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Necrotizing enterocolitis in premature infants: the importance of risk factors in its development

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Aim: to investigate the relationship between different risk factors and the neonatal development of necrotizing enterocolitis (NEC).

Material and methods. A prospective retrospective case-control study of premature infants with suspected of NEC in 2020–2021 was conducted. A total of 88 cases of preterm neonates with suspected NEC and 30 preterm neonates in the control group were identified and analyzed. NEC diagnosis was performed in 29 (32.5%) infants. The collected variables included pregnancy- and maternal-related risk factors, physical developmental indicators of infants, Apgar score, mechanical ventilation, mode and type of delivery, sex of infants. Statistical processing of indicators was carried out in the Windows SPSS20 system. Differences at $p<0.05$ were considered reliable.

Results. A relationship between the number of pregnancies and NEC in preterm infants was found. The birth of a newborn from the 3rd–4th pregnancy increased the risk of NEC development ($p=0.001$). In babies whose diagnosis of NEC is not confirmed, the height was 38.9±0.5 sm (min 30, max 47); with a confirmed diagnosis of NEC, it was 41.2±0.7 cm (min 34, max 48) ($p=0.019$).

Conclusions. The factors recognized by this case-control study that increased the risk of neonatal NEC contained heterogeneity. There were no significant differences in terms of other maternal, pregnancy and neonatal risk factors in the development of NEC.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Ethics Committee of Azerbaijan Medical University. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: premature infants, necrotizing enterocolitis, risk factors.

Некротичний ентероколіт у недоношених дітей: значення факторів ризику в його розвитку

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Мета: дослідити зв'язок між різними факторами ризику та неонатальним розвитком некротизуючого ентероколіту (НЕК).

Матеріал і методи. Було проведено проспективне ретроспективне дослідження типу «випадок-контроль» недоношених дітей із підозрою на НЕК у 2020–2021 роках. Виявлено та проаналізовано 88 випадків недоношених новонароджених із підозрою на НЕК та 30 недоношених контрольної групи. Діагностику НЕК проведено у 29 (32,5%) дітей грудного віку. До зібраних змінних належали фактори ризику, пов'язані з вагітністю та матері, показники фізичного розвитку немовлят, оцінку за шкалою Апгар, штучну вентиляцію легень, спосіб та тип пологів, стать немовлят. Статистичну обробку показників проведено в системі Windows SPSS20. Відмінності при $p<0,05$ вважалися надійними.

Результати. Виявлено зв'язок між кількістю вагітностей і НЕК у недоношених дітей. Народження новонародженого від 3–4-ї вагітності підвищувало ризик розвитку НЕК ($p=0,001$). У дітей, у яких не підтверджено діагноз НЕК, зріст становив 38,9±0,5 см (min 30, max 47); з підтвердженим діагнозом НЕК — 41,2±0,7 см (min 34, max 48) ($p=0,019$).

Висновки. Фактори, визнані в цьому дослідженні типу «випадок-контроль», що підвищували ризик неонатального НЕК, містили різнорідність. Не було виявлено суттєвих відмінностей щодо інших факторів ризику розвитку НЕК у матері, вагітної та новонародженого.

Дослідження виконано відповідно до принципів Гельсінської Декларації. На проведення досліджень отримано інформовану згоду пацієнток. Протокол дослідження ухвалений Етичним комітетом Азербайджанського медичного університету.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: недоношені діти, некротичний ентероколіт, фактори ризику.

Introduction

Necrotizing enterocolitis (NEC) is a devastating multifactorial disease in newborns, characterized by intestinal necrosis in the ileum, jejunum, and colon, with clinical signs such as abdominal distension, vomiting, bloody stool, septic shock, and in severe cases, signs of disseminated intravascular coagulation [17]. This disease leads to high service costs, prolonged hospitalization, long-term neurological (49%) and gastrointestinal (39%) complications [3,7]. Because the pathogenesis of the disease is multifactorial, it is difficult to predict which infants will develop NEC, as there are very few clear risk factors associated with NEC and many suspected risk factors [13]. In addition to the generally accepted neonatal risk factors [8,11,12,14] for the development of NEC, such as prematurity, low birth weight, artificial feeding, and neonatal infection, there is little information about maternal (prenatal) risk factors [10]. The observation of different relationships in different studies is likely due to geographic location, population diversity, and other environmental factors [9]. There is no general estimate of the in-

cidence of NEC worldwide. With the continuous increase in the survival of premature births, the risk factors related to NEC should be studied and used in the preparation of a plan for reducing the disease and its complications [2]. The identification of factors contributing to the development of NEC can lead to the selection of infants with risk factors for NEC and the creation of developmental strategies aimed at the prevention and early treatment of NEC [4].

Taking into consideration the above, we considered it important to study the relationship between maternal risk factors, pregnancy-related pathologies, physical development indicators and the occurrence of NEC.

All of the above confirms the relevance of this research work and creates conditions for conducting research on this basis.

The **aim** of the study: to investigate the role of risk factors in the development of neonatal NEC.

Material and methods of the study

The study is based on the results obtained from the study of the role of maternal risk factors, somatic diseases, pregnancy-related pathologies, physical development indicators of the newborn in the development of the disease in premature newborns with initial clinical signs of suspected NEC.

This prospective-retrospective case-control study was conducted at Scientific Research Institute of Pediatrics named after K. Farajova, Republican Perinatal Center, Baku Medical Plaza and Maternity hospital No. 5 named after Shamama Alasgarova (2020–2021). A total of 118 infants were included in the study. Of these, 88 were suspected of NEC, and 30 were healthy. Out of 88 babies, there were 43 girls and 45 boys, the average gestational age (GA) was 31.03±2.68 weeks (min 26, max 36), and the average weight was 1478.3±464.35 (min 800 g, max 2500 g). The average GA of 30 conventionally healthy preterm infants (15 girls and 15 boys) was 34.3±1.97; min 28, max 36 weeks; and the average weight was 2042.6±356.03 g; min 900 g, max 2500 g.

In turn, 88 sick children were divided into two groups: infants with symptoms of central nervous system damage along with suspicion of NEC were in the Group I (n=32), and those without the damage to central nervous system were in the Group II (n=56). After confirmation of the NEC diagnosis, all children were grouped into subgroups: A — confirmed (IA, n=9; IIA, n=20) and B — unconfirmed (IB, n=23; IIB, n=36) subgroups according to the confirmation of NEC diagnosis. The control group consisted of 30 premature infants without NEC.

The diagnosis of NEC was confirmed based on clinical, laboratory (blood cell count, C-reactive protein, stool test) and instrumental (abdominal X-ray and abdominal ultrasonography) indicators. The primary clinical symptoms of NEC in all patients are abdominal distention with foam, food intolerance, emesis, vomiting (mainly with bile), blood in stool, apnea and other signs.

Exclusion criteria in the study:

— congenital and chromosomal anomalies;

— infants without suspicion of NEC during the first 3 weeks.

The maternal and child risk factors (*in vitro* fertilization — IVF cases; the presence of preeclampsia and anemia during pregnancy, the number of pregnancies, GA, Apgar scores, CPAP (continuous positive airway pressure) therapy cases applied in the early neonatal period were studied. In addition, physical development indicators of the children (weight, height, head circumference, chest circumference) were measured. The weight of the children was measured by a hanging scale, height — in the supine position with a recumbent baby length scale.

Statistical processing of indicators was carried out in the Windows SPSS20 system. The arithmetic average indicators (based on all the quantitative indicators we received — mean (average indicator); SD — how much the indicators differ from the mean squared difference and minimum, maximum indicators are given (Mean±SD). The Chi-Square (χ^2) table was used for descriptive evaluation of quality indicators. The odds ratio (OR) with 95% confidence interval (CI) was also calculated by univariate (one variable) analysis and $p<0.05$ was considered statistically significant.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Local Ethics Committee of a participating institution. The informed consent of the patient was obtained for conducting the studies.

Results of the study

The data related to risk factors with the development of neonatal NEC was analyzed. The relationship between in vitro fertilization cases; the presence of preeclampsia and anemia during pregnancy, GA, Apgar scores, and CPAP

Table 1

The relationship of risk factors with the development of neonatal NEC

Risk factors		Group I (confirmed NEC)	Group II (no confirmed NEC)	Univariate OR (95% CI)	P
Test-tube baby (IVF)	No	27 (25%)	81 (75%)	0.8 (0.15–3.8)	0.725
	Yes	2 (20%)	8 (80%)		
Sex	Male	15 (25%)	45 (75%)	0.9 (0.41–2.2)	0.913
	Female	14 (24.1%)	44 (75.9%)		
Preeclampsia	No	26 (25%)	78 (75%)	0.818 (0.21–3.2)	0.771
	Yes	3 (21.4%)	11 (78.6%)		
Anemia	No	20 (24.1%)	63 (75.9%)	1.09 (0.44–2.7)	0.852
	Yes	9 (25.7%)	26 (74.3%)		
The number of pregnancies	1-2	13 (16.3%)	67 (83.8%)	4.5 (1.7–11.4)	0.001
	3-4	14 (46.7%)	16 (53.3%)		
Gestational age	>34 weeks	4 (13.8%)	25 (86.2%)	2.4 (0.8–7.7)	0.12
	⩽34 weeks	25 (28.1%)	64 (71.9%)		
Apgar score in the 1st min	>5 point	15 (27.8%)	39 (72.2%)	0.72 (0.31–1.68)	0.458
	⩽5point	14 (21.9%)	50 (78.1%)		
Apgar score in 5th min	>5 point	18 (21.2%)	67 (78.8%)	1.86 (0.76–4.54)	0.169
	⩽5 point	11 (33.3%)	22 (66.7%)		
CPAP therapy	No	17 (37%)	29 (63%)	0.68 (0.28–1.68)	0.403
	Yes	12 (28.6%)	30 (71.4%)		

therapy applied in the early neonatal period and the development of NEC was investigated and reflected in Table 1.

In the Group with confirmed NEC, newborns from the 1st and 2nd pregnancies accounted for 48.1%, and newborns from the 3rd–4th pregnancies — 51.9% (the expected count is 7.4, but the actual count is 14, which is related to crosstabulation) (χ^2=11.0; p=0.001). Thus, 5 children (18.5%) in the Subgroup IA (expected count is — 2.9) and 7 children (8.4%) (expected count — 9.1) in the Subgroup IB were born from the 4th pregnancy (χ^2=11.20; p=0.082).

The frequency of test-tube babies was more common in the Group II (n=9; 16.1%), while in the Group I only one baby (3.1%) was a test-tube baby (χ^2=8.125, p=0.017). However, the relationship between confirmation of the NEC diagnosis and NEC outcome (surgery or death) and test-tube infants was not noted.

Literature data assessing the relationship between maternal preeclampsia and the development of neonatal NEC are controversial [11]. L. Perger [15] and others in their study considered maternal preeclampsia as an independent risk factor in the development of NEC in some subgroups, while in other study, it was shown that there is a negative relationship between NEC and preeclampsia (PE) [1]. In our study, there was no relationship between groups and subgroups with the presence of PE and anemia during pregnancy. In particular, since these pathologies are more common in pregnant women and cause fetal hypoxia, these pathologies were investigated and the results are given in the Table 1.

There was no difference between Group I and Group II in maternal somatic diseases. There were: coagulation disorder — 1 (3.1%), hypothyroidism — 1 (3.1%) in the mothers of babies from Group I; in the Group II — 1 hypothyroidism (1.8%); HELLP syndrome was noted in 1 (1.8%), cardiovascular diseases in 2 (3.6%) (χ^2=7.18; p=0.304).

The literature data on type of delivery — vaginal or by caesarean section is controversial. In our study, according to the study of Yan Su et al. [17], no relationship was found between vaginal or cesarean delivery and the development of NEC. Thus, 24 (75%) in the Group I, and 42 (75%) in the Group II were delivered by caesarean section (χ^2=0.88, p=0.64). There was no relationship between the type of delivery and the confirmation of NEC diagnosis, as well as the results of NEC.

Among the indicators of physical development of the newborn, especially low birth weight is considered an important prognostic factor of NEC. In studies, more intrauterine growth retardation and low birth weight were considered risk factors for developing NEC [11].

Since the odds ratio of birth weight as a prognostic factor of NEC varies between 0.999 and 1.001, its relationship with NEC has been controversial [16]. In our study, the birth weight, height, head and chest circumference of all newborns were measured in the delivery room, and the

Table 2

The comparison of physical development indicators of infants within groups

Indicators	Groups	Mean	Std. Deviation	Std. Error	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Weight	Group I	1391.87	417.98	73.89	1241.17	1542.57	800.00	2200.00
	Group II	1527.76	485.55	64.88	1397.73	1657.80	800.00	2500.00
Height	Group I	39.21	3.53	0.62	37.94	40.49	32.00	47.00
	Group II	39.93	4.34	0.58	38.77	41.10	30.00	48.00
Head circumference	Group I	27.64	2.59	0.45	26.70	28.57	20.00	31.00
	Group II	28.16	2.86	0.38	27.39	28.92	22.00	34.00
Chest circumference	Group I	25.93	2.27	0.40	25.11	26.75	22.00	30.00
	Group II	26.28	2.84	0.38	25.52	27.04	20.00	32.00

comparison of the indicators by groups is given in the Table 2.

Indicators were not statistically different between the Group I and Group II.

In 88 infants suspected of NEC, when physical development indicators were compared according to the confirmation of the diagnosis, a statistical difference was noted only according to the height indicator. In babies whose diagnosis of NEC is not confirmed, the height was 38.9±0.5 cm (min 30, max 47); with confirmed diagnosis of NEC, it was 41.2±0.7 cm (min 34, max 48) (p=0.019). Considering that height, especially intrauterine development, is affected by various factors in the early fetal period of pregnancy, it is seen that there is no relationship between the progress of this period of pregnancy and NEC in these babies.

Although maternal hypertension is not statistically significant in the risk of neonatal NEC, children of these mothers had 2 times more cases of NEC. In our case, the statistical accuracy of height in the development of NEC suggests that this disease is more likely to be related to pathologies associated with the last trimester of pregnancy. Thus, in our study, the height of babies diagnosed with NEC is greater in Subgroup IA than Subgroup IB, and it is related to the normal course of fetal development in the 2nd trimester of pregnancy. The impact of these pathological factors mostly coincided with the 3rd trimester of pregnancy and caused premature birth.

No statistical difference was noted between groups and subgroups according to GA. Thus, GA was 30.7±0.48 weeks (min 26, max 36) in the Group I, and 31.2±2.66 weeks (min 26, max 35) in the Group II; in the Subgroup IA — 30.67±3.2 weeks (min 26, max 35); and in the Subgroup IB 30.74±2.6 weeks (min 27, max 36); 31.4±3.0 weeks (min 26, max 35) in the Subgroup IIA; in the Subgroup IIB it was 31.1±2.47 weeks (min 26, max 35) (p>0.05). The non-significance of a statistical difference in GA between subgroups was due to the fact that our groups were matched by weight and GA, as we wanted to reduce sampling errors, and other factors were our research objective.

Discussion

The condition of newborns in the early neonatal period is often formed depending on intrauterine developmental status. Also, adaptation disorders during this period can lead to NEC by causing intestinal ischemia. From this point of view, it is interesting to study the role of pathologies encountered in the early neonatal period in the development of NEC. First of all, when the baby is born, the baby's condition is assessed with the Apgar scale in the delivery room. Although the indicators of the assessment with the Apgar scale do not have prognostic significance, they dictate the necessary action plan by reflecting the current condition of the baby.

Although the infants of the control group were statistically significantly different from other groups according to Apgar scale scores (p=0.001), there was no statistically significant difference between the main and comparison groups. At the same time, 11 (37.9%) babies were diagnosed with NEC, the assessment with Apgar score in the 1st minute was 4–5 points (χ^2=6.206, p=0.102), and in 15 (55.7%), in the 5th minute it was estimated at 6–7 points (χ^2=5.7; p=0.126). Low Apgar scores at the 5th minute indicate the presence of early adaptation disorders of the baby and reflect the disorder of compensatory mechanisms. The results of our study deny the prognostic value of the Apgar score in the delivery room in confirming the diagnosis of NEC. The presence of hypoxia in these infants raised the suspicion of NEC due to general clinical signs in the early neonatal period.

There was no statistical difference between the groups according to the sex of the newborn. In the control and main groups, girls and boys had the same frequency, and in the comparison group, there were 29 (51.8%) boys, 27 (49.2%) girls (χ^2=0.012; p=0.913). A number of studies have also shown no relationship between the sex of the newborn and NEC [6].

Since 28 (87.5%) infants had signs of respiratory distress, CPAP therapy and mechanical ventilation were performed. The need for respiratory support in infants is associated with prematurity and surfactant deficiency. In our study, there was no statistically significant difference between CPAP therapy and the development of NEC (Table 1).

Study limitations. We could not compare the stages of the disease according to the degree of severity due to the small number of patients.

Conclusion

Thus, multiparity leads to the development of NEC, especially in cases where previous pregnancies ended in miscarriages, the number of current pregnancies did not correspond to the number of births, and in cases of complications of previous pregnancies. The research work has been informative for the diagnosis of NEC in low birth weight and very low birth weight children by demonstrating predictive performance in assessing risk factors, increasing the scope of early clinical interventions, improving survival and the quality of life of children affected by the disease, reducing the prolonged course of the disease and hospital costs.

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