A consensus statement on the management of pregnancy and delivery in women who are carriers of or have bleeding disorders

Scott M Dunkley, Susan J Russell, John A Rowell, Chris D Barnes, Ross I Baker, Megan I Sarson, Alison M Street on behalf of the Australian Haemophilia Centre Directors’ Organisation

Women with inherited bleeding disorders (Box) are at risk of bleeding complications from haemostatic challenges during pregnancy and childbirth. Although several groups have published “evidence-based” guidelines on management of inherited bleeding disorders that include management of pregnancy, these guidelines are often voluminous and not user-friendly. The Australian Haemophilia Centre Directors’ Organisation (AHCDO) has developed practical guidelines for the management of pregnancy and delivery in women with bleeding disorders, with the aim of improving and standardising care, and these guidelines are available online (http://www.ahcdo.org.au). However, as several different clinicians care for women with bleeding disorders (management involves a multidisciplinary team including, among others, an obstetrician, an anaesthetist and a haematologist), the AHCDO decided that the consensus statement would be valuable for the broader medical community.

All directors of haemophilia centres (adult and paediatric) throughout Australia are members of the AHCDO. The guidelines were developed initially by a working party (the listed authors) after extensive consultation, face-to-face meetings and revisions, and the final document represents a consensus opinion of all AHCDO members. Evidence-based literature and international guidelines were reviewed, and some are referenced. However, in many aspects of care in this area of medicine, evidence is lacking, and the recommendations are based on clinical experience and consensus opinion. The AHCDO recommendations are summarised at the beginning of each main topic.

Physiological response expected in pregnancy in women with bleeding disorders

In carriers of haemophilia A (carriers of the gene for factor VIII deficiency), coagulation factor VIII levels increase significantly during pregnancy, reaching a peak between 29 and 35 weeks. Although in a majority of these women, the levels will increase to within the normal range, the rise is variable and some may still have insufficient factor VIII levels for safe haemostasis at term. Similarly, in women with type 1, but not type 3, von Willebrand disease, levels of factor VIII and von Willebrand factor antigen (VWF:Ag) usually increase during pregnancy. In carriers of haemophilia B (carriers of the gene for factor IX deficiency), factor IX levels usually do not change significantly during pregnancy, and neither do factor XI levels in women with factor XI deficiency states.

Because the rise in factor levels is unpredictable during pregnancy, the levels should be checked at presentation, and checked again before any invasive procedure, and during the third trimester. After delivery, factor levels usually return to baseline after days to weeks, but may drop earlier. It should be noted that women with normal factor levels may still be haemophilia carriers.

Management of pregnancy and delivery

During pregnancy

- Women with most inherited bleeding disorders usually require no specific therapy antenatally.
- Genetic counselling is desirable, optimally before conception, if the mother is a haemophilia carrier, or if there is a family history of haemophilia.
- Factor levels should be measured at presentation and the measurement repeated during the third trimester (usually at 32–34 weeks’ gestation).
- Factor levels should be checked before invasive procedures and, if below the normal range, replacement therapy should be considered.

- Women who are carriers of the genes for factor VIII or factor IX deficiency (haemophilia A and B, respectively) may have plasma factor levels outside the normal range and, particularly when these levels are < 30% (classified as mild haemophilia), they may be at increased risk of bleeding. A majority of carriers of haemophilia A will develop “normal” factor levels as pregnancy progresses, and thus will not require replacement therapy. However, in carriers with a moderate-to-severe deficiency, factor levels may not adequately correct during pregnancy. Women with rare bleed-
ing disorders, such as fibrinogen or factor XIII deficiency, may require antenatal treatment to prevent fetal loss.

Women with type 1 von Willebrand disease (the most common and mildest form) also experience increased levels of factor VIII and VWF:Ag during pregnancy, with normal levels occurring in most women by delivery. Women with type 2 von Willebrand disease may also show an increase in factor VIII and VWF:Ag during pregnancy, but measures of VWF function (ristocetin cofactor and collagen binding assay) usually remain low. Further, thrombocytopenia associated with type 2B von Willebrand disease can worsen during pregnancy. Women with type 3 von Willebrand disease do not show any change in factor levels during pregnancy, and all require replacement therapy for delivery.

Measurement of factor levels should be repeated in the third trimester (32–34 weeks’ gestation) to allow planning of the appropriate management of labour and delivery and the need for prophylactic therapy.

The mother’s factor levels should also be checked before any invasive procedure, and, if below the normal range, replacement therapy should be provided. In general, normal equates to levels of factor VIII, factor IX and VWF:Ag being >50 IU/dL for haemophilia A, haemophilia B, and type 1 von Willebrand disease, respectively. Bleeding in women with factor XI deficiency is highly variable and provision of replacement therapy should be individualised; however, it is required if factor XI levels are <15 IU/dL. Treatment of women with rare bleeding disorders (Box) should be individualised.

Desmopressin (1-desamino-8-D-arginine vasopressin [DDAVP]) is a synthetic analogue of vasopressin that increases the plasma levels of VWF and factor VIII. DDAVP has been used in the treatment of women with haemophilia A and type 1 von Willebrand disease during pregnancy; it has a category B2 safety determination on obstetric grounds. Caesarean section does not eliminate the risk of cranial haemorrhage in the neonate, and elevates the risk of bleeding and the factor replacement requirements of the mother. In some series, the risk of cranial bleeding was in fact higher with caesarean section compared with vaginal delivery. However, the use of vacuum extraction is contraindicated because of the unacceptably high risk of cranial haemorrhage (about 60%). Also, the use of forceps and a prolonged labour should be avoided.

The mode of delivery should ultimately be determined on obstetric grounds.
A normal factor level in the mother (or, in women with von Willebrand disease, results of quantitative and functional assays for VWF) is desirable for delivery and, if the factor level is abnormal (see previous section), replacement therapy may be required.\textsuperscript{1,7,9,10}

**Obstetric anaesthesia**

- There are no guidelines that adequately cover epidural or spinal anaesthesia in patients with bleeding disorders.
- Epidural anaesthesia should only be considered in close consultation with an anaesthetist and a haematology team. As inherited bleeding disorders are associated with an increased risk of spinal haematoma, other forms of analgesia may be preferred.
- Coagulation factor levels should be maintained in the normal range (\(>50\) IU/dL) for the duration of catheter placement and for 12 hours (mild bleeding disorder) to 24 hours (moderate-to-severe bleeding disorder) after catheter removal.

As studies of epidural or spinal anaesthesia in patients with bleeding disorders are lacking, no guidelines comprehensively cover this topic. Patients with inherited bleeding disorders are at an increased risk of spinal haematoma.\textsuperscript{10,9} However, if a woman’s coagulation factor levels are in the normal range, or supported and maintained in the normal range, then regional anaesthesia is not contraindicated.\textsuperscript{1,2,18-20} Epidural anaesthesia is generally not recommended for women with severe type 2 or type 3 von Willebrand disease, but the decision should be made on an individual basis.\textsuperscript{5}

The AHDCO recommends that factor levels are maintained in the normal range for the duration of catheter placement, and for 12 hours (mild bleeding disorder) to 24 hours (moderate-to-severe bleeding disorder) after catheter removal.

**Postpartum care**

- In general, factor levels should be maintained in the normal range for 3–4 days after vaginal delivery and for up to 7 days after caesarean section.

Factor levels that may have normalised during pregnancy tend to return to baseline by 7–21 days after delivery, but may drop earlier and should be closely monitored.\textsuperscript{8,21} Women who have low baseline factor VIII or VWF:Ag levels are at continuing risk of postpartum haemorrhage during this time and should be advised to report symptoms.

To reduce the risk of postpartum haemorrhage and surgical bleeding, factor levels should be maintained in the normal range for at least 3–5 days after vaginal delivery and for up to 7 days after caesarean section.\textsuperscript{1,2,9,10}

**Postpartum haemorrhage**

- Active management of the third stage of labour should be practised.
- Women with early postpartum haemorrhage associated with low factor levels should be managed by factor replacement therapy, or DDAVP in carriers of haemophilia A or women with type 1 von Willebrand disease.
- Should late postpartum haemorrhage occur, first-line management includes tranexamic acid and oral contraceptives, and in the longer term, a levonorgestrel-releasing intrauterine device.

Carriers of haemophilia, women with von Willebrand disease, and those with factor XI deficiency have a significantly higher risk of both primary and secondary postpartum haemorrhage.\textsuperscript{1,2,10-13,21,22}

The risk of postpartum haemorrhage can be reduced by the active management of labour.\textsuperscript{23}

Women with early postpartum haemorrhage associated with low factor levels should be managed by factor replacement therapy, or by giving DDAVP to those with type 1 von Willebrand disease or haemophilia A.\textsuperscript{1,2,12,13} DDAVP has been detected in the breast milk of lactating women and thus is not recommended for use in such women.\textsuperscript{24}

Tranexamic acid can be used to control secondary postpartum haemorrhage.\textsuperscript{1,11} Tranexamic acid is safe in breastfeeding mothers and has a category B1 safety warning for use in pregnancy in Australia.\textsuperscript{15} The oral contraceptive pill and, in the longer term, a levonorgestrel-releasing intrauterine device are alternative therapies.\textsuperscript{23}

**Management of neonates**

**Infants at risk of a severe bleeding disorder**

- If the baby is at risk of a severe bleeding disorder, blood samples should be taken for measuring factor levels.
- In general, intramuscular injections should be avoided.
- Vitamin K is often given orally or subcutaneously to avoid the risk of intramuscular haematoma.
- In babies known to have, or suspected of having, a severe bleeding disorder, a transfontanel ultrasound examination should be considered soon after birth to check for intracranial haemorrhage.
- All at-risk neonates should be carefully observed for signs of intracranial haemorrhage and similarly examined with transfontanel ultrasonography.
- Even in neonates known to have a severe bleeding disorder, prophylactic factor replacement should not be given because of the potential risk of inhibitor development.
- All infants, including those already known to have bleeding disorders, should be immunised for hepatitis B.
- Neonates with an identified inherited bleeding disorder should be registered at a haemophilia treatment centre.

Testing of cord blood for inherited bleeding disorders is recommended in the guidelines of the Haemophilia Centre Doctors’ Organisation in the United Kingdom and is very useful in excluding severe disease.\textsuperscript{1} However, its value in milder disease (particularly haemophilia B) is controversial, and results should be confirmed by peripheral blood testing. In addition, adult levels of vitamin-K-dependent clotting factors and factor XI may not be present until after 6 months of age.

The risk of intracranial haemorrhage is around 4% in newborns with severe haemophilia.\textsuperscript{1,7,17} In haemophilia, predelivery ultrasound determination of the sex of the fetus is useful, because female infants do not ordinarily have an elevated risk of cranial haemorrhage. The risk of cranial haemorrhage is also increased in neonates with severe forms of von Willebrand disease,\textsuperscript{5} but is very rare in infants with factor XI deficiency.\textsuperscript{11}

The AHDCO recommends that neonates with a bleeding disorder receive a transfontanel ultrasound examination soon after birth to check for intracranial haemorrhage. Because intracranial haemorrhage may be delayed (median time after delivery is 4.5 days), mothers should be made aware of potential symptoms, such as vomiting, seizures and poor feeding.\textsuperscript{26}

Prophylactic factor replacement therapy should not be routinely given and may be associated with an increased risk of inhibitor development in children with haemophilia (inhibitor development is an immune response inhibiting factor replacement from stop-
Management of bleeding in neonates

- Neonates known (or suspected) to have haemophilia A or B, and who have evidence of either intracranial bleeding or severe bleeding elsewhere, should receive immediate factor replacement with recombinant factor VIII or IX, respectively.\(^1,7,9\)

- If haemophilia is suspected in a neonate with bleeding, but the type of haemophilia is unknown, both factor VIII and IX should be given until confirmation of specific factor levels.

- Neonates with severe haemophilia A or B and severe bleeding require 100% plasma factor levels. This can be achieved by giving, as appropriate, 75IU/kg recombinant factor VIII or 150IU/kg factor IX. Factor levels should be maintained in the normal range for at least 7–10 days, and a haemophilia specialist in a paediatric haemophilia treatment centre should coordinate therapy (consensus opinion).

Guidelines for the care of children with haemophilia are not covered in this document; however, continuing regular factor replacement prophylaxis in neonates with early exposure to factor replacement may reduce the risk of inhibitor formation.\(^3\)

Competing interests

None identified

Author details

Scott M Dunkley, BMed(Hons), FRACP, FRCPA, Haematologist,\(^1\) and Chairman\(^2\)
Susan J Russell, MB BS, FRACP, Haematologist\(^3\)
John A Rowell, MB BS, FRCPA, MBA, Haematologist\(^4\)
Chris D Barnes, MB BS, FRACP, FRCPA, Haematologist\(^5\)
Ross I Baker, MB BS, FRACP, FRCPA, Haematologist\(^6\)
Megan I Sarson, PhD, Research Project Officer\(^7\)
Alison M Street, MB BS, FRACP, FRCPA, Head of Haematology\(^8\)
1 Institute of Haematology, Royal Prince Alfred Hospital, Sydney, NSW.
2 Australian Haemophilia Centre Directors’ Organisation, Melbourne, VIC.
3 Centre for Children’s Cancer and Blood Disorders, Sydney Children’s Hospital, Sydney, NSW.
4 Haematology Department, Royal Brisbane Hospital, Brisbane, QLD.
5 Henry Ekert Haemophilia Treatment Centre, Royal Children’s Hospital, Melbourne, VIC.
6 Thrombosis and Haemophilia Service, Royal Perth Hospital, Perth, WA.
7 The Alfred Hospital, Melbourne, VIC.

Correspondence: scott.dunkley@sswhs.nsw.gov.au

References


(Received 19 Nov 2008, accepted 5 Aug 2009)