

## REVIEW ARTICLE

# Unresolved issues in diagnosis and management of inherited bleeding disorders in the perinatal period: A White Paper of the Perinatal Task Force of the Medical and Scientific Advisory Council of the National Hemophilia Foundation, USA

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**Summary.** Haemophilia and inherited bleeding disorders in newborns and their carrier mothers pose unique challenges. The pattern of bleeding and the causes and risk factors for bleeding are decidedly different than an older child or an adult with haemophilia/inherited bleeding disorder. This document outlines the needs for further research and education,

summarizes the state of the art background information and provides guidance regarding research, education and access to care issues in this population.

**Keywords:** bleeding, carrier, haemophilia, intracranial hemorrhage, neonatal, pregnancy

## Introduction

The Perinatal Task Force of the National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) was charged with developing a position paper regarding challenges and issues in newborns with bleeding disorders that would highlight and prioritize areas of research and education in this population. This paper outlines neonatal as well as maternal issues that need further research and educational efforts to improve patient care and prevent complications.

## Background

Bleeding in newborns with haemophilia and other inherited bleeding disorders may potentially be life-

threatening and continues to be a preventable cause of morbidity and mortality. Prompt recognition and early diagnosis of such newborns is crucial to ensure appropriate management including use of safer clotting factor concentrates, early prophylaxis and, perhaps in the future, early institution of gene therapy. Recent studies suggest that 15–33% of newborns with inherited bleeding disorders initially present with bleeding manifestations in the neonatal period [1].

To understand the issues of haemostatic disorders in newborns one must be aware of the differences in the haemostatic system between the newborn and older children and adults and also of extraneous factors that impact on the bleeding manifestations in this population. These include the following:

- 1 Maternal issues such as carrier status and mode of delivery influence manifestations of bleeding disorders in the newborn.
- 2 The coagulation system of the newborn is not well developed, resulting in lower than adult levels of most of the procoagulant and anticoagulant factors. Factor VIII (FVIII) levels, however, are normal in newborns.

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- 3 The blood volume of neonates is small, and relatively little amounts of blood loss can have major consequences.
- 4 Neonatal bleeds are almost always traumatic in origin (trauma of delivery, vitamin K injection and circumcision), and the pattern of bleeding is typically different than in older children.

## Maternal issues

### *Carrier testing*

All women who are potential carriers of haemophilia should be tested for carrier status, ideally before they become pregnant, because pregnancy raises FVIII, but not the factor IX (FIX), levels and may make diagnosis more difficult. DNA testing can identify with 100% accuracy those women who are carriers. Where there is a family history of haemophilia, direct DNA analysis is the most accurate method to determine carrier status. However, an affected individual in the family must be available to detect the mutation first. An alternative method, linkage analysis by restriction-fragment length polymorphisms, is laborious, time consuming, and expensive and may not give the correct answer to allow for accurate genetic counselling. Research is needed to determine the most appropriate age for carrier testing.

Hereditary coagulopathies can produce serious bleeding manifestations in pregnant affected carrier women, resulting in adverse fetal outcomes. While miscarriage and postpartum haemorrhage have been reported to be more common among haemophilia

carriers [2–6], studies have been limited to case series (Table 1). There are neither controlled studies nor are there studies from the USA. The prevalence of gynaecological and bleeding morbidity in carriers in the USA remains unknown. Obtaining data regarding the reproductive experiences of haemophilia carriers should be a research priority. Furthermore, preconceptional education and counselling should precede prenatal diagnosis in known haemophilia carriers and women with bleeding disorders. Such educational initiatives should provide adequate information not only concerning the genetics of bleeding disorders but also conception options and management of pregnancies.

### *Prenatal diagnosis*

While prenatal diagnosis is helpful in the management of carrier mothers and their newborns, one-third to one-half of the cases of haemophilia are sporadic with no family history. For early prenatal diagnosis, chorionic villus sampling (CVS) is performed between 10 and 12 weeks of gestation; it takes 3–4 days to determine fetal gender and 1 week to diagnose haemophilia [2]. European investigators, using new techniques, have reported that it is possible to obtain a diagnosis of haemophilia B within 24 h of a CVS. The advantage of CVS vs. amniocentesis is that it allows for first trimester diagnosis and avoids late termination of pregnancy, a distinct disadvantage of amniocentesis that is often performed after 14 weeks of gestation [7]. Once a diagnosis has been made, the potential parents can be

**Table 1.** Problems related to childbirth among haemophilia carriers.

Study	Sample size and population	Type of study	Prevalence
<b>Miscarriage</b>			
Kadir <i>et al.</i> (2)	82 pregnancies in 32 haemophilia carriers (24 with A; eight with B)	Case series	22/72 intended pregnancies (31%)
Yang <i>et al.</i> (3)	19 pregnancies among five women with factor IX deficiency	Case series	3/19 (16%)
<b>Other bleeding during pregnancy</b>			
Guy <i>et al.</i> (4)	One woman with haemophilia B	Case report	Subchorionic haemorrhage at 32 weeks
<b>Postpartum haemorrhage</b>			
Mauser Bunschoten <i>et al.</i> (5)	97 obligate carriers of haemophilia A	Case series	22%
Mauser Bunschoten <i>et al.</i> (5)	Eight obligate carriers of haemophilia B	Case series	0/8 women
Greer <i>et al.</i> (6)	34 term pregnancies in 18 obligate carriers of haemophilia A	Case series	3/34 (9%) secondary
Greer <i>et al.</i> (6)	12 pregnancies (nine term) in five obligate carriers of haemophilia B	Case series	1/9 (11%) secondary
Kadir <i>et al.</i> (2)	46 term pregnancies in obligate carriers of haemophilia A and B	Case series	10/46 (22%) primary 5/46 (11%) secondary
Yang <i>et al.</i> (3)	19 pregnancies among five women with factor IX deficiency	Case series	6/16 pregnancies carried to term with at least one secondary

provided with information concerning haemophilia. Despite availability, only 35% of carriers agree to prenatal testing [8]; the majority of the newborns with haemophilia are still being diagnosed following a bleeding episode. Research is needed to determine what factors influence acceptance of prenatal testing amongst pregnant carriers.

Among carrier women, newer technologies such as preimplantation genetic diagnosis and sperm sorting are being implemented to maximize chances of a female fetus. The former combines assisted reproductive technology with molecular genetics and cytogenetics to allow identification of abnormalities in embryos prior to implantation. Patients undergo *in vitro* fertilization followed by embryo biopsy; only female embryos are transferred to the uterus [9]. Sperm sorting, currently in clinical trial is another new method of maximizing chances of a female fetus by enriching the proportion of X-carrying sperms [9].

#### *Obstetrical management*

Uniform and national guidelines for obstetric management of carriers and their newborns are lacking. Research in the area of prenatal diagnosis may help with the development of such guidelines and may be useful for the management of pregnant as well as non-pregnant carriers. Perhaps genetic diagnosis of all potential carriers may prevent pre- and postpartum bleeding complications in this population.

#### *Mode of delivery*

In a recent study from the Netherlands of the impact of carrier status on the mode of delivery, 31% of the mothers of 73 haemophilia patients were not aware of their carrier status prior to delivery [10]. Instrumental delivery such as vacuum and forceps delivery occurred more frequently in mothers who were unaware (16%) compared with those who were aware (8%) of their carrier status. In contrast, a higher proportion of Caesarean deliveries were performed in known carriers compared with unaware carriers (22% vs. 8%). In the same study, head bleeds (intra- and extracranial) occurred in a total of seven newborns; of these, five occurred in nine instrumental deliveries and two in 53 spontaneous vaginal deliveries. None of the 11 Caesarean deliveries among women in this study resulted in head bleeds. Ljung *et al.* [11] reported a significant risk of cranial haematomas in newborns with haemophilia with vacuum deliveries and recommended vaginal delivery for pregnant haemophilia carriers. Further

research is needed to study the optimum mode of delivery of carriers of haemophilia as well as the influence of bleeding disorder on both the pregnant carrier and her baby.

#### **Newborn issues**

Despite advances in treatment of haemophilia and bleeding disorders, several major challenges persist in newborns with bleeding disorders.

- 1 A majority of the newborns are still being diagnosed following a bleeding episode.
- 2 Even though bleeding, e.g. intracranial haemorrhage (ICH), is recognized early, in the majority of cases, the diagnosis of a bleeding disorder such as haemophilia is often delayed; the median age of diagnosis of haemophilia is 7–9 months [12,13], and rare bleeding disorders are diagnosed much later.
- 3 Head bleeds (intra- and extracranial haemorrhage) remain a major cause of morbidity and mortality in this age group. The optimal imaging study for diagnosis and the timing of such a study in haemophilic newborns remains unknown.
- 4 Studies are needed to determine whether early exposure to factor concentrates constitutes a risk factor for later inhibitor development.
- 5 The feasibility, safety and efficacy of gene therapy in the newborn period and its potential use for inducing tolerance in severe haemophilia need further study.

Newborns with inherited bleeding disorders such as haemophilia A and B, von Willebrand's disease, factor VII (FVII), factor X (FX), factor V (FV), factor II (FII), factor I, FXIII and congenital platelet disorders may present with bleeding in vital areas such as the brain, lungs and abdomen. A majority of the bleeds may be iatrogenic, caused by intramuscular injections, venipuncture, and procedures such as circumcision. Birth trauma, resulting in scalp and ICH, remains a potential cause of mortality and morbidity. Of the 222 babies with bleeding disorders aged 0–2 years enrolled during 2004 and 2005 in a surveillance project sponsored by the Centers for Disease Control and Prevention (CDC), 77% were diagnosed in the first month of life; the most common reasons for diagnostic testing was a bleeding episode in 37%, mother a known carrier in 40%, and positive family history in 21%. The age at first bleed was <1 month of age in 37% of the cases. ICH was reported in 12 babies and was associated with delivery in five of 12 babies (CDC, unpublished data).

In the haemophilic newborn, besides organ damage due to bleeding, blood volume depletion due to

blood sampling for laboratory testing or blood loss from procedures such as circumcision and injections may further compromise the haemodynamic status and may be life-threatening. Such newborns can easily exsanguinate into the scalp, brain and other areas. To further confound the issue, the signs and symptoms of blood loss may be subtle and overlooked. Physiological changes during the newborn period such as immaturity of the liver coupled with vitamin K deficiency may result in decreased levels of clotting factors. These changes often cause a physiological prolongation of prothrombin time and activated partial thromboplastin time that can mask the diagnosis of an inherited coagulation defect.

#### *Intracranial haemorrhage*

An ICH in a newborn with inherited bleeding disorder may have a life-long impact, and therefore early recognition and appropriate management are crucial. Although in the general population, ICH has been reported in one of 860 infants delivered by vacuum extraction, one of 664 delivered with forceps, one of 907 delivered by Caesarean section during labour, one of 2750 delivered by Caesarean section before labour, and one of 1900 born spontaneously [15], it is not known how many of these babies had an inherited bleeding disorder as a cause of the ICH. In newborns with haemophilia, ICH is the leading cause of morbidity and mortality and can occur regardless of the mode of delivery. The overall incidence of ICH in individuals with haemophilia (all ages) is 2.2–7.5%; approximately 50% occur in the newborn period. The cumulative incidence of cranial haemorrhage (intra- and extracranial) in a retrospective study was 3.8% [16]. ICH has also been reported in 30% of newborns with FXIII deficiency, as well as in newborns with deficiencies of FII, FV, FVII, and FX and vitamin K deficiency. Because ICH can result in permanent disability or death, it is critical that every attempt be made to recognize and treat such bleeds promptly. Although a diagnosis of ICH is often made within a matter of days after birth, it takes an average of 6 months (range 6–18 months), to diagnose haemophilia [1,13]. This is most likely due to subtle and non-specific clinical signs and symptoms (such as anaemia, lethargy, hypotension and shock) coupled in many cases with an absence of a family history of haemophilia. Lack of awareness that ICH may be the first indicator of haemophilia and can occur regardless of the severity of haemophilia may further contribute to delays in diagnosis [17]. The consequences of ICH in newborns with haemophilia are long-term and include

psychomotor retardation and seizure disorder. In a recent survey of 30 cases (including 11 newborns) of ICH in haemophilia, psychomotor retardation and cerebral palsy were reported in 59%; neonates with ICH showed a poorer outcome compared with older children [18]. The prevalence of inherited coagulation disorders in premature and very low birth weight newborns that may contribute to the high risk of ICH is unknown.

#### *Age of initiation of factor administration*

Prophylactic administration of factor concentrate at birth remains an intensely debated issue [19]. A recent survey in the UK of current practices in the management of neonates [20] with haemophilia indicated that of the 45 centres responding, 41% would routinely obtain an ultrasound (US) of the head at birth; 38% would only under special circumstances (forceps delivery or prolonged labour), and 21% would in the presence of clinical signs suggestive of bleeding. With regards to prophylaxis, 19% would consider short-term primary prophylaxis, and 50% would treat following traumatic delivery. For rare bleeding disorders, 44% and 52% would consider prophylaxis in severe FX and FVII deficiency, respectively, and 66% would consider prophylaxis in severe FXIII deficiency.

In the CDC surveillance data, 8% of babies had received factor concentrates within 24 h after birth; 11 had received product for prophylaxis for bleeds and six for treatment of bleeding episodes (CDC, unpublished data). Rodriguez *et al.* [21] in a case report and review of institutional experience, described six of 18 newborns with haemophilia A that received prophylactic FVIII infusions at birth, all of whom were positive for a family history of bleeding disorder.

An important question is whether early administration of FVIII poses a risk for inhibitor formation. Data from the literature [22,23] have suggested that patients who receive FVIII concentrates prior to 6 months of age may have a higher incidence of inhibitor formation of 30–40%. In contrast, those that start factor at 6–12 months of age have an incidence of inhibitor development of 20–30%, and those that start factor at 12 months or later have an incidence of inhibitor development of 10%. Rivard *et al.* [24] used recombinant activated FVII (rFVIIa) to postpone exposure of infants to FVIII concentrates, however five of 11 subjects in the rFVIIa group developed inhibitors compared with two of eight in the FVIII group. Interpretation of the results of these studies is complicated by the fact that patients who start

treatment early may have more severe disease or that due to problems with venous access, early treatment may be more likely to be episodic rather than prophylactic. There are no published studies in which patients have been randomized to receive factor early vs. late or to initiate treatment with prophylactic vs. episodic administration.

In contrast to the clinical literature in patients, studies in mice and dogs have suggested that administration of FVIII or FIX concentrates in the newborn period can reduce the chance of subsequent inhibitor formation. A single dose of FVIII shortly after birth resulted in tolerance in 90% of mice that were challenged with clotting factor protein or gene therapy at an older age [25]. In contrast, only 20% of mice that were challenged as adults without neonatal FVIII injection were tolerant. Similarly, initiation of human FIX protein treatment at 3 days after birth given subcutaneously daily for 2 months resulted in tolerance in 60% of haemophilia B dogs, whereas 0% of dogs that started FIX challenge at an older age were tolerant [26]. This may be due to the immaturity of the immune system at birth, which might make it easier to develop tolerance.

#### *Gene therapy in the neonate*

Neonatal gene therapy in the animal model has also been remarkably effective at inducing tolerance. This was effective with a vector expressing FIX in 100% of mice and dogs [27] and with a vector expressing FVIII in 100% of mice if expression was above 10% of normal human FVIII levels (L. Xu, K. Ponder, unpublished data). However, lower expression was not effective, suggesting that it will be important to achieve high levels of clotting protein in blood to induce tolerance. Thus, studies in animals support the hypothesis that achieving high and constant levels of protein in blood in the newborn period may induce tolerance. However, this would be difficult to perform in humans due to problems with i.v. access, and it is possible that the immune system of humans could behave differently. Randomized trials will be necessary to determine the effect of age of onset of treatment in patients with haemophilia A. Another important variable to evaluate will be whether or not prophylactic treatment induces more tolerance than episodic treatment.

#### **Controversial and unresolved issues**

The following controversies and unresolved issues exist regarding newborns with haemophilia and other bleeding disorders:

- 1 What are the types of inherited bleeding disorders that present in the newborn period and are the bleeding patterns different?
- 2 What proportion of cases is diagnosed at or before birth and what factor(s) lead to the diagnosis (family history, mother a carrier, bleeding symptoms)?
- 3 What is the optimum modality for detection of cranial bleeds in newborns with inherited bleeding disorders? There are no published studies in this population regarding the utility of routine cranial US in the early detection of ICH. Furthermore, there is no data in the newborn with bleeding disorders comparing cranial US, computerized tomography (CT) scan and magnetic resonance imaging (MRI). It is a well-established fact that for subdural and subarachnoid haemorrhages CT or MRI is the modality of choice.
- 4 What is the optimal timing of scanning as well as repeat scanning for detection of ICH in newborns with inherited bleeding disorders?
- 5 What are the long-term effects of ICH and other organ bleeds? Is this population particularly susceptible to recurrent bleeding episodes in the brain and other organs?
- 6 Should all newborns at-risk for haemophilia receive factor concentrates at the time of birth and in some instances in utero? Should rFVIIa be administered to newborns with bleeding episodes (including those with rare bleeding disorders) pending diagnosis?
- 7 What is the appropriate dose of factor for treatment of a bleeding episode in a newborn? What is the pharmacokinetics of infused concentrate in the newborn? There is little data in the literature on recovery or continuous infusion of factor concentrates [28] in newborns.
- 8 What are the risks (inhibitor development, thrombosis) of administering factor concentrates to the newborn for prophylaxis or treatment? Is the immune response of newborns to factor different than an older child or adult?
- 9 What proportions of newborns with inherited bleeding disorders have central venous access devices placed, and what are the complications of such devices in this population?

#### *Research priorities*

The following are some of the priorities that should be addressed in newborns and their carrier mothers.

- 1 Encourage ongoing surveillance to identify and delineate the different types of inherited bleeding

- disorders in newborns (term and preterm) and patterns of bleeding in newborns with inherited coagulation disorders. This should also include preterm newborns and those with in utero bleeds.
- 2 Continue data capture on the Universal Data Collection forms of the Center for Disease Control regarding haemophilia and inherited coagulation disorders in babies.
  - 3 Encourage prenatal genetic diagnosis of carrier status in families at-risk for haemophilia.
  - 4 Promote controlled studies regarding reproductive experiences of carrier mothers.
  - 5 Support research and provide incentives for the development of micro-methods of laboratory diagnosis of bleeding disorders in newborns and infants.
  - 6 Determine the optimal method of diagnosis of ICH using bedside US vs. CT and MRI in newborns with inherited bleeding disorders.
  - 7 Determine optimal timing of obtaining US/CT/MRI and the need for rescanning in newborns with inherited bleeding disorders.
  - 8 Encourage a nationwide study to determine if prophylactic infusion of factor concentrate in newborns with haemophilia prevents haemorrhage and the impact of such infusion on immune status and inhibitor development.
  - 9 Promote research on pharmacokinetics of factor concentrates and optimal dosage and timing of factor replacement for bleeding episodes in the newborn.
  - 10 Determine safety and efficacy of rFVIIa for the treatment of term and preterm newborns with bleeding disorders, pending diagnosis.
  - 11 Promote research regarding the incidence and causes of inhibitor formation in newborns, the impact on the immune system of treatment with factor concentrates and other risk factors such as bleeding sites, central venous access devices, immunizations, injections, infections, etc.). Develop preventive strategies for inhibitor formation in the newborn.
  - 12 Encourage research in newborn animal model of haemophilia regarding the feasibility of gene therapy.
  - 13 Encourage long-term follow up regarding neurological and neuropsychological sequelae of ICH in neonates with haemophilia.

#### Education issues

- 1 Support education regarding bleeding problems in the neonate and in pregnant carriers in the pre- and postnatal period.

- 2 Educate obstetricians and OB nurses about the importance of collecting a cord blood sample for testing for a bleeding disorder if the mother is a carrier.
- 3 Develop guidelines for diagnosis and management of newborns with bleeding problems.

#### Access to care issues

- 1 Promote access to speciality care for carrier mothers and babies (HTC, high-risk OB and neonatology) to ensure safe delivery and appropriate diagnosis and management.
- 2 Promote insurance coverage for genetic testing of haemophilia and other bleeding disorders.

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