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LEADING ANTENATAL FACTORS OF CONGENITAL PNEUMONIA IN PREMATURE NEWBORNS WITH VITAMIN D DEFICIENCY

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Abstract

Relevance: The incidence of congenital pneumonia varies about 1% among full-term newborns, and in premature infants up to 10%. From 10 to 40% of cases occupy a leading place in the structure of neonatal mortality [1,2]. Nissen M.D. [13], described that pneumonia was the cause of about 1.2 million neonatal deaths per year worldwide [9]. The role of vitamin D in the functioning and regulation of the immune system is important, since 1,25-dihydroxyvitamin D can contribute to an innate immature response to a pathogen [6]. Some studies have revealed a link between respiratory infectious diseases and vitamin D deficiency in serum in children [18,14].

Objective: To assess risk factors and the level of vitamin D in the blood serum of premature newborns with congenital pneumonia.

Materials and methods: case - control. The study was conducted on the basis of the Regional Perinatal Center of Semey, Republic of Kazakhstan. The study included premature newborns in the number of 228 children. Informational consents were received from mothers of newborns to participate in the study. The mothers were informed about the processing of the received data, with the subsequent publication of the research results, without specifying personal data. *Inclusion criteria:* premature newborns (gestation period from 22 weeks to 37 weeks). *Exclusion criteria:* children with malformations, genetic diseases, full-term newborns. The data analysis was carried out using the SPSS package version 20.0. To check the statistical significance of the differences between the group of "cases" and "controls", the Pearson criterion $\chi 2$ is used, and the odds ratio is calculated taking into account the 95% confidence interval. Continuous data is presented in the form of (M) and standard deviation (CO).

Results: The leading risk factors for congenital pneumonia in premature newborns were: infections of the mother, such as acute respiratory viral infections, pathology of the urinary system, premature discharge of amniotic fluid (18 hours), chorioamnionitis, preeclampsia, placental abruption led to a threatening fetal condition and premature birth.

Conclusion: Leading antenatal factors and vitamin D deficiency in premature newborns may be associated with a higher risk of developing congenital pneumonia.

Keywords: *congenital pneumonia, risk factors, premature newborn, vitamin D.*

Резюме

ВЕДУЩИЕ АНТЕНАТАЛЬНЫЕ ФАКТОРЫ ВРОЖДЕННОЙ ПНЕВМОНИИ У НЕДОНОШЕННЫХ НОВОРОЖДЕННЫХ С ДЕФИЦИТОМ ВИТАМИНА D

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Актуальность: Встречаемость врожденной пневмонии варьирует около 1% среди доношенных новорожденных, а у недоношенных до 10%. От 10 до 40% случаев занимает ведущее место в структуре неонатальной смертности [1,2]. Nissen M.D. [13], описывал, что пневмония явилась причиной около 1,2 млн. неонатальных смертей в год во всем мире [9]. Важна роль витамина D в функционировании и регуляции иммунной системы, поскольку 1,25-дигидроксивитамин D может способствовать врожденному незрелому ответу на патоген [6]. В некоторых исследованиях выявили связь респираторных инфекционных заболеваний и недостаточности витамина D в сыворотке у детей [18,14].

Цель: Оценка факторов риска и уровня витамина D в сыворотке крови недоношенных новорожденных с врожденной пневмонией.

Материалы и методы: случай - контроль. Исследование проведено на базе Областного перинатального центра города Семей, Республики Казахстан. В исследование вошли недоношенные новорожденные в количестве 228 детей. Получены информационные согласия от матерей новорожденных на участие в исследовании. Матери были проинформированы об обработке полученных данных, с последующей публикацией результатов исследований, без указания персональных данных. *Критерии включения:* недоношенные новорожденные (срок гестации от 22 недель до 37 недель). *Критерии исключения:* дети с пороками развития, генетическими заболеваниями, доношенные новорожденные. Анализ данных проводился с использованием пакета SPSS версии 20.0. Для проверки статистической значимости различий между группой «случаев» и «контролей» используется критерий χ2 Пирсона, а отношение шансов рассчитывается с учетом 95% доверительного интервала. Непрерывные данные представлены в виде (M) и стандартного отклонения (CO).

Результаты: Ведущими факторами риска врожденной пневмонии у недоношенных новорожденных явились: инфекции матери, такие как ОРВИ, патология мочевыделительной системы, преждевременное излитие околоплодных вод (>18 часов), хориоамнионит, преэклампсия, отслойка плаценты привели к угрожающему состоянию плода и преждевременным родам.

Вывод: Ведущие антенатальные факторы и дефицит витамина D у недоношенных новорожденных могут быть связаны с более высоким риском развития врожденной пневмонии.

Ключевые слова: *врожденная пневмония, факторы риска, недоношенный новорожденный, витамин D.*

Түйіндеме

D ДӘРУМЕНІ ЖЕТІСПЕЙТІН ШАЛА ТУЫЛҒАН НӘРЕСТЕЛЕРДЕГІ ТУА БІТКЕН ПНЕВМОНИЯНЫҢ ЖЕТЕКШІ АНТЕНАТАЛЬДЫ ФАКТОРЛАРЫ

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Өзектілігі. Туа біткен пневмонияның пайда болуы жетіліп туған жаңа туған нәрестелер арасында шамамен 1%, ал шала туылған нәрестелерде 10% -ке дейін өзгереді. Бұл жағдайлардың 10-40% - ы неоналдық өлім құрылымында жетекші орын алады [1,2]. Nissen M. D. [13], пневмония бүкіл әлемде жылына шамамен 1,2 миллион неоналдық өлімге себеп болғанын сипаттады [9]. Иммундық жүйенің жұмысында және реттелуінде D витаминінің рөлі маңызды, себебі 1,25-дигидроксивитамин D, патогенге туа біткен жетілмеген реакцияға ықпал етуі мүмкін [6].

Кейбір зерттеулерде балалардағы респираторлық жұқпалы аурулар мен қан сарысуындағы D дәрумені жетіспеушілігінің байланысы анықталды [18,14].

Мақсаты: туа біткен пневмониямен ауыратын шала туылған нәрестелердің қан сарысуындағы D дәрумені деңгейін және қауіп факторларын бағалау.

Материалдар мен әдістер: жағдайды-бақылау дизайны. Зерттеу Қазақстан Республикасы, Семей қаласының Облыстық перинаталдық орталығының базасында жүргізілді. Зерттеуге 228 нәрестеден тұратын шала туылған нәрестелер кірді. Зерттеуге қатысуға жаңа туған аналардан ақпараттық келісім алынды. Аналарға алынған деректерді өңдеу, кейіннен зерттеу нәтижелерін жариялау, дербес деректерді көрсетілмейтіні хабарланды. *Қосу критерийлері:* шала туылған нәрестелер (жүктілік мерзімі 22 аптадан 37 аптаға дейін). *Шектеу критерийлері:* даму ақаулары, генетикалық аурулары бар балалар, жетіліп туған нәрестелер. Деректерді талдау SPSS 20.0 нұсқасының пакетін қолдана отырып жүргізілді. "Жағдайлар" тобы мен "бақылаулар" арасындағы айырмашылықтардың статистикалық маңыздылығын тексеру үшін Пирсонның χ2 критерийі қолданылды, ал коэффициенттер коэффициенті 95% сенімділік аралығын ескере отырып есептеледі. Үздіксіз деректер (M) және стандартты ауытқу (Co) түрінде ұсынылған.

Нәтижелер: шала туылған нәрестелердегі туа біткен пневмонияның жетекші қауіп факторлары: ананың ЖРВИ, зәр шығару жүйесінің патологиясы, амниотикалық сұйықтықтың мерзімінен бұрын төгілуі (18 сағаттан артық), хориоамнионит, преэклампсия, плацентаның уақытынан бұрын ажырауы, ұрықтың қауіпті жағдайына және мерзімінен бұрын босануға әкелді.

Қорытынды: жетекші антенатальды факторлар және шала туылған нәрестелердегі D дәрумені тапшылығы туа біткен пневмонияның даму қаупімен байланысты болуы мүмкін.

Түйін сөздер: *туа біткен пневмония, қауіп факторлары, шала туылған нәресте, D дәрумені.*

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Relevance:

Pneumonia is an inflammatory pulmonary process that can originate in the lung or be a focal complication of an adjacent or systemic inflammatory process. Airway obstruction and alveolar ventilation and perfusion often result from a variety of mechanisms. These disorders often significantly alter gas exchange and their dependent cellular metabolism in many tissues and organs, which determine survival and contribute to quality of life. Such pathological problems, superimposed on the main difficulties associated with the transition from intrauterine to extrauterine life, create critical problems for the immature body of the newborn. Recognition, prevention and treatment of these problems are the main factors in the care of high-risk newborns [11]. In the modern world, congenital pneumonia still remains an important, urgent problem. The incidence of this pathology varies about 1% among full-term newborns, and in preterm infants up to 10%. From 10 to 40% of cases occupies a leading place in the structure of neonatal mortality [1,2]. Some authors, in particular *Nissen M.D.* [13], noted that pneumonia was the cause of about 1.2 million neonatal deaths per year, which in turn accounted for 10% of child deaths worldwide.

According to a systematic analysis for the study of the global burden of disease, the incidence of congenital pneumonia remains a serious, formidable pathological process for modern healthcare, and especially in developing countries [9].

Numerous reports suggest a vital role for vitamin D in the functioning and regulation of the immune system, as 1,25-dihydroxyvitamin D may contribute to the innate immature response to a pathogen [6,3,4]. In addition, studies have identified an association between respiratory infections and serum vitamin D deficiency in children [18,14,20,8]. Biomarkers used in synergy with the clinical signs and symptoms of pneumonia may provide additional data on disease severity and differentiation between bacterial and viral etiologies [7,15,17].

Pneumonia is an important cause of neonatal infection and is responsible for significant morbidity and mortality in the neonatal period. The best way to reduce the high prevalence of pneumonia in this age group is to identify and address its risk factors. Congenital pneumonia is most often caused by bacterial pathogens associated with the early onset of sepsis. The maternal history should be carefully examined, as it is important to identify maternal risk factors associated with

congenital pneumonia and other pathogens. Any previous maternal history of bacterial or viral diseases, such as hepatitis viruses, herpes, gonorrhea, or syphilis, should be carefully examined as it may be passed on to the child. Maternal risk factors associated with the perinatal phase include preterm labor before 37 weeks' gestation, prolonged or premature rupture of membranes, maternal fever, and maternal chorioamnionitis. A complication during labor or delivery may increase the infant's risk of respiratory distress or conditions mimicking congenital pneumonia [16].

Target. Assessment of risk factors and serum vitamin D levels in preterm infants with congenital pneumonia.

Materials and research methods.

Study design: case - control.

Research materials: The study was conducted on the basis of the Regional Perinatal Center in the city of Semey, the Republic of Kazakhstan in the period from January 1, 2021 to December 31, 2021. The study included premature newborns in the amount of 228 children. Immediately after birth, cord blood samples were taken into a vacutainer without filler in a volume of 5.0 ml. Then this tube was placed in a Sky Line Centrefuge CM-6M, with parameters of 3000 rpm, 3 minutes. The resulting serum in a volume of 1.0 ml was placed in a test tube "Eppendorf 1 ml", followed by freezing at -20°C and transportation at a cooling temperature in a cold bag with ice packs to the "Center of the Research Laboratory of the Semey Medical University", Semey city, Republic of Kazakhstan. An enzyme immunoassay was performed to quantify 25OH-D3. Using the 25-OH Vitamin D kit, total ELISA - 96 samples. Demeditec 25-OH Vitamin D Total ELISA is a microplate ELISA. During the first 2 hours of incubation, at room temperature, the total 25-OH vitamin D (D2 and D3) present in the calibrators, controls, and samples is separated from the serum binding proteins to bind to the binding sites of the specific monoclonal antibody. After 1 wash, a certain amount of 25-OH vitamin D labeled with biotin in the presence of horseradish peroxidase (HRP), along with unlabeled 25-OH vitamin D2 and 25-OH vitamin D3, is present at the binding sites of a specific monoclonal antibody. After a 30 minute incubation at room temperature, the microplate is washed with water to stop the competing reaction. Added chromogenic solution (TMB), then incubated for 15 minutes. The reaction is terminated by the addition of stop solution and then the microtiter plate is read at the appropriate wavelength. The amount of substrate volume is determined colorimetrically by changing the absorption coefficient, which is inversely proportional to the concentration of total 25-OH vitamin D (D2 and D3). A calibration curve is constructed and the concentrations of total 25-OH vitamin D (D2 and D3) on the samples are determined by dose interpolation from the calibration curve.

The AIFR-01 UNIPLAN™ analyzer was used.

Informational consents were obtained from mothers of newborns to participate in the study. Mothers were informed about the processing of the received data, with the subsequent publication of the results of the studies, without specifying personal data.

Inclusion Criteria: premature newborns (gestational age from 22 weeks to 37 weeks). Exclusion criteria: children with congenital malformations, genetic diseases, full-term newborns.

Main group: premature newborns with congenital pneumonia (76 newborns).

Control group: premature newborns without congenital pneumonia (152 newborns).

Statistical block: Data analysis was carried out using SPSS version 20.0. Data analysis was carried out using SPSS version 20.0. Pearson's $\chi 2$ test is used to test for statistical significance of differences between the "cases" and "controls" group, and the odds ratio is calculated using a 95% confidence interval. Continuous data are presented as (M) and standard deviation (SD).

The study was approved by the Local Ethical Commission "Family Medical University" Protocol No. 2 dated October 28, 2020.

Results

228 children were examined, the main group included 76 (33.3%) children, the control group included 152 (66.7%) children. Of these, 111 (48.7%) were boys, 152 (66.7%) were girls. At the same time, in the main group there were 44 boys (57.9%), girls 32 (42.1%), in the control group there were 67 boys (44.1%), girls 85 (55.9%).

The mean age of mothers was 31.9 (95% CI: 31.1-32.7) years SD=6.06, the youngest mother was 19 years old, the oldest 44 years old. The average age of mothers in the main group was 32.5 (95% CI: 31.1-34.0) years SD = 6.26, the youngest mother was 19 years old, the oldest was 42 years old. The mean age of mothers in the control group was 31.6 (95% CI: 30.6-32.6) years SD = 5.95, the youngest mother in this group was 19 years old, the oldest was 44 years old.

The mean gestational age was 31.6 (95% CI: 31.2-32.0) weeks SD=2.88, the minimum gestational age was 24.0 weeks, and the maximum gestational age was 36.0 weeks. At the same time, in the main group, the average gestational age was 30.0 (95% CI: 29.4-30.5) weeks SD = 2.51, the minimum gestation period in this group was 24 weeks, the maximum gestational age was 35 weeks. The mean gestational age in the control group was 32.4 (95% CI: 32.0-32.9) weeks SD = 2.69, the minimum gestation period in this group was 25 weeks, the maximum gestational age was 36 weeks.

The mean birth weight of the children was 1761.6 (95% CI: 1687.3-1835.9) grams SD=569.3, the minimum weight was 470 grams, the maximum weight was 3000 grams. The average weight of children in the main group at birth was 1461.3 (95% CI: 1337.3-1585.3) grams SD = 542.7, the minimum birth weight of children in this group was 470 grams, the maximum weight was 3000 grams. The mean weight of children in the control group was 1911.8 (95% CI: 1828.1 -1995.5) grams SD = 522.4, the minimum birth weight of children in this group was 690 grams, the maximum weight was 3000 grams.

A caesarean section for delivery was used in 130 (57.0%) women, spontaneous delivery was in 98 (43.0%) women. In the main group, caesarean section was used in 25 (32.9%) women, spontaneous delivery in this group was in 51 (67.1%) women. In the control group, caesarean section was used in 105 (69.1%) women, spontaneous delivery in this group was in 47 (30.9%) women.

In total, there were 9 (3.9%) cases with an unfavorable outcome. 219 (96.1%) children were discharged home. At the same time, 8 (10.5%) children died in the main group, 68 (89.5%) children were discharged home. In the control group, 1 (0.7%) child died, 151 (99.3%) children were discharged. Table 1 presents the data (Table 1).

Most of the parity accounted for third births 53 (23.2%). At the same time, in both the main and control groups, most women had third births 19 (25.0%) and 34 (22.4%), respectively. Table 2 presents risk factors (Table 2).

Table 1.

Parity of childbirth.

	Total	Main group	Control group
First birth	45 (19,7%)	18 (23,7%)	27 (17,8%)
Second birth	48 (21,1%)	18 (23,7%)	30 (19,7%)
Third birth	53 (23,2%)	19 (25,0%)	34 (22,4%)
Fourth birth	45 (19,7%)	12 (15,8%)	33 (21,7%)
Fifth birth	22 (9,6%)	3 (3,9%)	19 (12,5%)
Sixth birth	10 (4,4%)	3 (3,9%)	7 (4,6%)
Seventh birth	5 (2,2%)	3 (3,9%)	2 (1,3%)

Table 2.

Risk factors.

	Main group		Control group		χ^2, df, p
	Yes	No	Yes	No	
Preeclampsia	33 (43,4%)	43(56,6%)	27 (17,8%)	125 (82,2%)	χ^2=17,202, df=1, p=0,000
SARS	10 (13,2%)	66 (86,8%)	46 (30,3%)	106 (69,7%)	χ^2=8,001, df=1, p=0,005
Pathology of the urinary system	36 (47,4%)	40 (52,6%)	32 (21,1%)	120 (78,9%)	χ^2=16,765, df=1, p=0,000
Premature rupture of amniotic fluid for more than 18 hours	21 (27,6%)	55 (72,4%)	39 (25,7%)	113 (74,3%)	χ^2=0,102, df=1, p=0,750
Placental abruption	23 (30,3%)	53 (69,7%)	13 (8,6%)	139 (91,4%)	χ^2=17,961, df=1, p=0,000
Chorioamnionitis	16 (21,1%)	60 (78,9%)	4 (2,6%)	148 (97,4%)	χ^2=21,485, df=1, p=0,000
Threatening condition of the fetus	42 (55,3%)	34 (44,7%)	27 (17,8%)	125 (82,2%)	χ^2=21,485, df=1, p=0,000

In the main group, preeclampsia was diagnosed in 33 (43.4%) women, in the control group in 27 (17.8%) women, while the difference was statistically significant (p=0.000).

In the main group, ARVI was in 10 (13.2%), in the control group in 46 (30.3%) women in labor, while the difference was statistically significant (p=0.005).

In the main group, the pathology of the urinary system was in 36 (47.4%), in the control group in 32 (21.1%) women, the difference was statistically significant (p=0.000).

In the main group, premature rupture of amniotic fluid for more than 18 hours was in 21 (27.6%), in the control group in 39 (25.7%) women in labor, the difference was statistically insignificant (p=0.750).

In the main group, placental abruption was in 23 (30.3%), in the control group in 13 (8.6%) women in labor, the difference was statistically significant (p=0.000).

In the main group, chorioamnionitis was diagnosed in 16 (21.1%) women, in the control group in 4 (2.6%) women, the difference was statistically significant (p=0.000).

In the main group, the threatening condition of the fetus was diagnosed in 42 (55.3%) women, in the control group in 27 (17.8%) women, the difference was statistically significant (p=0.000).

Vitamin D content was estimated based on data from *Holick M.F., Binkley N.C.* [10], the following criteria:

- normal rate 25 (OH) D within - 30–80 ng / ml,
- 0–30 ng/ml – deficiency
- 10–19 ng/mL is deficient
- less than 10 ng/ml - severe deficiency*

According to the severity of vitamin D deficiency, according to the accepted classification, the following data were obtained: in the main group, a pronounced deficiency was in 60 children (79%), deficiency in 11 (14%) children, deficiency in 5 (7%) cases, with a normal content of vitamin D There were no premature newborns with pneumonia. Figure 1 shows the data (Figure 1).

According to the severity of vitamin D deficiency in the control group, severe deficiency was in 20 children (13%), deficiency in 86 (57%) children, deficiency in 35 (23%) cases, with normal vitamin D content in 11 (7%) children. Figure 2 shows the data (Figure 2).

Discussion:

The study was carried out as part of a doctoral dissertation. In this case-control study, we report parity rates of preterm birth, mean maternal age, mean gestational age, route of delivery, mean baby weight, gender, and outcomes in groups with and without congenital pneumonia in preterm infants born in the Perinatal the center of the city of Semey, Republic of Kazakhstan.

Risk factors are described in many literature reviews, systematic reviews and meta-analyses [5,12,19]

Choudhury A.M., Nargis S., Mollah A.H., Kabir L.M., Sarkar R.N., the authors conducted a case-control study, described the causative factors of congenital pneumonia such as: average birth weight, inadequate prenatal care, home birth, birth by untrained personnel, that were significantly associated with pneumonia. The authors do not indicate the gestational age of the children and whether the newborns were full-term or premature [5].

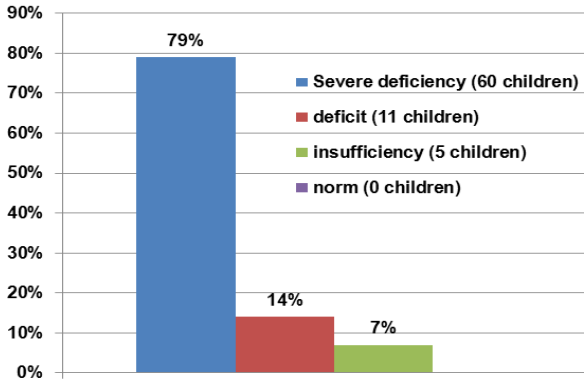

Figure 1. Vitamin D content in preterm infants with congenital pneumonia.

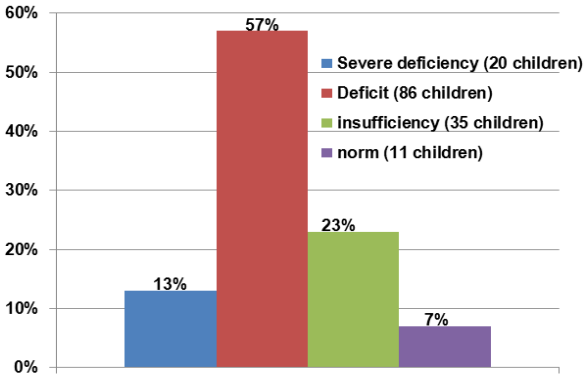

Figure 2. Vitamin D levels in preterm infants without congenital pneumonia.

The authors *Yang L, Zhang Y, Yu X, Luo M.* also described risk factors for pneumonia, the results of which are similar to those of previous authors *(A.M. Nargis S., Mollah A.H., Kabir L.M., Sarkar R.N.)* [19].

Walker V.P., Modlin R.L. in their study described the relationship between vitamin D and infections. For example, in the United States, vulnerable populations have been identified, including premature babies. Scientists indicated the ratio of vitamin D content in blood serum to the ability of immune cells to protect the body from infections [18].

Our study included a group of preterm infants with and without congenital pneumonia, gestational age between 22 weeks and 37 weeks, and determination of vitamin D levels. In this study of vitamin D deficiency in preterm infants with congenital pneumonia, the results showed that vitamin D levels in serum was significantly lower than in children without congenital pneumonia.

Conclusions

Thus, according to the results of the analysis of the leading risk factors for congenital pneumonia in premature newborns, maternal infections, such as SARS, pathology of the urinary system, premature rupture of amniotic fluid (>18 hours), chorioamnionitis, as well as preeclampsia, placental abruption, led to a threatening condition fetus and premature birth.

Also, in a study of vitamin D deficiency in premature infants with congenital pneumonia, the results showed that serum vitamin D levels were significantly lower in patients in the main group - with congenital pneumonia compared to the control group - without congenital pneumonia.

These results indicate that inadequate vitamin D concentrations in preterm infants may be associated with a higher risk of developing congenital pneumonia, as well as determine the severity of the inflammatory process.

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Publication Information: *The results of this case have not been previously published in other journals and are not pending in other publishers.*

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