

Risk Factors for Intraventricular Hemorrhage in Very Low Birth Weight Premature Infants: A Retrospective Case-Control Study

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ABSTRACT. *Objective.* High-grade intraventricular hemorrhage (IVH) is an important cause of severe cognitive and motor neurologic impairment in very low birth weight infants and is associated with a high mortality rate. The risk of IVH is inversely related to gestational age and birth weight. Previous studies have proposed a number of risk factors for IVH; however, lack of adequate matching for gestational age and birth weight may have confounded the results. The purpose of this study was to identify variables that affect the risk of high-grade IVH, using a retrospective and case-control clinical study.

Methods. From a cohort of 641 consecutive preterm infants with a birth weight of <1500 g, 36 infants with IVH grade 3 and/or 4 were identified. A control group of 69 infants, closely matched for gestational age and birth weight, was selected. Maternal factors, labor and delivery characteristics, and neonatal parameters were collected in both groups. Results of cranial ultrasound examinations, whether routine or performed in presence of clinical suspicion, were also collected. Univariate analysis and multivariate logistic regression analysis were performed.

Results. High fraction of inspired oxygen in the first 24 hours, pneumothorax, fertility treatment (mostly in vitro fertilization), and early sepsis were associated with an increased risk of IVH. A higher number of suctioning procedures, a higher first hematocrit, and a relatively low arterial pressure of carbon dioxide during the first 24 hours of life were associated with a lower occurrence. In the multivariate logistic regression model, early sepsis (odds ratio [OR]: 8.19; 95% confidence interval [CI]: 1.55–43.1) and fertility treatment (OR: 4.34; 95% CI: 1.42–13.3) were associated with a greater risk of high-grade IVH, whereas for every dose of antenatal steroid treatment there was a lower risk of high-grade IVH (OR: 0.52; 95% CI: 0.30–0.90) and each decrease in a mmHg unit of arterial pressure of carbon dioxide during the first 24 hours was associated with a lower risk of IVH (OR: 0.91; 95% CI: 0.83–0.98). This multivariate model had a sensitivity of 77%, a specificity of 75%, and a positive predictive value of 76%. The area under the curve derived from the receiver operator characteristic plots is 0.82.

Conclusions. Our results confirm that the development of IVH is associated with early sepsis and failure to give antenatal steroid treatment. We propose that fertility treatment (and especially in vitro fertilization) may be a

new risk factor, and more research is needed to assess its role. *Pediatrics* 2003;111:e590–e595. URL: <http://www.pediatrics.org/cgi/content/full/111/5/e590>; *intraventricular hemorrhage, premature infants, risk factors.*

ABBREVIATIONS. IVH, intraventricular hemorrhage; VLBW, very low birth weight; IVF, in vitro fertilization; FIO₂, fraction of inspired oxygen; Paco₂, arterial pressure of carbon dioxide; HMD, hyaline membrane disease; OR, odds ratio; CI, confidence interval.

Intraventricular hemorrhage (IVH) is an important cause of morbidity and mortality in very low birth weight (VLBW) infants. More than 50% of bleeding episodes occur during the first 24 hours of life, with <5% occurring after day 4/5.^{1,2} Although the incidence of IVH is decreasing,³ it remains a serious problem in the VLBW infant.

A number of risk factors have been proposed for the development of IVH: low birth weight and gestational age,^{1–8} maternal smoking,⁹ breech presentation,⁵ gender,^{5,7,10} premature rupture of membranes,^{6,11} intrauterine infection,^{6,11–13} mode of delivery,^{5,10,11,14,15} prolonged labor,^{1,16} postnatal resuscitation and intubation,^{1,7,16} transfer from one unit to another,^{7,16} early onset of sepsis,^{17,18} development of respiratory distress syndrome^{7,11} or pneumothorax,² recurrent endotracheal suctioning,^{1,16} metabolic acidosis and rapid bicarbonate infusion,^{10,16} and high-frequency ventilation.¹⁹ Pregnancy-induced hypertension is associated with a lower rate of IVH.^{5,20} For reducing the incidence of IVH, several pharmacological interventions have been proposed, including antenatal steroids,^{5,8,10,15,21,22} prenatal tocolytic therapy,^{8,23} postnatal administration of low-dose indomethacin,^{24,25} and surfactant.^{26,27}

However, many of the above studies failed to undertake multivariate analysis to identify independent risk factors for IVH. Furthermore, although low birth weight and low gestational age are major risk factors, they may simply describe a population at higher risk. Many studies have not adequately controlled for this, and their results may have been confounded by these 2 variables. We therefore performed a retrospective, case-control study with a high degree of matching for birth weight and gestational age to increase the sensitivity of detection of potential risk and protective factors that could be altered by medical intervention, in the hope of reducing the incidence of IVH.

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METHODS

The neonatal department at the Rabin Medical Center prospectively collects data on all VLBW infants. The data include prenatal demographic details, maternal pregnancy history and antenatal care, details of the delivery, the infant's status at delivery, diagnoses, procedures and complications during hospitalization, and outcome at discharge. A total of 641 VLBW preterm infants (<1500 g) were born at the Rabin Medical Center during the 5-year period from January 1, 1995, to December, 31 1999. From the cohort, we retrospectively identified all 36 premature infants (5.6%) with IVH grades 3 and/or 4, which composed our study group. A control group composed of 2 infants for each case, matched for gestational age (± 1 week) and birth weight (± 100 g), was selected on the basis of the first compatible live-born infant before and after each study infant.

In 3 cases, only a single control infant could be matched according to our criteria; hence, the control group consists of 69 infants. Data regarding maternal attributes, labor and delivery characteristics, and postnatal parameters were collected retrospectively from the fertility unit, high-risk pregnancy department delivery room, and neonatal charts in both groups. Maternal attributes included maternal age, fertility treatment (including clomiphene, Pergonal, and in vitro fertilization [IVF]), smoking during pregnancy, amniocentesis, cervical incompetence and cervical cerclage suture, maternal hypertension and the presence of preeclampsia, maternal steroids/antibiotics/tocolytic therapy/other medication (type, week of gestation when commenced, number of doses and dosage, reason for treatment), reason for induction of premature labor, reason for early delivery (premature contractions, premature rupture of membranes), placental abruption, placenta previa, and amnionitis (diagnosis on the basis of maternal fever $>37.8^{\circ}\text{C}$ orally or 38°C rectally, measured twice within 1 hour with no other source of fever identified, supported either by a positive culture result from amniotic fluid or by a high white blood cell count with elevated neutrophils in the amniotic fluid).

Labor, delivery, and newborn characteristics were: gender; singleton or twin or triplet; mode of delivery (vaginal, C-section, breech, instrumental: forceps and vacuum); gestational age (determined according to at least 2 of the following parameters: last menstrual period, first prenatal ultrasound, and Dubowitz score); birth weight; appropriateness for gestational age; Apgar score at 5 minutes; cord blood pH, bicarbonate and base excess; and delivery room resuscitation (use of oxygen, bag and mask or mechanical ventilation, intubation, cardiac massage, and epinephrine). Parameters for the first 24 hours of life included highest fraction of inspired oxygen (FiO_2); highest mean airway pressure; blood gases (highest and lowest arterial pressure of carbon dioxide [PaCO_2], arterial oxygen pressure, pH); highest and lowest mean blood pressure; first hematocrit, lowest hemoglobin; lowest platelet count; treatment with bicarbonate (dose); and number of suction procedures per day. For the neonatal course, the presence of any of the following neonatal diagnoses was recorded: hyaline membrane disease (HMD; diagnosed in infants who required either supplemental O_2 or mechanical ventilation, together with radiographic evidence of HMD), respiratory support (requirement for O_2 , nasal continuous positive airway pressure, intermittent mandatory ventilation, high-frequency ventilation, use of nitric oxide), pneumothorax, patent ductus arteriosus (if present, mode of treatment), necrotizing enterocolitis, retinopathy of prematurity (stage, zone), and presence of sepsis (early or late sepsis; early defined as within 72 hours of birth¹⁸). Sepsis was defined as positive microbial growth on 1 or more bloodstream cultures with accompanying clinical signs of sepsis. The diagnosis of sepsis caused by *Staphylococcus-coagulase-negative* was determined according to the Vermont Oxford Network Database²⁸; bacterial growth and antibiotics given (type, dosage); requirement for inotropes; requirement for surfactant (type, dosage); prophylactic indomethacin treatment (0.1 mg/kg given as a bolus during the first 72 hours); and administration of vitamins (type, dosage, age when commenced). Ultrasound evaluations were assessed by 2 independent radiologists. When present, the grade of IVH was determined according to Papile et al,²⁹ together with any posthemorrhagic hydrocephalus or periventricular leukomalacia. The routine protocol in the neonatal intensive care unit was for the first ultrasound scan to be performed on the third day of life, with follow-up scans at 14 and 28 days, and then monthly until

discharge.³⁰ When there was clinical suspicion of bleeding, additional ultrasound examinations were performed. The first day of bleeding and day of maximal hemorrhage were defined as the days on which hemorrhage was first identified or highest degree of hemorrhage seen, respectively. Any pathologic or neurologic findings were noted, including the occurrence of convulsions and results of brainstem-evoked potential tests. The need for recurrent lumbar punctures or ventricular taps, ventriculoperitoneal shunt insertion, or ventriculostomy was recorded. Outcome data were also obtained, either discharge data (day of discharge, age, weight, height, head circumference, medical treatment at time of discharge, and all neurologic findings) or age and cause of death. At discharge, a physical neurologic examination performed by a qualified neurologist and brainstem-evoked responses were obtained from all infants.

Statistical Analysis

Statistical analysis was performed with the BMDP Statistical Software.³¹ Univariate analysis was performed to identify differences between the study and control groups, using the *t* test, Pearson χ^2 test, and Mann-Whitney nonparametric test, as appropriate. Statistical significance was defined as $P \leq .05$. Those variables in which the univariate analysis was demonstrated as $P < .1$ were entered into a stepwise logistic regression model. Because we had only 36 infants with high-grade IVH and 69 controls with no possibility of enlarging these 2 groups, we did only the power analysis regarding survival with a result of 97%.

RESULTS

Between 1995 and 1999, 36 infants developed IVH grade 3 and/or 4, an incidence of 5.6%. Eleven of these (31%) developed posthemorrhagic hydrocephalus, with 1 infant requiring ventriculoperitoneal shunt insertion. In 86% of cases, the hemorrhage occurred during the first week of life, with 70% of cases diagnosed before or on the third day. In 31%, propagation of the bleed occurred during the first week. The overall mortality of infants born at <1500 g during the 5-year period was 13.4%. Among infants with IVH grades 3/4, the mortality was 75%, with a rate of 20.5% in the control group. None of the infants died within the first 24 hours. In the IVH group, 8 infants (22%) died within the first 3 days and 17 (47%) died within the first week compared with 2 (2.9%) within the first 3 days and 3 (4.3%) within the first week in the control group. Periventricular leukomalacia was present in 19.4% of infants with IVH, compared with 5.8% in the control group ($P = .05$). There were 9 survivors in the study group, 2 of whom had abnormal neurologic findings at discharge, whereas only 2 (of 52 survivors) in the control group had similar findings. Table 1 includes the important parameters and ultrasound findings of the study subjects, control subjects, and total population.

TABLE 1. Important Parameters and Ultrasound Findings of the Study Subjects, Control Subjects, and VLBW Population

	VLBW Population (N = 641)	Grade 3/4 IVH (N = 36)	Controls (N = 69)
Mortality	86 (13.4%)	27 (75%)	17 (20.5%)
Survivors	555 (86.6%)	9 (25%)	52 (75%)
Fertility treatment	198 (30.9%)	23 (64%)	27 (39%)
IVF	172 (26.8%)	18 (50%)	21 (30%)
In utero steroids	316 (49.3%)	22 (61%)	55 (80%)
Early sepsis	19 (3%)	7 (19%)	4 (6%)
Grade 1-2 IVH	61 (9.5%)	0	0
PVL	23 (3.6%)	7 (19.4%)	4 (6.2%)

PVL indicates periventricular leukomalacia.

There were no differences between the study and control groups in terms of demographic data, including gestational age and birth weight, as shown in Table 2. The results of the univariate analysis are shown in Tables 2–5. The factors found to be associated with a statistically significantly higher incidence of IVH were fertility treatment (63.9% vs 39.1% in controls; $P = .02$), which usually was through IVF treatment ($P < .03$). Ninety-two percent of all of the fertility treatments and 94% of the IVF treatments were performed by specialists of the fertility unit at the Rabin medical center. The percentage of twins and triplets and the incidence of infants who were small for gestational age was found to be similar in the 2 groups (Table 2). In 2 pregnancies, fetal death was recorded, 1 in each group; a higher incidence of early sepsis (19.4% vs 5.8%; $P < .05$); 86% of patients with early sepsis had Gram-negative sepsis all identified by positive blood cultures; only 1 infant had positive cerebrospinal fluid culture (early sepsis rate in the VLBW population was 3%), and pneumothorax (41.7% vs 20.3%; $P < .05$) in the IVH group compared with controls; a relatively lower first hematocrit level during the first 24 hours (44.0 ± 7.9 vs 49.3 ± 11.2 ; $P < .02$); and a higher F_{iO_2} during the first 24 hours of life in the study group ($P < .02$). No difference was observed in the arterial oxygen pressure. Variables associated with a lower incidence of IVH were a lower P_{aCO_2} during the first 24 hours (30.7 ± 6.6 in the controls vs 33.6 ± 5.8 ; $P < .05$) and a higher number of suctioning procedures during the first 24 hours (4.7 ± 2.9 in controls vs 3.3 ± 2.4 ; $P < .05$). There was no significant difference in maternal antenatal treatment with steroids between the 2 groups. Eighty percent of infants without IVH were born to mothers who had received antenatal steroid therapy, compared with 61% in the IVH group. However, a negative association was observed be-

tween the number of steroid doses and the occurrence of IVH grade 3 and/or 4 ($P = .03$).

The multivariate logistic regression analysis included all parameters with $P < .1$ in the univariate analysis (fertility treatment, premature rupture of membranes, antenatal steroids, highest F_{iO_2} , lowest pH, lowest P_{aCO_2} , number of suction procedures in 24 hours, highest first hematocrit, lowest first hemoglobin, early sepsis, pneumothorax, nitric oxide, inotropes), and the results are shown in Table 6. The analysis identified that early sepsis (odds ratio [OR]: 8.19; 95% confidence interval [CI]: 1.55–43.1) and fertility treatment (OR: 4.34; 95% CI: 1.42–13.3) were associated with a greater risk of high-grade IVH, whereas for every dose of antenatal steroid treatment there was a lower risk of high-grade IVH (OR: 0.52; 95% CI: 0.30–0.90) and each decrease in a mmHg unit of P_{aCO_2} during the first 24 hours was associated with a lower risk of IVH (OR: 0.91; 95% CI: 0.83–0.98). The multivariate model performed on 96 cases (as a result of 9 cases with missing value) had a sensitivity of 77% and a specificity of 75%, with a positive predictive value of 76%. The receiver operator characteristic curve area is 0.82 (Table 7).

We tried to determine the associations among the 4 independent variables that were found to affect the occurrence of high-grade IVH. The only significant association found was between fertility treatment and antenatal steroid treatment. Among mothers whose pregnancy was achieved by fertility treatment, there was a higher percentage of antenatal steroids exposure as well as higher frequency of multiple steroid doses ($P < .05$).

DISCUSSION

Our main objective was to identify risk factors for the development of high-grade IVH. The prenatal factors associated with increased risk of IVH were fertility treatment and especially IVF, which was identified as an independent risk factor in the multivariate analysis, something previously unreported in the literature. A recent study found that infants born after IVF have a higher incidence of neurologic impairment, particularly cerebral palsy, and it was proposed that the higher rates of multiple pregnancies and prematurity in IVF pregnancies may account for this.³² Another study demonstrated an association between assisted conception and retinopathy of prematurity.³³ IVF is a known risk factor for prematurity, largely as a result of the higher occurrence of multiple pregnancies. However, in our study, controlled for birth weight and gestational age, there was no difference in the incidence of multiple pregnancies between the study and control groups, an observation consistent with previous findings,⁶ and an alternative explanation is necessary. It is possible that the maternal problem preventing spontaneous pregnancy is also influencing the environmental conditions of the embryo in utero, increasing the risk of IVH. Alternatively, medication used during IVF treatment may increase the risk of IVH, perhaps by an effect on vasoreactivity or platelet aggregation. During the 5-year period, various techniques for IVF were introduced. The database

TABLE 2. Demographic Data and Delivery Characteristics

Parameter	IVH Group (n = 36)	Control Group (n = 69)	P Value
Maternal age (y)	28.7 ± 6.1	30.2 ± 5.9	.203
Gender			
Male	22 (61%)	39 (57%)	.103
Female	14 (39%)	30 (44%)	
Multiple pregnancy	19 (53%)	31 (45%)	.538
Twins	14 (39%)	23 (33%)	.74
Triplets	5 (14%)	8 (12%)	
SGA	2 (5.6%)	7 (10%)	
Gestational age (wk)	25.7 ± 1.7	25.3 ± 1.8	.228
Mode of delivery			
Vaginal	12 (33%)	22 (32%)	1.00
C-Section	24 (67%)	47 (68%)	
Birth weight (g)	803 ± 268	838 ± 243	.495
Apgar score at 5 min	7.5 (2–10)*	8.5 (1–10)*	.13
Cord blood			
pH	7.29 ± 0.09	7.29 ± 0.13	.929
HCO ₃ ⁻ (mEq)	20.39 ± 3.41	19.33 ± 4.11	.404
Base excess (mM)	-6.58 ± 5.14	-6.48 ± 5.51	.953
Delivery room intubation	33 (92%)	57 (83%)	.253

SGA indicates small for gestational age.

Data shown as number of cases (%) or mean ± standard deviation.

* Data shown as median (range).

TABLE 3. Univariate Analysis of Prenatal Data

Parameter	IVH Group (n = 36)	Control Group (n = 69)	P Value
Fertility treatment (including IVF)	23 (64%)	27 (39%)	.023
Maternal smoking	3 (9%)	9 (13%)	.536
Cervical incompetence	15 (42%)	20 (29%)	.2
Cervical encercage	5 (14%)	9 (13%)	1.00
Amniocentesis	3 (8%)	3 (4%)	.106
Premature contractions	26 (72%)	47 (68%)	.824
Preeclampsia	1 (3%)	3 (4%)	1.00
Amnionitis	6 (17%)	19 (28%)	.136
Placenta abruptio/previa	6 (17%)	10 (14%)	.78
Antenatal steroids	22 (61%)	55 (80%)	.09
Tocolytic therapy	15 (42%)	32 (46%)	.833
Premature rupture of membranes	10 (28%)	33 (48%)	.089

TABLE 4. Univariate Analysis of NICU Parameters During the First 24 Hours

Parameter	IVH Group	Control Group	P Value
Highest F _{IO} ₂ (%)	80.83 ± 23.38	68.67 ± 24.60	.016
Blood gases (mmHg)			
pH			
Lowest	7.19 ± 0.12	7.26 ± 0.11	.084
Highest	7.41 ± 0.09	7.42 ± 0.07	.224
PaCO ₂			
Lowest	33.58 ± 5.84	30.74 ± 6.65	.035
Highest	57.93 ± 14.98	56.76 ± 17.74	.740
Max Δ PaCO ₂ *	24.35 ± 15.37	26.02 ± 19.24	.657
PaO ₂			
Lowest	46.45 ± 20.59	47.22 ± 14.53	.826
Highest	149.49 ± 63.2	156.79 ± 85.74	.658
Highest mean airway pressure (cm H ₂ O)	6.61 ± 4.79	6.87 ± 4.14	.791
No. of suction procedures	3.33 ± 2.38	4.72 ± 2.93	.020
Hematology			
Hematocrit (first)	43.96 ± 7.94	49.29 ± 11.18	.018
Hemoglobin (lowest)	12.53 ± 2.66	13.54 ± 2.51	.067
Platelet count (lowest)	172.1 ± 77.77	186.1 ± 67.27	.355
Mean BP (mmHg)			
Highest	43.09 ± 9.14	42.71 ± 7.97	.832
Lowest	25.36 ± 4.78	27.00 ± 5.24	.136
Max ΔBP†	17.73 ± 8.16	15.71 ± 8.44	.260

NICU indicates neonatal intensive care unit; BP, blood pressure.

Data shown as mean ± standard deviation.

* Calculated as the difference between highest PaCO₂ and lowest PaCO₂.

† Calculated as the difference between highest BP and lowest BP.

TABLE 5. Univariate Analysis of Neonatal Course

Parameter	IVH Group (n = 36)	Control Group (n = 69)	P Value
Early sepsis	7 (19%)	4 (6%)	.044
Pneumothorax	15 (42%)	14 (20%)	.024
HMD	31 (86%)	51 (74%)	.214
Nitric oxide	8 (22%)	6 (9%)	.075
High-frequency ventilation	6 (17%)	7 (10%)	.361
Inotropes	29 (81%)	46 (67%)	.060
Surfactant	34 (94%)	60 (87%)	.324
Prophylactic indomethacin	21 (58%)	46 (67%)	.664
Intravenous bicarbonate	19 (53%)	30 (43%)	.295

does not record the specific technology used in each individual case; hence, we are not able to ascribe the outcomes reported to any specific technology. A prospective study evaluating the outcome of infants in relation to the different therapeutic modalities is currently being undertaken. Additional investigation using larger, controlled prospective trials are needed to clarify this finding.

Antenatal steroid treatment has been reported as conferring protection against the development of IVH.^{20,21} Although this study failed to corroborate this with statistical significance, we did observe that the protection provided by steroids may be related to the number of steroid doses received (Table 8). Therefore, repeated doses of maternal antenatal steroids may reduce the risk of IVH in high-risk populations, but the possible benefits of such an intervention need to be assessed further before any recommendations can be made. This study did not find any influence on the incidence of high-grade IVH by other maternal and perinatal factors such as preeclampsia, method of delivery, premature rupture of membranes, and chorioamnionitis.

Early sepsis was associated with an 8-fold increase in the incidence of IVH, in agreement with previous studies.¹⁷ In this study, early sepsis was not related to chorioamnionitis. An association among chorioamnionitis, sepsis, and IVH in the preterm infant has been reported previously,¹¹ and the risk of IVH and

TABLE 6. Parameters Influencing the Development of Grade 3 and/or 4 IVH, Identified by Logistic Regression Analysis

Parameter	OR	95% CI
Early sepsis	8.19	1.55–43.1
Fertility treatment (including IVF)	4.34	1.42–13.3
Antenatal steroids (doses)	0.52	0.30–0.90
Low PaCO ₂ during first 24 h	0.91	0.83–0.98

TABLE 7. Sensitivity, Specificity, and Positive Predictive Value

	Predicted as Normal	Predicted as IVH	Total
Control	49	16	65
IVH 3/4	7	24	31
Total	56	40	96

Sensitivity, 24/31 = 77%; specificity, 49/65 = 75%; positive predictive value + 73/96 = 76%.

TABLE 8. Number of In Utero Steroid Doses in the 2 Groups

	0	1	2	>2
IVH (N = 36)	12 (33%)	11 (31%)	10 (28%)	3 (8%)
Controls (N = 69)	13 (19%)	18 (26%)	19 (27.5%)	19 (27.5%)

P = .03.

early sepsis is reduced when antenatal antibiotics are given.¹⁶ Pneumothorax is also described as a risk factor for IVH² but was not found to be a significant risk factor in the multivariate analysis.

Suctioning procedure has been reported to increase intracranial pressure and hence has been associated with an increased incidence of IVH. Our study, however, shows in the univariate analysis a significant inverse relationship between the incidence of IVH and the number of suction procedures performed during the first 24 hours of life. This contradicts the minimal handling theory recommended for very small premature infants,^{2,15} and additional research is needed before proper recommendations as to airway suction procedures in very small infants during the first 24 hours of life can be made.

Infants who developed IVH required a higher FIO₂ during the first 24 hours to maintain the same degree of oxygenation as controls. This suggests that these infants may be commencing life with a more severe degree of respiratory compromise. This factor was not found to be an independent factor in the logistic regression analysis. The incidence of HMD in both groups was statistically similar. Lower PaCO₂ during the first 24 hours of life was found to be associated with a lower incidence of IVH in the multivariate analysis, a finding reported elsewhere.³⁴ Potentially, a lower PaCO₂ may reduce the risk of IVH by causing arterial vasoconstriction. However, low PaCO₂ has been described as a risk factor for periventricular leukomalacia and a poor neurologic prognosis,¹⁹ so there is a need for caution in interpreting this finding.

A relatively lower first hematocrit during the first 24 hours of life correlated with a higher incidence of IVH, a finding consistent with previous reports.¹⁴ Although a low hematocrit might accelerate cerebral

blood flow, thus contributing to the hemorrhage,¹⁴ it is difficult to determine whether the low hematocrit levels contributed to the development of IVH or were a consequence of the bleed itself.

This study is limited by its retrospective nature and the small sample size. However, to our knowledge, this is the first study in the literature in which study and control groups were closely matched for gestational age and birth weight, with similar rates of multiple pregnancies in both groups. By reducing the confounding effects of these factors, the sensitivity of this study to detect other independent variables that affect the incidence IVH was increased.

CONCLUSIONS

We have demonstrated that early sepsis and fertility treatment may be risk factors for the development of grade 3 and/or 4 IVH in VLBW infants, whereas antenatal steroids and a lower PaCO₂ may confer a degree of protection. The relationship between IVF and IVH has not been mentioned previously, and a large prospective study is required to clarify this finding. If these factors can be validated further, then it may be possible for medical interventions to reduce the incidence of IVH, thus decreasing mortality and preventing the associated long-term severe neurologic sequelae in the VLBW neonate.

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