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CAUSAL RISK FACTORS FOR MACROSOMIA OF NEWBORNS WITH VITAMIN D DEFICIENCY

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Abstract

Relevance: In the modern world, the frequency of macrosomia is growing dynamically. The World Health Organization (WHO) has recognized obesity, type 2 diabetes mellitus and non-communicable diseases as global epidemics [2]. Macrosomia is defined as a birth weight of more than 4000 g regardless of gestational age and occurs in 3-15% of all pregnancies worldwide [4,9,22]. Vitamin D deficiency during pregnancy is associated with an increased risk of gestational diabetes and preeclampsia, which may indirectly affect the health of offspring [5,6,21].

Objective: To assess risk factors and the level of vitamin D in umbilical cord blood in macrosomal newborns.

Materials and methods of research. Case - control. The study was conducted in the period from January 2021 to April 2021 at the clinical bases "Perinatal Center of Semey and Ust-Kamenogorsk. The study included full-term newborns in the number of 100 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*: full-term children with macrosomia. *Exclusion criteria*: children with defects, genetic diseases, premature 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 and Mann-Whitney $\chi 2$ criterion was used, and the odds ratio is calculated taking into account the 95% confidence interval. Continuous data is presented in the form of (Me) and standard deviation (CD).

Results: According to the results of the analysis of risk factors, the cause of macrosomia was maternal diabetes mellitus. The study showed that the pronounced vitamin D deficiency in serum was significantly lower in patients with macrosomia compared to normal-weight children.

Conclusion: the leading risk factor for macrosomia was diabetes mellitus of pregnant women. In newborns with macrosomia, a pronounced deficiency of 25(OH) D.

Keywords: *macrosomia, large for gestational age; obesity; overweight, risk factors, newborn, vitamin D.*

Резюме

ПРИЧИННЫЕ ФАКТОРЫ РИСКА МАКРОСОМИИ НОВОРОЖДЕННЫХ С ДЕФИЦИТОМ ВИТАМИНА D

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Актуальность: В современном мире частота макросомии динамично растет. Всемирная организация здравоохранения (ВОЗ) признала ожирение, сахарный диабет 2 типа и неинфекционные заболевания глобальными эпидемиями [2]. Макросомия определяется как масса тела при рождении более 4000 г независимо от гестационного возраста и встречается в 3-15% всех беременностей по всему миру [4,9,22]. Дефицит витамина D во время беременности связан с повышенным риском гестационного диабета и преэклампсии, которые могут косвенно влиять на здоровье потомства [5,6,21].

Цель: Оценка факторов риска и уровня витамина D в пуповинной крови у макросомных новорожденных.

Материалы и методы исследования. Случай - контроль. Исследование проводилось в период с января 2021 г. по апрель 2021 г. на клинических базах «Перинатальный центр города Семей и города Усть-Каменогорск. В исследование вошли доношенные новорожденные в количестве 100 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:* доношенные дети с макросомией. *Критерии исключения:* дети с пороками, генетическими заболеваниями, недоношенные новорожденные.

Анализ данных проводился с использованием пакета SPSS версии 20.0. Для проверки статистической значимости различий между группой «случаев» и «контролей» использовался критерий χ2 Пирсона и Манна-Уйтни, а отношение шансов рассчитывается с учетом 95% доверительного интервала. Непрерывные данные представлены в виде (Me) и стандартного отклонения (CD).

Результаты: По результатам анализа факторов риска причиной макросомии, явился сахарный диабет матери. Исследование показало, что выраженный дефицит витамина D в сыворотке был значительно ниже у пациентов с макросомией по сравнению с нормовесными детьми.

Вывод: ведущим фактором риска макросомии явился сахарный диабет беременных. У новорожденных с макросомией, выявлен выраженный дефицит 25(OH) D.

Ключевые слова: *макросомия, сахарный диабет, гестационный диабет, факторы риска, новорожденный, витамин D.*

Түйіндеме

D ДӘРУМЕНІ ТАПШЫЛЫҒЫ БАР ЖАҢА ТУҒАН НӘРЕСТЕЛЕРДІҢ МАКРОСОМИЯСЫНЫҢ СЕБЕП-САЛДАРЛЫҚ ҚАУІП ФАКТОРЛАРЫ

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Өзектілігі. Қазіргі әлемде макросомия жиілігі қарқынды өсуде. Дүниежүзілік денсаулық сақтау ұйымы (ДДҰ) семіздікті, 2 типті қант диабетін және жұқпалы емес ауруларды жаһандық эпидемия екенін мойындады [2]. Макросомия жүктілік мерзіміне қарамастан 4000 г-нан асатын дене салмағы ретінде анықталады және бүкіл әлем бойынша жүктіліктің 3-15% кездеседі [4,9,22]. Жүктілік кезіндегі D дәрумені жетіспеушілігі гестациялық қант диабеті мен преэклампсия қаупінің жоғарылауымен байланысты, бұл ұрпақтың денсаулығына жанама әсер етуі мүмкін [5,6,21].

Мақсаты: макросомиямен дүниеге келген жаңа туған нәрестелердегі кіндік қанындағы D дәрумені деңгейін және қауіп факторларын бағалау.

Зерттеу материалдары мен әдістері. жағдайды бақылау. Зерттеу 2021 жылғы қаңтар айы мен 2021 жылғы сәуір аралығында "Семей қаласы мен Өскемен қаласының перинаталдық орталықтарында" жүргізілді. Зерттеуге 100 толық мерзімді жаңа туған нәрестелер кірді. Зерттеуге қатысуға жаңа туған нәрестелердің аналарынан ақпараттық келісім алынды. Аналарға алынған деректерді өңдеу, кейіннен зерттеу нәтижелерін жариялау, дербес деректерді көрсетпейтіні хабарланды. *Қосу критерилері*: макросомиясы бар толық мерзімді балалар. *Шектеу критерилері*: тума ақаулары бар, генетикалық аурулары бар балалар, шала туылған нәрестелер. Деректерді талдау SPSS 20.0 нұсқасының пакетін қолдана отырып жүргізілді. "Жағдайлар" тобы мен "бақылаулар" арасындағы айырмашылықтардың статистикалық маңыздылығын тексеру үшін Пирсон мен Манн-Уитнидің χ2 критерийі қолданылды, ал коэффициенттер коэффициенті 95% сенімділік аралығымен есептеледі. Үздіксіз деректер (Me) және стандартты ауытқу (CD) түрінде ұсынылған.

Нәтижелер: қауіп факторларын талдау нәтижелері бойынша макросомияның себебі ананың қант диабеті болды. Зерттеу қалыпты балалармен салыстырғанда макросомиямен ауыратын науқастарда қан сарысуындағы D дәруменінің жетіспеушілігі айтарлықтай төмен екенін көрсетті.

Қорытынды: макросомияның жетекші қауіп факторы жүкті әйелдердің қант диабеті болды. Макросомиясы бар жаңа туған нәрестелерде айқын 25(OH) D тапшылығы анықталды.

Түйінді сөздер*: макросомия, қант диабеті, гестациялық қант диабеті, қауіп факторлары, жаңа туған нәреста, D дәрумені.*

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Relevance

Every year, the frequency of macrosomia is dynamically increasing. This is due to the high probability of obstetric as well as neonatal complications. The World Health Organization (WHO) has recognized obesity, type 2 diabetes and noncommunicable diseases as global epidemics. The 2015 U.S. Vital Statistics Report indicated that seven percent of babies had a birth weight of more than 4,000 grams, and one percent had a birth weight of more than 4,500 grams [2, 3, 16,17,20]. The prevalence of macrosomia ranged from 0.5% in India to 13.9% in China, while the prevalence of large for gestational age ranged from 4.3% in Korea to 22% in China, which determines the differences in epidemiology within the countries of Central Asia [9].

Risk factors for macrosomia or large for gestational age at birth: multiple parous, maternal age, maternal weight and height, maternal overweight and obesity, excessive maternal weight gain during pregnancy, pregestational diabetes, and gestational diabetes mellitus [7,11]. Understanding the factors influencing macrosomal delivery entails immediate and long-term risks of adverse maternal and child outcomes. In the short term, newborns are at risk of perinatal asphyxia, birth trauma, hypoglycemia, and perinatal death, and mothers are at risk of caesarean section, prolonged labor, bleeding, and perineal injury. Long-term consequences for infants include an increased risk of being overweight, childhood obesity, and developing diabetes [9].

Morbidity and mortality associated with macrosomia can be divided into maternal, fetal, and neonatal. A study investigating the effect of birth weight on fetal mortality shows that higher rates of fetal mortality are associated with birth weights greater than 4250 g in mothers without diabetes and birth weights of 4000 g in mothers with diabetes [18].

Macrosomia is defined as birth weight greater than 4000 g regardless of gestational age and occurs in 3-15% of all pregnancies worldwide [4]. The authors Ng S.K., Olog A., Kerényi Z. describe the concept of macrosomia - a large fetus determined by the maximum weight, or as large for gestational age. [1,14,19]. Vitamin D during pregnancy is associated with an increased risk of gestational diabetes and preeclampsia, which may indirectly affect the health of the offspring [5,6,21]. It is also associated with direct offspring health effects such as birth weight, poor skeletal health, impaired brain development, autoimmune diseases, obesity, and insulin resistance [5]. Pregnancy diabetes can be gestational diabetes, insulin dependent or drug-induced/chemical diabetes. Jordan Peterson in 1920 hypothesized that maternal hyperglycemia is associated with fetal hyperinsulinemia and fetal hyperglycemia, which ultimately leads to excessive use of glucose by the fetus and therefore to abnormal growth acceleration [8]. There is currently an epidemic of maternal obesity around the world, which in turn poses a significant risk of developing diabetes in all demographic groups. It is maternal obesity that is associated with a 4-12-fold increase in the likelihood of developing macrosomia in the fetus. The standard metabolic basis of macrosomia is increased insulin resistance and hyperinsulinemia. However, it may contribute to maternal diabetes and obesity, which are more important causes. Women with a parity of more than three are prone to the birth of macrosomal children [20]. With each pregnancy, there may be an associated weight gain of 100-150 grams, which increases the risk of macrosomia in the long term in this group of patients. Previous LGA (large for gestational age) babies: Women who have had previous macrocosmic babies are five to ten times more likely to have another macrosomal baby. Prolonged pregnancy beyond 42 weeks is most likely associated with an increased risk of macrosomia due to the constant supply of nutrients and oxygen rich blood to the developing fetus [2].

Birth weight is an important predictor of the nutritional status and development of newborns in utero and plays an important role in neonatal survival. The incidence of macrosomia worldwide in recent decades has been 4.7–13.1%. Macrosomia is characterized by asymmetrical growth of the abdominal circumference and excess accumulation of fat. Newborns with macrosomia are associated with a high risk of caesarean section, birth complications and subsequent obesity, metabolic disorders, and certain types of cancer. Thus, the study of macrosomia and its risk factors has important public health implications. Studies have shown that gestational week at birth, pre-pregnancy body mass index, body weight gain during pregnancy, fetal sex, season of birth, gestational diabetes status, and genetic factors may influence

macrosomia. Whether maternal vitamin D deficiency is related to infant weight remains a matter of debate. Due to the growth needs of the fetus, inadequate vitamin D intake, and limited exposure to sunlight, vitamin D deficiency is very common in pregnant women. The association of maternal vitamin D levels with fetal growth has been studied in numerous observational studies and randomized controlled trials, most of which focused on fetal macrosomia. 25(OH)D, a measure of vitamin D levels, was measured in maternal serum or cord blood in most studies. Some studies have provided evidence that there is an inverted U-shaped relationship between 25(OH)D concentrations and fetal growth, and it has been suggested that low 25(OH)D concentrations are associated with a higher risk of macrosomia. Some cohort studies have found that women with 25(OH)D <37.5 nmol/L had higher birth weight babies in a linear regression model [8].

Aim: Evaluation of risk factors and cord blood vitamin D levels in macrosomal neonates.

Materials and research methods. The study was conducted within the framework of the grant project "El Basy", "Assessment of the status of vitamin D, trace elements and mineral metabolism in children of the East Kazakhstan region" in the period from January 2021 to April 2021 in the period from January 2021 to April 2021 for the clinical base "Perinatal Center Semey City" and the Center "Mother and Child City Ust-Kamenogorsk", Republic of Kazakhstan.

The study included full-term newborns in the amount of 100 children. 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: term infants with macrosomia (gestational age from 37 weeks to 42 weeks). *Exclusion criteria*: children with congenital malformations, genetic diseases, premature newborns.

Main group: newborns with large weight (4000g and more) - 50 newborns

Control group: full-term newborns with normal weight (2500-4000g) - 50 newborns

Data analysis was carried out using SPSS version 20.0. The Pearson and Mann-Whitney χ2 test was 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 (Me) and standard deviation (CD).

Study design: case - control. Immediately after birth, cord blood samples were taken into a vacutainer with a coagulation activator and separating gel in a volume of 5.0 ml. Then this test tube was transported at the cooling temperature in a cold bag with ice packs to the Clinical Diagnostic Laboratory "Olimp", the cities of Semey and Ust-Kamenogorsk, the Republic of Kazakhstan, where enzyme immunoassay was carried out for the quantitative determination of 25OH-D3.

The study was approved by the Local Ethical Commission "Family Medical University" Protocol No. 1.1 dated September 25, 2020.

Research results: According to the results of a study of maternal risk factors for the threat of abortion in the main group (Table 1), 70% (n=35) of women were absent and 30% (n=15) had.

Table 1. **Risk factors.**

Risk factors		Main group n(%)	Control group n(%)
Threat of abortion	Yes	15(30%)	8(16%)
	No	35(70%)	42(84%)
Maternal iron deficiency anemia	Mild degree	27(54%)	17(34%)
	Intermediate degree	2(4%)	1(2%)
	Severe degree	1(2%)	0(0%)
	No	20(40%)	32(64%)
Thyroid diseases	No	40(80%)	42(84%)
	Mild hypothyroidism	2(4%)	2(4%)
	Moderate hypothyroidism	6(12%)	3(6%)
	Autoimmune thyroiditis	2(4%)	3(6%)
Maternal obesity	No	33(66%)	39(78%)
	Obesity 1 degree	8(16%)	8(16%)
	Obesity 2 degrees	5(10%)	1(2%)
	Obesity 3 degrees	2(4%)	0
	Overweight	2(4%)	2(4%)
Maternal hypertension	No	36(72%)	36(72%)
	Gestational hypertension	7(14%)	8(16%)
	Arterial hypertension of the 1st degree	1(2%)	0
	Arterial hypertension 2nd degree	6(12%)	6(12%)
Maternal diabetes	No	36(72%)	44(88%)
	Diabetes mellitus 1	2(4%)	0
	Diabetes mellitus 2	2(4%)	0
	Gestational diabetes	5(10%)	3(6%)
	Impaired glucose tolerance	5(10%)	3(6%)
Maternal gastrointestinal disease	No	35(70%)	36(72%)
	Gastritis	5(10%)	5(10%)
	Cholecystitis	8(16%)	3(6%)
	pancreatitis	2(4%)	6(12%)

In the control group, the threat was not 84% (n=42) of cases, and was noted in 16% (n=8). Iron deficiency anemia in the main group was observed in 60% (n=30) of women, while 40% (n=20) were not observed. In the control group, 64% (n=32) of cases were absent and 36% (n=18) did. Disease of the thyroid gland in the main group was observed in 20% (n=10), in the control group 16% (n=8). Obesity in the main group was not observed 66% (n=33), in the control group 78% (n=39). In the main group with 1st degree of obesity was noted in 16% (n=8), 2nd degree 10% (n=5), 3rd degree 4% (n=2), overweight 4% (n=2), in the control group with 1st degree of obesity was observed in 16% (n=8), 2nd degree 2% (n=1), 3rd degree was not observed, overweight 4% (n=2). Gestational hypertension in the main group was observed in 14% (n=7) of pregnant women, Arterial hypertension 1-2% (n=1), Arterial hypertension 2-12% (n=6), while in the control group gestational hypertension was observed in 16 % (n=8) of pregnant women, Arterial hypertension 1- none, Arterial hypertension 2-12% (n=6) cases. Maternal diabetes in the main group was absent in 72% (n=36), while in the control group it was absent in 88% (n=44). In the group with macrosomia, type 1 diabetes mellitus, type 2 diabetes mellitus were observed in the same values of 4% (n=2). Gestational diabetes was observed in 10% (n=5) of cases, impaired glucose tolerance in 10% (n=5). In the group of born newborns with normal weight, no one had diabetes mellitus type 1 and 2. Gestational diabetes and impaired glucose tolerance were observed in equal amounts of 6% (n=3). The data are presented in table 1 (Table 1).

In terms of severity of vitamin D deficiency in our study, we focused on the accepted classification of *Holick M.F., Binkley N.C., Bischoff-Ferrari H.A.* [12].

Table 2 shows the frequency of occurrence of deficiency severity by levels. In the main group, severe vitamin D deficiency was detected in 20 (40%), in the control group in 10 (20%). Vitamin D deficiency was observed in the main group in 30 (60%), in the control group 38 (76%), vitamin D deficiency was not observed in the main group, in the control group it was noted in 2 (4%) newborns. There were no sufficient levels of vitamin D in both groups. The difference in the results of the study was statistically significant p=0.043 (Table 2).

Table 2. **Vitamin D contingency table by levels.**

Contingency table of Vitamin D by levels						p
			Group		Total	
			Main	Control		
Vitamin D content by levels	Severe vitamin D deficiency	Frequency	20	10	30	0,043
		Expected frequency	15,0	15,0	30,0	
	Vitamin D deficiency	Frequency	30	38	68	
		Expected frequency	34,0	34,0	68,0	
	Failure Vitamin D	Frequency	0	2	2	
		Expected frequency	1,0	1,0	2,0	
Total		Frequency	50	50	100	
		Expected frequency	50,0	50,0	100,0	

Discussion: The study was conducted within the framework of the grant project "El Basy", "Assessment of the status of vitamin D, trace elements and mineral metabolism in children of the East Kazakhstan region" in the period from January 2021 to April 2021 in the period from January 2021 to April 2021 for the clinical base "Perinatal Center Semey City" and the Center "Mother and Child City Ust-Kamenogorsk", Republic of Kazakhstan. In this case-control study, we report on the leading risk factors for macrosomia, which are also described in many sources [7,9,11]. *Harvey L., van Elburg R. and van der Beek E.M.,* also assessed risk factors for macrosomia and large gestational age in Asia. The authors noted the body mass index before pregnancy or at the first visit to the clinic and associated the subsequent birth of a newborn with macrosomia [9]. Other authors *James-Todd T.M., Karumanchi S.A., Hibert E.L., Mason S.M., Vadnais M.A., Hu F.B., Rich-Edwards J.W.,* express the highest risk of macrosomia of 23.5% in parturient women with gestational diabetes mellitus [13]. In our study, we report the frequency of risk factors for macrosomia, such as threatened miscarriage, maternal IDA, thyroid disease, maternal obesity, arterial hypertension, maternal diabetes, and gastrointestinal disease. *Harvey L., van Elburg R. and van der Beek E.M.* published the main risk factors for macrosomia and a modern view of this pathology [9]. The results of our study are consistent with the literature data by authors from different countries.

Conclusion: Thus, according to the results of the analysis of macrosomia risk factors, the leading factor was maternal diabetes mellitus. The study focused on vitamin D in macrosomic neonates and the results showed that severe serum vitamin D deficiency was significantly lower in macrosomic patients and large for gestational age compared to normal weight infants. The analysis showed that newborns with macrosomia had a pronounced deficiency of 25(OH)D. In order to reduce the birth rate of children with macrosomia or large for gestational age, where early and late perinatal outcomes occur, we think about the need for antenatal prophylaxis with vitamin D. For confirmation of this statement requires randomized controlled trials.

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