Guideline on the management of haemophilia in the fetus and neonate*

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Summary

Evidence-based guidelines are presented for the management of haemophilia in the fetus and neonate. This includes information regarding the management of pregnancy and delivery as well as aspects of management during the early neonatal period. Specific issues regarding the mode of delivery and the risk of intra-cranial and extra-cranial haemorrhage are discussed.

Keywords: haemophilia, pregnancy, neonatal haematology, bleeding disorders, fetal medicine.

Methodology

This guidance was produced with reference to relevant publications since 1990. Publications known to the writing group were supplemented with additional papers identified by searching PubMed for publications in the last 20 years using key words (Haemophilia, Pregnancy, Newborn) and limits (humans, core clinical journals, English language).

The writing group produced the draft guideline which was subsequently revised by consensus by members of the United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO) Advisory Board. It was reviewed by the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology (BCSH) and the sounding board of the British Society of Haematology, comments being incorporated where appropriate. Criteria used to define strength of recommendations and levels and grades of evidence are according to the GRADE system (Atkins *et al* 2004). Strong recommendations (grade 1, 'recommended') are made when there is confidence that the benefits either do or do not outweigh the harm and costs of treatment. Where the magnitude of benefit or not is less certain, a weaker grade 2 recommendation ('suggested') is made. Grade 1 recommendations can be applied uniformly to most patients whereas grade 2 recommendations require a more individualized application. The quality of evidence is graded as A (high quality randomized clinical trials), moderate (B), or low (C) (Guyatt *et al*, 2008a,b; http://www.bcshguidelines.com).

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Management of the fetus at risk of haemophilia during pregnancy and at delivery

General antenatal management

Haemophilia A and B are inherited as X-linked recessive bleeding disorders and maternal carriers therefore have a 50% chance of delivering an affected male infant. In women who are known carriers of haemophilia the opportunity exists to manage pregnancy, delivery and the early neonatal period in such a way as to try to minimize the increased risk of bleeding in both the mother and affected fetus/neonate. Specific issues relating to the management of women with haemorrhagic disorders during pregnancy have been the subject of previous guidelines (Haemostasis and Thrombosis Task Force, 1994; Lee *et al*, 2006).

In the presence of a positive family history of haemophilia, pregnancy should be managed by an obstetric unit with experience of haemophilia and access to both laboratory monitoring and appropriate factor replacement therapy. This should include access to coagulation screening and factor assays on a 24-h basis. Where possible, delivery should take place in an obstetric unit affiliated to a haemophilia centre, although this may not always be possible because of geographical or social factors. Good communication between

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the involved haematologist, obstetrician and neonatologist is of paramount importance. Written protocols and individual treatment plans should be agreed by all those involved, and should be readily available.

Awareness of all neonates at risk of haemophilia is not possible antenatally. It is estimated from molecular studies that at least 30% of newly diagnosed cases of haemophilia occur as a consequence of a new mutation, affecting either the male propositus or a female carrier in whom there may be no personal history of bleeding problems (Giannelli & Green, 1996). It is also evident that a positive family history of haemophilia is not always ascertained antenatally, and may result in inappropriate management during the perinatal period and delays in the diagnosis of haemophilia (Conway & Hilgarter, 1994; MacLean *et al*,2004).

Recommendations

- **The antenatal care of known or potential carriers of haemophilia should be undertaken by obstetric units in close liaison with a haemophilia centre (1C).**
- **Written management plans should be readily available. These plans should reflect input from the multidisciplinary team and include the haemostatic management of the mother and baby (1C).**

Genetic screening and fetal sexing

There should be adequate provision for genetic screening and counselling, which should, ideally, be completed pre-pregnancy. Preimplantation genetic diagnosis (PGD) can now be utilized in number of genetic conditions including haemophilia and may be considered by some couples in preference to conventional invasive prenatal diagnosis by chorionic villous sampling (CVS) (Lavery, 2009). First trimester pre-natal diagnosis should be available for couples who wish to consider this option. Issues related to genetic testing and prenatal diagnosis are covered in detail in a separate UKHCDO guideline (Ludlam *et al*, 2005).

In the presence of a continuing pregnancy, where the mother is a confirmed or suspected carrier of haemophilia A or B, fetal sexing should be performed as part of antenatal care as this will be helpful in managing pregnancy and delivery. This should be offered even if the mother wishes to remain unaware of the result. Fetal sexing can be performed either by ultra-sound (US) examination at 18–20 weeks gestation or by testing circulating cell-free fetal DNA from maternal blood for Y-chromosome-specific sequences (Bustamante-Aragones *et al*, 2008). The latter technique may not be available at all centres but has been successful from the seventh week of gestation. It does therefore have the potential to provide a result at an earlier stage of pregnancy and may help inform decisions about CVS for prenatal diagnosis.

For women wishing to avoid the miscarriage risk associated with first trimester prenatal diagnosis, but who do wish information that would influence their intrapartum management (see Management of delivery) there is an option for third trimester amniocentesis. There is probably a 1% risk of causing labour (Royal College of Obstetricians and Gynaecologists, 2010), but if performed at 35–36 weeks gestation this is unlikely to be associated with adverse clinical consequences.

Recommendations

- **Fetal sexing should be undertaken either by maternal blood sampling at around 10 weeks gestation or by US scan at between 18 and 20 weeks (1C).**
- **Third trimester amniocentesis may be considered where confirmation of an affected male fetus will influence management at delivery (2C).**

Management of delivery

The optimal mode of delivery for a fetus at risk of haemophilia remains the subject of debate due to continuing uncertainty regarding the risk of intra-cranial and extra-cranial bleeding and opinions and recommendations vary (Kulkarni *et al*, 1999; Dunkley *et al*, 2009; Medical and Scientific Advisory Council (MASAC) of the National haemophilia Foundation (2009); Ljung, 2010; James & Hoots, 2010). A number of publications have addressed the relationship between mode of delivery and the risk of intra-cranial and extra-cranial bleeding in both normal neonates and in those with haemophilia and other inherited bleeding disorders (Ljung *et al*, 1994; Towner *et al*, 1995; Klinge *et al*, 1999; Kulkarni & Lusher, 1999 & Kulkarni *et al*, 2009; Whitby *et al*, 2003; Stieltjes *et al*, 2005; Tarantino *et al*, 2007; Richards *et al*, 2009).

In a large retrospective study Towner *et al* (1995) evaluated morbidity in 583 000 live born singleton infants weighing between 2·5 and 4·0 kg. The risk of intracranial haemorrhage was 1/860 (0·12%) following ventouse extraction, 1/664 (0·15%) following forceps delivery, 1/907 (0·11%) following caesarean section performed during labour, 1/1900 (0·05%) following spontaneous delivery and 1/2750 (0·035%) following caesarean section without labour. Underlying haemorrhagic disorders and other factors which could have predisposed to bleeding were not recorded. The authors concluded that while the overall risk of intracranial haemorrhage (ICH) appeared low, the risk was highest in those delivered by ventouse extraction, forceps or by caesarean section during labour. Similarly, in a prospective study where 111 apparently normal babies underwent a cranial magnetic resonance imaging (MRI) scan within 48 h of delivery, the risk of subdural bleeding was highest following forceps or ventouse delivery and lowest following caesarean section (Whitby *et al*, 2003).

In keeping with these data, the increased risk of intra-cranial and extra-cranial bleeding secondary to birth trauma appears to be mirrored in neonates with haemophilia (Ljung *et al*,

1994; Klinge *et al*, 1999; Stieltjes *et al*, 2005; Tarantino *et al*, 2007; Richards *et al*, 2009). In one of the first studies to address this issue, Ljung *et al* (1994) reported data on 117 severe and moderate haemophiliacs born in Sweden between 1970 and 1990. There were 17/117 (14·5%) cases of cranial bleeding, 4/117 (3·5%) ICH, 12/117 (10·3%) extra-cranial haemorrhage (ECH) and 1/117 (0·8%) retro-orbital bleeding (Ljung *et al*, 1994). Of the 12 subgaleal/cephalic haematomas, 10 had been delivered by ventouse extraction and among the four cases of ICH, one followed ventouse extraction, one followed premature delivery by caesarean section and the other two followed apparently normal vaginal delivery. There was therefore a clear relationship between ventouse at delivery and ECH, but a less clear association with ICH. Several subsequent studies did however show a more definite relationship between ICH and instrumentation at delivery (Klinge *et al*, 1999; Stieltjes *et al*, 2005; Tarantino *et al*, 2007; Richards *et al*, 2009). In a German registry study (Klinge *et al*, 1999) 9/11 cases of ICH were associated with trauma at delivery although the details were not specified and Stieltjes *et al* (2005) reported instrumentation at delivery in 7/10 cases of ICH. In a large population-based study the overall incidence of ICH in the presence of haemophilia or von Willebrand disease was 3·4%, which dropped to 1·9% following exclusion of ventouse deliveries and other co-morbidities (Tarantino *et al*, 2007).

While it seems clear that instrumentation at delivery is associated with an increased risk of both ICH and ECH, it has been more difficult to define the relative risk of ICH in uncomplicated spontaneous vaginal delivery (SVD) compared with caesarean delivery. In a literature review Kulkarni and Lusher (1999) reported details on 47 haemophiliacs with ICH. 22/47 and 19/47 cases followed SVD with and without instrumentation respectively and 1/47 and 5/47 followed elective and emergency caesarean delivery. In a more recent population-based study the same author reported 17 cases of ICH, 2 of which were associated with assisted delivery while 14 followed SVD and 1 followed emergency caesarean delivery (Kulkarni *et al*, 2009).

These data suggest that the risk of ICH is reduced by avoiding instrumentation during vaginal delivery, but is not prevented, and moreover appears less frequently reported following elective caesarean delivery. Caesarean delivery may however be associated with increased maternal morbidity, which may be higher in haemophilia carriers, especially haemophilia B carriers where low baseline factor IX (FIX) levels will not increase during pregnancy and should therefore be taken into account when planning delivery (Haemostasis and Thrombosis Task Force, 1994; Lee *et al*, 2006).

Decisions regarding the management of labour in a carrier of haemophilia are dependent on both obstetric issues and the potential or known haemophilia status of the fetus. For vaginal delivery a number of constraints are placed on the intrapartum management of women carrying a confirmed or potentially affected male fetus in order to avoid procedures that have an increased risk of cranial bleeding.

Ventouse extraction, rotational and mid-cavity forceps are associated with a significant risk of cranial bleeding and should be avoided. If the clinical findings meet the criteria for use of low cavity forceps, this is likely to be a less traumatic mode of delivery than a full dilatation caesarean section. Similarly fetal scalp blood sampling or the use of intrapartum scalp electrodes may increase the risk of bleeding. There is little data to inform the management of breech presentation at term in the context of haemophilia. However, there would be similar concerns regarding the potential for ICH in association with external cephalic version or vaginal breech delivery.

Potential constraints on monitoring and concerns about traumatic delivery will result in a lower threshold for delivery by emergency caesarean section and may also result in consideration of elective caesarean section. These constraints will have proved unnecessary in a woman carrying a male fetus of unknown haemophilia status who is subsequently found to be unaffected. The woman may have been exposed to operative intervention, and its future sequelae, which could have been avoided. Third trimester amniocentesis, avoiding the risk of first trimester miscarriage, would identify a group of unaffected pregnancies that could have routine intrapartum management. This could be of particular relevance for women living in remote geographical areas who would otherwise have had to travel to a central unit.

Recommendations

- **Mode of delivery should be informed by both obstetric and haemostatic factors; haemophilia carrier status itself is not a contraindication to vaginal delivery (1C).**
- **The option of elective caesarean section in an attempt to reduce the risk of neonatal ICH may be considered on an individual basis, taking into account knowledge of the fetal haemophilia status and potential maternal morbidity (2C).**
- **Ventouse extraction, rotational and mid-cavity forceps are associated with an increased risk of bleeding and should be avoided (1A).**
- **Invasive monitoring procedures, such as placement of intrapartum scalp electrodes and fetal scalp blood sampling, should be avoided (1C).**
- **Decisions regarding the management of labour should always involve a consultant (1C).**

Diagnosis of haemophilia in the newborn infant

At delivery a cord blood sample should be obtained for coagulation screening and factor VIII (FVIII) and FIX assays as appropriate. Where severe haemophilia A or B is suspected, the diagnosis should be confirmed by factor assay ideally within the first few hours after delivery. Testing cord blood avoids potential trauma to the neonate but care should be taken to avoid maternal blood contamination and if there is any uncertainty about the result a venous sample should be

obtained from the baby. Intramuscular vitamin K prophylaxis should be withheld until the results of these investigations are available but if there is likely to be any significant delay oral vitamin K should be administered. If haemophilia is diagnosed further dosing with oral vitamin K should be given according a standard regimen (Cornelissen *et al*, 1997).

Both Haemophilia A and B typically result in an isolated prolongation of the activated partial thromboplastin time (APTT), which should be interpreted using age-specific normal ranges. Where the mother is a possible carrier, FVIII/FIX assays should be carried out regardless of the APTT. In the normal neonate, FVIII levels at birth are within the normal adult range or mildly increased (Andrew *et al*, 1987). Adult levels are also achieved in preterm infants (Andrew *et al*, 1988) and it is therefore possible to diagnose most cases of haemophilia A at birth. The only exception is in mild haemophilia A where a FVIII result at the lower end of the normal range should be repeated when the infant is around 6 months of age. Unlike FVIII, FIX levels are significantly reduced at birth and are further reduced in preterm infants (Andrew *et al*, 1987, 1988). While it is usually possible to make a diagnosis of severe or moderate haemophilia B, infants who may be mildly affected will require repeat screening at 3–6 months of age.

Recommendations

- **The diagnosis of haemophilia should be established using uncontaminated cord blood as soon as possible following delivery (1C).**
- **Results should be interpreted using age (gestation)-adjusted normal ranges (1B).**
- **FVIII/IX assays should be carried out on the cord sample regardless of the APTT (1C).**
- **Intramuscular vitamin K should be withheld until haemophilia is excluded. Oral vitamin K should be given if there is a delay in diagnosis or if haemophilia is confirmed (1C).**

Management of the newborn infant with haemophilia

Management of bleeding

Treatment for acute bleeding during the neonatal period should be undertaken urgently after discussion with a haematologist with experience of haemophilia management. The pattern of bleeding seen in neonates with haemophilia is quite different to that typically observed in older children, where muscle and joint bleeds predominate. Many neonatal bleeds are iatrogenic in origin and continued oozing or excessive haematoma formation following venepuncture, heel stab sampling or the administration of intramuscular vitamin K are relatively common. Post-surgical bleeding, post-delivery cephalohaematomas and intra-cranial bleeding are also well documented.

Guidelines on the selection and use of therapeutic products to treat haemophilia have been published by the UK Haemophilia Centres Director's Organisation (Keeling *et al*, 2008). Recombinant factor VIII and recombinant factor IX concentrates carry the lowest risk of transmitting viral infection and are the treatment of choice for haemophilia A and B.

There is little information available on the pharmacokinetics of replacement therapy in neonates and dosing is therefore based on schedules used in older children and adults (Rickard, 1995). There is some evidence to suggest that neonates, especially preterm infants, may have reduced recovery and increased clearance of FVIII and may therefore require higher doses (Gale *et al*, 1998; Kraft *et al*, 2008). *In vivo* recovery following recombinant FIX may also be lower in neonates than in older children and adults and monitoring of levels is recommended (Abshire *et al*, 1998; Poon *et al*, 2002; Guilcher *et al*, 2005).

The administration of desmopressin (DDAVP) may result in dilutional hyponatraemia with consequent seizures, and should not be used for the treatment of neonates with mild haemophilia A.

Haemophilia is not infrequently diagnosed in the absence of a family history and its initial presentation can be bleeding in the neonatal period. In a neonate with clinically significant ongoing haemorrhage, where haemophilia is suspected based on a prolonged APTT, it may be appropriate to administer fresh frozen plasma (FFP) while the results of appropriate factor assays are awaited. Large doses are required in severe haemophilia and 15–25 ml/kg may be required to raise the FVIII/FIX concentration to haemostatic levels. In keeping with current UK guidelines, non-UK sourced virally inactivated FFP should be used. Once the diagnosis is made, appropriate doses of factor concentrate should be given to obtain satisfactory factor levels.

Heel stab sampling or careful venepuncture for other neonatal screening procedures e.g. Guthrie, should not be omitted in the neonate with haemophilia but should be undertaken with pressure being applied to the puncture site until haemostasis is achieved.

Recommendations

- **Recombinant factor VIII or IX concentrate is the treatment of choice for Haemophilia A or B and should be immediately available (1C).**
- **Replacement therapy during the neonatal period should be monitored as neonates may require higher doses to achieve desired factor levels and may demonstrate a shortened factor half life (1B).**
- **Virally-inactivated fresh frozen plasma 15–25 ml/kg may be given if treatment is urgently required before the diagnosis of haemophilia has been confirmed (1C).**
- **Desmopressin should not be given to a neonate as treatment for haemophilia (1C).**
- **Heel stab sampling or careful venepuncture for other neonatal screening procedures should not be omitted and should be carried out with care by experienced staff (1C).**

Early detection and prevention of intra-cranial and extra-cranial bleeding

Both ICH and ECH are observed in newborn infants with haemophilia and the incidence of ICH in neonates with severe haemophilia is estimated to be 1–4% (Ljung *et al*, 1994; Klinge *et al*, 1999; Kulkarni & Lusher, 1999 & Tarantino *et al*, 2007; Kulkarni *et al*, 2009; Richards *et al*, 2009).

In a literature review ICH was more common that ECH and the most frequent site of haemorrhage was subdural (Kulkarni & Lusher, 1999). The mean age at presentation was 4·5 d. Although ICH and ECH may present dramatically, clinical features can equally be subtle and non-specific and a high level of clinical awareness is therefore important. The outcome of these events is not always adequately recorded in the literature but it is clear that morbidity and mortality are significant, with at least one-third of survivors of ICH reported to develop long term sequelae with neuro-developmental problems. ECH is also associated with a significant risk of mortality as a consequence of massive blood loss even in apparently normal infants (Plauche, 1980).

As well as instrumentation at delivery, severity of haemophilia has been identified as a risk factor for cranial bleeding (Kulkarni & Lusher, 1999). Preterm delivery may also increase the risk of ICH although the numbers of cases in the literature are too small to assess the magnitude of risk (Bidlingmaier *et al*, 2005).

The ability to identify those neonates at highest risk of cranial bleeding could facilitate early intervention either in terms of investigations aimed at detection of asymptomatic bleeding or the administration of short-term factor replacement therapy to try to reduce the risk of bleeding triggered by trauma at delivery.

Recommendation

- **Where there is a strong clinical suspicion of ICH (or other bleeding), factor concentrate should be given immediately and not withheld pending definitive imaging studies (1C).**

Radiological assessment of intracranial bleeding

Cranial US has been proposed as a readily available, non-invasive method to detect early signs of ICH. However, the place of routine cranial US in the management of neonates with haemophilia currently remains controversial and data on cranial US findings from large prospective series are lacking. Controversial issues include the optimal timing of scanning and the need for sequential scanning during the first few days of life. It is also clear that cranial US is not the most sensitive imaging technique for the detection of sub-dural bleeding which represents the most common site of ICH in this patient group (Smith *et al*, 2008).

The current level of knowledge suggests that routine cranial US cannot be relied upon to detect all cases of early ICH but it may be a useful screening investigation. In neonates with non-specific symptoms that could represent ICH, or in neonates with a documented ECH, computed tomography (CT) or MRI scanning should be considered even in the presence of an apparently normal cranial US.

Recommendations

- **Cranial US should be undertaken prior to discharge in all neonates with severe or moderate haemophilia (2C).**
- **Due to the low sensitivity of US for the detection of subdural bleeding, cranial MRI or CT scan should be undertaken in symptomatic neonates even if an US is normal (1C).**

Prophylactic treatment of neonates with factor concentrate

Short-term neonatal prophylaxis with either FVIII or FIX is a potential approach to reducing the risk of ICH and other significant haemorrhagic problems in the newborn period but has not been the subject of any systematic studies to date. Proponents of early prophylaxis have argued that it is illogical to manage potential cranial trauma in the neonate expectantly, when older children, even following relatively minor head trauma, generally receive prompt replacement therapy. Potential disadvantages of this treatment include the risk of trauma during the administration of factor concentrates and the likelihood that time in hospital post-delivery will be prolonged. Perhaps more importantly, it has been suggested that early exposure to FVIII in severe haemophilia A is associated with an increased risk of inhibitor development: these data however, have not been confirmed in subsequent studies (Lorenzo *et al*, 2001; Van der Bom *et al*, 2003; Chalmers *et al* 2007; Gouw *et al*, 2007).

Other areas of uncertainty include the timing and number of doses required to confer potential benefit. It seems likely that in order to be effective, treatment should be administered as soon as possible following delivery, but should only be given after the diagnosis has been confirmed to avoid treating unaffected infants. A single dose of factor replacement is unlikely to provide adequate protection for any significant degree of bleeding and more frequent doses for an extended period of time are likely to be more effective.

A recent survey of practice in the UK suggested that routine prophylaxis was infrequent but was likely to be considered following potentially traumatic delivery (Chalmers *et al*, 2005). Primary neonatal prophylaxis in all cases of severe haemophilia A and B is not justified based on current evidence but may be appropriate in high risk situations e.g. following instrumental or other potentially traumatic delivery. Other unconfirmed risk factors may include prolonged second stage labour (primigravid >3 h; parous >2 h), delivery of preterm infants and infants born with evidence of superficial cranial bruising, as this may indicate a degree of excessive trauma (RCOG, 2005).

Given these uncertainties and the lack of a strong evidence base, all such proposed interventions should be discussed with

parents before delivery. It is also crucial to future developments in this area that neonatal management is prospectively monitored to assess the effectiveness and side effects of these interventions.

Recommendations

- **Following confirmation of diagnosis, short term prophylactic replacement therapy should be given in neonates at increased risk of bleeding e.g. following traumatic delivery, instrumental delivery (particularly Ventouse or forceps extraction), or a prolonged second stage of labour (1C).**
- **Short term prophylaxis should be considered following preterm delivery (1C).**

Information on diagnosis

Once a diagnosis of haemophilia has been made it is important that the affected infant is referred promptly to his local haemophilia treatment centre. The diagnosis and its implications should be discussed with the parent(s) or carers before discharge from hospital. Neonatal bleeding problems not infrequently occur following discharge and it is therefore important that parents are adequately counselled about potential problems, including those which could relate to major bleeding such as ICH. The community midwife & general practitioner should be informed of the diagnosis and be aware of the early signs and symptoms of ICH. If appropriate, e.g. in more remote geographical areas, a small supply of factor concentrate should be given to parents to have at home in case of emergencies.

Recommendations

- **Parents of an affected neonate should be informed of the diagnosis and presenting features of significant bleeding prior to discharge from hospital (2C).**
- **Early follow up by Haemophilia clinician should be arranged prior to discharge (2C).**

Female carriers

Female infants who are potential carriers of haemophilia appear to be at low risk of bleeding during the neonatal period. Occasional cases will however have particularly low factor levels due to extreme Lyonization and any abnormal bleeding should be appropriately investigated. There are no reports of serious neonatal bleeding in female carriers of either haemophilia A or B and standard obstetric and fetal/neonatal management should therefore be followed.

Recommendation

- **Newborn haemophilia carriers or potential carriers should receive routine obstetric and neonatal management (1C).**

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the UKHCDO, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

Disclosures

Disclosures made annually by all authors to Chairman of UKHCDO.

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