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Mode of delivery in hemophilia: vaginal delivery and Cesarean section carry similar risks for intracranial hemorrhages and other major bleeds

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ABSTRACT

The optimal mode of delivery for a pregnant hemophilia carrier is still a matter of debate. The aim of the study was to determine the incidence of intracranial hemorrhage and other major bleeds in neonates with moderate and severe hemophilia in relationship to mode of delivery and known family history. A total of 926 neonates, 786 with severe and 140 with moderate hemophilia were included in this PedNet multicenter study. Vaginal delivery was performed in 68.3% (n=633) and Cesarean section in 31.6% (n=293). Twenty intracranial hemorrhages (2.2%) and 44 other major bleeds (4.8%) occurred. Intracranial hemorrhages occurred in 2.4% of neonates following vaginal delivery compared to 1.7% after Cesarean section (P =not significant); other major bleeds occurred in 4.2% born by vaginal delivery and in 5.8% after Cesarean section (P =not significant). Further analysis of subgroups (n=813) identified vaginal delivery with instruments being a significant risk factor for both intracranial hemorrhages and major bleeds (Relative Risk: 4.78-7.39; P <0.01); no other significant differences were found between vaginal delivery without instruments, Cesarean section prior to and during labor. There was no significant difference in frequency for intracranial hemorrhages and major bleeds between a planned Cesarean section and a planned vaginal delivery. Children with a family history of hemophilia (n=466) were more likely to be born by Cesarean section (35.8% vs. 27.6%), but no difference in the rate of intracranial hemorrhages or major bleeds was found. In summary, vaginal delivery and Cesarean section carry similar risks of intracranial hemorrhages and major bleeds. The 'PedNet Registry' is registered at *clinicaltrials.gov* identifier: 02979119.

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Introduction

The optimal mode of delivery for a known hemophilia carrier, i.e. either vaginal delivery (VD) or Cesarean section (CS), is still a matter of debate. A carrier may have an increased bleeding risk herself that might need to be taken into account in the obstetric planning but, from the fetal point of view, the key question is how the mode of delivery may impact on the risk of major bleeds, and in particular intracranial hemorrhages (ICH). These life threatening bleeds can also impair the outcome in survivors due to serious neurological sequelae.^{1,2} Moreover, the require-

ment for intensive replacement therapy has been identified as a risk factor for inhibitor development in patients with hemophilia A.³

Several studies have been published with quite a uniform consensus that around 3-4% of boys with hemophilia born in countries with a good standard of obstetric care have had ICH diagnosed during the neonatal period.^{2,4-6} It has also been shown that instrumental delivery using forceps or vacuum extraction (VE) is a major risk factor for intra- and extracranial bleeds in neonates with hemophilia.^{5,7,8} However, figures for bleeds associated with uncomplicated VD and CS and, consequently, recommendations on mode of delivery vary between publications and guidelines.^{7,9-11} It is undisputed that the risk of a neonatal bleed in a child with hemophilia is considerably higher than that expected in a non-hemophilia population, although few figures are available. The largest series, among the few studies published on mode of delivery in the normal population, suggests an incidence of ICH of 1 per 1,900 in spontaneous VD, 1 per 2,750 in CS with no labor, 1 per 907 delivered by CS during labor, 1 per 860 deliveries with VE, and 1 per 664 delivered with the use of forceps.¹² Using these numbers as a reference, the risk for ICH in hemophilia boys is 60 times higher compared to healthy neonates born by VD.

Knowledge of carrier status in a pregnant woman, or the knowledge of confirmed hemophilia in the fetus following prenatal diagnosis (PND), may impact on obstetric care, especially when planning the mode of delivery. In recent cohorts, around 50% of all cases of hemophilia are sporadic, i.e. newly diagnosed boys without family history of hemophilia or without any knowledge of carrier status in the mother at birth.¹³ Many published studies on the delivery of a hemophilia child have not been able to distinguish between sporadic cases and cases with a known family history of hemophilia. Some studies include neonates with mild hemophilia and, furthermore, it is not always possible to distinguish between CS performed as a result of the baby having hemophilia or for other reasons, and this complicates comparisons between studies.

The PedNet Registry is a prospective, multicenter database that includes all children born since 1st January 2000 diagnosed with hemophilia A (HA) or B (HB) of all severities and treated in the 31 participating hemophilia centers in Europe, Canada and Israel.¹⁴ Baseline data regarding the neonatal period are collected on mode of delivery, neonatal events, family history of hemophilia, and gestational age. This longitudinal prospectively collected cohort study makes it possible to address questions of interest on obstetric and neonatal issues.

The aim of this paper was to study the frequency of ICH and other major bleeds in neonates with hemophilia and the association with mode of delivery to improve counseling of pregnant carriers in the future. Furthermore, the results will be stratified according to the presence or absence of a prior knowledge of hemophilia in the family.

Methods

Study group

Data were retrieved from the 'PedNet Registry' which is owned and administered by the 'PedNet Haemophilia Research Foundation', consisting of 31 international hemophilia treatment centers and registered at *clinicaltrials.gov* identifier: 02979119. The

purpose of the registry is to promote and facilitate research and healthcare development in children with hemophilia. The PedNet Registry includes all consecutive patients diagnosed and treated in each center born after 1st January 2000. The aim of the PedNet registry is to establish large well-documented birth cohorts of patients with hemophilia enabling studies on side effects and outcome of treatment. Patient data are collected from birth onwards prospectively and consist of all data concerning treatment, side effects and outcome of treatment. Information is collected on mode of delivery and during the first 75 exposure days of treatment with factor concentrate; all major bleeds including ICH are registered with detailed information. Approval for data collection was obtained from the institutional review boards of each of the 31 centers taking part in the study, and written informed consent was obtained from the parents or guardians of all participants in accordance with the Declaration of Helsinki. The data quality in the PedNet Registry is monitored regularly and independent audits are carried out in all participating centers.¹⁴

Study population

All children included in the Registry by 1st January 2015 with severe (factor VIII/IX activity, < 0.01 IU/mL) or moderate (factor VIII/IX activity, 0.01-0.05 IU/mL) HA and HB and with at least one follow up covering the neonatal period after the initial baseline report were enrolled. This resulted in 926 children born between 1st January 2000 and 1st January 2015 with data on mode of delivery and the neonatal period, defined as 28 days after birth. Prematurity was defined as up to 36 weeks of gestational age.

Data collection

We uniformly collected data on the mode of delivery (including vaginal, vaginal instrumental, CS), and major bleeds including ICH in the neonatal period. Data were also recorded on whether an affected newborn belonged to a family with a known history of hemophilia or was a sporadic case.

Statistical analysis

The primary outcome was ICH and major bleeds, the latter defined as a bleed requiring treatment with factor concentrate and not resolving within 24 hours during the neonatal period. The determinants of outcome were mode of delivery and family history of hemophilia, either known or unknown. Statistical comparisons between different groups were made using χ^2 test or Fisher's exact test at a significance level of 0.05. In the comparison of four subgroups on mode of delivery, an overall test was performed to compare the frequencies between all groups simultaneously. If an overall test was significant, it was followed by pairwise comparisons between the groups. The results of the pairwise comparisons were corrected for multiple testing by Bonferroni correction. Statistical power was shown by the width and magnitude of the 95% Confidence Interval (95%CI) according to the CONSORT guidelines. All analyses were performed using IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp., NY, USA, or R: A language and environment for statistical Computing, version 3.4.2. Vienna, Austria, R Foundation for Statistical Computing.

Results

Cohort demography

A total of 926 patients were included, 140 with moderate and 786 with severe hemophilia comprising those with HA [$n = 803$ (86.7%)], and HB [$n=123$ (13.3%)]. MOD in the 926 patients was vaginal in 633 (68.4%) and

CS in 293 (31.6%). Sixty-two (6.7%) of the included patients were preterm. For more detailed information on cohort demographics see Table 1.

Intracranial hemorrhages and major bleeds

Twenty ICH (2.2%) and 44 other major bleeds (4.8%) were recorded in the 926 children. The majority of major bleeds were soft tissue bleeds (n=14), followed by muscle bleeds (n=7) and mucous membrane bleeds (n=3). One patient each suffered from a shoulder bleed, subgaleal bleed, scalp bleed, cephalohematoma, hematemesis, and a hepatic bleed; in 14 patients the bleeds were not further defined. No significant difference was observed in the frequency of bleeds when comparing HA to HB or moderate to severe hemophilia.

In the whole cohort, major bleeds occurred at a frequency of 4.3% (27 of 633) after all vaginal deliveries and 5.8% (17 of 293) after CS ($P=0.32$). The frequencies of ICH after all vaginal deliveries was 2.4% (15 of 633), compared to 1.7% after CS (5 of 293), with no significance ($P=0.631$).

Term and preterm neonates

Data on gestational age was available in 849 of 926 neonates. When comparing major bleeds in term and preterm deliveries, major bleeds occurred in 5.2% (41 of 787) of term and in 6.4% (3 of 62) of preterm babies with no significant statistical difference between the groups ($P=1.0$). The frequency of ICH in the term delivery group was 2.5% (20 of 787) and no cases of ICH was reported in the preterm delivery group (n=62). In the preterm group, neonates were born at a median of 35 gestational weeks (range 26-36 weeks) and only 11 of 62 (17.7%) neonates were very or extremely preterm (born before the 33rd gestational week). Unfortunately, in 77 cases, gestation at delivery was not recorded, but no major bleeds were reported in this group (Table 2). Because there was no difference between the groups based on gestational age, all further analysis was carried out on the whole cohort.

Mode of delivery

In 813 of 926 patients, more information about the mode of delivery was available and further subgroups could be defined: non-instrumental vaginal delivery (n=541), vaginal with instruments, e.g. forceps or vacuum extraction (n=68), CS prior to labor (n=125), and CS during labor (n=79). The frequencies for ICH were 1.5% (8 of 541) for non-instrumental vaginal delivery, 10.2% (7 of 68) for instrumental vaginal delivery, 1.6% (2 of 125) CS prior to labor, and 2.5% (2 of 79) during labor. Regarding major bleeds, the frequencies showed 2.6% (14 of 541) for non-instrumental vaginal delivery, 19.1% (13 of 68) for instrumental vaginal delivery, 4.0% (5 of 125) CS prior to labor, and 8.9% (7 of 79) for CS during labor. The results identify vaginal instrumental delivery as a significant risk factor in comparison to vaginal delivery without instruments and CS prior to labor for both major bleeds and ICH: the Relative Risk (RR) for ICH was 6.96 (95%CI: 2.61-18.6; $P=0.0005$) and the RR for major bleeds was 7.39 (95%CI: 3.63-15.05; $P<0.0001$) for comparison with vaginal delivery without instruments; compared to CS prior to labor the RR was 6.43 (95%CI: 1.37-30.12; $P=0.010$) for ICH and 4.78 (95%CI: 1.78-12.84; $P=0.0012$) for major bleeds. Regarding major bleeds only at a significance level of $P<0.05$, vaginal delivery without instruments was significantly safer than CS during labor ($P=0.011$; RR 3.42, 95%CI: 1.43, 8.22) but no difference for ICH could be seen ($P=0.37$). All other groups showed no significances in comparison; there was no significant difference in the rate of ICH or major bleeds when comparing instrumental vaginal delivery with CS during labor. For more details see Tables 3 and 4.

A subanalysis of moderate *versus* severe hemophilia was made showing similar results regarding ICH: 2.14% (3 of 140) ICH for moderate and 2.16% (17 of 786) for severe hemophilia without statistical significance. However, major bleeds were significantly more often reported in severe hemophilia 5.5% (43 of 786) than in moderate

Table 1. Basic characteristics of study group.

	n (%)
Type and severity of hemophilia	
Moderate hemophilia A	110 (11.9)
Severe hemophilia A	693 (74.8)
Moderate hemophilia B	30 (3.2)
Severe hemophilia B	93 (10.0)
Family history of hemophilia	
No known family history	445 (48.1)
Known family history	466 (50.3)
No data on family history	15 (1.6)
Mode of delivery	
Vaginal delivery	633 (68.4)
Cesarean section	293 (31.6)
Gestational age	
Born term	787 (85.0)
Born preterm	62 (6.7)
No data term/preterm	77 (8.3)
Total	926

Table 2. Major bleed and intracranial hemorrhage (ICH) in term or preterm delivery in the first 28 days.

	All	Major bleed n (%)	ICH n (%)
Term	787	41 (5.2)	20 (2.5)
Preterm	62	3 (6.4)	0 (0)
Missing data term/preterm	77	0 (0)	0 (0)
Total	926	44	20

Table 3. Intracranial hemorrhage (ICH) and major bleeds and mode of delivery.

	All n	ICH n (%)	Major bleeds n (%)
Vaginal delivery without instruments	541	8 (1.5)	14 (2.6)
Vaginal instrumental	68	7 (10.2)	13 (19.1)
Cesarean prior to labor	125	2 (1.6)	5 (4.0)
Cesarean during labor	79	2 (2.5)	7 (8.9)
No detailed information on MOD	113	1 (0.8)	5 (4.4)
Total	926	20	44

MOD: mode of delivery.

hemophilia 0.7% (1 of 140) ($P=0.009$) where only one major bleed in the neonatal period was reported.

The analysis of major bleeds in severe hemophilia only showed the same significant results regarding vaginal instrumental delivery as a risk factor compared to vaginal delivery without instruments ($P<0.0001$; RR 7.28) and CS prior to labor ($P=0.0004$; RR 6.05) (Table 3); therefore, these groups were kept together in the further analysis.

Family history of hemophilia

In 466 neonates there was a known family history of hemophilia. In 445 cases, no family history of hemophilia was known; these patients represent sporadic cases where no influence on mode of delivery could be made. The rate of CS differed significantly between the groups ($P=0.009$): 35.8% (167 of 466) in the group with known family history were born by CS and 27.6% (123 of 445) of the sporadic cases (Table 5). The reason for planned CS in the group of known family history was hemophilia carrier status and/or known hemophilia status of the child in 45.2% (38 of 84 cases), in 14.3% (12 of 84 cases) due to a combination of hemophilia status and maternal/fetal issues, and in 29.8% not related to hemophilia ($n=16$ cases, maternal; $n=9$ cases, fetal). The reasons recorded for a planned CS in the group with no known family history of hemophilia ($n=49$) were maternal reasons in 65.3% ($n=32$), fetal reasons in 24.5% ($n=12$), combined reasons in 4.1% ($n=2$), and Other in 6.1% ($n=3$). Vaginal instrumental deliveries occurred less often when a family history was known (18 of 466) than in the group with no known family history (48 of 445) ($P=0.00038$).

However, there was no significant difference in the frequency of major bleeds and ICH between the group with known family history (KFH) and the group with no known family history (NFH) ($P=0.87$ and $P=0.37$, respectively). In the KFH group, we found an overall frequency of 4.7% (22 of 466) for major bleeds and 1.7% (8 of 466) for ICH. In comparison, in NFH the frequency was of 4.5% (20 of 445) for major bleeds and 2.7% (12 of 445) for ICH. For more detailed information see Table 5.

Prenatal diagnosis

Prenatal diagnosis was performed in 13.7% (62 of 466) of the children with a known family history of hemophil-

ia. In this group, the rate of CS was significantly higher (32 of 62; 51.6% vs. 135 of 404, 33.4%) than in the group with known family history and no PND ($P=0.0068$).

Mortality

One child with no known family history died after CS in labor due to ICH in the neonatal period. The patient was diagnosed with ICH at six days of age and the diagnosis of hemophilia A was made on the same day; this child was included in the analysis.

No other deaths related to major bleeds or ICH were reported.

Counseling of a pregnant carrier of hemophilia

In counseling a pregnant carrier, the decision to be taken is between a planned CS (in most cases prior to labor) compared to planned vaginal delivery which can result in vaginal delivery with or without instruments or CS during labor. Patients with planned vaginal delivery ($n=703$) had a non-instrumental vaginal delivery in 77% (541 of 703), an instrumental delivery in 9.7% (68 of 703), and a CS during labor in 9.9% (70 of 703); in 24 patients it was unknown if the vaginal delivery was with or without instruments (3.4%). Patients with planned CS ($n=134$) had a CS prior to labor in 93.2% (125 of 134) and in 9 patients the CS was performed in labor (6.8%) (Table 6). We compared planned CS ($n=134$) to planned vaginal delivery ($n=703$) for the whole cohort, and no significant difference could be seen for both ICH ($P=0.75$) and major bleeds ($P=0.82$). The frequencies for ICH were 1.5% (2 of 134) for planned CS and 2.4% (17 of 703) for planned vaginal delivery. Frequencies for major bleeds were 3.7% (5 of 134) for planned CS and 4.8% (34 of 703) for planned vaginal delivery. (See Table 6 for an overview.) We also compared the subgroup of patients with known family history of hemophilia and compared the number of major bleeds and ICH in planned CS ($n=84$) and planned vaginal delivery ($n=327$); even here, there was no significant difference ($P=0.777$ for major bleeds, $P=1$ for ICH).

Discussion

In this multicenter study, no statistical difference was

Table 4. Pairwise comparisons between groups on mode of delivery.

Reference group	Comparison group	ICH P-value; RR (95%CI)	Major bleeding P-value; RR (95%CI)/severe hemophilia only
Vaginal delivery without instruments	Vaginal instrumental	**0.0005; 6.96 (2.61,18.60)	**<0.0001; 7.39 (3.63,15.05)/ **<0.0001; 7.28 (3.60,14.72)
Vaginal delivery without instruments	Cesarian prior to labor	1.0000; 1.08 (0.23,5.03)	0.3758; 1.55 (0.57,4.21)/ 0.3408; 1.20 (0.4,3.58)
Vaginal delivery without instruments	Cesarian during labor	0.3709; 1.71 (0.37,7.92)	*0.0110; 3.42 (1.43,8.22)/ *0.0209; 3.20 (1.34; 7.66)
Cesarian prior to labor	Vaginal instrumental	*0.0100; 6.43 (1.37,30.12)	**0.0012; 4.78(1.78,12.84)/ **0.0004; 6.05 (2.07, 17.72)
Cesarian during labor	Vaginal instrumental	0.0814; 4.07 (0.87,18.92)	0.0918; 2.16 (0.91,5.10)/ 0.1263; 2.27 (0.97, 5.32)
Cesarian prior to labor	Cesarian during labor	0.6417; 1.58 (0.23,11.01)	0.2207; 2.22 (0.73,6.74)/ 0.09396; 2.66 (0.81, 8.76)

ICH: intracranial hemorrhage; RR: relative risk; CI: Confidence Interval. *Significant at significance level $P<0.05$; *significant after Bonferroni correction $P<0.0083$.

Table 5. Known and unknown family history of hemophilia.

	All	Known family history of hemophilia	Unknown family history of hemophilia	Family history not known
	n	n (%)	n (%)	n
ICH	20	8 (1.7)	12 (2.7)	0
Major bleeds	44	22 (4.7)	20 (4.5)	2
Vaginal delivery	633	299 (64.2)	322 (72.4)	12
VD without instruments	541	285	274	5
VD instrumental	68	14	48	6
Not known with/without instruments	24	13	10	1
Cesarean section	293	167 (35.8)*	123 (27.6)	3
Planned CS	134	84	49	1
Reason:				
Hemophilia		37	–	0
Combined hemophilia and maternal or fetal status		12	–	0
Maternal		16	32	1
Fetal		9	12	0
Combined maternal/fetal		0	2	0
Other/unknown		9/1	3/0	0
Total number	926	466	445	15

*Significant at $P < 0.05$ in comparison to unknown family history of hemophilia. n: number; ICH: intracranial hemorrhage; VD: vaginal delivery; CS: Cesarean section.

found in the rate of major bleeds and intracranial hemorrhage in neonates with moderate and severe hemophilia between vaginal delivery and Cesarean section: major bleeds occurred in 4.3% neonates born by VD and in 5.8% after CS (P =not significant, ns); ICH in 2.4% following VD and 1.7% after CS (P =not significant, ns). Further analysis of subgroups by MOD (VD with and without instruments, CS prior to and during labor) revealed instrumental VD as a risk factor for major bleeds and intracranial hemorrhage compared to non-instrumental VD (RR 7.39 major bleed; 6.96 ICH) and CS prior to labor. Neonates with moderate hemophilia had a similar risk regarding ICH compared to severe hemophilia, but a lower risk for other major bleeds. No other significant differences were found between the subgroups of vaginal delivery without instruments, CS prior and CS during labor. The CS rate was higher in neonates with a known family history and reason was hemophilia in more than half of the cases. However, no significant difference was found between the group with and without a known family history of hemophilia regarding major bleeds and ICH. The comparison of planned CS (including CS prior to labor in 93.2% but also including some cases during labor) to planned VD (including VD without instruments in 77% and also instrumental VD and CS during labor) also showed no significant difference in the group with known family history.

To our knowledge, this study represents the largest prospective, monitored series recording comprehensive data on mode of delivery and neonatal bleeds in patients with moderate and severe hemophilia. The data come from countries with a good and quite uniform standard of health care which should make the results relevant and applicable for these countries, although the results may also be applicable to countries with different health care standards. Due to the inclusion of all consecutive cases in the participating centers, selection bias should be low but cannot be totally excluded. Missing data is a problem for

most registries. Earlier publications of the PedNet registry show high quality data regarding baseline data and first 75 exposure days including bleeds, with only 4% missing data.¹⁴ The subanalysis on detailed information on mode of delivery (vaginal with instruments, CS prior to or during labor, reason for CS) was available in 813 of 926 (87.8%) patients, which means that in 12.2% of included patients these data are missing, which is still acceptable for analysis. However, the frequencies for both major bleeds and ICH are low, and small differences between the groups analyzed cannot be detected due to the limited number of included patients. For example, to show a difference between ICH in vaginal delivery of 2.4% to CS of 1.7%, over 12,000 patients would have to be included, which is not feasible. We excluded mild hemophilia from our analysis since the diagnosis in these patients is often made at an older age and undiagnosed cases born during the study period have not yet been included in the PedNet Registry.¹⁵

Both term and preterm neonates were included in the calculations and one could question if data should have been presented separately since ICH is a well-known complication of, in particular, delivery of an extremely premature neonate.¹⁶ Our series included 849 children with data on gestational week of birth, of whom 62 (7.3%) were born prematurely, but only 11 children (1.3%) were born before the 33rd gestational week, i.e. very or extremely premature. There were three major bleeds in the premature group (5.2%) and no cases of ICH. In term births, 41 major bleeds in 787 neonates (6.4%) occurred, and 20 ICH (20 of 787; 2.5%). Since there was no significant difference in the frequency of bleeds between the term and preterm groups we considered it justified to merge them together in the calculations. The premature group was still a rather small group, and a much larger group would be needed in order to draw any conclusions between the more extremely premature and less premature on this issue. In another neonatal series,

Richards *et al.*,⁸ with an overall head bleed rate of 3.5% and some data on prematurity (29 premature children; 6.0% in the series), had the same issue. It is, however, possible that extreme prematurity is under-represented in the registry due to mortality before diagnosis.

The frequency of major bleeds and ICH for all neonates was similar to previous studies.^{9,17,18} When splitting the group into instrumental VD and non-instrumental VD, and CS prior to and during labor, only instrumental VD was identified as a risk factor. A recent study from the UK on ICH in bleeding disorders had similar findings and identified instrumental delivery as a clear risk factor with a RR of 10.6.¹⁹ This is also known from the normal population, but in lower frequencies: Towner *et al.* reported ICH frequencies of 1 of 860 for VE and 1 of 664 for forceps and VE, which means that the risk for ICH in hemophilic neonates born by instrumental delivery is roughly 80-fold higher in our series.¹² In a recent published meta-analysis from Davies and Kadir, CS was proposed as a safer option for children born with hemophilia, but the comparison was made with historical cohorts.⁷ In our prospective cohort, there was no difference in incidence of major bleeds and ICH in neonates born by vaginal delivery (both instrumental and non-instrumental) compared to CS (prior to and during labor): 5.2% *versus* 6.4% in major bleeds, and 2.3% *versus* 1.7% for ICH. A planned CS with the intention to perform CS prior to labor did not prevent neonates from experiencing ICH or major bleeds in comparison to planned VD. This information is important when counseling a pregnant carrier. It has also been shown in other studies that CS does not prevent neonatal bleeds.^{4,8,9} Studies from the normal population with 583,340 births included show that vaginal delivery without instruments and CS prior to labor were the safest option but ICH still occurred (1 of 2,750 CS prior to labor, and 1 of 1,900 delivered spontaneously).¹²

A known family history of hemophilia (KFH) had some influence on the mode of delivery: 36% (167 of 466) were delivered by CS in the KFH group compared to 28% (123 of 445) in the no known family history group (NFH) ($P=0.00038$). The group of neonates in the NFH group present the 'true risk' of neonatal bleeds in a child with hemophilia, since no precautionary measures had been taken with respect to hemophilia on the obstetric procedures. However, there was no significant difference in the rate of major bleeds and ICH between KFH and NFH. Regarding vaginal delivery, 4.5% of the children in the NFH group compared to 4.7% in the KFH had a major bleed and 2.7% had ICH in the NFH-group compared to 1.7% in the KFH-group. This may be explained by our findings, that the mode of delivery (CS *vs.* vaginal delivery) did not impact the rate of major bleeds and ICH. Similar findings were shown in a recent study of Kulkarni *et al.* in which 547 neonates with all severities of hemophilia were included.²⁰ The reason to choose a planned CS was hemophilia in 45%; but in 55%, other maternal and fetal reasons played a role illustrating that the planning of a delivery is a complicated and multifactorial task.

Prenatal diagnosis was performed in 14% (62 of 466) of known carriers, and in these cases it was definitely known that they were carrying a child with hemophilia. In this subgroup, 51.6% were delivered by CS, demonstrating a statistically significant impact on the decision to choose a CS delivery. We do not have data on how many carriers terminated pregnancy after PND with an affected fetus, so

Table 6. Planned vaginal delivery versus planned Cesarean section – major bleeds and intracranial hemorrhage (ICH).

	n	ICH n (%)	Major bleeds n (%)
Planned VD	703	17 (2.4)	34 (4.8)
VD without instruments	541	10	18
VD instrumental	68	7	13
CS during labor	70	0	3
VD not known with or without instruments	24	0	0
Planned CS	134	2 (1.5)	5 (3.7)
CS prior to labor	125	2	5
CS during labor	9	0	0
Planning not known	89	1	5
<i>P</i> -value; RR (CI)		0.753; 1.62 (0.38,6.93)	0.822; 1.30 (0.52,3.25)

VD: vaginal delivery; CS: Cesarean section; RR: relative risk.

the numbers on PND might be underestimated. However, recent figures from Sweden indicate that carriers today often choose PND in order to prepare for having a hemophilia child and not for termination of the pregnancy; but this may not be the case in all participating centers.²¹

One child died from ICH, representing 1 of 786 boys with severe hemophilia (0.13%), and 1 of 20 of all ICH (5%). These numbers are low compared to historical data, but they are in line with a recent CDC report that included all ICH with a mortality rate of around 2.5%.²² These numbers may be underestimated due to undiagnosed or unreported cases.

It would have been of interest to analyze the risks and outcomes for the carrier mothers who gave birth to a child with hemophilia according to delivery mode, but our registry is limited to pediatric data.

In summary, vaginal delivery and Cesarean section carry similar risks of ICH and major bleeds in neonates with severe and moderate hemophilia, and pregnant carriers of hemophilia should be informed about different options for mode of delivery and their potential risks.

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