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Ante-, peri- and postnatal factors associated with intraventricular hemorrhage in very premature infants

Martin Poryo[a,*], Judith Caroline Boeckh[b], Ludwig Gortner[c], Michael Zemlin[c], Perrine Duppré[d], Daniel Ebrahimi-Fakhari[d], Stefan Wagenpfeil[e], Matthias Heckmann[f], Eva Mildenberger[g], Anne Hilgendorff[h,1], Andreas W. Flemmer[h,1], Georg Frey[i], Sascha Meyer[c,j], On behalf of the PROGRESS study consortium and NGFN - Nationales Genomforschungsnetz Deutschland

[a] Department of Pediatric Cardiology, Saarland University Medical Center, Homburg/Saar, Germany
[b] Department of Internal Medicine, Katharinenhospital Klinikum Stuttgart, Stuttgart, Germany
[c] Department of Pediatrics and Neonatology, Saarland University Medical Center, Homburg/Saar, Germany
[d] University of Saarland, Medical School, Homburg/Saar, Germany
[e] Institute for Medical Biometry, Epidemiology and Medical Informatics, Saarland University, Campus Homburg/Saar, Germany
[f] Department of Neonatology and Pediatric Intensive Care, University Medicine Greifswald, Germany
[g] Department of Neonatology, University Medical Center, Johannes Gutenberg University Mainz, Germany
[h] Department of Neonatology, University Medical Center, Ludwig-Maximilian-University Munich, Germany
[i] Department of Pediatric Cardiology and Neonatology, Darmstaedter Kinderkliniken Prinzessin Margaret, Darmstadt, Germany
[j] Department of Pediatric Neurology, Saarland University Medical Center, Homburg/Saar, Germany

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ABSTRACT

Background: Intraventricular hemorrhage (IVH) is one of the most serious complications in preterm infants and is associated with neurological sequelae and mortality. Over the past few decades, the rate of IVH has decreased due to improved neonatal intensive care. However, up to 15–25% of very and extremely premature infants (< 32 and < 28 weeks of pregnancy (WOP) respectively) still suffer from IVH.

Study purpose.

The aim of this study was to perform an updated, multicenter analysis to identify ante-, peri, and postnatal factors other than gestational age/birth weight associated with IVH of any grade in a large cohort of very and extremely premature infants.

Methods: We performed a retrospective analysis in a prospectively conducted multicenter cohort study between 01/01/1998–31/12/2012 at 5 level 3 perinatal centers. All relevant ante-, peri- and neonatal data were collected and univariate as well as multivariate logistic regression analysis was performed.

Results: 765 inborn infants with a gestational age < 32 WOP were enrolled into this study (369 (48.2%) female; 396 (51.8%) male). Birth weight ranged from 315 g to 2200 g (mean 1149.7 g, SD 371.9 g); 279 (36.5%) were born ≤ 27 + 6 WOP and 486 (63.5%) ≥ 28 + 0 WOP. IVH was seen in 177 (23.1%) patients.

Multivariate analysis revealed that in addition to higher gestational age (OR 0.7, CI [0.6–0.8]), antenatal steroid treatment (OR 0.3, CI [0.2–0.6]) and caesarian section without uterine contraction (OR 0.6, CI [0.4–0.9]) were associated with a lower rate of IVH while RDS (OR 5.6, CI [1.3–24.2]), pneumothorax (OR 2.8, CI [1.4–5.5]) and use of catecholamines (OR 2.7, CI [1.7–4.5]) were associated with an increased risk of IVH. After exclusion of gestational age and birth weight from multivariate analysis, early onset sepsis (OR 1.6, CI [1.01–2.7]) and patent ductus arteriosus (OR 1.9, CI [1.1–3.1]) were associated with a higher rate of IVH. In addition, univariate analysis revealed that Apgar scores at 5 min ($p < 0.001$), BDP/ROP/NEC (p < 0.001),

Abbreviations: AIS, amniotic infection syndrome; ANS, antenatal steroids; BPD, bronchopulmonary dysplasia; CBF, cerebral blood flow; CI, confidence interval; CRIB score, critical risk index for babies score; CPAP, continuous positive airway pressure; CRP, C-reactive protein; CUSS, cranial ultrasonography scans; EOS, early onset sepsis; ELBW infants, extremely low birth weight infants; ELGAN, extremely low gestational age neonates; GA, gestational age; g, grams; IVH, intraventricular hemorrhage; LBW infants, low birth weight infants; UA-pH, umbilical arterial pH; NGFN, Nationales Genomforschungsnetz Deutschland; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; iNO, inhalative nitric oxide; PDA, patent ductus arteriosus; pPROM, preterm premature rupture of membranes; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SD, standard deviation; US, ultrasound; VLBW infants, very low birth weight infants; VLGAN, very low gestational age neonates; WOP, weeks of pregnancy

* Corresponding author at: Department of Pediatric Cardiology, Saarland University Medical Center, Kirrberger Straße, 66421 Homburg/Saar, Germany.
E-mail address: martin.poryo@uks.eu (M. Poryo).

[1] Member of the German Center for Lung Diseases (DZL), Germany.

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mechanical ventilation ($p < 0.001$) and inhalative nitric oxide ($p < 0.001$) were significantly associated with IVH.

Conclusions: Our comprehensive analysis demonstrated that the occurrence of IVH in very premature infants is significantly associated with ante-, peri- and postnatal factors being either related to the degree of immaturity or indicating a critical clinical course after birth. The analysis reiterates the necessity for a very close cooperation between obstetricians and neonatologists to reduce the incidence of IVH in this susceptible cohort.

1. Introduction

Intraventricular hemorrhage (IVH) in preterm neonates is one of the most serious complications seen in this high risk patient cohort, and it is associated with significant long-term morbidity and mortality. The etiology for IVH is thought to be multifactorial [1] and related to both ante- and post-natal factors including altered hemostasis [2].

One of the main reasons for morbidity and mortality in very low and extremely low gestational age neonates (< 32 weeks of pregnancy (WOP) = VLGAN; < 28 WOP = ELGAN) is the occurrence of intraventricular hemorrhage (IVH) [3–6]. A significant decline of the incidence of IVH could be seen in the 1980–1990s [5] when routine implementation of antenatal steroids (ANS) increased. Nowadays the rate of IVH is estimated at around 15–25% in VLGAN [5,7,8].

A number of ante-, peri-, and postnatal factors have been linked to the occurrence of IVH [7,9–13]. Pharmacologic prevention trials have been conducted [14] because of the importance of IVH for long-term prognosis, but so far they delivered unconvincing and conflicting data with regard to the effective reduction of IVH.

Moreover, other studies examined the importance of coagulopathy and their potential treatment on the development and severity of IVH [2,15]. The lowest activities of many coagulation factors were seen in extremely low birth weight infants (ELBW) infants, but results from these studies are conflicting. Nevertheless, recommendations with regard to the use of platelets and humoral clotting factors in this susceptible cohort have been published [16–20].

Of note, previous data sets referred to specific subsets of risk factors (either ante-, peri- or postnatal) for the occurrence of IVH in premature infants [2] or relied on older data [10] obtained from more mature neonates often collected before the year 2000. These studies included analyses of potentially relevant clinical parameters (e.g., Apgar score, body temperature at admission, etc.), specific laboratory findings (e.g., clotting factors, etc.) as well as specific interventions (ANS, administration of clotting factors, mechanical ventilation, use of catecholamines). Thus, the main aim of this study was to present an updated, comprehensive and integrative analysis of potential ante-, peri- and postnatal factors associated with the occurrence of IVH in a highly susceptible cohort of VLGAN and ELGAN. Moreover, it was our aim to analyze changes over time by comparing two a priori defined time intervals.

2. Patients and methods

This retrospective study was performed as a multicenter cohort study in five large tertiary neonatal intensive care units (NICU) with annual admission rates of VLGAN between 50 and 100, located mainly in German university hospitals (University Medical Center Giessen; Saarland University Medical Center, Homburg/Saar; University Medical Center of the Johannes Gutenberg University Mainz; Darmstaedter Kinderkliniken Prinzessin Margaret; University Medical Center of the Ludwig-Maximilian-University, Grosshadern/Munich). Standard neonatal intensive care treatment was comparable between participating centers. Data evaluation was a sub-project within the prospective Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis (PROGRESS), and the Nationales Genomforschungsnetz Deutschland (NGFN) sponsored by the German Federal Ministry of Education and Research (BMBF).

Data were collected from infants born from 01/01/1998 to 31/12/2012. The study was approved by the local ethics committee (Ethikkommission des Saarlandes, Saarbrücken, Germany) as well as by the local ethics committees of all participating centers. Inclusion criteria were: gestational age (GA) of < 32 WOP, informed parental consent. Patients were not included in study analysis in case of early neonatal death (< 12 h of life) because of lack to obtain parental consent, or if missing data was in excess of 25%.

All relevant ante-, peri- and postnatal data were retrieved from an electronic database (SAP, Walldorf, Germany) and included information about the course of pregnancy as well as the delivery, perinatal maternal infectious parameters (amniotic infection syndrome (AIS) and/or preterm premature rupture of membranes (pPROM)), peri- and neonatal information, the critical risk index for babies score (CRIB score), laboratory parameters within the first 72 h of life, the clinical course and diagnoses (e.g. retinopathy of prematurity (ROP), IVH, hemodynamically relevant patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD)), parameters related to respiratory support (e.g. continuous positive airway pressure (CPAP), mechanical ventilation, etc.) as well as pharmacological therapies. Definitions of ROP, BPD, IVH, PVL and NEC have been provided previously [2]. Hemodynamically relevant PDA was characterized by echocardiography and either the need for a change in medical treatment (e.g. fluid restriction, use of inotropes, escalation of ventilatory support), the use of either ibuprofen or indomethacin for PDA closure or surgical PDA ligation.

Included neonates were subdivided into two groups with regard to GA: group 1 corresponded to neonates delivered ≤ 27 + 6 WOP (ELGAN) and group 2 were all neonates born between ≥ 28 + 0 and < 32 + 0 WOP (VLGAN).

Furthermore, two a priori defined time intervals, 1998–2005 and 2006–2012, were used to examine changes in the occurrence of IVH over time.

In all NICUs, serial cranial ultrasonography scans (CUSS) were performed based on the unit protocol by the attending neonatologist with expertise and training in ultrasonography on at least day 1, 3, and 7. Routinely, ultrasound studies were then repeated at 14, 21, 42 days of life, and then at term-corrected gestation with individual modifications made as deemed necessary. The *Papile* grading system for IVH [21] was used for assessment of IVH. The definition is as follows:

(1) Grade 1: Blood in the periventricular germinal matrix regions or germinal matrix hemorrhage.
(2) Grade 2: Blood within the lateral ventricular system without ventricular dilatation.
(3) Grade 3: Blood acutely distending the lateral ventricles.
(4) Grade 4: Blood within the ventricular system and parenchyma.

Primary data were entered into Microsoft Excel 2010 and further statistical analysis was performed using IBM SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Data are presented as minimum, maximum, mean, median and standard deviation, as appropriate. Comparison of variables between the groups of presence and absence of associated factors was performed using contingency tables, Chi^2-test, Mann-Whitney-U test and t-test for two independent samples, respectively. Two-sided *p*-values < 0.05 were defined as statistical significant. Due to the

explorative nature of investigation we did not correct for multiple testing. Independent influential variables for IVH were determined by univariate logistic regression analysis. In a second step significant parameters were included as independent variables in multiple logistic regression analysis. Since GA and birth weight are known to be associated with IVH, multiple logistic regression analysis was performed excluding these two parameters in addition to determine further important influential variables.

3. Results

3.1. Study population

In total, 765 neonates with a GA < 32 WOP were enrolled into this study; 369 (48.2%) female, 396 (51.8%) male. Birth weight ranged from 315 g to 2200 g (mean 1149.7 g, SD 371.9 g); 132 (17.3%) were low birth weight infants (LBW), 336 (43.9%) were very low birth weight infants (VLBW) and 297 (38.8%) were extremely low birth weight infants (ELBW). GA ranged from 23 + 3 WOP to 31 + 6 WOP, while 279 (36.5%) were born ≤ 27 + 6 WOP and 486 (63.5%) ≥ 28 + 0 WOP. 33 were excluded from study participation due to lack of parental consent or incomplete data sets. No significant differences existed between participating centers with regard to included patients and rate and severity of IVH.

In 571 (74.6%) infants antenatal steroids were given to the mother prior to birth; in 97 (12.7%) cases ANS were not administered, and in 97 (12.7%) sufficient data with regard to ANS use were not available. Overall 51 (6.7%) infants were born vaginally and 671 (87.7%) by caesarian sections, whereof 381 (49.8%) were done before and 290 (37.9%) after the onset of labor. One third of pregnancies (261; 34.1%) were multi parities. Tocolysis was used in 500 (65.4%) pregnancies; in 134 (17.5%) cases of preeclampsia/HELLP syndrome, and in 596 (77.9%) cases of threatened preterm birth including pPROM, AIS and perinatal infection respectively.

Apgar scores at 1 min and 5 min ranged from 1 to 10 (median 7.0, range 1–10) and 0–10 (median 8.0, range 0–10), respectively, and umbilical arterial pH (UA-pH) from 6.78–7.57 (mean 7.30, SD 0.0). CRIB scores ranged from 0 to 17 (mean 3.9, SD 0.1).

A total of 177 (23.1%) infants suffered from IVH. In these infants IVH I° occurred in 54 (7.1%), IVH II° in 44 (5.8%), IVH III° in 37 (4.8%), and IVH IV° in 42 patients (5.5%). IVH of any grade was equally distributed in girls and boys (82; 46.3% and 95; 53.7%, respectively,

Table 1
Frequency of IVH in presence/absence of suspected maternal predictors.

Risk factor		IVH in presence of risk factor n/n (%)	IVH in absence of risk factor n/n (%)	*p*-Value (2-sided)[a]
Perinatal maternal infection	Overall	142/596 (23.8)	35/169 (20.7)	0.39
	≤ 27 + 6 WOP	107/237 (45.1)	18/42 (42.9)	0.78
	28 + 0–32 + 0 WOP	35/359 (9.7)	17/127 (13.4)	0.26
	ELBW infant	95/238 (39.9)	19/59 (32.2)	0.28
	VLBW infant	38/253 (15.)	14/83 (16.9)	0.67
	LBW infant	9/105 (8.6)	2/27 (7.4)	1.0
Preeclampsia/HELLP syndrome	Overall	28/134 (20.9)	143/594 (24.1)	0.62
	≤ 27 + 6 WOP	19/45 (42.2)	102/221 (46.2)	0.63
	28 + 0–32 + 0 WOP	9/89 (10.1)	41/373 (11.0)	0.81
	ELBW infant	20/66 (30.3)	92/221 (41.6)	0.1
	VLBW infant	8/61 (13.1)	40/262 (15.3)	0.67
	LBW infant	0/7 (0.0)	11/111 (9.9)	1.0
Antenatal steroids	Overall	123/571 (21.5)	39/97 (40.2)	< 0.001
	≤ 27 + 6 WOP	87/203 (42.9)	30/44 (68.2)	0.002
	28 + 0–32 + 0 WOP	36/368 (9.8)	9/53 (17.0)	0.11
	ELBW infant	82/217 (37.8)	26/47 (55.3)	0.03
	VLBW infant	33/264 (12.5)	10/35 (28.6)	0.01
	LBW infant	8/90 (8.9)	3/15 (20.0)	0.19
Tocolysis	Overall	122/500 (24.4)	41/211 (19.4)	0.15
	≤ 27 + 6 WOP	85/260 (47.8)	30/82 (36.6)	0.09
	28 + 0–32 + 0 WOP	37/322 (11.5)	11/129 (8.5)	0.36
	ELBW infant	75/271 (39.1)	31/104 (29.8)	0.01
	VLBW infant	38/230 (16.5)	9/87 (10.3)	0.17
	LBW infant	9/103 (8.7)	1/20 (5.0)	1.0
Caesarian section (prior to onset of labor)	Overall	77/381 (20.2)	95/341 (27.9)	0.02
	≤ 27 + 6 WOP	48/133 (36.1)	74/136 (54.4)	0.003
	28 + 0–32 + 0 WOP	29/248 (11.7)	21/184 (10.2)	0.62
	ELBW infant	48/160 (38.9)	64/128 (50.0)	0.001
	VLBW infant	*n* = 25/172 (15.6)	24/143 (16.8)	0.58
	LBW infant	4/49 (8.2)	7/70 (10.0)	1.0
Caesarian section (after onset of labor)	Overall	79/290 (27.2)	93/432 (21.5)	0.08
	≤ 27 + 6 WOP	61/113 (54.0)	61/156 (39.1)	0.016
	28 + 0–32 + 0 WOP	18/177 (10.2)	32/276 (11.6)	0.64
	ELBW infant	53/106 (50.0)	59/182 (32.4)	0.003
	VLBW infant	20/128 (15.6)	29/187 (15.5)	0.98
	LBW infant	6/56 (10.7)	5/63 (7.9)	0.60
Vaginal delivery	Overall	16/51 (31.4)	156/671 (23.2)	0.19
	≤ 27 + 6 WOP	13/23 (56.5)	109/246 (44.3)	0.26
	28 + 0–32 + 0 WOP	3/28 (10.7)	47/425 (11.1)	1.0
	ELBW infant	11/22 (50.0)	101/266 (38.0)	0.27
	VLBW infant	4/15 (26.7)	45/300 (15.0)	0.22
	LBW infant	1/14 (7.1)	10/105 (9.5)	1.0

Weeks of pregnancy – WOP.
Low birth weight infants – LBW infants.
Extremely low birth weight infants – ELBW infants.
Very low birth weight infants – VLBW infants.
[a] Fisher's exact test if one of the expected cell frequencies was < 5; Chi^2 test if all the expected cell frequencies were ≥ 5.

$p = 0.31$). 600 (78.4%) patients suffered from RDS, with a positive association between more severe forms of RDS and higher grade IVH ($p < 0.001$). 350 (45.8%) infants developed a hemodynamically relevant PDA, 311 (40.7%) suffered from BPD, ROP and/or NEC, and in 67 (8.8%) patients pneumothoraces were seen while 271 (35.4%) infants developed early onset sepsis (EOS).

464 (60.7%) infants were mechanically ventilated; of those 33 (4.3%) received inhaled nitric oxide (iNO). 35.3% ($n = 164$) of mechanically ventilated infants suffered from IVH, whereas only 4.4% ($n = 12$) of the spontaneous breathing babies ($n = 271$) had IVH. Catecholamines were used in 282 (36.9%) patients and 458 (59.9%) had surfactant therapy. Of the 282 infants who received catecholamines, 112 (39.7%) developed IVH compared to only 64 out of 478 (13.4%) infants without catecholamine treatment ($p < 0.001$). Mortality rate was 5.4% ($n = 41$)

3.2. Factors associated with IVH

The frequency of IVH in presence or absence of a suspected factor potentially associated with IVH, presence or absence of major complications, and presence or absence of a particular therapy is depicted in Tables 1-3.

Over two a priori defined time intervals, the occurrence of some relevant factors potentially associated with IVH changed significantly while the overall occurrence of IVH remained unchanged (1998–2005: $n = 93/362$, 25.7% versus 2006–2012: $n = 84/403$, 20.8%; $p = 0.11$). However, grade 3 and 4 IVH decreased non-significantly over time (1998–2005: $n = 43/362$, 11.9% versus 2006–2012: $n = 36/403$, 8.9%; $p = 0.65$). The variables with significant differences are shown in Table 4.

Variables which were determined by univariate logistic regression to be independently and statistically significant associated with IVH are listed in Table 5.

Overall, higher GA, ANS and caesarian section before onset of labor were found to be associated with a reduced risk of IVH, while RDS, pneumothoraces and the use of catecholamines were found to associated with an increased risk of IVH for all enrolled neonates (Table 6). Results after subdivision by gestational age (VLGAN vs. ELGAN) are also demonstrated in Table 6.

After exclusion of GA and birth weight from multivariate logistic regression to control for confounder impact, ANS, caesarian section before onset of labor were found to be associated with a reduced risk of IVH while RDS, pneumothoraces, EOS, PDA and the use of catecholamines were associated with an increased risk of IVH (Table 7). Results after stratifying according to gestational age (VLGAN vs. ELGAN) are also demonstrated in Table 7.

4. Discussion

In our large, multi-center retrospective study including 765 neonates with a GA < 32 WOP, we demonstrated an overall incidence of IVH in 23.1% of infants. To the best of our knowledge, this is one of the

Table 2
Frequency of IVH in presence/absence major complications.

Risk factor		IVH in presence of risk factor n/n (%)	IVH in absence of risk factor n/n (%)	*p*-Value (2-sided)[a]
RDS	Overall	170/600 (28.3)	7/155 (4.5)	< 0.001
	≤ 27 + 6 WOP	123/268 (45.9)	2/11 (18.2)	0.12
	28 + 0–32 + 0 WOP	47/332 (14.2)	5/144 (3.5)	0.001
	ELBW infant	112/277 (40.4)	2/19 (10.5)	0.10
	VLBW infant	50/248 (20.2)	2/83 (2.4)	< 0.001
	LBW infant	8/75 (10.7)	3/53 (5.7)	0.36
Pneumothorax	Overall	38/67 (56.6)	136/681 (20.0)	< 0.001
	≤ 27 + 6 WOP	31/46 (67.4)	91/230 (39.6)	0.001
	28 + 0–32 + 0 WOP	7/21 (33.3)	45/451 (10.0)	0.005
	ELBW infant	26/37 (70.3)	85/255 (33.3)	< 0.001
	VLBW infant	10/24 (41.7)	42/304 (13.8)	0.001
	LBW infant	2/6 (4.)	9/122 (7.4)	0.084
EOS	Overall	108/271 (39.9)	69/494 (14.0)	< 0.001
	≤ 27 + 6 WOP	86/165 (52.1)	39/114 (34.2)	0.003
	28 + 0–32 + 0 WOP	22/106 (20.8)	30/380 (7.9)	< 0.001
	ELBW infant	76/158 (48.1)	38/139 (27.3)	< 0.001
	VLBW infant	28/98 (28.6)	24/238 (10.1)	< 0.001
	LBW infant	4/15 (26.7)	7/117 (6.0)	0.023
BPD/ROP/NEC	Overall	102/311 (32.8)	55/424 (13.0)	< 0.001
	≤ 27 + 6 WOP	87/202 (43.1)	20/52 (38.5)	0.55
	28 + 0–32 + 0 WOP	15/109 (13.8)	35/372 (9.4)	0.19
	ELBW infant	79/205 (38.5)	17/65 (26.2)	0.07
	VLBW infant	22/89 (24.7)	28/245 (11.4)	0.003
	LBW infant	1/17 (5.9)	10/114 (8.8)	1.0
PDA	overall	115/350 (32.9)	54/367 (14.7)	< 0.001
	≤ 27 + 6 WOP	94/198 (47.5)	28/75 (37.3)	0.13
	28 + 0–32 + 0 WOP	21/152 (13.8)	26/292 (8.9)	0.11
	ELBW infant	85/194 (43.8)	24/92 (26.1)	0.004
	VLBW infant	26/127 (20.5)	25/192 (13.0)	0.075
	LBW infant	4/29 (13.8)	5/83 (6.0)	0.234
Mortality	overall	32/41 (78.0)	145/724 (20.0)	< 0.001
	≤ 27 + 6 WOP	29/35 (82.9)	96/244 (39.3)	< 0.001
	28 + 0–32 + 0 WOP	3/6 (50.0)	49/480 (10.2)	0.02
	ELBW infant	26/34 (76.5)	88/263 (33.5)	< 0.001
	VLBW infant	6/6 (100.0)	46/330 (13.9)	< 0.001
	LBW infant	0/1 (0.0)	11/131 (8.4)	1.0

Weeks of pregnancy – WOP.
Low birth weight infants – LBW infants.
Extremely low birth weight infants – ELBW infants.
Very low birth weight infants – VLBW infants.
[a] Fisher's exact test if one of the expected cell frequencies was < 5; Chi^2 test if all the expected cell frequencies were ≥ 5.

Table 3
Frequency of IVH in presence/absence of a particular therapy.

Risk factor		IVH in presence of risk factor n/n (%)	IVH in absence of risk factor n/n (%)	*p*-Value (2-sided)[a]
Mechanical ventilation	Overall	164/464 (35.3)	12/271 (4.4)	< 0.001
	≤ 27 + 6 WOP	121/255 (47.5)	3/17 (17.6)	0.02
	28 + 0–32 + 0 WOP	43/209 (20.6)	9/254 (3.5)	< 0.001
	ELBW infant	111/253 (43.9)	2/37 (5.4)	< 0.001
	VLBW infant	45/169 (26.6)	7/156 (4.5)	< 0.001
	LBW infant	8/42 (19.0)	3/78 (3.8%)	002
iNO	Overall	20/33 (60.)	155/699 (22.2)	< 0.001
	≤ 27 + 6 WOP	17/25 (68.0)	106/246 (43.1)	0.02
	28 + 0–32 + 0 WOP	3/8 (37.5)	49/453 (10.8)	0.05
	ELBW infant	16/24 (66.7)	96/264 (36.4)	0.004
	VLBW infant	4/8 (50.0)	48/316 (15.2)	0.03
	LBW infant	0/1 (0.0)	11/119 (9.2)	1.0
Catecholamines	Overall	112/282 (39.7)	64/478 (13.4)	< 0.001
	≤ 27 + 6 WOP	83/159 (52.2)	41/118 (34.7)	0.004
	28 + 0–32 + 0 WOP	29/123 (23.6)	23/360 (6.4)	< 0.001
	ELBW infant	75/154 (48.7)	38/141 (27.0)	< 0.001
	VLBW infant	32/105 (30.5)	20/229 (8.7)	< 0.001
	LBW infant	5/23 (21.7)	6/108 (5.6)	0.02

Weeks of pregnancy – WOP.
Low birth weight infants – LBW infants.
Extremely low birth weight infants – ELBW infants.
Very low birth weight infants – VLBW infants.
[a] Fisher's exact test if one of the expected cell frequencies was < 5; Chi^2 test if all the expected cell frequencies were ≥ 5.

Table 4
Change of the incidence of factors associated with IVH, major complications and specific therapies over two a priori defined time intervals depicted as mean and absolute number respectively.

Risk factor	1998–2005	2006–2012	*p*-Value (2-sided)
Gestational age	Mean 28.8 WOP	Mean 28.6 WOP	$p = 0.32$[a]
Birth weight	Mean 1183.5 g	Mean 1119.4 g	$p = 0.02$[a]
UA-pH	Mean 7.28	Mean 7.31	$p < 0.001$[a]
Apgar 5 min	Mean 8.2	Mean 7.98	$p = 0.047$[a]
Perinatal maternal infection	272/326 (75.1%)	324/403 (80.4%)	$p = 0.08$[b]
Preeclampsia/HELLP syndrome	52/327 (15.9%)	82/401 (20.4%)	$p = 0.12$[b]
Antenatal steroids	197/270 (73.0%)	374/398 (94.0%)	$p < 0.001$[b]
Tocolysis	218/318 (68.6%)	282/393 (71.8%)	$p = 0.35$[b]
Caesarian section (prior to onset of labor)	195/319 (61.1%)	186/403 (46.2%)	$p < 0.001$[b]
Caesarian section (after onset of labor)	91/319 (28.5%)	199/403 (49.4%)	$p < 0.001$[b]
Vaginal delivery	33/319 (10.3%)	18/403 (4.5%)	$p = 0.002$[b]
RDS	274/357 (76.8%)	326/398 (81.9%)	$p = 0.08$[b]
Pneumothorax	38/345 (11.0%)	29/403 (7.2%)	$p = 0.07$[b]
EOS	153/362 (42.3%)	118/403 (29.3%)	$p < 0.001$[b]
PDA	154/317 (48.6%)	196/400 (49.0%)	$p = 0.91$[b]
BPD/ROP/NEC	128/350 (36.6%)	183/385 (47.5%)	$p = 0.003$[b]
Mechanical ventilation	208/332 (62.7%)	256/403 (63.5%)	$p = 0.81$[b]
iNO	18/335 (5.4%)	15/397 (3.8%)	$p = 0.30$[b]
Catecholamines	100/361 (27.7%)	182/399 (45.6%)	$p < 0.001$[b]
Surfactant	214/362 (59.1%)	244/403 (60.5%)	$p = 0.69$[b]

Umbilical arterial pH – UA-pH.
Respiratory distress syndrome – RDS.
Early onset sepsis – EOS.
Patent ductus arteriosus – PDA.
Retinopathy of prematurity – ROP.
Bronchopulmonary dysplasia – BPD.
Necrotizing enterocolitis – NEC.
Inhalative nitric oxide – iNO.
[a] *t*-Test.
[b] Fisher's exact test if one of the expected cell frequencies was < 5; Chi^2 test if all the expected cell frequencies were ≥ 5.

largest and most up-to-date cohorts of preterm infants analyzed with respect to the occurrence of IVH. Thus, we were able to perform a more comprehensive analysis of factors (ante-, peri- and postnatal) associated with IVH. In our cohort we identified a number of factors associated with the development of IVH – most importantly the occurrence of RDS, pneumothoraces, EOS, PDA and use of catecholamines. In contrast antenatal steroids and caesarian section before onset of labor were associated with a significantly reduced risk for IVH. Of note, no significant differences with regard to the rate and severity of IVH were seen between participating centers. Moreover, similar treatment and diagnostic modalities were employed in all 5 centers.

Preeclampsia and HELLP syndrome have been described as potentially protective factors with regard to the development of grade 3 and 4 IVH [22]. This may be related to the greater rate of caesarian sections

Table 5
Result of univariate logistic regression – significant independent influential variables for IVH.

Risk factor	*p*-Value	Corrected R^2	Regression coefficient beta
Gestational age	< 0.001	0.15	− 0.072
Birth weight	< 0.001	0.09	< 0.001
UA-pH	0.07	0.003	0.3
Apgar 5 min	< 0.001	0.04	− 0.06
Perinatal maternal infection	0.4	< 0.001	0.03
Preeclampsia/HELLP syndrome	0.43	− 0.001	− 0.03
Antenatal steroids	< 0.001	0.02	− 0.19
Tocolysis	0.15	0.002	0.05
Caesarian section (prior to onset of labor)	0.016	0.01	− 0.08
Caesarian section (after onset of labor)	0.08	0.003	0.06
Vaginal delivery	0.19	0.001	0.08
RDS	< 0.001	0.05	0.24
Pneumothorax	< 0.001	0.06	0.37
EOS	< 0.001	0.09	0.26
PDA	< 0.001	0.04	0.18
BPD/ROP/NEC	< 0.001	0.06	0.2
Mechanical ventilation	< 0.001	0.12	0.31
iNO	< 0.001	0.03	0.38
Catecholamines	< 0.001	0.09	0.26

Umbilical arterial pH – UA-pH.
Respiratory distress syndrome – RDS.
Early onset sepsis – EOS.
Patent ductus arteriosus – PDA.
Retinopathy of prematurity – ROP.
Bronchopulmonary dysplasia – BPD.
Necrotizing enterocolitis – NEC.
Inhalative nitric oxide – iNO.

Table 6
Results of the multivariate logistic regression displayed as Odds ratio (OR) and 95% - confidence interval (CI).

Risk factor	Overall	≤ 27 + 6 WOP	28 + 0–32 + 0 WOP
Gestational age	0.7 [0.6–0.8]		
Antenatal steroids	0.3 [0.2–0.6]	0.2 [0.1–0.6]	
Caesarian section (prior to onset of labor)	0.6 [0.4–0.9]	0.3 [0.1–0.6]	
RDS	5.6 [1.3–24.2]		
Pneumothorax	2.8 [1.4–5.5]	2.5 [1.03–5.9]	
Catecholamines	2.7 [1.7–4.5]	2.1 [1.1–3.9]	3.5 [1.7–7.3]

Table 7
Results of the multivariate logistic regression displayed as Odds ratio (OR) and 95% - confidence interval (CI) after exclusion of gestational age and birth weight.

Risk factor	Overall	≤ 27 + 6 WOP	28 + 0–32 + 0 WOP
Antenatal steroids	0.4 [0.2–0.8]	0.2 [0.1–0.6]	
Caesarian section (without uterine contraction)	0.5 [0.3–0.8]	0.3 [0.1–0.6]	
RDS	5.0 [1.1–22.7]		
Pneumothorax	2.9 [1.5–5.6]	2.5 [1.03–5.9]	
Early Onset Sepsis	1.6 [1.01–2.7]		
PDA	1.9 [1.1–3.1]		
Catecholamines	2.3 [1.4–3.7]	2.1 [1.1–3.9]	3.5 [1.7–7.3]

that is a standard procedure in most cases of manifest preeclampsia/HELLP syndrome. Interestingly, we found no significant reduction of IVH in these patients. However, it must be noted that preeclampsia/HELLP syndrome are risk factors for prematurity [10], which is in itself associated with a higher risk for IVH [23].

To induce fetal maturation of the lung, antenatal steroids (ANS) have become standard of care if preterm delivery is expected. Latest studies and a recently published Cochrane meta-analysis demonstrated a clear reduction in IVH when ANS were given to the mother prior to preterm birth [24]. This effect is at least partly attributed to a reduction in RDS, and to a reduced need for mechanical ventilation. Similar findings could be shown in our cohort with an OR of 0.4 for ANS. 74.6% of our study participants received ANS, which is in line with other studies [25]. However, it must also be conceded that in a relevant number of pregnancies (97/765, 12.7%), insufficient data on the use of ANS was available.

The impact of tocolysis on IVH remains controversial. Groome et al. demonstrated an increased incidence of IVH when using beta-sympathomimetics but not magnesium sulfate or no tocolysis [26]. Berkman et al. even found no correlation between the use of any tocolytic drug and IVH [27]. The same findings could be shown in our study, where we were not able to differentiate between different tocolytic drugs.

In a previous study, multiple pregnancy was suggested to be a further risk factor [28] for the development of IVH. However, this finding could not be substantiated by others [29]. Papiernik et al. conducted a large European study with 1254 gemini and 3586 singletons demonstrating a significant higher risk for IVH in gemini with GA of 24–27 WOP compared to singletons of the same gestational age [30]. In the present study we were not able to find a significant difference with respect to the occurrence of IVH when comparing singletons and gemini ($p = 0.77$).

Our data suggest that caesarian section before onset of labor in this cohort may help prevent IVH. This finding is supported by previous studies that also found caesarian section prior to the onset of labor is beneficial compared to spontaneous vaginal delivery [31,32]. It can be speculated that deformation of the head during vaginal delivery as well as hemodynamic fluctuations during labor may result in an increased risk of vascular damage in the brain [1].

The two single most important risk factors for developing IVH are prematurity and low birth weight because of an increased vulnerability of the immature vessels of the germinal matrix [1]. In line with previous reports, we were able to demonstrate an association between GA and birth weight (univariate logistic regression) with a significantly higher risk for IVH ($p < 0.001$) [33]. Especially ELGANs had higher grade IVH than those of 28–32 WOP. However, in contrast to previous reports our multivariate logistic regression demonstrated that only increased maturity but not higher birth weight had a protective effect with regard to the rate of IVH.

Prematurity bears the risk of several severe complications including EOS. In chorioamnionitis cytokine release as well as disturbances of the fetal cardio-circulatory regulation are important contributing factors for developing IVH [34] as well as PVL [35]. However, we and other authors [36,37] were not able to confirm these findings. This may at least in part be attributable to different definition of chorioamnionitis in the different studies.

One of the most common complications in premature infants is RDS, which occurs in about 30–80% of VLGAN [38,39]. It may be associated with IVH by rapid changes in intra-thoracic and venous pressure ratios, which in turn will result in a fluctuating cerebral perfusion and cerebral venous drainage. We demonstrated that more severe forms of RDS were associated with higher grade IVH ($p < 0.001$), and multivariate logistic regression found RDS to increase the risk of IVH (OR 5.0). Moreover, many of these infants will require mechanical ventilation, which is also associated with an increased risk for IVH [40]. This is presumably caused by variations in intra-thoracic pressure ratios, which consecutively will affect cerebral blood flow. In our analysis mechanical ventilation was not found to be associated with a higher occurrence of IVH; this finding is new and not in line with previous reports [40–43].

Fluctuations in cerebral perfusion can also be caused by a

pneumothorax secondary to impaired cerebral venous drainage, or a PDA [1] with inadequate cerebral perfusion. We found a 2.9-times increased probability of IVH when neonates suffered from pneumothoraces; also a hemodynamically relevant PDA was significantly correlated with the occurrence of IVH ($p < 0.001$, OR 1.9).

Data on the use of iNO application is inconsistent. Some studies reported a decreased rate of IVH in this context, while others describe an early termination due to an increased incidence of IVH while in other reports brain injury was unchanged [44–47]. A recent Cochrane meta-analysis failed to demonstrate significant changes in the rate of IVH in preterm neonates with respiratory failure that were treated with iNO [48]. We found that neonates who were treated with iNO had more severe IVH than those without iNO therapy and univariate logistic regression also found iNO to be an independent influential factor for IVH. However, multivariate logistic regression could not verify this association.

Further relevant complications of prematurity include ROP, BPD and NEC. Of note, we were able to determine that higher grade of IVH was associated with the occurrence of one or more of these three complications. This is of particular interest since they appear in the later course, and cannot be linked directly to the appearance of an IVH. Moreover, we found an increase in the occurrence of these complications over the two a priori defined time intervals – most likely caused by treatment and inclusion of smaller neonates as reflected by significantly lower birth weight and possibly by an improved detection rate of IVH secondary to better and more sophisticated ultrasonography studies.

The need for catecholamines is another potential factor associated with IVH in this cohort possibly because of relevant fluctuations in both blood pressure and cerebral perfusion, thus contributing to the development of IVH due to damage to and rupture of immature cerebral vessels [23] as reflected by a 2.3-times higher number of IVH when using catecholamines. Conversely, sicker neonates with IVH may have developed more often cardiovascular compromise, thus mandating the use of inotropes and vasopressors for cardio-circulatory stabilization. Thus, a uniform, straightforward causal and temporal relationship between the use of catechoalmines and the incidence of IVH is difficult to establish.

While some studies suggest a substantial reduction in the rate of IVH in the last decades because of improved ante- and post-natal care [5,49], only a small, non-significant decrease in the occurrence of IVH irrespective of severity was seen in our cohort over time.

The overall mortality in our cohort was 5.4% which is lower than described in the literature with mortality rates ranging from 8 to 20% for the same gestational age group [49]. This may in part be attributed to different selection criteria with exclusion of neonates who died within the first 12 h of life and lack of parental consent.

The strength of our retrospective data analysis was the large number of VLGAN and ELGAN studied with respect to the occurrence of IVH and potential risk factors. Limitations of our study included the retrospective nature of our data and the missing data. Moreover, due to data quality and availability, we were not able to analyze some very specific factors that may have contributed to the occurrence of IVH, e.g. presence/absence of senior medical staff (consultant) at initial resuscitation, core body temperature at admission, cellular and humoral clotting factors, use of fibrinogen, etc. Also, it was difficult to assess the temporal relationship (before/after) between IVH and certain measures (e.g. use of catecholamines).

5. Conclusion

In our large multi-center study including 765 patients we were able to perform an up-to-date comprehensive analysis over time of potential ante-, peri-, and postnatal factors linked to the occurrence of IVH. Our data indicate that in order to reduce the rate of IVH in this susceptible cohort, management strategies require an optimal interdisciplinary cooperation between obstetricians and neonatologists. Amenable factors likely to reduce the rate of IVH include more frequent administration of ANS, reduction of early onset sepsis, avoidance of pneumothoraces, optimal therapeutic approach of hemodynamically significant PDA, and possibly prudent use of catecholamines.

Conflict of interests

The authors declare that no conflict of interests exists. All authors have seen and approved the final version of the manuscript. The manuscript has solely been submitted to Early Human Development for review and possible publication.

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