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# PRECONDITIONS FOR EARLY AND LATE INTRAVENTRICULAR HEMORRHAGES IN PRETERM VERY LOW BIRTH WEIGHT INFANTS

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The risk factors for early and late intraventricular hemorrhages (IVH) in very preterm newborns were investigated in a cohort study. One hundred eleven infants with a mean gestation age of 29.59±2.59 wks. were under observation. The risk factors connected to the development of early and late hemorrhages were different. Opposite to the early IVH, development of the late hemorrhages was neither dependent on birth weight and gestation age, nor on infectious pathology of perinatal period. The relevant risk was determined by infant's condition at birth and arterial hypotension that developed within the first 24 hrs. of newborn's hospitalization. Development of severe respiratory distress syndrome (RDS) was reliably connected with IVH independently on infant's age. According to the results of logistic regression analysis, the risk of early IVH was significantly associated with RDS severity (odds ratio [OR]: 6.05; 95% confidence interval [CI]: 1.35–27.17), and the probability of late IVH was significantly influenced by arterial hypotension within the first 24 hrs. of hospitalization (OR: 16.6; 95% CI: 2.69–102.43).

**Keywords:** intraventricular hemorrhages, age of occurrence, risk factors, prevention, very preterm infants.

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Intraventricular hemorrhage (IVH) often complicates the neonatal period in very preterm (gestational age <32 weeks) infants and represents one of the most severe perinatal brain lesions. Its development is associated with high mortality and may be an important independent cause of long-term neurological and cognitive impairment in surviving infants [9, 11].

Approximately half of the cases of hemorrhage in infants with very low birth weight occur during the first 6 hours of life, and 38% – after 24 hours of life [1]. IVH is considered early if detected within the first 72 h of life and late if diagnosed after 72 h [15].

The high prevalence of IVH in the group of least mature newborns, the association of this complication with high mortality, and the threat of severe long-term consequences and disability determine the importance of studying the risk factors for IVH and possible mechanisms of their occurrence.

**The purpose** of the study was to determine the risk factors for early and late IVH in the modern cohort of very preterm infants.

**Materials and methods.** A cohort of 111 very preterm infants with birth weight less than 1.500 g was under observation in specialized neonatology departments of the Lviv Regional Clinical Hospital (LRCH). The inclusion criteria were hospitalization within the first 3 days of life and the absence of significant malformations.

IVH were diagnosed using cranial ultrasound (CUS), which was performed on the third day of life. To assess the evolution of existing hemorrhages and diagnose late IVH, according to the developed protocol, further examinations were performed on 5-7, 9-11, 14-16 and 24-28 days of life, as well as at postmenstrual age of 36 weeks or before discharge from the hospital. CUS was also performed regardless of the infant's age if there were clinical signs indicating the possible development of IVH. Digitae Sonoace 5500 ultrasound machine (Medison, South Korea) and 5–7.5 MHz convex sensors were used. The severity of the hemorrhages was assessed using the Papille classification.

All children were distributed into 2 groups depending on the presence of hemorrhage. The main group included 21 (19%) infants with IVH diagnosed within 3 days of life, and the control group consisted of 90 (81%) newborns in whom no hemorrhage was detected at this age. Late hemorrhage developed in 17 (15%) infants from the latter group, these babies were included into the main subgroup, and 73 (66%) newborns, who did not have this CNS pathology before discharge from the hospital, were attributed to the control subgroup.

The obtained data were analyzed using standard descriptive statistics methods, categorical, and multivariate logistic regression analysis. Categorical data are presented as numbers (%). The measurements with normal distribution are presented as means (±standard deviations). Nonparametric data are presented as medians [interquartile ranges]. Parametric continuous measurements were compared using t-test and medians were compared with the Mann–Whitney U test for non-parametric data. The chi-squared test was applied to categorical data. A *p* value less than 0.05 was considered significant.

**Results of the study and their discussion.** The mean gestational age of infants in the study was 29.59±2.59 weeks. Seventeen infants (15%) had birth weight less than 1000 g, 1000–1249 g – 32 (29%) and 1250–1500 g – 62 newborns (56%). The mean age of babies in the main group at the time of hospitalization was 8 [3–19] h versus 10.5 [4–25] h for infants in the control group (p=0.51).

Newborns with early hemorrhage had a lower gestational age (28.048±1.91 weeks vs. 29.94±2.61 weeks in the control group; p=0.002) and birth weight (respectively 1147.62±236.81 g vs. 1255.22±236.004 g; p=0.063). At the same time, these indicators did not differ significantly in infants from the main and control subgroups (respectively 28.82±1.88 weeks vs. 29.72±2.69 weeks; p=0.19; and 1204.12 ±284.65 g vs. 1240.43 ±230.95 g; p=0.57). The main group also differed from the control by a significantly larger proportion of infants with weight less than 1250 g (15 (71.4%) vs. 34 (37.7%); p=0.014). Instead, late hemorrhages were more common in bigger children.

Early IVH were significantly more often severe than late ones (p<0.05) (Fig. 1), and were more likely to cause death of infants accordingly (9 (42.9%) cases in the main versus 6 (6.7%) in the control group; p=0.001).

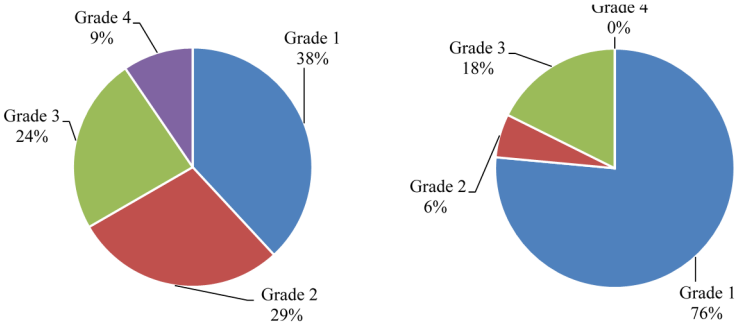


Fig. 1. Comparative distribution of early and late IVH by severity (p<0.05).

A comparative analysis of medical and social risk factors showed that mothers of infants with early IVH were more likely to be under 17 years of age (respectively 3 (14.3%) vs. 3 (3.3%) cases; p=0.046). At the same time, the majority of other risk factors in mothers of infants with IVH were not associated with either type of the hemorrhage. Only the frequency of stillbirths was significantly higher in mothers whose children had late IVH (respectively 3 (17.6%) vs. 1 (1.4%) cases; p=0.003).

Antenatal steroid prophylaxis most significantly reduced the risk of early hemorrhages. Hemorrhages within the first 72 hours of life were less likely to develop in infants with intrauterine growth retardation. Instead, early IVH were significantly more often diagnosed in babies from mothers with bleeding in the first half of pregnancy or preeclampsia (table 1).

Table 1

**Comparative frequency of pregnancy and delivery complications in groups and subgroups**

| Risk factors | Groups | | *p* | Subgroups | | *p* |
|---|---|---|---|---|---|---|
| | Main (n=21) | Control (n=90) | | Main (n=17) | Control (n=73) | |
| Preeclampsia | 11 (52.4) | 24 (26.7) | **0.035** | 3 (17.6) | 21 (28.8) | 0.62 |
| Bleeding in the first half of pregnancy | 7 (33.3) | 9 (10.0) | **0.006** | 3 (17.7) | 6 (8.2) | 0.26 |
| Bleeding in the last trimester of pregnancy | 7 (33.3) | 10 (11.1) | 0.098 | 0 (0) | 10 (13.7) | 0.16 |
| Cesarean section | 1 (4.8) | 17 (18.9) | 0.13 | 0 (0) | 1 (1.4) | 0.63 |
| Rapid delivery | 3 (14.3) | 30 (33.3) | 0.087 | 2 (11.8) | 15 (20.5) | 0.46 |
| Duration of delivery > 24 h | 5 (23.8) | 16 (17.8) | 0.55 | 4 (23.5) | 16 (21.9) | 0.91 |
| Placental abruption | 5 (23.8) | 11 (12.2) | 0.18 | 1 (5.9) | 10 (13.7) | 0.38 |
| IUGR | 0 (0) | 15 (16.7) | 0.052 | 1 (5.9) | 14 (19.2) | 0.22 |
| Multiple pregnancy | 3 (14.3) | 16 (17.9) | 0.71 | 3 (17.7) | 13 (17.8) | 0.99 |
| Antenatal steroids | 6 (28.6) | 63 (70.0) | **0.001** | 14 (82.3) | 49 (67.1) | 0.21 |

Notes: number of cases (%). IUGR–intrauterine growth retardation.

The risk of early IVH increased in case of chorioamnionitis (respectively 6 (28.6%) vs. 4 (4.4%) cases; p=0.001), fever during labor (respectively 3 (14.3%) vs. 1 (1.1%) case; p=0.003), or stained amniotic fluid (respectively 13 (61.9%) vs. 17 (18.9%) cases; p=0.001), however, effective antibacterial therapy reduced this risk (2 (9.5%) versus 36 (40.0%) cases respectively; p=0.009). At the same time, no significant associations have been established between infectious diseases in mothers and the occurrence of late IVH in their children. Early hemorrhages were significantly more common in infants with hypothermia, severe RDS, pneumothorax, early sepsis, clinical signs of patent ductus arteriosus (PDA), as well as in those who required controlled ventilation or early administration of dobutamine (table 2).

On the first day of hospitalization, infants with early hemorrhages were ventilated with significantly higher mean airway pressure (11.14±2.57 cm Hg vs. 9.064±1.89 cm Hg; p=0.002). They also had a lower pH (7.19±0.083 vs. 7.33±0.082; p=0.001) and higher partial pressures of $CO_2$ ($paCO_2$) (48 [38.3–54] cm Hg vs. 33 [28.4–38.9] mm Hg; p=0.001).

Resuscitation at birth with epinephrine and (or) chest compressions, hypotension with dopamine administration, severe RDS, pneumothorax, surfactant administration and use of controlled mechanical ventilation were associated with higher incidence of late IVH (table 2).

According to the results of LRA, occurrence of early hemorrhages was significantly associated only with the severity of RDS (odds ratio (OR) – 6.05; 95% confidence interval (CI): 1.35–27.17), hypotension within the first 24 hours of hospitalization reliably and independently affected the probability of late hemorrhage occurrence (OR–16.6; 95% CI: 2.69–102.43).

Table 2

**Early neonatal period data in groups and subgroups[1]**

| Risk factors | Groups | | *p* | Subgroups | | *p* |
|---|---|---|---|---|---|---|
| | Main (n=21) | Control (n=90) | | Main (n=17) | Control (n=73) | |
| Intubation and MV | 6 (28.6) | 29 (32.2) | 0.79 | 7 (41.2) | 22 (30.1) | 0.34 |
| Chest compressions | 3 (14.3) | 4 (4.4) | 0.1 | 3 (17.6) | 1 (1.4) | **0.003** |
| Epinephrine administration | 3 (14.3) | 4 (4.4) | 0.1 | 3 (17.6) | 1 (1.4) | **0.003** |
| Apgar<4 at 5 min | 4 (19.0) | 9 (10) | 0.25 | 1 (5.9) | 8 (10.9) | 0.53 |
| MV at birth | 14 (66.7) | 44 (48.9) | 0.16 | 11 (64.7) | 33 (45.2) | 0.17 |
| CPAP at birth | 1 (4.8) | 13 (14.4) | 0.23 | 1 (5.9) | 12 (16.4) | 0.26 |
| Hypothermia at the time of hospitalization (<36.6°C) | 20 (95.2) | 6 (6.7) | **0.001** | 0 (0) | 6 (8.2) | 0.22 |
| Arterial hypotension[2] | 7 (33.3) | 15 (16.7) | 0.091 | 12(70.6) | 3(4.1) | **0.001** |
| Dobutamine[2] | 4 (19.1) | 1 (1.1) | **0.001** | 0 (0) | 1 (1.4) | 0.63 |
| Dopamine[2] | 6 (28.6) | 14 (15.6) | 0.17 | 12 (70.6) | 2 (2.7) | **0.001** |
| Hypotension / dopamine at the age of >3 days | 0 (0) | 0 (0) | – | 2 (11.8) | 0 (0) | **0.003** |
| Severe RDS | 14 (66.7) | 29 (32.2) | **0.004** | 17 (100) | 11 (15.1) | **0.001** |
| Initial controlled MV | 11 (52.4) | 24 (26.7) | **0.024** | 8 (47.1) | 16 (21.9) | **0.04** |
| Surfactant therapy | 8 (38.1) | 18 (20.0) | 0.084 | 7 (41.2) | 11 (15.1) | **0.02** |
| Pneumothorax at the age of 1–3 days | 1 (4.8) | 0 (0) | **0.04** | 0 (0) | 0 (0) | – |
| Pneumothorax at the age of >3 days | 0 (0) | 9 (10) | 0.13 | 9 (52.9) | 0 (0) | **0.001** |
| Clinical signs of PDA at the age of 1–3 days | 6 (28.6) | 3 (3.3) | **0.001** | 1 (5,9) | 2 (2.7) | 0.53 |
| Early onset sepsis | 13 (61.9) | 2 (2.2) | **0.001** | 0 (0) | 2 (2.7) | 0.49 |

Notes: 1–number of cases (%); 2–the first 24 hours of hospitalization; MV–mechanical ventilation; RDS – respiratory distress syndrome; PDA– patent ductus arteriosus; CPAP– continuous positive airway pressure.

In this study, we found that infants who developed IVH within the first 72 hours of life were more likely to be born to mothers whose pregnancies were complicated by preeclampsia and bleeding in the first half of pregnancy. Intrauterine growth retardation reduced the risk of this complication (table 1). Because preeclampsia was much more common in mothers of infants with early hemorrhages, and the incidence of intrauterine growth retardation was higher in babies without IVH, it could be thought that only severe or prolonged preeclampsia reduced the risk of IVH.

Our results confirm the known fact of the prophylactic effect of antenatal steroids on the occurrence of early IVH [14] but indicate a lack of such a protective effect against the late hemorrhages (table 1). The incidence of the latter type of IVH did not depend on the complicated course of pregnancy and childbirth (table 1) but was associated with the condition of infant at birth (table 2).

A comparative analysis of the frequency of infectious risk factors revealed a significant association between the presence of an infectious process in the mother's body before and during childbirth and the occurrence of early IVH. Studies by other authors have also established an association between chorioamnionitis and a higher incidence of IVH [8, 9]. Our results suggest that effective maternal antibacterial therapy is likely to reduce the risk of neonatal hemorrhage, as confirmed by other authors [3]. At the same time, we did not prove the effect of infectious diseases in mothers on the risk of late IVH in their infants.

According to the literature, birth asphyxia, and the use of resuscitation measures in the delivery room, as well as the need for mechanical ventilation immediately after birth are associated with a high risk of early IVH [7, 9]. Infants in the main group were more likely to require resuscitation after birth and had lower 5 min Apgar scores, but differences in the frequency of resuscitation interventions were not significant. In contrast, infants who required extended or complete resuscitation, were much more likely to develop late IVH (table 2).

In our study, children who did not have early IVH, were significantly more likely to be born by elective or urgent cesarean section, although no statistically significant differences were found between the groups. The elective cesarean section may have advantages in the prevention of IVH in newborns with gestational age of <30 weeks compared not only to vaginal delivery but also to the emergency cesarean section [6]. Meta-analysis data, which took into account all cases of cesarean section, showed its advantage in the prevention of IVH in premature infants with gestational age of <28 weeks, who required active resuscitation after birth. Should cases of elective cesarean section be the only ones considered, the results could have been better, as the need for an emergency cesarean section could be determined by conditions that increase the risk of IVH [4].

Treatment with constant positive airway pressure (CPAP) or mechanical ventilation did not significantly increase the risk of IVH occurrence within the first 72 hours of life, although initial controlled ventilation was a significant risk factor for both types of hemorrhage. Infants with early IVH were ventilated with significantly higher mean airway pressures during the first day of hospitalization, consequently, a larger tidal volume was used increasing the risk of IVH development [10]. Such infants were also significantly more likely to have acidosis and higher levels of paCO2, which were connected to the occurrence of IVH by other authors [8].

The early IVH occurred much more often in younger and more immature infants with hypothermia at hospitalization, severe RDS, pneumothorax, sepsis, and clinical signs of PDA (Table 2). At the same time, we could not objectively assess the association between the onset of the early IVH and PDA because the routine echocardiographic examination was not possible during the study. Dobutamine administration was also associated with a higher risk of early IVH.

The risk of late IVH was significantly associated with primary resuscitation, which included epinephrine administration and/or chest compressions, hypotension, and its treatment with dopamine, severe RDS or pneumothorax, controlled mechanical ventilation, and surfactant treatment (table 2). The occurrence of IVH has been associated with the therapeutic use of surfactant by other authors [2], which indicates the reality of such an association in our settings. Significant associations between the development of IVH and hypotension, the use of inotropic drugs [8, 12], the presence of RDS [8], and its complications [13] have also been established in other studies.

Thus, the risk factors of early and late IVH differ, which confirms the idea of different mechanisms of their occurrence. Our data suggest a significant association between the severity of the condition of the premature infant, development of RDS, peculiarities of its course, and effectiveness of treatment with the occurrence of IVH not only within the first days after birth but also during the late neonatal period. This emphasizes the importance of adequate obstetric care, rational use of surfactant, and physiological respiratory support immediately after birth, including the use of CPAP, which can prevent the development of severe RDS and reduce the need for surfactant treatment [5, 14].

## Conclusions

1. The severity of RDS in a premature infant is the main factor that significantly and independently determines the risk of IVH within the first 72 hours of life. Additional factors that increase this risk are complicated course of RDS, using asynchronous mechanical ventilation with rigid parameters, inotropes administration, mother`s or infant`s infection diseases (complications), and acidosis development. The incidence of early hemorrhages can be reduced with antenatal steroids administration. The onset of early IVH significantly increases the risk of infant death.

2. Late IVH, which occurs beyond 72 hours of life, is a common problem of very premature infants. The occurrence of this complication is significantly associated with impaired hemodynamics in the early postnatal period, increasing severity and complicated course of RDS, as well as methods of RDS treatment.

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## Реферати

### ПЕРЕДУМОВИ ВИНИКНЕННЯ РАННІХ ТА ПІЗНІХ ВНУТРІШНЬОШЛУНОЧКОВИХ КРОВОВИЛИВІ У НЕДОНОШЕНИХ НОВОНАРОДЖЕНИХ З ДУЖЕ МАЛОЮ МАСОЮ ТІЛА

**Добрянський Д.О., Горинець І.Б., Меньшикова А.О., Содомора О.О., Мацюра О.І.**

У когортному дослідженні вивчені чинники ризику виникнення ранніх та пізніх внутрішньошлуночкових крововиливів (ВШК) у значно недоношених новонароджених. Під спостереженням перебували 111 немовлят із середнім гестаційним віком 29,59±2,59 тиж. Установлено відмінність між чинниками ризику, що пов'язані з розвитком ранніх і пізніх крововиливів. На відміну від ранніх ВШК, імовірність виникнення пізніх крововиливів не залежала від маси тіла і гестаційної зрілості дитини, а також інфекційної патології перинатального періоду. Натомість, відповідний ризик визначався важкістю стану немовляти після народження і наявністю артеріальної гіпотензії в першу добу госпіталізації. Розвиток важкого респіраторного дистрес-синдрому (РДС) був вірогідно пов'язаний з виникненням ВШК незалежно від віку дитини. За підсумками логістичного регресійного аналізу ризик виникнення ранніх крововиливів достовірно визначався важкістю РДС (коефіцієнт співвідношення шансів (КСШ) – 6,05; 95% довірчий інтервал (ДІ): 1,35–27,17), а на ймовірність розвитку пізніх ВШК вірогідно впливала артеріальна гіпотензія в перші 24 год госпіталізації (КСШ – 16,6; 95% ДІ: 2,69–102,43).

**Ключові слова:** внутрішньошлуночкові крововиливи, вік на момент виникнення, чинники ризику, профілактика, значно недоношені новонароджені.

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### ПРЕДПОСЫЛКИ ВОЗНИКНОВЕНИЯ РАННИХ И ПОЗДНИХ ВНУТРИЖЕЛУДОЧКОВЫХ КРОВОИЗЛИЯНИЙ У НЕДОНОШЕННЫХ НОВОРОЖДЕННЫХ С ОЧЕНЬ МАЛОЙ МАССОЙ ТЕЛА

**Добрянский Д.А., Горинец И.Б., Меньшикова А.А., Содомора О.А., Мацюра О.И.**

В когортном исследовании изучены факторы риска возникновения внутрижелудочковых кровоизлияний (ВЖК) у глубоко недоношенных новорожденных. Под наблюдением находились 111 младенцев со средним гестационным возрастом 29,59±2,59 недель. Установлено отличие факторов риска, связанных с развитием ранних и поздних кровоизлияний. В отличие от ранних ВЖК, вероятность возникновения поздних кровоизлияний не зависела от массы тела и гестационной зрелости ребенка, а также от инфекционной патологии перинатального периода. Соответствующий риск определялся тяжестью состояния младенца после рождения и наличием артериальной гипотензии в первые сутки госпитализации. Развитие тяжелого респираторного дистрес-синдрома (РДС) было достоверно связано с возникновением ВЖК независимо от возраста ребенка. По итогам логистического регрессионного анализа риск возникновения ранних кровоизлияний достоверно зависел от тяжести РДС (коэффициент соотношения шансов (КСШ) – 6,05; 95% доверительный интервал (ДИ): 1,35–27,17), а на вероятность развития поздних ВЖК существенно влияла артериальная гипотензия в первые 24 часа госпитализации (КСШ – 16,6; 95% ДИ: 2,69–102,43).

**Ключевые слова:** внутрижелудочковые кровоизлияния, возраст на момент возникновения, факторы риска, профилактика, глубоко недоношенные новорожденные.

Рецензент Похилько В.І.