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

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ABSTRACT

- Pregnancy and delivery are critical times for women with bleeding disorders, with mothers, and possibly their affected infants, being exposed to a variety of haemostatic challenges.
- Management of women with bleeding disorders during pregnancy involves a multidisciplinary team including, but not limited to, an obstetrician, an anaesthetist and a haematologist.
- This consensus document from the Australian Haemophilia Centre Directors' Organisation (AHCDO) provides practical information for clinicians managing women with bleeding disorders during pregnancy. Included are:
  - ➢ the expected physiological response in pregnancy in such women;
  - ➢ management of pregnancy, labour and delivery, as well as obstetric anaesthesia issues, postpartum care, and reducing and treating postpartum haemorrhage; and
  - ➢ management of infants at risk of a bleeding disorder and of bleeding in neonates.
- The guidelines were developed after extensive consultation, face-to-face meetings and revisions. The final document represents a consensus opinion of all AHCDO members. Where evidence is lacking, recommendations are based on clinical experience and consensus opinion.

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Women with inherited bleeding disorders (Box) are at risk of bleeding complications from haemostatic challenges during pregnancy and childbirth.[1-5] 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.[1,2,6,7] 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.[8,9] 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.[1,8,9] 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.[1,8,9] 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.[1,7,10,11]

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.[1,2,9,10] After delivery, factor levels usually return to baseline after days to weeks, but may drop earlier.[1,8] 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.[7] A majority of carriers of haemophilia A will develop "normal" factor levels as pregnancy progresses, and thus will not require replacement therapy.[1,7,12] However, in carriers with a moderate-to-severe deficiency, factor levels may not adequately correct during pregnancy.[1,7,12] Women with rare bleed-

Bleeding disorders that may increase the risk of bleeding in pregnant women[1-4]

Disorder	Factor affected	Bleeding phenotype in women
Haemophilia A	Factor VIII levels decreased*	Mild to moderate when levels <40IU/dL†[4]
Haemophilia B	Factor IX levels decreased	Mild to moderate when levels <40IU/dL†[4]
Factor XI deficiency	Factor XI levels decreased	Highly variable; risk increased with levels <15IU/dL[1]
von Willebrand disease[2]		
Type 1	von Willebrand factor levels decreased*	Mild to moderate
Type 2	Dysfunctional von Willebrand factor	Variable, usually moderate
Type 3	von Willebrand factor absent	Severe (von Willebrand factor antigen undectable; factor VIII <10IU/dL)
Rare coagulation factor deficiencies	Afibrinogenaemia; factor II, factor V, combined factor V and VIII, factor VII, factor X and factor XIII deficiencies	Highly variable, mild to severe, not always predictable on factor levels. Recurrent fetal loss associated with factor II and factor XIII deficiencies

* Levels may normalise during pregnancy.[1] † Women with factor VIII or IX above 40%, but below the lower limit of the normal reference range (laboratory "normal" ranges vary based on methodology), may also have increased bleeding tendencies.[5] ◆

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.[1,7,13] 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.[1,2,10] 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.[1]

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.[1,6,7]

The mother's factor levels should also be checked before any invasive procedure, and, if below the normal range, replacement therapy should be provided.[1,9,10] In general, normal equates to levels of factor VIII, factor IX and VWF:Ag being >50IU/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 <15IU/dL.[1,10,11] Treatment of women with rare bleeding disorders (see 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;[1,7,14] it has a category B2 safety warning for use in pregnancy in Australia.[15] However, DDAVP can stimulate uterine contraction and cause premature labour, as well as hyponatraemia.[13] Importantly, in most patients with type 1 von Willebrand disease, who would respond to DDAVP, factor levels will have risen during pregnancy, but in patients with type 2 and type 3 von Willebrand disease, who have the greatest need for elevation of VWF, the response to DDAVP is generally poor.[16] As such, if treatment is needed, the AHCDO recommends administration of VWF-containing concentrates in the antenatal treatment of von Willebrand disease, although DDAVP may be a suitable alternative in women who are carriers of haemophilia A.

Labour and delivery

- Spontaneous vaginal delivery is preferred. An inherited bleeding disorder in the mother or fetus, by itself, is not an indication for delivery by caesarean section. The mode of delivery should be determined by obstetric indications.
- Ideally, women with severe bleeding disorders, or who are at risk of delivering a boy with haemophilia, should be managed by an obstetric unit with facilities for caring for high-risk infants, and a haemophilia treatment centre.
- Treatment in bleeding disorders should be individualised and specific treatment protocols followed (eg, http://www.ahcdo.org.au; http://www.nba.gov.au).
- 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.
- If needed, factor replacement should be given to the mother as close to the time of delivery as possible. (Note: this does not normalise the baby's factor levels.)
- Vacuum extraction is contraindicated. Use of forceps, fetal scalp blood sampling, and scalp electrodes should be avoided, if possible.
- DDAVP has poor efficacy in type 2 and type 3 von Willebrand disease, but may be used in carriers of haemophilia A. DDAVP may cause fluid retention with hyponatraemia, hypotension, uterine contractions and premature labour.

Normal vaginal delivery is recommended for women with inherited bleeding disorders.[1,2,6,7,9-13] 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.[1,7] In some series, the risk of cranial bleeding was in fact higher with caesarean section compared with vaginal delivery.[1,7] 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.[1,7,17] 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.[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.[18,19] However, if a woman's coagulation factors are in the normal range, or supported and maintained in the normal range, then regional anaesthesia is not contraindicated.[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.[1]

The AHCDO 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.[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.[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.[1,2,10-13,21,22] The risk of postpartum haemorrhage can be reduced by the active management of labour.[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.[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.[24]

Tranexamic acid can be used to control secondary postpartum haemorrhage.[1,13] Tranexamic acid is safe in breastfeeding mothers and has a category B1 safety warning for use in pregnancy in Australia.[15] The oral contraceptive pill and, in the longer term, a levonorgestrel-releasing intrauterine device are alternative therapies.[25]

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.[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.[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,[2] but is very rare in infants with factor XI deficiency.[11]

The AHCDO 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.[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-

ping a bleeding episode).[1,3,27] Similarly, the use of prophylactic recombinant factor VIIa has not been shown to improve clinical outcomes.[3]

In neonates with haemophilia or severe subtypes of von Willebrand disease, vitamin K should be given orally or subcutaneously.[1] Immunisation should be given subcutaneously or intradermally.[1,3]

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

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References

1 Lee CA, Chi C, Pavord SR, et al. The obstetric and gynaecological management of women with inherited bleeding disorders — review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2006; 12: 301-336.
2 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.
3 Gouw SC, van der Bom JG, van den Berg HM, et al. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study. *Blood* 2007; 109: 4648-4654.
4 White GC 2nd, Rosendaal F, Aledort LM, et al. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost* 2001; 85: 560.
5 Plug I, Mauser-Bunschoten EP, Bröcker-Vriends AH, et al. Bleeding in carriers of hemophilia. *Blood* 2006; 108: 52-56.
6 Canadian Hemophilia Society. Women with inherited bleeding disorders. http://www.hemophilia.ca/en/bleeding-disorders/women-with-inherited-bleeding-disorders/ (accessed Sep 2009).
7 Street AM, Ljung R, Lavery SA. Management of carriers and babies with haemophilia. *Haemophilia* 2008; 14 Suppl 3: 181-187.
8 Stirling Y, Woolf L, North WR, et al. Haemostasis in normal pregnancy. *Thromb Haemost* 1984; 52: 176-182.
9 Kadir R, Lee CA. Obstetrics and gynecology: hemophilia. In: Lee CA, Berntorp EE, Hoots WK, editors. Textbook of hemophilia. Oxford: Blackwell, 2005: 249-256.
10 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.
11 Bolton-Maggs PH. The management of factor XI deficiency. *Haemophilia* 1998; 4: 683-688.
12 Kadir RA, Economides DL, Braithwaite J, et al. The obstetric experience of carriers of haemophilia. *Br J Obstet Gynaecol* 1997; 104: 803-810.
13 Kouides PA. Obstetric and gynaecological aspects of von Willebrand disease. *Best Pract Res Clin Haematol* 2001; 14: 381-399.
14 Mannucci PM. Use of desmopressin (DDAVP) during early pregnancy in factor VIII-deficient women. *Blood* 2005; 105: 3382.
15 Australian Drug Evaluation Committee. Prescribing medicines in pregnancy. 4th ed. Canberra: Therapeutic Goods Administration, 1999 [this document is being updated]. http://www.tga.gov.au/DOCS/HTML/medpreg.htm (accessed Aug 2009).
16 Federici AB, Mazurier C, Berntorp E, et al. Biologic response to desmopressin in patients with severe type 1 and type 2 von Willebrand disease: results of a multicenter European study. *Blood* 2004; 103: 2032-2038.
17 Ljung R, Lindgren AC, Petrini P, Tengborn L. Normal vaginal delivery is to be recommended for haemophilia carrier gravidae. *Acta Paediatr* 1994; 83: 609-611.
18 Haljamäe H. Thromboprophylaxis, coagulation disorders, and regional anaesthesia. *Acta Anaesthesiol Scand* 1996, 40: 1024-1040.
19 Horlocker TT, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg Anesth Pain Med* 2003; 28: 172-197.
20 Stedeford JC, Pittman JA. von Willebrand's disease and neuroaxial anaesthesia. *Anaesthesia* 2000; 55: 1228-1229.
21 Sánchez-Luceros A, Meschengieser SS, Marchese C, et al. Factor VIII and von Willebrand factor changes during normal pregnancy and puerperium. *Blood Coagul Fibrinolysis* 2003; 14: 647-651.
22 Hoveyda F, MacKenzie IZ. Secondary postpartum haemorrhage: incidence, morbidity, and current management. *BJOG* 2001; 108: 927-930.
23 Prendiville WJ, Elbourne D, McDonald S. Active versus expectant management in the third stage of labour. *Cochrane Database Syst Rev* 2000; (3): CD000007.
24 MediMedia Australia. MIMS annual. 31st ed. Sydney: MediMedia Australia, 2007.
25 Demers C, Derzko C, David M, Douglas J; Society of Obstetricians and Gynaecologists of Canada. Gynaecological and obstetric management of women with inherited bleeding disorders. *J Obstet Gynaecol Can* 2005; 27: 707-732.
26 Kulkarni R, Lusher JM. Intracranial and extracranial hemorrhages in newborns with hemophilia: a review of the literature. *J Pediatr Hematol Oncol* 1999; 21: 289-295.
27 Veldman A, Josef J, Fischer D, Volk WR. A prospective pilot study of prophylactic treatment of preterm neonates with recombinant activated factor VII during the first 72 hours of life. *Pediatr Crit Care Med* 2006; 7: 34-39.

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