C level and with haemophilic genotype. *Haemophilia* 2012; 18: 50–55.
44. Holmberg L, Nilsson IM, Borge L, et al. Platelet aggregation induced by 1-desamino-8-D-arginine vasopressin (DDAVP) in type IIB von Willebrand's disease. *New Eng J Med* 1983; 309: 816–821.

45. Kouides PA. Obstetric and gynaecological aspects of von Willebrand disease. *Best Pract Res Clin Haematol* 2001; 14: 381–399.
46. Trigg DE, Sterigiotou I, Peitsidis P, et al. A systematic review: the use of desmopressin for treatment and prophylaxis of bleeding disorders in pregnancy. *Haemophilia* 2012; 18: 25–33.
47. Kadir RA, Lee CA, Sabin CA, et al. Pregnancy in women with von Willebrand's disease or factor XI deficiency. *Br J Obstet Gynaecol* 1998; 105: 314–321.
48. Prendiville WJ, Elbourne D and McDonald S. Active versus expectant management in the third stage of labour. *Cochrane Database Syst Rev* 2000; 3: CD000007.
49. Yamanaka Y, Takeuchi K, Sugimoto M, et al. Dysfibrinogenemia during pregnancy treated successfully with fibrinogen. *Acta Obstet Gynecol Scand* 2003; 82: 972–973.
50. Peyvandi F and Mannucci PM. Rare coagulation disorders. *Thromb Haemost* 1999; 82: 1207–1214.
51. Philipp CS. Platelet disorders. In: Lee CA, Kadir RA and Kouides PA (eds) *Inherited bleeding disorders in women*. Oxford: Wiley Blackwell, 2009, pp.65–69.
52. Pavord S and Maybury H. How I treat postpartum hemorrhage. *Blood* 2015; 125: 18.