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A.M. Aliyeva[1], A.A. Polukhova[1,2], S.R. Nasirova[1], S.A. Mekhdiyeva[1], N.M. Mammadova[2], A.I. Adilova[2]

The role of perinatal risk factors in the development of necrotizing enterocolitis in preterm infants

[1]Scientific Research Pediatrics Institute named after K.Y. Farajova, Baku, Azerbaijan
[2]Azerbaijan Medical University, Baku

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Necrotizing enterocolitis (NEC) is one of the most severe perinatal diseases and is associated with high mortality among preterm infants.
Aim – to investigate the role of perinatal risk factors in the development of NEC.
Material and methods. The study involved 69 infants with NEC treated in the Neonatal Intensive Care Unit and the Preterm Infants Unit (study groups I and II). The control (III) group consisted of 31 conditionally healthy infants. The diagnosis of NEC was established according to Bell's criteria. In turn, each group was subdivided into two subgroups: infants weighing less than 1500 g and those weighing more than 1500 g. In order to determine the role of antenatal risk factors in the development of NEC among the infants included in the study, genital and extragenital pathologies, as well as the course of pregnancy and delivery, were evaluated in 100 mothers and analyzed across the study groups.
Results. Thus, based on the results of the present study, in mothers of infants in Groups I and II, turbid amniotic fluid ($p<0.001$), intrauterine infection ($p<0.001$), and birth asphyxia ($p<0.001$), as well as in mothers of infants in Group II, arterial hypertension ($p<0.05$), preeclampsia ($p<0.05$), and operative delivery ($p<0.001$), are significant ante- and intranatal risk factors for the development of NEC. In addition, respiratory distress syndrome ($p<0.05$) and hypoxic-ischemic encephalopathy ($p<0.05$) were identified as postnatal risk factors for the development of NEC in low birth weight newborns.
Conclusion. The findings of the present study demonstrate that both antenatal and intranatal factors play a significant role in the development of NEC in newborns, particularly in low birth weight infants.
The study complied with the principles of the Declaration of Helsinki and was approved by the institutional Ethics Committee. Informed consent was obtained from the patients prior to participation.
The authors declare no conflict of interest.
Keywords: necrotizing enterocolitis, preterm infant, perinatal risk factors.

Роль перинатальних факторів ризику в розвитку некротизуючого ентероколіту в недоношених дітей

A.M. Aliyeva[1], A.A. Polukhova[1,2], S.R. Nasirova[1], S.A. Mekhdiyeva[1], N.M. Mammadova[2], A.I. Adilova[2]
[1]Науково-дослідний інститут педіатрії імені К.Й. Фараджової, м. Баку, Азербайджан
[2]Азербайджанський медичний університет, м. Баку

Некротизуючий ентероколіт (НЕК) є одним із найважчих перинатальних захворювань і пов'язаний із високою смертністю серед недоношених дітей.
Мета – дослідити роль перинатальних факторів ризику в розвитку НЕК.
Матеріали та методи. Обстежено 69 дітей із НЕК, які пройшли лікування у відділенні інтенсивної терапії новонароджених та відділенні для недоношених дітей (дослідницькі групи I та II). Контрольну (III) групу становила 31 умовно здорова дитина. Діагноз НЕК встановлено за критеріями Белла. Кожну групу поділено на дві підгрупи: немовлята вагою менше 1500 г та ті, хто важив більше 1500 г. Для визначення ролі антенатальних факторів ризику в розвитку НЕК у немовлят, включених у дослідження, у 100 матерів було оцінено генітальні та екстрагенітальні патології, а також перебіг вагітності та пологів, які були проаналізовані в усіх досліджуваних групах.
Результати. У матерів немовлят I та II груп каламутна амніотична рідина ($p<0,001$), внутрішньоутробна інфекція ($p<0,001$) та асфіксія при народженні ($p<0,001$), а також у матерів немовлят II групи артеріальна гіпертензія ($p<0,05$), прееклампсія ($p<0,05$) та оперативні пологи ($p<0,001$) є значними антенатальними та інтранатальними факторами ризику розвитку НЕК. Крім того, респіраторний дистрес-синдром ($p<0,05$) та гіпоксично-ішемічна енцефалопатія ($p<0,05$) були визначені як постнатальні фактори ризику розвитку НЕК у новонароджених із низькою вагою при народженні.
Висновок. Результати цього дослідження демонструють, що як антенатальні, так і інтранатальні фактори відіграють значну роль у розвитку НЕК у новонароджених, особливо в дітей із низькою вагою при народженні.
Дослідження відповідало принципам Гельсінської декларації та було схвалено комітетом з етики установи. Інформовану згоду було отримано від пацієнтів перед участю.
Автори заявляють про відсутність конфлікту інтересів.
Ключові слова: некротизуючий ентероколіт, недоношена дитина, перинатальні фактори ризику.

Despite numerous scientific studies devoted to necrotizing enterocolitis (NEC) at present, investigation into more sensitive and specific risk factors involved in the development of this disease continues. Identification, prevention, and elimination of NEC risk factors would contribute not only to earlier diagnosis but also to a reduction in the incidence and severity of the disease. According to several sources, gestational age, birth weight, Apgar scores, prolonged labor, maternal chronic diseases (arterial hypertension, chorioamnionitis, respiratory disorders), resuscitation measures, use Continuous Positive Airway Pressure (CPAP) support of respiratory support in CPAP mode, type of feeding, bacterial intestinal colonization, congenital heart defects, sepsis, intracranial hemorrhage, fortification of breast milk, central venous catheterization, red blood cell transfusion, elevated hemostatic indices, and the presence of respiratory disorders are considered risk factors for NEC [1,2,4–6].

The aim of the study was to investigate the perinatal risk factors of NEC in preterm infants.

Materials and methods of the study

The study involved 69 infants with NEC treated in the Neonatal Anesthesiology and Intensive Care Unit and the Preterm Infants Unit of the Scientific Research Institute of Pediatrics named after K.Y. Farajova (study group). The Control group consisted of 31 conditionally healthy infants examined at Maternity Hospital No. 7. The diagnosis of NEC was established according to Bell's criteria.

All infants enrolled in the study were divided into two groups: the main (NEC) group and the control group. In turn, each group was subdivided into two subgroups: Group I consisting of 25 patients with NEC and a body weight of less than 1500 g, Group II consisting of 44 patients with NEC and a body weight of more than 1500 g, Group IIIa the Control group consisting of 9 newborns with a body weight of less than 1500 g, Group IIIb the Control group consisting of 22 newborns with a body weight of more than 1500 g.

To determine the role of perinatal risk factors in the development of NEC, a retrospective analysis was performed.

In order to determine the role of antenatal risk factors in the development of NEC among the infants included in the study, genital and extragenital pathologies, as well as the course of pregnancy and delivery, were evaluated in 100 mothers and analyzed across the study groups. To assess the clinical characteristics of NEC, clinical data from the neonatal period of 69 preterm infants diagnosed with NEC were compared with the outcomes of 31 infants without NEC.

All numerical data obtained during the study were statistically analyzed using IBM SPSS Statistics version 26, applying variation, discriminant, and analysis of variance (ANOVA) methods. The level of statistical significance was set at $p<0.05$.

Results of the study and discussion

The frequency of extragenital diseases among the children's mothers included in the study groups differed significantly between the groups. Arterial hypertension (between Groups II and IIIb, $p=0.034$) and a history of certain intrauterine infections in mothers (herpes, cytomegalovirus, toxoplasmosis) were more frequently observed among the children's mothers in the study groups (Group I vs. Group IIIa, $p=0.022$; Group II vs. Group IIIb, $p<0.001$) (Table 1).

In both the study and comparison groups, mothers of infants in Groups I and IIIa had a higher incidence of threatened miscarriage during pregnancy (36% and 44%, respectively). This difference indicates a more complicated course of intrauterine development in very low birth weight preterm infants.

As shown in Table 1, the incidence of preeclampsia among mothers of infants in Group II was statistically significantly higher compared with the Control group ($p=0.016$). In mothers of infants in both Groups I and IIIa, this indicator was also elevated (24% and 33%, respectively); however, no statistically significant difference was observed between these subgroups.

The presence of turbid amniotic fluid was higher in both subgroups of the study group (Groups I and II) compared with the Control groups (Groups IIIa and IIIb), and this difference was statistically significant ($p<0.001$ for both subgroups).

Based on the Apgar score assessment performed at the 1st and 5th minutes, it is evident that intrapartum asphyxia occurred more frequently in infants belonging to the study subgroups. A statistically significant difference was identified in the 1-minute Apgar scores (comparison of Groups I and IIIa: $p=0.001$; comparison of Groups II and IIIb: $p<0.001$). The 5-minute Apgar score differences were $p=0.001$ and $p=0.311$, respectively. Most likely,

Table 1

Characteristics of the course of pregnancy among mothers across the study groups

Pregnancy-related pathologies	Groups	N	Absolute number, %	Pχ2	PU
Preeclampsia	I	25	6 (24.0%)	0.586	0.592
	IIIa	9	3 (33.3%)		
	II	44	10 (22.7%)	0.015*	0.016*
	IIIb	22	0 (0%)		
Turbid amniotic fluid	I	25	23 (92.0%)	<0.001*	<0.001*
	IIIa	9	3 (33.3%)		
	II	44	28 (63.6%)	<0.001*	0.001*
	IIIb	22	4 (18.2%)		
Arterial hypertension	I	25	8 (32%)	0.223	0.230
	IIIa	9	1 (11.1%)		
	II	44	8 (18.2%)	0.033*	0.034*
	IIIb	22	0 (0%)		
Intrauterine infection (IUI)	I	25	14(56.0%)	0.020*	0.022*
	IIIa	9	1 (11.1%)		
	II	44	19 (43.2%)	<0.001*	<0.001*
	IIIb	22	0 (0%)		
Threatened miscarriage	I	25	9 (36.0%)	0.888	0.889
	IIIa	9	4 (44.4%)		
	II	44	10 (22.7%)	1.000	0.502
	IIIb	22	5 (22.7%)		

Note: statistical significance of differences between subgroup indicators; $P\chi^2$ – according to the Pearson chi-square test; Pu – according to the Mann-Whitney U test; * – the null hypothesis is rejected.

birth asphyxia in the infants included in the study was not solely related to intrapartum factors, but also to chronic intrauterine hypoxia and inadequate antenatal development, leading to exhaustion of the compensatory and protective mechanisms of the organism (Table 2).

Completion of pregnancy by cesarean section occurred at a markedly higher frequency than vaginal delivery in infants of the study groups compared with the regional average (Groups I and IIIa: 72% and 55.6%, respectively, p=0.373; Groups II and IIIb: 59.1% and 13.6%, respectively, p=0.001). Mothers of infants with a birth weight below 1500 g (Group I) more frequently underwent operative delivery, and mortality among these infants was significantly higher ($p<0.05$). In both NEC groups, birth asphyxia and a pathological course of the early neonatal period were noted, and the infants' condition at hospital admission was severe ($p<0.001$).

A pathological course of the early neonatal period was observed in 90–100% of infants with NEC, regardless of gestational age and birth weight. This finding reflects the adverse impact of unfavorable ante- and intranatal conditions on the adaptation of newborns to extrauterine life and the more severe manifestation of neonatal pathologies.

In both subgroups of the study group (Groups I and II), the incidence of respiratory distress syndrome (RDS) was significantly higher compared with the Control groups. Among infants in the study group, particularly those with a birth weight below 1500 g, cardiorespiratory adaptation was more severe, necessitating more frequent use of mechanical ventilation (MV) and CPAP for respiratory support.

Neurosonographic findings across the study groups, including the incidence of intracranial hemorrhage of varying severity and periventricular leukomalacia (PVL), did not differ statistically significantly between the subgroups. Although the higher incidence of PVL and grade III intracranial hemorrhage in Group I did not reach statistical significance, it indicates a more severe course of central nervous system injury compared with the other

Table 2

Assessment of newborns according to the Apgar score

Indicator	Groups	N	M±m (min-max)	PF	PU
1-minute Apgar scores	I	25	4.5±0.3 (1–7)	0.004*	0.001*
	IIIa	9	6.3±0.2 (5–7)		
	II	44	5.7±0.2 (2–7)	<0.001*	<0.001*
	IIIb	22	6.7±0.2 (4–7)		
5-minute Apgar score	I	25	5.6+0.3 (3–7)	0.004*	0.001*
	IIIa	9	7.0±0.2 (6–8)		
	II	44	6.6±0.2 (3–8)	0.319	0.311
	IIIb	22	6.8±0.1 (5–7)		

Note: statistical significance of differences between subgroup indicators: PF – according to Fisher's exact test; Pu – according to the Mann-Whitney U test; * – the null hypothesis is rejected.

Table 3

Selected early neonatal indicators of the newborns included in the study groups.

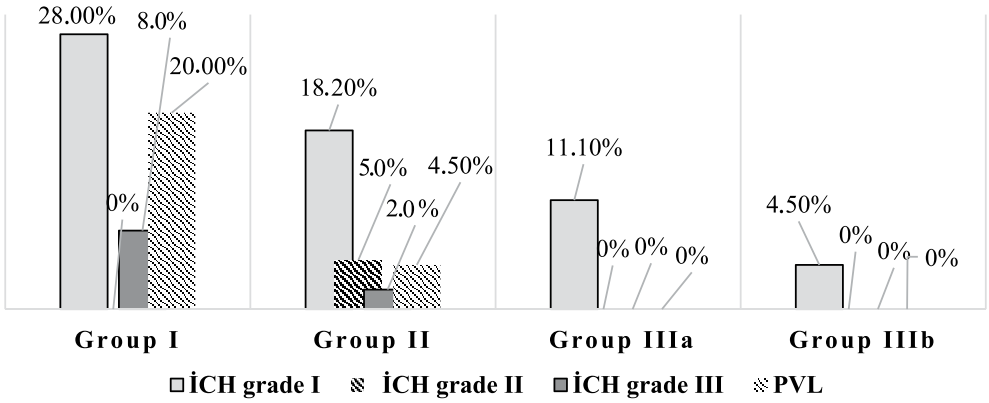
Indicator	Groups	N	Absolute number, %	Pχ^2	PU
RDS	I	25	8 (32.0 %)	0.223	0.230
	IIIa	9	1 (11.1 %)		
	II	44	11 (25.0 %)	0.042	0.044*
	IIIb	22	1 (4.5 %)		
MV in the early neonatal period	I	25	6 (24.0%)	0.105	0.111
	IIIa	9	0 (0%)		
	II	44	3 (6.8%)	0.210	0.213
	IIIb	22	0 (0%)		
CPAP in the early neonatal period	I	25	7 (28.0%)	0.075	0.079
	IIIa	9	0 (0%)		
	II	44	5 (11.4%)	0.100	0.103
	IIIb	22	0 (0%)		

groups. The higher frequency of grade II and III hemorrhages in the study Groups I and II is most likely associated with morphofunctional immaturity, hypoxic-ischemic and infectious-toxic inflammation, weakness of the germinal matrix, and increased permeability of cerebral vessels in infants with NEC (Figure 1).

Severe hypoxic-ischemic encephalopathy was observed at a significantly higher frequency in both subgroups of the study (Groups I and II) and demonstrated statistical significance in infants with a birth weight above 1500 g (comparison of Groups II and IIIb, $p<0.001$).

Analysis of feeding characteristics revealed that among preterm infants who developed NEC, the proportion of infants who had not received enteral feeding was significantly higher ($p<0.05$), whereas the proportion of those receiving breast milk was significantly lower ($p<0.05$). Failure to implement minimal enteral feeding and preference for formula feeding cannot be excluded as contributing factors to the development and complicated course of NEC (Figure 2).

Studies have demonstrated that breast milk feeding, compared with formula feeding, reduces the incidence of NEC in preterm infants. Breastfeeding is beneficial not only for the prevention of NEC but also for the postoperative rehabilitation of newborns. In addition, in low birth weight infants, the initiation of minimal enteral feeding prior to establishing full enteral nutri-



Notes: ICH – intracranial hemorrhage, PVL – periventricular leukomalacia.
Fig. 1. Results of cranial ultrasound examination across the study groups

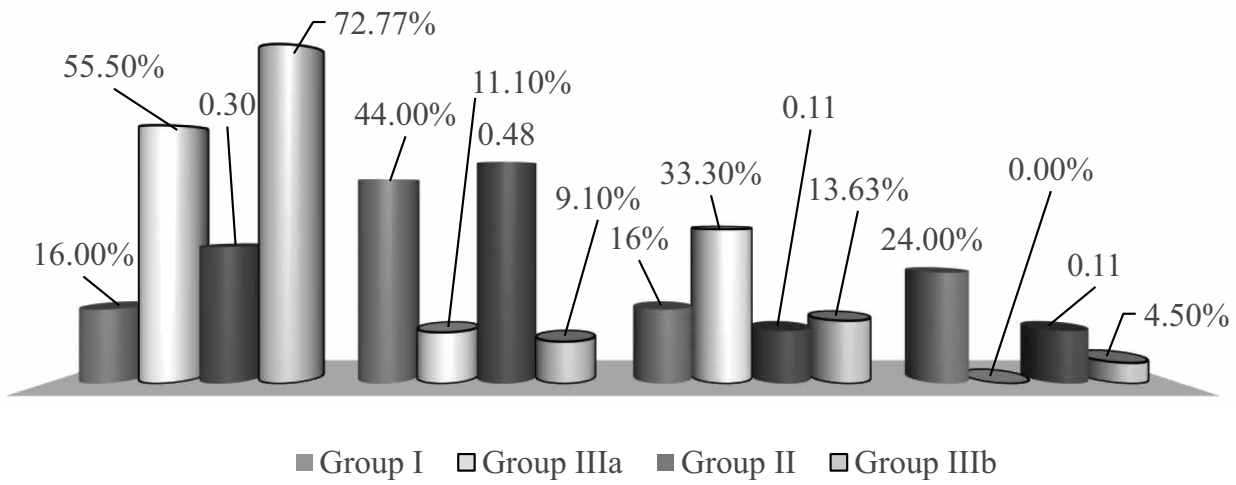


Fig. 2. Feeding characteristics of infants across the study groups

tion represents a safer alternative and contributes to a reduction in the incidence of NEC [3,7,8].

Thus, based on the results of the present study, in both NEC groups, turbid amniotic fluid ($p<0.001$), intrauterine infection ($p<0.001$), and birth asphyxia ($p<0.001$), as well as arterial hypertension ($p<0.05$), preeclampsia ($p<0.05$), and operative delivery ($p<0.001$) in mothers of infants in Group II, constitute significant ante- and intranatal risk factors for the development of NEC. Furthermore, RDS ($p<0.05$) and hypoxic-ischemic encephalopathy ($p<0.05$) were identified as postnatal risk factors for NEC in low birth weight infants.

Conclusion

The findings of the present study demonstrate that both antenatal and intranatal factors play a significant role in the development of necrotizing enterocolitis in newborns, particularly in low birth weight infants. Turbid amniotic fluid, intrauterine infection, and birth asphyxia were identified as major risk factors in both NEC groups, while maternal arterial hypertension, preeclampsia, and operative delivery were additionally associated with an increased risk of NEC in infants of Group II. Moreover, RDS and hypoxic-ischemic encephalopathy were determined to be important postnatal risk factors contributing to the development of NEC. These findings highlight the multifactorial nature of NEC and emphasize the importance of early identification and careful monitoring of high-risk infants during the perinatal and neonatal periods.

The authors declare no conflict of interest.

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Відомості про авторів:
Aliyeva Aytakin Mahir – Department of newborn pathology, Scientific Research Institute of Pediatrics named after K.Y. Farajova. Address: Azerbaijan Republic. Baku city, AZ 1022 acad. M. Mirgasimov str. 1A. https://orcid.org/0000-0003-2685-6790.
Polukhova Aynur Ali – PhD in Medical Sciences, Associate Professor, Scientific Research Institute of Pediatrics named after K.Y. Farajova. Address: Azerbaijan Republic. Baku city, AZ 1022 acad. M. Mirgasimov str. 1A. https://orcid.org/0009-0005-5647-4840.
Nasirova Sevinj Ramiz – PhD in Medical Sciences, Associate Professor, Scientific Research Institute of Pediatrics named after K.Y. Farajova. Address: Azerbaijan Republic. Baku city, AZ 1022 acad. M. Mirgasimov str. 1A. https://orcid.org/0000-0002-3113-3282.
Mekhtiyeva Sevinj Amil – PhD in Medical Sciences, Scientific Research Institute of Pediatrics named after K.Y. Farajova. Address: Azerbaijan Republic. Baku city, AZ 1022 acad. M. Mirgasimov str. 1A.
Mammadova Naiba Mirzali – PhD in Medical Sciences, Department of Child desease II, Azerbaijan Medical University. Address: Azerbaijan Republic, Baku, Samad Vurgun, 163. https://orcid.org/0009-0009-6377-0890.
Adilova Aytekin İsmail – PhD in Medical Sciences, Associate Professor, Department of Child desease II, Azerbaijan Medical University. Address: Azerbaijan Republic. Baku, Samad Vurgun, 163. https://orcid.org/0009-0005-3105-0304.
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