The obstetric experience of carriers of haemophilia

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Objective To review the obstetric problems, pregnancy outcome and management of carriers of haemophilia.

Design Retrospective review of haemophilia and maternity unit records.

Setting Haemophilia Comprehensive Care Centre.

Participants Thirty-two carriers of haemophilia (24 haemophilia A, eight haemophilia B) who had their obstetric care at the Royal Free Hospital over a 10-year period (1985–1995).

Main outcome measures Uptake and results of prenatal diagnosis, changes in factor levels during pregnancy, effect of knowledge of fetal gender on obstetric management and neonatal outcome, and maternal haemorrhagic complications.

Results There were 82 pregnancies and 32 resulted in miscarriage or social abortion. The option of prenatal diagnosis was taken up in only 35% (17/48) of pregnancies. There were five affected male fetuses diagnosed prenatally but only three women opted for termination of the pregnancy. Knowledge of fetal gender was unavailable to the attending obstetrician in 46% (21/46) of pregnancies. A fetal scalp electrode was applied in eight, fetal blood sampling was performed in four, and ventouse delivery was conducted in one of these pregnancies. No adverse effects were reported from the first two procedures, but the ventouse delivery was associated with a huge cephalhaematoma requiring blood transfusion. On the other hand, in five cases fetal blood sampling was withheld because fetal gender was unknown. Four of the eight caesarean sections performed might have been avoided if the gender had been known. The incidence of primary and secondary postpartum haemorrhage was high, 22% (including two cases with massive haemorrhage) and 11%, respectively.

Conclusion Carriers of haemophilia A and B require special obstetric care with close liaison with the haemophilia centre, and management guidelines should be available and observed. Knowledge of fetal gender is very valuable for management in labour and should be determined antenatally even if the mother declines prenatal diagnosis.

INTRODUCTION

Haemophilia A and B are uncommon conditions with a prevalence in the general population of 1 to 2 per 10,000 and 1 to 2 per 100,000, respectively. The genetic defect on the X chromosome results in an absent or low level of plasma factor VIII in haemophilia A, and factor IX in haemophilia B. The advent and appropriate use of clotting factor concentrates have dramatically improved the life expectancy and quality of life of patients with clotting factor deficiencies. This increased longevity and the obvious improvement in the general and reproductive fitness among men with haemophilia over the last 40 years has resulted in an increase in the birth of daughters who are obligate carriers.

Since female carriers have a second normal gene from one parent the clotting factor level is expected to be around 50% of normal, which is generally sufficient for normal haemostasis. However, a wide range of functional activities has been reported and in 10% to 20% of carriers extreme Lyonisation results in significantly low levels of factor VIII and IX (less than 40%) and an increase of haemorrhagic problems specially in those with very low levels (5% to 10%). In addition, 50% of male fetuses of carriers of haemophilia are likely to be affected. If mothers reject prenatal diagnosis their male infants may be unknowingly at risk of traumatic haemorrhage.

There are few studies addressing the haemorrhagic problems for carriers of haemophilia and their fetuses in pregnancy and delivery. The Royal Free Hospital has a large, comprehensive care centre for haemophilia and many carrier women have their pregnancy care at this
hospital. The aim of this study was to assess pregnancy outcome with particular regard to bleeding problems in both mother and fetus.

METHODS

Thirty-two carriers of haemophilia (24 haemophilia A, eight haemophilia B) registered at the Royal Free Hospital Haemophilia Centre who had obstetric care at this hospital over a 10-year period (1985–1995) were investigated. Twenty four were known as obligate carriers, carrier status was suspected in six of the women during the antenatal period and was confirmed in the postnatal period, and diagnosis of carrier status was made in the remaining two after birth of an affected male.

These women had a total of 82 pregnancies and both the Haemophilia Centre and maternity casenotes were reviewed with particular emphasis on the obstetric experiences and coagulation status during pregnancy and the puerperium. Information recorded included: 1. baseline (nonpregnant) clotting factor levels and any changes in pregnancy; 2. uptake and results of prenatal diagnosis; 3. occurrence of bleeding during pregnancy and postpartum period including primary postpartum haemorrhage (blood loss in excess of 500 mL during the 24 hours after the birth of the infant) and secondary postpartum haemorrhage (bleeding in excess of normal lochial loss after first 24 hours of delivery to 6 weeks); 4. mode of delivery including indications for instrumental deliveries and caesarean sections; 5. Neonatal outcome with special emphasis on haemorrhagic complications and impact of invasive monitoring techniques and mode of delivery on these complications.

Student’s $t$ test was performed to test for significant changes in clotting factor levels during pregnancy.

RESULTS

Prenatal diagnosis and antenatal care

Of the 82 pregnancies, 32 resulted in miscarriage or termination for social reasons (Fig. 1). Of the remaining 50, prenatal diagnosis was offered to the women in 48 pregnancies (in two pregnancies the carrier status was discovered postnatally). The women opted for prenatal diagnosis in only 17/48 (35%) pregnancies. The methods used and results are shown (Fig. 1). Termination of pregnancy was performed in 3 cases with an affected fetus and there was one miscarriage of an unaffected male fetus following cordocentesis.
Among the 46 ongoing pregnancies, the gender of the fetus was determined in 13 from prenatal diagnosis, and was requested by the obstetrician in a further 14 pregnancies. The fetal genital area was visualised antenatally by ultrasound at 18 to 20 weeks of gestation in 12 of these 14 cases. In these 12 there was correct gender assignment. There was failure to visualise the genital area in two cases and no later attempts at gender assignment were made. In five others pregnancies, the mothers specifically did not want fetal sexing. In 14 pregnancies with known carrier status, no gender diagnosis was offered. Therefore, in 21/46 (46%) pregnancies, fetal gender was not available to the attending obstetrician during labour.

The nonpregnant mean factor VIII level in carriers of haemophilia A was 52.5 IU/dL (median 56, range 18–96) and nonpregnant mean factor IX level in haemophilia B was 57 IU/dL (median 48, range 16–80). Factor levels were checked in nine and three pregnancies in the second and/or third trimesters in haemophilia A and B carriers, respectively (Fig. 2). Most of the carriers of haemophilia A showed a significant increase in factor VIII levels ($P < 0.001$) but there was no significant increase in factor IX in carriers of haemophilia B.

**Labour and mode of delivery**

The mean gestation at delivery was 39.2 weeks (range 34–42). Fetal scalp electrodes were used for fetal monitoring in labour in eight pregnancies where the fetal gender was not known. Two of these fetuses were subsequently found to be affected males. Fortunately there were no adverse affects from the use of fetal scalp electrodes in these cases. On the other hand fetal scalp electrodes were required for fetal monitoring in three cases but withheld due to lack of knowledge of the gender. Fetal blood sampling was considered essential in nine pregnancies where gender was not known but was not performed in five of them because of this. In two of these five cases, emergency caesarean section was performed (Table 1; case no. 7, 9), another two had forceps delivery (Table 1; case no. 1, 3) and in the fifth case cardiotocogram (CTG) improved while the woman was being prepared for caesarean section and she had a vaginal delivery. However, among the four cases where the procedure was performed, there was one affected male fetus who suffered no adverse effect.

The mode of delivery was a normal vaginal delivery in 32 pregnancies (intact perineum in 14, vaginal tears in nine, episiotomy in nine). Details of the forceps, ventouse and caesarean section deliveries are shown in Table 1. A severe cephalhaematoma developed subsequent to ventouse delivery in one fetus later found to be an affected male, infant of a known carrier mother. Of the eight caesarean section deliveries, knowledge of gender might have influenced management in four cases (Table 1; case no. 7, 8, 9, 12).

None of the caesarean sections was performed under regional anaesthesia. However, epidural analgesia was the method of pain relief during labour in six of the total group. Factor levels were > 50% in five of these but was unknown in the sixth patient as her haemophilia carrier status was diagnosed postnatally. There were no reported complications from the procedure in any of the six cases.

**Maternal haemorrhagic complications**

These were all postpartum. There were 10 primary postpartum haemorrhages (Table 2), two of which were massive. Two caesarean sections were followed by significant postpartum haemorrhage. Although the factor levels were below 50% in six of these cases, prophylactic treatment was not arranged to cover delivery and the postpartum period. Desmopressin (1-deamino-8-arginine vassopressin [DDAVP]) was administered prophylactically immediately after delivery in only three women and in another who had a postpartum haemorrhage within 30 minutes of delivery. This resulted in an increase in factor level in these patients (mean factor level was 46 IU/dL before and 84 IU/dL after DDAVP administration, respectively). Intravenous access in labour was established in 15 women but in only four of them was this because of the haemophilia carrier status. There were five secondary postpartum haemorrhages and retained products of conception were obtained in only one (Table 2).

**Neonatal complications**

Of the 46 infants born 24 were male (eight were confirmed to have haemophilia) and 22 were female. The mean birthweight was 3.25 kg (range 2.34–4.26). There were three neonatal problems in affected male
infants as a result of haemophilia. One infant suffered a huge cephalhaematoma after a ventouse delivery resulting in subsequent anaemia (haemoglobin 5.2 g/dL) requiring transfusion but there was no intraventricular haemorrhage. A second infant already known to be an affected male, was delivered by caesarean section after a 2 hour second stage and there was marked bruising and a cephalhaematoma but again no intraventricular haemorrhage. A third infant was inadvertently given intramuscular vitamin K before the diagnosis of haemophilia was made and developed extensive deep bruising around the site which settled with conservative management and did not require blood transfusion. Admission to the intensive care unit was required for six infants. In two (Table 1; case no. 6, 11) this was directly associated with bleeding complications. Preterm delivery, meconium aspiration and low Apgar scores were reasons for admission in the other four.

**DISCUSSION**

The little published information on the obstetric problems of carriers of haemophilia A and B involves only a small number of women. Our study represents the largest detailed assessment of the obstetric outcome of carriers of haemophilia from one centre and illustrates the problems of pregnancy for both mother and fetus.

Recent advances in molecular genetic procedures have resulted in accurate DNA-based prenatal diagnosis and have therefore increased the available options for carrier women. However, there was a low uptake of prenatal diagnosis (35%) in our study and termination was chosen in only half of the affected pregnancies. Similarly, Varekamp et al. evaluating the attitudes toward prenatal diagnosis among 549 nonpregnant potential and obligate carriers of haemophilia found that only 31% of the study group would favour prenatal diagnosis, with the implication of a possible abortion in early pregnancy, and half of them would choose this option even at 16 to 20 weeks. Most of the women who objected to prenatal diagnosis did so because they did not consider haemophilia to be a sufficiently serious disorder to justify an abortion. Nowadays, with the availability of genotype analysis (by linked polymorphism or direct identification of the gene causing the disease), chorionic villus sampling has become the main method of prenatal diagnosis and determination of fetal clotting factors by cordocentesis is used only in special circumstances (e.g. when the mother’s DNA analysis is noninformative or adequate information about the family cannot be obtained). Therefore, accurate prenatal diagnosis is not only possible but also important in the management of the pregnancy.
Most female carriers of haemophilia have factors VIII and IX levels within the normal range, although the reported range is wide. In our study group the non-pregnant mean value was 52.5 IU/dL (range 18–86) and 57 IU/dL (range 16–80) for factor VIII and IX, respectively. Mean factor VIII levels of 54 IU/dL (range 22–116) and 96 IU/dL (range 44–136) have been reported in carriers of haemophilia and normal females, respectively, and factor VIII has been shown to be less than 30 IU/dL in 2% of carriers of haemophilia A.<sup>6</sup> Pregnancy induces a rise in factor VIII levels in normal women<sup>7</sup> and in carriers of haemophilia A<sup>6</sup>. A significant increase in factor VIII concentration (average 37 IU/dL) was found among our patients who had their factor levels checked during pregnancy (Fig. 2). However, this rise seems to be variable, unpredictable and inconsistent, and not all patients attain normal factor levels (i.e. > 50 IU/dL)<sup>9</sup>. Factor IX levels, in contrast, often do not rise in pregnancy<sup>9,10</sup> and this trend was also observed in our patients (Fig. 2). Affected male fetuses are potentially at risk of scalp haemorrhage from fetal scalp electrode application and fetal blood sampling but there is a lack of published data to support this. In our study these procedures were performed when fetal gender was unknown in some cases, including three affected male fetuses, without any apparent injury. In other cases these procedures were clinically indicated but not performed due to the lack of knowledge of fetal gender. The inconsistencies in the use of both fetal blood sampling and fetal scalp electrodes may well be attributed to imprecise instructions within obstetric notes or poor understanding of haemophilia by the attending obstetricians. Lack of prior knowledge of fetal gender also influenced the method of delivery resulting in unnecessary caesarean section (Table 1). In pregnancies where karyotyping has not been performed fetal gender can be assessed accurately by ultrasound in the mid-trimester<sup>12</sup>. Indeed, with the advances in transvaginal sonography this can be determined as early as the first trimester<sup>11</sup>. It may sometimes be difficult to visualise the fetal genital area due to fetal position and in these cases ultrasound examination should be repeated until positive diagnosis of the gender is made. Although some patients would not wish to know, this information should be available to the attending obstetrician to help intrapartum care.

Labour and delivery are critical periods for affected male haemophiliacs. They are at risk of serious scalp haemorrhage, including scalp abrasions, cephalohaematoma, subgaleal haematoma and intracranial haemorrhage, from the process of birth, invasive monitoring techniques or instrumental deliveries. The
incidence of intracranial haemorrhage in haemophilic newborn infants has been reported to be 1% to 4%\(^\text{13,14}\). This is more likely to occur in association with traumatic delivery\(^\text{15}\). Ljung et al.\(^\text{16}\) reviewed mode of delivery and perinatal bleeding in 117 infants with moderate or severe haemophilia. They concluded that the risk of serious bleeding in normal vaginal delivery is small and that delivery of all fetuses known to be at risk of haemophilia by caesarean section is not expected to eliminate the risk. However, the use of vacuum extraction was shown in the same study to constitute a significant risk factor as 10 of 12 infants with subgaleal cephalhaematoma were delivered by this instrument. Indeed, in our study the one affected male infant delivered by ventouse extraction developed a huge cephalhaematoma extending distally to the neck, necessitating blood transfusion and prolonged neonatal admission. The association of intracranial haemorrhage with traumatic deliveries was also reported by Kletzel et al.\(^\text{17}\) in three of four haemophilic infants with post-delivery head bleeding, with use of forceps in two and vacuum extraction in one. Therefore, fetuses at risk of haemophilia should be delivered by the least traumatic method. Prolonged labour, and especially prolonged second stage of labour, should be avoided and early recourse to caesarean section should be considered. Although vacuum extraction should not be used, low forceps delivery may be considered less traumatic than caesarean section when the head is deeply engaged in the pelvis and delivery can be achieved as an easy outlet procedure and performed by an experienced obstetrician. Mid cavity forceps and forceps involving the rotation of the head should not be used.

Epidural and spinal anaesthesia in the presence of a coagulation defect may cause an epidural haematoma if a blood vessel inside the spinal canal is punctured and may lead to permanent neurological damage\(^\text{18}\). However, it has been suggested that, provided the coagulation screen is normal in patients with haemostatic disorder, there is no contraindication to insertion of an epidural catheter\(^\text{19}\). In our unit regional block is used unless factor levels are below 50 IU/dL. In case of caesarean section, spinal block is regarded as a safer option because a smaller needle is used and is less likely to injure a blood vessel\(^\text{20}\).

Carriers of haemophilia have a significantly higher tendency to bruise, and also have prolonged bleeding from small wounds and post-operatively\(^\text{21}\). We have demonstrated an increased incidence of primary and secondary postpartum haemorrhage compared with the general obstetric population (22% versus 5%, and 11% versus 0.7%, respectively)\(^\text{22,23}\). Assessment by questionnaire of postpartum haemorrhage in carrier women reported an incidence of 22%\(^\text{21}\). Greer et al.\(^\text{9}\) also reported five postpartum haemorrhages and a large perineal haematoma in 43 pregnancies of carrier women. The tendency to bleed in carriers of haemophilia has been explained by the low plasma levels of factor VIII and IX. This was also observed in our study as most of the significant postpartum haemorrhage occurred in patients with pre-pregnancy factor levels below 50 IU/dL (Table 2).

DDAVP is a synthetic analogue of antidiuretic hormone. Administration results in an increase in factor VIII and Von Willebrand’s factor via V2 receptors\(^\text{24}\). There have been no controlled studies of the use of DDAVP during pregnancy and its safety and efficacy in obstetric practice has not yet been determined. Some haematologists and obstetricians recommend that DDAVP should be avoided during pregnancy. However, there have been several publications in the management of pregnant women with diabetes insipidus using DDAVP with no harm to the fetus. DDAVP is very specific to V2 receptors and has little effect on smooth muscle V1 receptors and consequently does not cause uterine contraction\(^\text{25}\). In the few patients we have treated immediately post-delivery the results have been very encouraging. DDAVP has no effect on factor IX levels and factor IX concentrates would be required to cover delivery in carriers of haemophilia B with low levels. High-purity factor IX concentrate should be used as, factor IX concentrate containing factors II, VII and X is potentially thrombogenic\(^\text{26,27}\). Plasma derived concentrates of coagulation factor VIII carry a small risk of transmitting hepatitis A and parvovirus B19\(^\text{28}\). The latter is of particular importance in pregnant women as it can cause severe fetal infection and hydrops fetales. Therefore, recombinant factor VIII should be used when administration of this factor is indicated.

Even in our obstetric unit where the help of the local haemophilia centre is easily available and carriers of haemophilia are more commonly encountered and managed by obstetricians there were many management inconsistencies. For most carriers of haemophilia prenatal diagnosis is performed at tertiary referral centres where the expertise to obtain chorionic villi or fetal blood is available and where prompt evaluation of the fetal haemophilia status can be quickly assessed. Consequently, after prenatal diagnosis the remainder of the pregnancy may well be managed at a different hospital where expertise in haemophilia is not present and thus management inconsistencies are more likely. This clearly shows the importance of a protocol of management, as well as the active involvement of a local haemophilia centre, for these patients. As a consequence of our and other investigators’ findings\(^\text{9}\) and the recommendations of the Haemostasis and Thrombosis Task Force\(^\text{29}\) we propose the following guidelines to aid consistent and appropriate management:

1. Pre-pregnancy counselling should be offered, to discuss prenatal diagnosis and other aspects of pregnancy management. Women who may require blood product therapy should be immunised against hepatitis B. When there is any doubt about a woman's carrier status, genetic testing with DNA probes should be offered.

2. There should be a multidisciplinary approach to the prenatal diagnosis involving experts in the fields of fetal medicine, genetic counselling, haemophilia care and molecular genetics.

3. For couples who do not wish to have prenatal diagnosis, we strongly recommend sexing by ultrasound at 18 weeks of gestation when anomaly scan is performed. The importance of this should be emphasised to the couple. If they do not wish to know the gender of the baby, this information should be available to the obstetrician in charge and written in the notes.

4. The pregnancy should be managed in close liaison with a local haemophilia centre. The mother's factor level should be checked at booking and at 28 and 34 weeks of gestation. This is especially important in patients with low pre-pregnancy levels (< 50 IU/dL) who would need prophylactic treatment for any invasive prenatal diagnostic procedures, spontaneous abortion, termination of pregnancy and during labour.

5. During labour maternal coagulation screen and appropriate factor assays should be checked. It may sometimes be difficult to assess factor levels in labour. In this situation, it is acceptable to rely on the third trimester factor levels to formulate plan of management. When the factor level is < 50 IU/dL, an intravenous line should be established and prophylactic treatment given. The risk of post-partum haemorrhage could be further reduced by minimising maternal genital and perineal trauma.

6. The use of invasive fetal monitoring techniques and instrumental deliveries, especially vacuum extraction, should be avoided in affected male fetuses or when fetal sex or coagulation status if male is unknown.

7. Providing the coagulation screen is normal in patients with an inherited bleeding disorder, there is no contraindication to epidural analgesia. In our department, regional block for labour or caesarean section is allowed when the factor level is ≥ 50 IU/dL.

8. A cord blood sample should be collected in a citrated tube and transferred to haemophilia laboratories within two hours. Results of clotting factors should be conveyed to the parents by the person most involved in counselling, usually a staff member from the Haemophilia Centre.

9. Intramuscular injections must be avoided in affected male infants or when coagulation status is not known. Vitamin K should be given orally, and routine immunisations should be given carefully intradermally or subcutaneously.

10. Parents should be given follow up counselling and haemophilic babies should be registered with, and reviewed regularly by, a haemophilia centre.

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References


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