Impact of the Induction of Labor on Hemophilia Carriers and Their Newborn Infants

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Abstract

Hemophilia is a risk for severe hemorrhage in newborns during the perinatal period and excessive postpartum hemorrhage (PPH) in hemophilia carriers. Vacuum extraction or use of forceps should be avoided to prevent neonatal intracranial hemorrhage (ICH). Optimal modes of delivery such as vaginal or cesarean section are open to debate. The safety of the induction of labor is also worthy of investigation. Here we ask if labor induction is a safe delivery mode for pregnant women who are hemophilia carriers and their infants. We looked at 13 deliveries by hemophilia carriers at our hospital from 2005 to 2018. Two of the five male neonates complicated by hemophilia suffered ICH complications (40%). Both were delivered by induced labor. No deliveries by carriers had PPH which required treatment. Our data indicate that the induction of labor may provoke ICH in infants with hemophilia. We suggest that induction of labor is not a preferable delivery method for hemophilia carriers to avoid neonatal ICH.

Keywords: Hemophilia carrier; Vaginal delivery; Cesarean section; Induced labor

Introduction

Hemophilia is a hereditary disease caused by reduced coagulation factor activity. Hemophilia A (HA) is caused by a deficiency of factor VIII (FVIII), and hemophilia B (HB) by factor IX (FIX) deficiency. Hemophilia is uncommon; the morbidity of HA is one in five thousand, and HB morbidity is one in thirty thousand. Both HA and HB follow X-linked recessive inheritance, 50% of males born to hemophilia carriers are affected. Hemophilia causes severe bleeding in newborns during the perinatal period, and excessive postpartum hemorrhages (PPH) in carriers.

In hemophilia cases, carrier diagnosis, sex determination of infants, and selection of delivery mode are critical factors. The British guidelines for perinatal management of hemophilia (2011) recommend avoiding vacuum extraction and forceps in delivery to prevent neonatal intracranial hemorrhage (ICH) [1]. The guidelines do not provide whether vaginal delivery (VD) or cesarean section (CS) is preferred. Upon delivery cord blood samples should be taken to measure clotting factor levels and the diagnosis of hemophilia [1-3]. Excessive bleeding necessitating administration of coagulation factors should be anticipated, and hemophilia-related deliveries require planning. Induction of labor (IOL) is often selected to assist in coordinating the obstetrics and neonatal staff.

Based on data from deliveries of hemophilia carriers at our hospital, we clarified the problems of perinatal management retrospectively, and evaluated the appropriate mode of delivery.

Case Report

Thirteen carriers of hemophilia, registered at the University of Occupational and Environmental Health, Japan, who had obstetric care at this hospital between 2005 and 2018 were investigated.

Patients were classified as either obligate or possible carriers. Obligate carriers were defined as all daughters of a father with hemophilia, mothers with one son with hemophilia and who have at least one other family member with hemophilia, or mothers with two or more sons with hemophilia. Possible carriers were defined as all daughters of a carrier, mothers with one son with hemophilia but who do not have any other family members with hemophilia, sisters, mothers, maternal grandmothers, aunts, nieces, and female cousins of carriers [4].

Fetal sexing was performed by ultrasound (US) examination. Planned VD cases were performed by IOL before natural labor pain, employing cervical balloon dilatation and uterine medications (oxytocin, prostaglandin E2).

We defined neonatal bleeding as that occurring within 28 days after birth except for subcutaneous hemorrhage. We also
investigated PPH and defined it as more than 500 mL bleeding in VD cases or more than 1,000 mL in CS cases within 24 h after parturition.

The mothers’ data of activated partial thromboplastin time (APTT) and coagulation factor activity were collected and adopted at the 34th - 36th weeks of pregnancy. The cord blood samples were taken to measure clotting factor levels and APTT.

Among the 13 cases, 10 were carriers of HA (76.9%), and three were carriers of HB (23.1%). There were four obligate carriers of HA (30.8%), six possible carriers of HA (46.1%), and three possible carriers of HB (23.1%). There was no sporadic case. All infants were correctly identified as male pre-delivery by US scan.

VD was performed in 10 cases (76.9%) and CS in three cases (23.1%). One VD case was breech presentation, all others were cephalic deliveries. All CS were planned to avoid neonatal ICH, and no delivery was performed during labor. No instrumental delivery was performed. Nine cases of the 10 VD cases (90%) included IOL (Table 1).

Two cases had PPH (15.3%). Both of them were VD but needed no treatment for bleeding (Table 2). Five neonates were diagnosed with hemophilia (38.5%). Two neonates exhibited ICH (15.4%). Both cases were born by IOL.

The first ICH case was scheduled for elective CS because of a pelvic presentation. However, the mother experienced a premature rupture of the membrane (PROM) and had strongly requested VD, which was performed by IOL with oxytocin. The male infant’s APTT was less than 100 s and his FVIII activity was less than 1%. HA was accordingly diagnosed. The infant’s color appeared pale and his hematocrit decreased at 7 days of age. We diagnosed ICH by head computerized tomography. In the second ICH case IOL with PGE2 and oxytocin required 2 days. The male infant had apnea at 4 days of age. HA and ICH were diagnosed similarly. Both cases had severe neurological sequelae.

### Discussion

Hemophilia is a risk for severe bleeding in newborns during the perinatal period. Critically, the mortality of ICH is high, as is the morbidity of long-term sequelae [5, 6]. Carrier diagnosis, sex determination of infants, and selection of delivery mode are important. Less invasive delivery modes should be selected and instrumental delivery such as the use of suction and forceps should be avoided [1]. However, it is not clear whether VD or CS is preferred. Some papers report that normal VD is safe [7, 8], while others propose CS for hemophilia carriers [9]. The optimal mode of delivery is open to some debate. One report suggests no significant difference in the risk of ICH in newborns between planned VD and planned CS among carriers of hemophilia [10], but no study evaluates the presence or absence of IOL, as far as we know.

In our study, two out of the five hemophilia male infants experienced ICH complications (40%), and both were delivered by IOL. The risk of neonatal ICH of hemophilia is high (3.5-4%), compared to full-term healthy neonates (0.04%) [11, 12]. The morbidity due to ICH in our study was much higher, and we suspect that the cause was IOL. The reason that we chose IOL for hemophilia carriers was to prepare for PPH and fetal complications. However, IOL tends to have a longer delivery time. One report describes the active phase of labor as longer when induced compared to spontaneous labors in nulliparous women [13]. IOL is also likely to induce a mechanical delivery and an emergency CS and induced nulliparous pregnancy may also have an increased risk of PPH and CS [14]. Therefore, we recommend not to choose IOL as the mode of delivery for hemophilia carriers, especially among nulliparous women.

In the first case of fetal ICH was performed IOL because...
the mother expected to have VD, though selective CS had been recommended due to a breech presentation. Infants delivered in vaginal breech had 6.7 times higher odds of ICH [15]. If they have hemophilia, further morbidity can be expected. In the second case IOL preceded VD without invasive treatment but required two days. Some papers report that IOL by oxytocin leads to oligodendrocyte cell death in neonatal mouse brain and anoxia in neonatal rat one [16, 17]. One study observed that IOL at term was associated with cerebral palsy and speculated that one of the causes was a decrease in oxygen supply due to excessive uterine contraction [18]. Encephalopathy and hypoxic encephalopathy caused by IOL may indirectly induce ICH. We suspect the prolonged delivery led to ICH. We suggest that spontaneous VD or elective CS were appropriate for a delivery in hemophilia. Even in spontaneous VD cases, switching to emergency CS must be judged early in order to avoid prolonged deliveries.

The mode of delivery in hemophilia carriers should be scheduled for early diagnosis of bleeding after the child is born, and medicating blood coagulation factor preparations if necessary. No serious PPH that required treatment occurred including both VD and CS cases in our study. One study observed that selective CS had less incidence of ICH than natural delivery [9]. In order to avoid complications in infants, the number of cases that choose selective CS is increasing. Therefore, for hemophilic neonates, we suggest that cesarean delivery is preferred to prevent ICH. If a mother wishes a VD, we recommend spontaneous delivery without the induction of labor.

Conclusions

We looked at thirteen deliveries of hemophilia carriers at our hospital from 2005 to 2018. Of the five male neonates diagnosed with hemophilia, two suffered complications of ICH (40%). Both were delivered by induced labor. These data indicate that IOL may provoke ICH in infants with hemophilia. We suggest that IOL is not preferable for pregnant women who are hemophilia carriers to avoid neonatal ICH. According to the literature and our data, selective CS or VD without IOL is safer delivery mode for newborn infants affected with hemophilia.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable because the manuscript has been sufficiently de-identified to protect the patient.

Author Contributions

M. Shibahara, T. Sakuragi, S. Amimoto, H. Mori and S. Aramaki treated the patients. M. Shibahara wrote the manuscript.

| Case no. | Comments | MOD | IOL | PPH (mL) | APTT(s) | Coagulation factor activity (%) |
|----------|----------|-----|-----|----------|---------|----------------------------------|
|          |          | M   | F   |          | M       | F       | M       | F       | M       |
| 1        | HA, obligate | HA, ICH | VD  | +  | 150 | 28.8 | 104.7 | 99 | < 1 |
| 2        | HB, possible | VD  | -  | 330 | 29.8 | 85 |
| 3        | HB, possible | VD  | +  | 546 | 28.2 |
| 4        | HB, possible | VD  | +  | 556 |
| 5        | HA, possible | VD  | +  | 223 | 28.6 | 48.6 | 66 |
| 6        | HA, possible | VD  | +  | 130 | 25.7 | 33.1 |
| 7        | HA, possible | HA  | VD  | +  | 342 | 36.5 | 128.3 | 67 | < 1 |
| 8        | HA, obligate | VD  | +  | 328 | 33.2 | 40.3 | 37 | 107 |
| 9        | HA, possible | HA, ICH | VD  | +  | 279 | 27 | 125.3 | 89 | < 1 |
| 10       | HA, possible | HA  | CS  | -  | 450 | 37.7 | 101.2 | 47 | < 1 |
| 11       | HA, possible | HA  | CS  | -  | 364 | 27.1 | 37.8 | 198 | 75 |
| 12       | HA, obligate | HA  | CS  | -  | 430 | 44.7 | 118.7 | 54 | < 1 |
| 13       | HA, obligate | CS  | -  | 900 | 30.7 | 54.1 | 90 | 52 |

MOD: mode of delivery; IOL: induction of labor; APTT: activated partial thromboplastin time; M: mother; F: fetus; HA: hemophilia A; HB: hemophilia B; VD: vaginal delivery; CS: cesarean section; ICH: intracranial hemorrhage; PPH: postpartum hemorrhages.
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**Data Availability**

The authors declare that data supporting the findings of this study are available within the article.

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