# PEDIATRICS

## CAUSES OF INTRAVENTRICULAR HEMORRHAGES IN EXTREMELY PREMATURE NEWBORNS AND FEATURES OF THEIR EARLY OUTCOMES

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## ABSTRACT

***The aim.*** *To study the predisposing factors for the development and timing of development of intraventricular hemorrhage (IVH) in extremely premature newborns.*
***Materials and methods.*** *We carried out retrospective analysis of 32 case histories of children born at a gestational age of less than 32 weeks. The children were divided into three groups: group 1 (n = 13) – children death was caused by non-traumatic IVH; group 2 (n = 12) – surviving infants with IVH; group 3 (comparison group; n = 7) – premature infants without IVH. We assessed risk factors for the development of IVH, their severity, and main indicators predisposing to death in newborns of these groups.*
***Results.*** *Children of the group 1 had statistically significantly low values of body weight – 670 [640–860] g ($p_{1-2}$ = 0.007; $p_{1-3}$ = 0.012), head circumference – 23 [22–24] cm ($p_{1-2}$ = 0.008; $p_{1-3}$ = 0.049), gestational age – 24.5 [23.5–25.5] weeks ($p_{1-2}$ = 0.002; $p_{1-3}$ = 0.007). Gender differences were revealed: in the group 1, there were 92.3 % of boys, in the group 2 – 33.3 % ($p_{1-2}$ = 0.008). Maternal smoking increased the risk of fatal IVH by 3.5 ± 0.15 times, polyhydramnios – by 3.3 ± 0.37 times, chorioamnionitis – by 12.8 ± 0.47 times, placenta previa – by 3.2 ± 0.15 times. In newborns of the group 1, seizures developed on the day 1 of life in 84.6 % (more often than in group 2; p = 0.00001), and shock in the first 3 hours of life was recorded in 46.1 % of cases ($p_{1-2}$ = 0.034), which increased the risk of death by 4.3 ± 0.47 times. In newborns of group 1, compared with newborns of groups 2 and 3, pulmonary hypertension was more often detected (60.8 [50.1–69.2] mm Hg; $p_{1-2}$ = 0.028; p1–3 = 0.047).*
***Conclusion.*** *Confirmed infectious diseases in the mother, clinical manifestation of convulsions, pulmonary hypertension, development of multiple organ failure and shock in extremely premature newborns increase the risk of intraventricular hemorrhage and the frequency of deaths.*

***Key words:*** *prematurity, intraventricular hemorrhage, risk factors*

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# ПРИЧИНЫ РАЗВИТИЯ ВНУТРИЖЕЛУДОЧКОВЫХ КРОВОИЗЛИЯНИЙ У ГЛУБОКО НЕДОНОШЕННЫХ НОВОРОЖДЁННЫХ И ОСОБЕННОСТИ ИХ РАННИХ ИСХОДОВ

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## РЕЗЮМЕ

***Цель исследования.*** *Изучить предрасполагающие факторы развития и сроки реализации внутрижелудочковых кровоизлияний (ВЖК) у глубоко недоношенных новорождённых.*

***Материалы и методы.*** *Ретроспективно проанализированы 32 истории болезни детей, рождённых на сроке гестации менее 32 недель. Дети были разделены на три группы: 1-я группа (n = 13) – дети, причиной смерти которых стало нетравматическое ВЖК; 2-я группа (n = 12) – выжившие младенцы с ВЖК; 3-я группа (сравнения; n = 7) – недоношенные дети, у которых не развились ВЖК. Оценивали факторы риска развития ВЖК, их тяжесть, основные показатели, предрасполагающие к летальному исходу у новорождённых этих групп.*

***Результаты.*** *У детей 1-й группы получены статистически значимо низкие показатели массы тела – 670 [640–860] г ($p_{1-2}$ = 0,007; p1–3 = 0,012), окружности головы – 23 [22–24] см ($p_{1-2}$ = 0,008; $p_{1-3}$ = 0,049), срока гестации – 24,5 [23,5–25,5] недели ($p_{1-2}$ = 0,002; $p_{1-3}$ = 0,007). Выявлены гендерные различия: в 1-й группе преобладали мальчики (92,3 %), во 2-й группе их доля составила 33,3 % ($p_{1-2}$ = 0,008). Увеличивали риск ВЖК с летальным исходом курение матери – в 3,5 ± 0,15 раза, многоводие – в 3,3 ± 0,37 раза, хориоамнионит – в 12,8 ± 0,47 раза, предлежание плаценты – в 3,2 ± 0,15 раза. У детей 1-й группы судороги развились в 1-е сутки жизни у 84,6 % (чаще, чем во 2-й группе; p = 0,00001), а шок в первые 3 часа жизни регистрировался у 46,1 % ($p_{1-2}$ = 0,034), повышая риск летального исхода в 4,3 ± 0,47 раза. У детей 1-й группы по сравнению с детьми 2-й и 3-й групп была чаще выявлена лёгочная гипертензия (60,8 [50,1–69,2] мм рт. ст.; $p_{1-2}$ = 0,028; $p_{1-3}$ = 0,047).*

***Заключение.*** *Наличие инфекционных заболеваний у матери, клиническое проявление судорог, лёгочной гипертензии, развитие полиорганной недостаточности и шока у глубоко недоношенных новорождённых увеличивают риск реализации ВЖК и частоту летальных исходов.*

***Ключевые слова:*** *недоношенность, внутрижелудочковые кровоизлияния, факторы риска*

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Premature birth remains an important medical problem. A special group of newborns requiring the use of modern medical technologies for nursing are infants with a gestational age (GA) of less than 32 weeks. Premature babies with very and extremely low body weight most often develop life-threatening diseases, one of which is intraventricular hemorrhage (IVH) of hypoxic and hemorrhagic genesis [1–3].

According to European researchers, the highest incidence of non-traumatic IVH is associated with the very fact of prematurity, that is, with the anatomical, physiological, and morphological features of the vascular wall structure of the brain germinal matrix, imperfect autoregulation of cerebral blood flow, and the state of the hemostasis system of premature infants. The likelihood of non-traumatic IVH is aggravated by conditions accompanied by chronic intrauterine hypoxia, birth asphyxia, and the development of hypocoagulation, including primary coagulopathy, generalized purulent-septic and viral diseases [4, 5]. Coagulation mechanisms in premature infants are characterized by low hemostatic potential, as reflected in the studies of P. Monagle et al. [6]. As gestational age (GA) increases, the probability of IVH decreases, which is certainly associated with neuronal and migratory regression of the germinal matrix. This is also associated with the tectonics of IVH localizations of different GAs. The most important independent risk factor for IVH is GA. At 28–32 weeks of GA, the germinal matrix is preserved for the longest time on the surface of the caudate nucleus head and in the caudate sulcus, and it is in this area that hemorrhages form in children with such GAs [7].

The above factors explain the negative relationship between the frequency of IVH and its severity in very premature infants. IVH is diagnosed in 20–30 % of very premature infants with a GA of less than 29 weeks and increases the frequency of fatal outcomes [8–11]. In the USA, the share of IVH among the causes of neonatal mortality is 1.7 % [12, 13].

## THE AIM OF THE STUDY

To study the predisposing factors for the development and timing of development of intraventricular hemorrhage in extremely premature newborns.

## MATERIALS AND METHODS

The study was conducted in the neonatal intensive care unit of the Trans-Baikal Regional Perinatal Center (Chita). Retrospectively, for the period 2020–2021, risk factors on the part of the mother and the child were assessed in 32 premature newborns with a GA of less than 32 weeks, using the following registration forms: No. 096/u-20 "Medical record of a pregnant woman, a woman in labor, and a postpartum woman receiving medical care in stationary conditions", and form No. 097u "Medical history of the development of a newborn". The mothers were examined for their somatic health indicators, obstetric and gynecological history, and the characteristics of the current pregnancy and childbirth.

Gestational, anthropometric, and gender characteristics of the newborns under study were assessed, the Apgar score, respiratory disorders, cardiovascular failure, hemostasis (coagulogram in the first hours after birth), metabolic, and electrolyte abnormalities (venous and capillary blood) were studied, general clinical laboratory diagnostic methods (blood, urine), as well as methods of therapeutic measures to stop the identified abnormalities were used. The venous blood coagulogram was studied using the STA Compact Max device (Stago, France); the results were compared with the reference values given in the instructions for this device. In order to identify the causes of hypocoagulation, infant diseases that affect hemostasis and the development of IVH were analyzed.

X-ray examinations were performed to verify the causes of respiratory disorders, were included in the standard examination of newborns with congenital pneumonia or respiratory distress syndrome. The study was conducted on equipment included in the perinatal center. Echocardiography was performed on all newborns to assess hemodynamic changes, including pulmonary hypertension, determine the volume of drug therapy, exclude heart defects and infectious myocardial damage.

The diagnosis of IVH was made after a neurosonographic (NSG) examination using the ALOKA SSD 1700 (Hitachi, Japan) device [14]. The severity of hemorrhage was determined according to the classification of M. Levene et al. [15, 16] and K.V. Vatoli et al. [17, 18]. The cause of death was confirmed by the results of autopsies according to D.A. Duskaliev et al. [19].

**The inclusion criteria were:** prematurity at less than 32 weeks; development of non-traumatic IVH of varying severity in children.

The children were divided into groups:

Group 1 – premature newborns with a fatal outcome, the cause of death was non-traumatic IVH and posthemorrhagic hydrocephalus ($n = 13$).

Group 2 – premature infants with the development of IVH who survived ($n = 12$).

**Inclusion criteria for the comparison group** (3rd group): prematurity; GA less than 32 weeks; absence of IVH ($n = 7$).

**Exclusion criteria:** prematurity after 32 weeks of gestation; presence of congenital malformations; fatal cases caused by generalized infectious diseases, anoxia ($n = 6$).

Statistical processing was performed using Statistica 6.0 (StatSoft Inc., USA), MS Excel 2010 (Microsoft Corp., USA). Groups of children were compared for normal distribution using the Kolmogorov – Smirnov method. Due to the non-normal distribution in the groups, the description is given as a median (Me) and 25-75th quantiles. Comparison of non-parametric indicators was performed using the Fisher's criterion. Risk factors were assessed by calculating the odds ratio (OR) ± standard error (SE, standard error) [95% confidence interval (95% CI)]. Differences were considered statistically significant at $p < 0.05$.

To predict an unfavorable outcome, a logistic regression model (logit regression) was calculated; indicators with a statistically significant resulting feature were included in the equation [20].

The work complied with ethical standards; the participants signed voluntary informed consent; the work was approved by the Ethics Committee of the Chita State Medical Academy of the Ministry of Health of the Russian Federation (Protocol No. 128 dated November 14, 2023).

## RESULTS

The characteristics of the study groups are presented in Table 1. When assessing the anthropometric parameters, infants with a fatal outcome and diagnosed IVH had the lowest body weight and length, head circumference, chest circumference and gestational features compared to newborns in groups 2 and 3. Weight fluctuations in group 1 were 490–990 g, in group 2 – 540–1400 g, in the group without IVH – 800–1300 g with a statistically significant difference ($p_{1-2}$ = 0.007; $p_{1-3}$ = 0.012). The body length of infants had a range from 28 to 37 cm and corresponded to the average percentile indicators for gender and GA, but had no statistically significant differences in the comparison groups.

The infants' height ranged from 28 to 37 cm and corresponded to the average percentile values for gender and GA, but had no statistically significant differences in the comparison groups. The head circumference values were statistically significantly lower in the 1st group and ranged from 21 to 27 cm, in the 2nd group Me was 24.2 cm (from 22 to 28 cm; $p_{1-2}$ = 0.008), in the 3rd group Me = 26 cm (from 23 to 29 cm; $p_{1-3}$ = 0.049). Smaller chest circumference was also found in the infants of the 1st group – from 18 to 24 cm ($p_{1-2}$ = 0.041), in the 2nd group – from 15 to 24 cm, in the 3rd group – from 18 to 27 cm. Small anthropometric values corresponded to the GA of premature infants.

In the group of infants who developed IVH with an unfavorable outcome, GA was statistically significantly lower – 24 [22; 27] weeks, that is, the infants were extremely immature; in the 2nd group, infants were born with a GA of 26 [26; 28] weeks, although they were extremely premature, but were more mature than the children in the 1st group ($p$ = 0.002). Extreme immaturity of newborns (GA – 22-26 weeks) increased the risk of developing IVH and a fatal outcome from it by 27.5 ± 0.5 times [95% CI: 10.21-74.01]. Infants who did not develop IVH were born at an average gestational age of 27 weeks (minimum 25 weeks 4 days, maximum 29 weeks), which also statistically significantly differed from children in group 1 ($p$ = 0.007).

**TABLE 1**

**ANTHROPOMETRIC, GESTATIONAL AND GENDER INDICATORS OF THE STUDIED GROUPS**

| Indicators | Comparison groups, Me [Q25–Q75] | | | |
|---|---|---|---|---|
| | Group 1 ($n$ = 13) | Group 2 ($n$ = 12) | Group 3 ($n$ = 7) | $p$ |
| Weight, g | 670 [640–860] | 960 [845–985] | 940 [870–1260] | **$p_{1-2}$ = 0.007*** $p_{2-3}$ = 0.703* **$p_{1-3}$ = 0.012*** |
| Height, cm | 31 [30–33] | 33 [30–35.5] | 34 [33–38] | $p_{1-2}$ = 0.513* $p_{2-3}$ = 0.204* $p_{1-3}$=0.079* |
| Head circumference, cm | 23 [22–24] | 24.25 [24–27] | 26 [23–28] | **$p_{1-2}$ = 0.008*** $p_{2-3}$ = 0.703* **$p_{1-3}$ = 0.049*** |
| Chest circumference, cm | 20 [19–22] | 22.5 [21–24] | 22 [20–23] | **$p_{1-2}$ = 0.041*** $p_{2-3}$ = 0.767* $p_{1-3}$=0.292* |
| Gestation age, weeks | 24.5 [23.5–25.5] | 26.6 [26.4–28] | 27 [25.6–28.1] | **$p_{1-2}$ = 0.002*** $p_{2-3}$ = 0.582* **$p_{1-3}$ = 0.007*** |
| Gender, $n$ (%) | | | | |
| Boys | 12 (92.3) | 4 (33.3) | 6 (85.7) | **7.034; $p_{1-2}$ = 0.008#** 2.99; $p_{2-3}$ = 0.064# |
| Girls | 1 (7.7) | 8 (66.7) | 1 (14.3) | 0.096; $p_{1-3}$ = 0.755# |

**Note.** $p_{1-2}$ – statistically significant differences between groups 1 and 2 ($p$ < 0.05); $p_{2-3}$ – statistically significant differences between groups 2 and 3 ($p$ < 0.05); $p_{1-3}$ – statistically significant differences between groups 1 and 3 ($p$ < 0.05); * – Mann – Whitney test; # – Fisher's test.

Among infants with a fatal outcome associated with IVH, boys predominated (12 out of 13 children), which was statistically significantly different from children in group 2, in which girls predominated **($p_{1-2}$ = 0.008).** Male gender increased the odds of an adverse outcome with IVH by **24.0 ± 0.48 times [95% CI: 9.18–62.6].**

To assess the impact of maternal diseases and the perinatal period course on the IVH development and its lethal outcome in the comparison groups, the socio-biological and obstetric-gynecological anamnesis were assessed. When assessing a possible lethal outcome, the risk assessment of their development was calculated against the background of the IVH development (OR ± SE; 95% CI). In all observation groups, a favorable age for childbirth was noted for mothers – from 20 to 35 years; the proportion of mothers over 35 years of age did not have statistically significant differences in the groups (from 15 to 28 %).

Nicotine dependence of mothers in the 1st group was recorded in more than half of the observations (53.8 %), in the 2nd group – in a quarter, in the 3rd group – in every 6th case. No statistically significant differences were found. However, maternal smoking increased the risk of IVH and its unfavorable outcome by **3.5 ± 0.15 times [95% CI: 3.01–4.06].**

When analyzing the somatic history of mothers in all study groups, no statistically significant differences were obtained. Burdened obstetric history in the study groups was diagnosed in 2/3 of women, which affected the likelihood of premature delivery, but statistically significant differences between the groups were not established. Preeclampsia was detected in mothers of the 2nd and 3rd groups (8.3 % and 28.6 %, respectively), and fetoplacental insufficiency (FPI) was diagnosed in all observation groups. At the same time, the subcompensated form was registered in 8 out of 13 patients (61.5 %) in the 1st group and in 2/3 of observations in the 2nd group; decompensated – in 15 % in the 1st group and in 16.7 % in the 2nd. In the group of children without IVH, decompensated FPI was not detected; subcompensated FPI was detected in 85.7 %, compensated – in 14.3 %. No statistically significant differences were found between the groups. Complications of pregnancy with the threat of termination in all observation groups were noted in almost half of the cases, the development of isthmic-cervical insufficiency – in every 4th case, which is associated with premature birth. Oligohydramnion was diagnosed in the 1st and 2nd groups with a frequency of 23 % and 8 %, respectively, which increased the probability of developing IVH with a fatal outcome by **3.3 ± 0.37 times [95% CI: 1.6–6.77].** In the 3rd observation group, polyhydramnios was detected in 14.3 %. Emergency operative delivery was required in all observation groups in more than half of the cases (53.8 %, 58.3 % and 57.1 %, respectively).

Pregnancy was complicated by infectious factors. Cervicitis was registered in almost every 3rd case (30.8 % in group 1; 25.0 % in group 2; 28.6 % in group 3). Chorioamnionitis during labor in group 1 occurred in 7 of 13 cases (53.8 %), in group 2 – in 1 of 12 (8.3 %), in group 3 – in 1 of 7 (14.3 %) and statistically significantly prevailed in the group of newborns with IVH that ended in death **($p_{1-2}$ = 0.03).** This pathology increased the probability of death from IVH by **12.8 ± 0.47 times [95% CI: 5.05–32.44].** Endometritis was also registered statistically significantly more often in the 1st group – in 10 of 13 observations (76.9 %), against 33.3 % in the 2nd group **($p_{1-2}$ = 0.047)**, and 28.6 % in the 3rd group. Bacterial inflammation of the endometrium increased the chance of IVH with a fatal outcome by **6.7 ± 0.5 times [95% CI: 2.48–18.03].** Placenta previa was detected only in the group with IVH and led to a fatal outcome in 5 of 13 cases. In the 2nd group, transverse fetal position was diagnosed in 1 patient, the risk of IVH development was increased by **3.2 ± 0.5 times [95% CI: 1.2–8.5].**

An increase in the placental-fetal coefficient (PFC) as a marker of the placental infectious process by more than 0.23 was diagnosed in all observations (100 %) of the 1st group, in 75 % of the 2nd group, and in 85.7 % of the 3rd group. The PFC Me in the 1st group was 0.36 [0.32–0.42], the minimum value was 0.28, and the maximum was 0.48, which is statistically significantly higher than the level of this indicator in the 2nd group: Me = 0.295 [0.225–0.34], the minimum value was 0.11, and the maximum was 0.46 **($p_{1-2}$ = 0.005)**; in the 3rd group Me = 0.34 [0.25–0.4], the minimum value is 0.23, the maximum is 0.52 ($p_{2-3}$ = 0.404; $p_{1-3}$ = 0.579). A prolonged anhydrous period (more than a day) in premature infants of the comparison groups was detected with a frequency of 46 % in the 1st group, 33.3 % in the 2nd group, and 43 % in the 3rd group.

Among the pathological conditions in newborns leading to the IVH development, convulsions are the most common, in the development of which, in addition to hypoxia, the implementation of infection plays a special role. In infants of the 1st group, convulsions were recorded in the first day in 11 of 13 cases (84.6 %), on average, the development time was 3 hours from the moment of birth [1 hour 10 minutes – 6 hours], minimum – 30 minutes, maximum – the 4th day of life. At the age of over 1 day, convulsions developed in 2 children (15.4 %). In the 2nd group, convulsions developed in 3 newborns (25.0 %) at the age of over 24 hours (Me = 2 days 7 hours). Convulsions were not recorded in 9 of 12 newborns (75.0 %) of the 2nd group. In the 3rd observation group, convulsions were diagnosed in 3 of 7 children (42.8 %), Me age – 8 days 8 hours. Statistically significant differences were revealed when comparing the 1st group with the 2nd and 3rd **($\chi^2$ = 26.692; $p$ = 0.0001).**

Clinical and functional manifestations of various types of shock in premature infants in the 1st group were diagnosed in the first 3 hours of life in 6 of 13 cases (46.1 %) compared to the 2nd group (2 of 12 children (16.7 %)), increasing the risk of developing IVH with a fatal outcome by **4.3 ± 0.47 times [95% CI: 1.69–10.89].** Shock was diagnosed at the age of 3–6 hours in 3 (23.1 %) children in the 1st group, and after 6 hours of life – in 4 (30.7 %) newborns; in the 2nd group, the clinical picture of shock developed at the age of 3–6 hours in 3 (25.0 %) children, and after 6 hours – also in a quarter. In the group of children without IVH, shock was diagnosed less frequently

– in the first 3 hours of life in 2 (28.6 %) children, at the age of over 6 hours – in 1 (14.3 %) infant. When comparing the timing of shock, statistically significant differences were obtained in the comparison groups **($\chi^2$ = 10.420; $p$ = 0.034).**

Persistent pulmonary hypertension (PPH) in infants of group 1 was detected in 12 of 13 cases (92.3 %), Me = 60.8 [50.1–69.2] mmHg, from 31.8 to 89.6 mmHg. In group 2, the frequency of PPH was recorded in 9 of 12 children (75 %) at a level of 44.1 [34.1–52.1] mmHg, from 23 to 78.7 mmHg, statistically significantly differing in the groups **($p_{1-2}$ = 0.028)**. PPH in group 3 was detected in 4 of 7 children (57.1 %), Me = 44 [28.6–57] mmHg, from 23 to 64.8 mmHg, in comparison with the 1st group, the differences are statistically significant **($p_{1-3}$ = 0.047)**.

Neurosonographic (NSG) criteria of IVH in the 1st group were detected in the first day of life in 6 (46.2 %) infants; bilateral IVH of grade III was detected in 53.8 % of cases from the 2nd to the 5th day of life. In the 2nd group, IVH was detected in 5 (41.6 %) children on the 1st day of life, in 1 child – of grades II-III, with the development of posthemorrhagic hydrocephalus. At the age of 3 to 6 days, IVH was realized in 50 % in the form of subependymal hemorrhage.

According to the acid-base balance (ABB) assessment, all infants had uncompensated mixed acidosis and increased lactate levels after birth: in group 1 Me = 4.35 [3.3–5.95] mmol/l, minimum – 2.2 mmol/l, maximum – 9.7 mmol/l; in group 2 Me = 4.4 [2.3–5.6] mmol/l, minimum – 1.4 mmol/l, maximum – 11.3 mmol/l; in group 3 Me = 5.1 [3.4–7.9] mmol/l, minimum – 2.5 mmol/l, maximum – 12.5 mmol/l; no statistically significant differences were found.

The base deficit in infants of group 1 was –9.1 [–7.05 ÷ –11.6] mmol/l, minimum –0.6 mmol/l, maximum –14.6 mmol/l; in group 2 Me = –9.35 [–5.9 ÷ –11.25] mmol/l, minimum –1.7 mmol/l, maximum –15 mmol/l; in group 3 Me = –6.4 [–4.8 ÷ –11.7] mmol/l, minimum –4.8 mmol/l, maximum –15 mmol/l; no statistically significant differences were found. These changes were nonspecific and were associated not with the fact of IVH, but with prematurity, the implementation of an infectious disease, and the presence of respiratory failure.

In order to identify violations of vascular-platelet hemostasis parameters and insufficiency of the blood coagulation system, laboratory criteria (platelet level), coagulogram parameters (activated partial thromboplastin time (APTT), fibrinogen level, international normalized ratio (INR)) were studied. The results are presented in Table 2.

In all study groups, thrombocytopenia was diagnosed in the first hours after birth. In the 1st group, the minimum platelet level was 92 × 109/l, the maximum was 252 × 109/l; in the 2nd group, the range of values was from 93 to 325 × 10 9/l; in the 3rd group – from 107 to 251 × 109/l.

In the coagulogram, the fibrinogen level in all groups corresponded to the average gestational values. In the 1st group, the minimum fibrinogen value was

**TABLE 2**

**LABORATORY PARAMETERS OF HEMOSTASIS IN THE STUDIED GROUPS AT BIRTH, ME [Q25–Q75]**

| | Comparison groups | | | |
|---|---|---|---|---|
| **Hemostasis parameters at birth** | **Group 1 ($n$ = 13)** | **Group 2 ($n$ = 12)** | **Group 3 ($n$ = 7)** | **$p$** |
| Platelets, thousand | 163.5 [141.5–232.5] | 198 [163–239.5] | 183 [121–247] | $p_{1-2}$ = 0.270<br>$p_{2-3}$ = 0.735<br>$p_{1-3}$ = 0.799 |
| Fibrinogen, g/l | 1.38 [1.14–1.9] | 2.2 [1.3–2.4] | 1.3 [0.81–3.6] | $p_{1-2}$ = 0.426<br>$p_{2-3}$ = 1.0<br>$p_{1-3}$ = 0.853 |
| APTT, s | 52 [42–57] | 47.35 [29.7–60.8] | 43.8 [41.1–46.6] | $p_{1-2}$ = 0.624<br>$p_{2-3}$ = 0.865<br>$p_{1-3}$ = 0.267 |
| INR | 1.87 [1.44–2.28] | 1.42 [1.2–2.45] | 1.72 [1.59–5.7] | $p_{1-2}$ = 0.602<br>$p_{2-3}$ = 0.361<br>$p_{1-3}$ = 0.609 |

**Note.** $p_{1-2}$ – statistically significant differences between groups 1 and 2 ($p < 0.05$; Mann – Whitney test); $p_{2-3}$ – statistically significant differences between groups 2 and 3 ($p < 0.05$; Mann – Whitney test); $p_{1-3}$ – statistically significant differences between groups 1 and 3 ($p < 0.05$; Mann – Whitney test).

0.75 g/l, the maximum – 4.1 g/l; in the 2nd group, its level was from 0.8 to 4.2 g/l; in the 3rd group – from 0.81 to 3.6 g/l; statistically significant differences were not revealed. In the group of children with a fatal outcome, an increase in APTT was determined from 41.4 to 118.9 s, in the group of surviving children with IVH – from 25.7 to 109 s. In the group of children who did not have developing IVH, APTT corresponded to the standard values – from 41.1 to 46.6 s. In all study groups, INR indicated hypocoagulation; statistically significant differences were not revealed. The indicators in the 1st group ranged from 1.26 to 2.8, in the 2nd – from 1.14 to 3.24, in the 3rd – from 1.59 to 5.7; statistically significant differences were not identified.

Based on the obtained statistical data, a logit regression equation was calculated, which made it possible to predict the implementation of an unfavorable outcome of IVH in the early neonatal period [21, 22].

**Y = exp (0.1 – 8.05 chorioamnionitis + 10.89 endometritis + 9.86 PFC + 12 gender – 6.43 maternal smoking – 1.17 placenta previa – 1.05 PPH – 5.6 shock in the first 3 hours – 45.8 convulsions in the first 3 hours) / 1 + exp (0.1 – 8.05 chorioamnionitis + 10.89 endometritis + 9.86 PFC + 12 gender – 6.43 maternal smoking – 1.17 placenta previa – 1.05 PPH – 5.6 shock in the first 3 hours – 45.8 convulsions in the first 3 hours); $\chi^2$ = 34.29641; df = 9; *p* = 0.0000797.**

## DISCUSSION

IVH in premature infants has a multifactorial genesis. There are three groups of factors: antenatal, intranatal and postnatal. According to the results of our study, antenatal factors include: maternal smoking; infectious processes causing oligohydramnios; chorioamnionitis; endometritis. Intranatal factors include: complicated delivery; abnormal placenta previa. Postnatal factors are: fluctuations in systemic arterial pressure, which is manifested by shock; PPH; coagulopathy; oxidative stress, confirmed by the data of the acid-base balance study. As is known, germinal matrix cells are rich in mitochondria and are very sensitive to oxygen deficiency, which explains the importance of germinal matrix hypoxia in the pathogenesis of IVH development [23].

## CONCLUSION

Thus, our observations established that extreme prematurity, infectious diseases of the mother, bad habits, and placental pathology exert their adverse effects on the fetus through pathophysiological processes. IVH is realized as a result of a violation of hemodynamic autoregulation and structural immaturity at the level of the germinal matrix. The clinical picture of shock, persistent pulmonary hypertension, and convulsions in the first hours of life can aggravate the severity of IVH and lead to death.

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**Conflicts of interest**

No potential conflict of interest relevant to this article reported.

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Kocherova V.V. – collected and analysed the data; performed the statistical data calculations; wrote the manuscript (34 %).

Popova N.G. – developed the concept; worked with literature sources; wrote the manuscript (33 %).

Shcherbak V.A. – worked with literature sources; wrote the manuscript; edited the manuscript (33 %).