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 PedN et 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: 02979449.
Management for intensive replacement therapy has been identified as a risk factor for inhibitor development in patients with hemophilia.\(^\text{3,4}\) 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.\(^\text{3,5}\) 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.\(^\text{3,6-8}\) However, figures for bleeds associated with uncomplicated VD and CS and, consequently, recommendations on mode of delivery vary between publications and guidelines.\(^\text{3,9-11}\) 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 VB, and 1 per 664 delivered with the use of forceps.\(^\text{12}\) 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.\(^\text{13}\) 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 1\(^{st}\) 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.\(^\text{14}\) 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 1\(^{st}\) 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.\(^\text{14}\)

**Study population**

All children included in the Registry by 1\(^{st}\) 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 1\(^{st}\) January 2000 and 1\(^{st}\) 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 \(\chi^2\) 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. Amonk, 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 635 (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=0.52). 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=0.651).

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% (8 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 in 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 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: 3.68-15.05; P<0.0001) for comparison with vaginal delivery without instruments; compared to CS prior to labor the RR was 6.43 (95% CI: 1.57-30.12; 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

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### Table 1. Basic characteristics of study group.

| Type and severity of hemophilia | n (%) |
|---------------------------------|-------|
| Moderate hemophilia A           | 110 (11.9) |
| Severe hemophilia A             | 683 (74.8) |
| Moderate hemophilia B           | 30 (3.2) |
| Severe hemophilia B             | 93 (10.0) |

| Family history of hemophilia    | n (%) |
|---------------------------------|-------|
| No known family history         | 445 (48.1) |
| Known family history            | 466 (50.3) |
| No data on family history       | 15 (1.6) |

| Mode of delivery                | n (%) |
|---------------------------------|-------|
| Vaginal delivery                | 633 (68.4) |
| Cesarean section                | 283 (31.6) |

| Gestational age                 | n (%) |
|---------------------------------|-------|
| Born term                       | 787 (85.0) |
| Born preterm                    | 62 (6.7) |
| No data term/preterm            | 77 (8.3) |

### 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)     |

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

|                      | All | ICH n (%) | Major bleeds n (%) |
|----------------------|-----|-----------|--------------------|
| Vaginal delivery     | 541 | 8 (1.5)   | 14 (2.5)           |
| Cesarean section     | 283 | 0 (0)     | 0 (0)              |

### Table 4. Intracranial hemorrhage (ICH) and mode of delivery.

|                      | All | ICH n (%) | Major bleeds n (%) |
|----------------------|-----|-----------|--------------------|
| 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)            |

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 (KHF) and the group with no known family history (NFH) (P=0.87 and P=0.37, respectively). In the KHF 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 hemophilia. 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

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**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)/** 0.37, respec-   |
| 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 (0.42,3.58) |
| 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 (1.84,6.66) |
| 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 (0.87,19.82)   | 0.0916; 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)/0.0938; 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.
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 VA and in 5.8% after CS (P=not significant, ns); ICH in 2.4% following VA and 1.7% after CS (P=not significant, ns). Further analysis of subgroups by MOD (VA with and without instruments, CS prior to and during labor) revealed instrumental VA as a risk factor for major bleeds and intracranial hemorrhage compared to non-instrumental VA (RR 7.89 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 to and 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 VA (including VA without instruments in 77% and also instrumental VA 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,

### Table 5. Known and unknown family history of hemophilia.

| Known family history of hemophilia | Unknown family history of hemophilia | Family history not known |
|-----------------------------------|-------------------------------------|--------------------------|
| n                   | 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 (46.2)               | 322 (72.4)                | 12 |
| VA without instruments| 541                              | 285                      | 274                      | 5 |
| VA instrumental      | 68                                 | 14                       | 48                       | 6 |
| Not known with/instruments| 24                            | 13                       | 10                       | 1 |
| Cesarean section     | 293                                | 167 (55.5)*              | 123 (27.6)                | 3 |
| Planned CS           | 134                                | 84                       | 49                       | 1 |
| Reason:              |                                    |                          |                          |    |
| Hemophilia           |                                    |                          |                          |    |
| Combined hemophilia and maternal | 37                      | 12                       | 0                       |    |
| or fetal status      |                                    |                          |                          |    |
| Material             |                                    |                          |                          |    |
| Fetal                |                                    |                          |                          |    |
| Combined maternal/fetal| 16                  | 32                       | 1                       |    |
| 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; VA: vaginal delivery; CS: Cesarean section.
Richards et al., 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. When splitting the group into instrumental 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. 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. In a recent published meta-analysis (0.38,6.93) that included all ICH with a mortality rate of around 2.5%. 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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### Appendix
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**Table 6. Planned vaginal delivery versus planned Cesarean section – major bleeds and intracranial hemorrhage (ICH).**

| Mode of Delivery | n (%) | ICH (%) | Major bleeds (%) |
|------------------|-------|---------|------------------|
| Planned VD       | 703   | 17 (2.4)| 34 (4.8)         |
| VD without instruments | 541 | 10 (1.9) | 18               |
| VD instrumental  | 68    | 7 (1.1) | 13               |
| CS during labor  | 70    | 0 (0.0) | 3                |
| **VD not known with or without instruments** | 24 | 0 (0.0) | 0                |
| Planned CS       | 134   | 2 (1.5) | 5 (3.7)          |
| CS prior to labor| 125   | 2 (1.6) | 5                |
| CS during labor  | 9     | 0 (0.0) | 0                |
| Planning not known | 89 | 1 (1.1) | 5                |

*P*-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.
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