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BODY COMPOSITION OF FULL-TERM NEWBORNS AGAINST THE BACKGROUND OF INCREASED PROTEIN INTAKE IN THE INTENSIVE CARE UNIT

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Summary

To evaluate the effects of increased protein and L-carnitine supplementation in the feeding program of term infants with perinatal conditions on improving physical development outcomes, changes in body composition and hospital outcomes.

***The aim** is to evaluate the effect of short-term increased protein intake in term infants and L-carnitine supplementation on body composition and key indicators of physical development in children.*

***Material and methods.** To test the proposed hypothesis of neonatal nutrition, we studied the vital signs of 59 term infants randomized into two groups. The first group (n = 30) received standard breastmilk (BM) or formula feeding, and the second group (n = 29) received a protein-fortified (PF) formula and L-carnitine supplementation during the hospital stay. At the beginning and end of treatment, the children's physical development and body composition were assessed using bioelectrical impedance.*

The study protocol was agreed and approved by the Regional Bioethics Committee of the Zaporizhzhia State Medical and Pharmaceutical University. The study was conducted in accordance with the moral and ethical standards of the IGH/GCP, the Declaration of Helsinki (1964 with amendments of 1975, 1983, 1989, 1996, 2000), the Convention of the Council of Europe on Human Rights and Biomedicine, and the legislation of Ukraine. Written informed consent was obtained from the parents of the patients before the start of the study.

All statistical analyses were performed using the software Statistica 13.0, TIBCO Software Inc (licence number JPZ804I382130ARCN10-J) and Microsoft Excel 2013 (licence number 00331-10000-00001-AA404). The probability of the difference in the absolute values of the means was determined using non-parametric methods of statistical analysis: the Mann-Whitney test (U) for unrelated groups and the Wilcoxon signed rank test (T) for related groups. Statistical significance was defined as $p < 0.05$.

The study was conducted within the framework of the research work of the Department of Anaesthesiology and Intensive Care Medicine of the Zaporizhzhia State Medical and Pharmaceutical University of the Ministry of Health of Ukraine – «Optimization of diagnosis and intensive care of multi etiological lesions of the brain, gastrointestinal tract, kidneys in newborns and older children», state registration number 0118U007142.

***Results.** Infants in both groups had similar characteristics of weight, length and head circumference at baseline. The proportions of infants of both sexes were within the 50 % percentile. In general, the proposed feeding strategy contributed to better indicators of infant physical development and a statistically significant, faster recovery of body weight in the fortified group. Thus, the generalised indicator of body weight of children in the GZ group was 3966.90 ± 439.08 g, compared to 3554.62 ± 452.28 g in the SC group, p = 0.0033. In general, the children who consumed more protein were transferred out of intensive care sooner – 10.00 (8.00, 12.00) days vs. 12.00 (11.00, 16.00) days, U = 235.00; p = 0.0024; discharged from hospital sooner – 21.00 (19.00, 27.00) days vs. 26.50 (22.00, 31.00) days, U = 267.00, p = 0.0109. This strategy proved to be safe, as evidenced by normal phenylalanine and urea levels at all stages of the children's examination. Percentage analysis of body composition showed an increase in the formation of more dry mass in children on the standard diet, without protein fortification and without carnitine supplementation. Thus, the percentage of FFM in the children on the standard diet was 84.71 (83.27; 85.47) % at the end of the study, compared with 83.09 (81.93; 83.96) % in the GZ group, U = 117.00; p = 0.0020. The total cohort indicator was influenced by the changes in body composition found in the women: in the GZ group, the percentage was 82.21 (81.55;83.10) % versus 84.71 (83.65;85.30) % in the SC group, U = 8.0; p = 0.0051. Thus, increased protein supplementation in term girls was associated with greater accumulation of fat mass, even with short-term supplementation.*

***Conclusions.** Consumption of more protein and carnitine supplementation in term neonates in the intensive care unit promotes better growth against a background of body composition with higher fat content in females, a fact that limits the use of this strategy without further studies.*

***Key words:** Body composition; Hypoxic-ischemic Encephalopathy; Neonates; Children; Physical Development; Bioelectrical Impedance; Breast Milk.*

Introduction

In the care of neonates in the intensive care unit, considerable attention is paid to nutritional support in addition to the management of perinatal conditions. The goal of feeding preterm infants is to mimic the intrauterine growth rate and, after 36 weeks postmenstrual age, to maintain the growth rate of a full-term infant who is breastfed [1]. Optimal physical development in full-term infants corresponds to rapid recovery of postnatal weight loss and standard daily growth. A proven strategy to improve children's physical development is to provide sufficient protein in breast milk or formula for both term and preterm infants. Exogenous protein is an indispensable source of essential amino acids for the synthesis of protein required for growth.

The problem of physical developmental delay is most prevalent in the low-birth-weight group. Only a limited number of studies have looked at the optimal protein intake for term infants, who have fewer perinatal morbidities than preterm infants [2, 3]. This is due to well-known and well-studied factors: impaired intracellular insulin signaling, impaired glucose uptake and reduced mitochondrial

efficiency during critical illness. Even in term infants requiring intensive care, such mechanisms contribute to increased protein catabolism and the need for additional energy to overcome illness and ensure physical growth [4, 5]. A large number of observational studies and surveys of the nutritional status of term infants treated for critical illness show that the prescribed and actually delivered macronutrient intakes are usually lower than recommended intakes, and that cumulative protein and energy deficiencies during hospitalization can reach 40-45 % [4]. The severity of illness and nutritional deficiencies correlate with the duration of mechanical ventilation. For example, the Canadian National Network of Intensive Care Units reports a similar problem [6].

One method of preventing this deficiency in preterm infants is early initiation of parenteral nutrition, but a recent multicentre study has shown possible risks of this strategy with potentially negative consequences for this population, so improving the outcomes of enteral nutrition is still relevant [7]. Another strategy that has been explored in recent years is to improve neonatal outcomes by supplementing the nutritional support program with L-carnitine. It plays an important role in fatty acid oxidation by facilitating the transport of long-chain fatty acids across the mitochondrial membrane. The resulting energy can contribute to improved protein synthesis. Carnitine is a conditionally essential nutrient found in breast milk and is added to infant formula. Recent evidence suggests a positive association between carnitine intake and brain size and physical development in children [8]. Almost no studies have been conducted in preterm infants requiring intensive care, but the lack of adequate nutrition in term infants in the first few weeks of life contributes to the accumulation of secondary carnitine deficiency.

During critical illness, proteolysis is enhanced. The release of cytokines, cortisol and growth hormone contributes to the breakdown of skeletal muscle so that certain amino acids can be redirected and used as substrates for the synthesis of additional energy in the liver. This may play an important role in stunted growth in infants with limited protein and energy reserves or in cases where energy intake is delayed [4]. Weight gain in the preterm infant cohort can be achieved with current formulae and breast milk fortification, but there is a risk that the weight gain will be at the expense of fat and a reduction in lean mass and will not meet the reference growth charts for newborns [9-11].

In recent years, studies have been carried out not only in the preterm category to investigate the effects of increased protein intake. In a multicentre study by V. Koletzko, the effect of increased protein intake in healthy term infants over the course of one year was investigated in comparison with the exclusive breastfeeding group. Assessment of body composition and anthropometric parameters at the age of 6 years showed a 2.6-fold reduction in the adjusted odds of obesity in the breastfed group, indicating the risks of high protein intake [12]. However, the short-term consumption of high protein intakes within the guidelines for critically ill preterm infants and the possible outcomes of such a strategy have been little studied [4]. Disorders of body composition in early life may play a key role in the «metabolic» programming of several future health conditions, including hypertension, stroke, type 2 diabetes mellitus, and obesity, which are grouped together in the definition of «metabolic syndrome» [13].

Accurate assessment of neonatal body composition is therefore essential for determining, predicting and monitoring nutritional outcomes in order to develop optimal feeding strategies. Conventional methods used in clinical settings to assess physical development and body composition in children are largely based on anthropometric measurements (such as length, weight and skinfold thickness). Body mass index (BMI) is commonly used to accurately assess the body composition of young children [13]. BMI reflects fat mass (FM) and fat-free mass (FFM) as a single value. Accurate methods for analyzing body composition in neonates include: air displacement plethysmography (ADP), water diluted isotope (TBW) method, bioelectrical impedance analysis (BIA), dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging (MRI). Each of these methods has been validated as an affordable way to determine body composition in newborns, although none of them provides the most accurate data [14-18]. In addition, all methods except BIA cannot be used in intensive care units for neonates with critical perinatal conditions. The latter, based on changes in tissue electrical conductivity, is fast, relatively inexpensive and BIA can be used in any patient [19].

The aim of the study. To evaluate the effect of short-term increased protein intake in term infants and L-carnitine supplementation on body composition and key indicators of physical development in children.

Material and Methods. When designing the study, we hypothesized that early administration of a guaranteed higher protein supplement (relative to the usual intake in the intensive care program) and the addition of L-carnitine to the nutritional program of term, critically ill infants would improve the physical development of the children. In addition, we hypothesized that an increase in body weight with increased protein intake would be accompanied by a decrease in adipose tissue content – fat mass (FM) – due to an increase in lean body mass – fat-free mass (FFM).

The study participants were treated in the neonatal intensive care unit of the Zaporizhzhia Regional Clinical Children's Hospital. The center provides tertiary care for infants delivered from medical institutions of the Zaporizhzhia region or the city of Zaporizhzhia of the second level of care and is the clinical base of the Zaporizhzhia State Medical and Pharmaceutical University.

A prospective, randomized, controlled trial was conducted in children of different gestational ages from 24 to 42 weeks at birth. The children were stratified into 4 groups according to their degree of maturity. This publication focuses on the group of children born at term. In the period from 2017 to 2020, 59 infants born at 37 to 41 weeks were selected. The children were evacuated from maternity hospitals and hospitals in critical condition. The

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universal criterion for inclusion in the study was the need for prolonged artificial lung ventilation for more than 72 hours due to critical perinatal diseases. Intensive care was provided in accordance with existing protocols of the Ministry of Health of Ukraine and international standards for neonatal care.

Exclusion criteria included children who were small or large for gestational age (assessed using the Fenton 2013 nomograms for fetal physical development [20]), children with congenital malformations requiring surgical intervention, children with congenital metabolic disorders, chromosomal abnormalities, and children with end-stage liver disease. Thus, 63 children were included in the study at the screening stage, but 4 infants were subsequently excluded from the study due to congenital heart disease with surgical correction (1), development of end-stage multiorgan failure (1), and 2 children were classified as large for gestational age by anthropometry (Fig. 1).

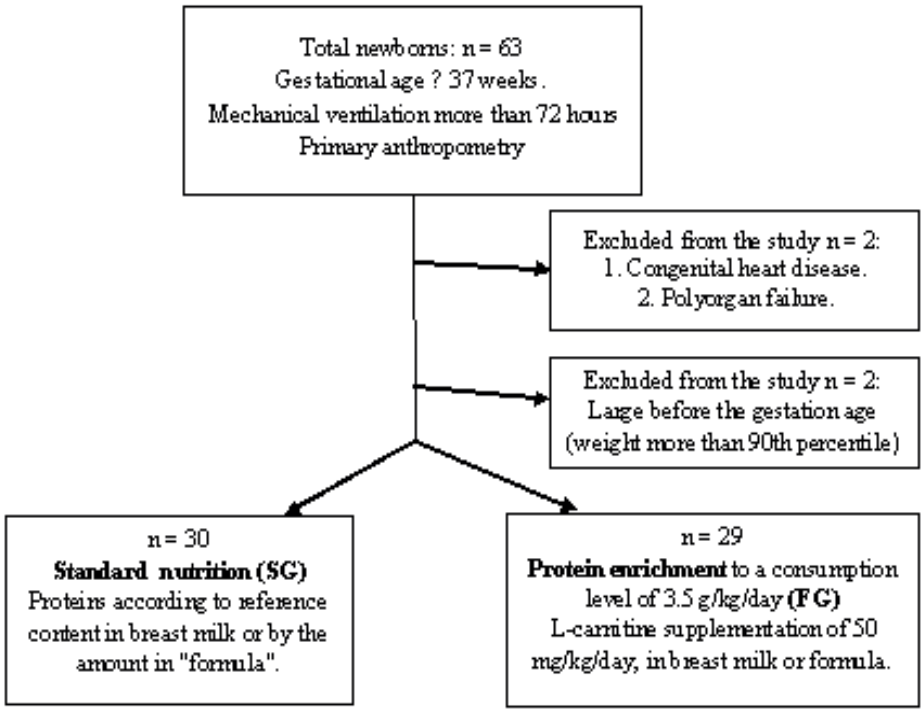

Fig. 1. Study design and organization.

All infants were randomly divided into 2 groups using the method of random numbers generated by the Statistica program. The standard feeding group consisted of 30 (50 %) infants who received mainly breast milk. At the initial stage of care, the infants received tube feeding, and when swallowing was regained, they received breast or bottle feeding. The amount of food was gradually increased each day based on clinical signs of food tolerance.

In the study group (29 children), protein supplementation was used up to a consumption of 3.5 g/kg/day using a protein fortifier, a casein hydrolysate. Fortification was started at an enteral absorption of approximately 80-90 ml/kg/day. The required dose of fortifier was calculated daily by adding the required amount to milk or formula. For the calculation, we used the average data on the protein content in breast milk of women who gave birth at term and the protein content according to the instructions for formula feeding [21]. Usually, the daily amount of fortifier was evenly distributed over all portions for tube feeding and in 4 portions for self-swallowing. In addition, L-carnitine supplements were administered to prevent the accumulation of carnitine deficiency at a daily dose of 50 mg/kg/day of the active ingredient until discharge from the hospital. Until the child was able to receive adequate enteral nutrition, L-carnitine was administered as an infusion by adding the daily dose to a prepared mixture of fluids and electrolytes, which was administered at a steady rate throughout the day. The enteral administration of carnitine was started when the feeding volume reached 90-100 ml/kg/day. The daily dose of carnitine was administered in three doses by adding it to the formula or breast milk.

The physical development of the children was assessed on the day of birth and then weekly or on the day of discharge from the hospital. The main anthropometric parameters (body weight, head circumference, body length) were measured. All measurements were standardized according to WHO recommendations [22]. Measurements were performed twice by two specialists independently of each other. Weight was measured to the nearest 5 g on a calibrated electronic scale. If the difference between the two measurements exceeded 50 g for weight, 0.7 cm for length, and 0.5 cm for head circumference, both personnel repeated the measurements.

The data obtained were compared with Fenton's nomograms of physical development and a comparative analysis was performed between the groups. In addition, a comprehensive assessment of the infants' somatic and neurological status was performed. The biochemical profile of the neonates was studied weekly. Plasma free carnitine and phenylalanine levels were assessed at baseline and during the last week of treatment using liquid

chromatography-mass spectrometry (LC MS-Agilent 1260 Infinity HPLC system, USA).

The variability of neonatal body composition was studied using the bioelectrical impedance (BIA) method. Impedance measurements were performed simultaneously with anthropometry. A Bodystat® 1500MDD device (Bodystat Ltd, Isle of Man, UK) and special disposable electrodes from the same manufacturer (Bodystat Electrode Pads) were used for impedance analysis. The device automatically performs a calibration during each measurement. Two electrodes were placed on the neonates in the supine position: on the back of the hand and on the right foot. Measurements were performed with a signal frequency of f = 50 KHz, an electric current amplitude of 200 microamperes, and a measurement accuracy of 2 ± Ω (ohm). The impedance index (impedance index – Ht2/I, (cm2/Ω)) as a variable (calculated as height in square centimeters divided by bioelectrical impedance in Ω) was calculated separately for each child to assess FFM. Impedance analysis using similar devices has demonstrated diagnostic capabilities in neonatal cohorts to measure FM and FFM with high accuracy [19, 23, 24]. A comparative analysis of the data obtained was performed at the time of birth and at the third postnatal week, which coincided with the discharge of most children in the fortification group.

In the text and tables, data are presented as M ± SD (arithmetic mean ± standard deviation) in the case of normal distribution of the trait, Me (Q1; Q3) (median of the sample with interquartile range reported as upper (75 %) and lower (25 %) quartiles in the case of non-normal distribution). Categorical variables are expressed as the absolute number of cases (n) in the group and frequency as a percentage (%). Nonparametric methods of statistical analysis, such as the Mann-Whitney U test, were used to assess the significance of the difference in absolute values of means between independent samples. The Wilcoxon signed rank test (T) was used for paired groups. The p level < 0.05 was defined as significant in all tests.

The study protocol was agreed and approved by the Regional Bioethics Committee of the Zaporizhzhya State University of Medicine and Pharmacy. The study was conducted in accordance with the moral and ethical standards of the IGH/GCP, the Declaration of Helsinki (1964 with amendments in 1975, 1983, 1989, 1996, 2000), the Convention of the Council of Europe on Human Rights and Biomedicine, and the legislation of Ukraine. Written informed consent was obtained from the parents of the patients before the start of the study.

The study was conducted within the framework of the research work of the Department of Anesthesiology and Intensive Care Medicine of the State Institution «Zaporizhzhya State Medical and Pharmaceutical University of the Ministry of Health of Ukraine» – «Optimization of diagnosis and intensive care of polyetiological lesions of the brain, gastrointestinal tract, kidneys in newborns and older children», state registration number 0118U007142.

All statistical analyses were performed with the software Statistica 13.0, TIBCO Software Inc. (license number JPZ804I382130ARCN10-J) and Microsoft Excel 2013 (license number 00331-10000-00001-AA404). The probability of the difference in absolute values of means was determined using nonparametric methods of statistical analysis: the Mann-Whitney test (U) for unrelated groups and the Wilcoxon signed rank test (T) for related groups. The statistical significance was defined as $p < 0.05$.

Results. The study included 59 neonates, 30 in the standard diet group (SN) and 29 in the protein and carnitine enrichment group (FG). The characteristics of the infant groups are shown in Table 1. The enrolled infants were similar in terms of gestational age and anthropometric characteristics. In each group, boys predominated with 70 % and 62 %, respectively. Children in both groups had manifestations of hypoxic-ischemic encephalopathy at birth, initially determined by the Sarnat scale. A small percentage of children were born by cesarean section, the frequency of intervention did not differ between subgroups and was 16.67 % in the SN group and 20.69 % in the FG group, p=0.96. As expected, the children were comparable in terms of perinatal morbidity. The main problem was moderate hypoxic-ischemic encephalopathy (86.67 % and 86.21 %, without statistically significant difference). The main product of infant feeding was breast milk, 86 % in the SN group and 90 % in the FG group, p=0.69.

The proportions of birth weight and head circumference were within the 50 % percentile for both sexes. For birth length, both cohorts had values within the <90th and >50th percentiles, which were statistically equivalent (Table 1).

Table 1

Demographic and clinical data of infants enrolled in the study

Indicator, units of measurement	SN (n = 30)	FG (n = 29)	p-level
Gestational age, weeks	38,73 ± 1,26	39,00 ± 1,13	0,39
Weight at birth, g	3265,13 ± 366,60	3452,24 ± 413,58	0,07
Body length, cm	52,17 ± 2,32	53,16 ± 2,13	0,09
Head circumference, cm	34,27 ± 1,17	34,69 ± 1,01	0,14
Boys, n (%)	21,00 (70,00 %)	18,00 (62,07 %)	0,53
Apgar score at the first minute, points	6,13 ± 1,72	5,69 ± 2,00	0,36
Apgar score at the fifth minute, points	7,20 ± 1,71	6,76 ± 1,60	0,31
Cesarean section, n (%)	5,00 (16,67 %)	6,00 (20,69 %)	0,69
Hypoxic-ischemic encephalopathy, n (%)	26,00 (86,67 %)	25,00 (86,21 %)	0,96
Neonatal sepsis, n (%)	1,00 (3,33 %)	2,00 (6,90 %)	0,54
Meconium aspiration, n (%)	3,00 (10,00 %)	2,00 (6,90 %)	0,68

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A gradual increase in the daily feeding volume provided tolerance to the nutritional load, which in the groups at the end of the first week of life was respectively: for the FG 141.81 ± 20.18 ml/kg/day and for the SN 131.87 ± 30.63 ml/kg/day, p = 0.13; on day 14: for the FG 163.43 ± 9.46 ml/kg/day and for the SN 156.12 ± 13.25 ml/kg/day, p = 0.07. These data indicate a good tolerance of food intake in full-term infants, which allowed protein supplementation during the first week after birth. The increase in volume was stopped when the daily intake reached 150-165 ml/kg. Parenteral nutrition with lipid emulsions and amino acids was not performed according to the strategy adopted by the hospital [4,7].

In the fortification group (FG), it was possible to provide protein supplementation of approximately 3.5 g/kg/day from the 7th day of life. This corresponded to the protein intakes of critically ill term infants (2.0-3.50 g/kg/day) who had entered a stable «recovery» phase, according to the ESPGHAN 2021 recommendations [4]. At the same time, the level of deviation from the average was low, achieved by the automatic calculation of the infant formula. Thus, on days 14 and 21, the infants continued to consume 3.5 (3.4; 3.6) g/kg/day and 3.5 (3.5; 3.5) g/kg/day, respectively, of protein from fortification, and 2.3 (2.3; 2.5) g/kg/day and 2.4 (2.3; 2.6) g/kg/day, respectively, of protein from breast milk or formula.

The protein intake of the infants on the standard formula was 2.35 (2.3; 2.5) g/kg/day on average and 2.4 (2.3; 2.5) g/kg/day on days 14 and 21, which was also within the recommendations. When comparing the intake of total protein in the stable phase of lactation, a statistically significant difference was found between the groups: 3.5 (3.4, 3. 6) g/kg/day versus 2.35 (2.3, 2.5) g/kg/day, at U = 80.00; p = 0.0001 on day 14, and 3.5 (3.5, 3.5) g/kg/day versus 2.4 (2.3, 2.5) g/kg/day, at U = 50.00; p = 0.0001 on day 21.

Increased protein intake did not lead to an increase in plasma phenylalanine reference values. The international database, which includes results from 133 laboratories, reports a mean phenylalanine cut-off value of 130 mmol/L (range 65-234 mmol/L). In our study, the mean plasma phenylalanine level before the start of fortification was 91.18 mmol/L (65.56; 112.61), and at the end of fortification it was 88.07 mmol/L (62.49; 112.40), with U = 429.00; p = 0.76. No child was found to exceed the threshold for the above amino acid. Urea levels did not differ between groups during the first week of life or during weekly monitoring of biochemical parameters. Thus, the urea in the blood plasma of children with CH was 6.39 (3.45; 9.73) mmol/l, while the index in the fortified group was 4.92 (3.65; 7.10) mmol/l, with U = 429.00; p = 0.76. In the second week of breastfeeding this trend continued: in the SC group 4.14 (2.85; 5.22) mmol/l versus 4.56 (4.10; 6.46) mmol/l, with U = 291.00; p = 0.03. At the end of the treatment, the data obtained finally indicated the safety of the proposed strategy. At the end of the third week of treatment, newborns in the lower protein intake group had a urea level of 3.39 (2.71; 4.55) mmol/L, compared with a urea level of 4.47 (3.04; 6.01) mmol/L in the supplementation group, U = 376.00; p = 0.2.

In our study, infants in both groups had limited enteral feeding opportunities during the first two weeks and thus did not receive adequate carnitine supplementation from breast milk. This increased the risk of secondary carnitine deficiency. It should be noted that the reference values for free carnitine (FC) in newborns vary. According to the results of the study by H. Snares, the normal level of FC in term infants is 46.41±20.73 mmol/L [25]. Other authors point out the limit values of free carnitine in the range of 20-26 mmol/L, which can vary during the first month of life, so the data vary in recent years. One observational study reports that hypoxic-ischemic encephalopathy is a proven risk factor for secondary carnitine deficiency. In the group of children with HIE, a statistically lower level of carnitine was found compared to healthy children, reaching 13.2±6.8 mmol/L [26]. This prompted us to offer carnitine supplementation to the study group. As a result, serum carnitine levels in the group not taking prophylactic carnitine were below the reference value of 13.67 mmol/L (10.08; 18.61) at baseline and below the reference value of 24.97 mmol/L (18.99; 38.85) before discharge. In the fortification group, the initial carnitine level was also below the reference value, which increased after supplementation. Thus, in the last measurements, the level of free carnitine averaged 96.18 mmol/L (76.33; 119.32), in the first samples of this group – 24.17 mmol/L (20.22; 36.29), U = 35.0000; p = 0.0001. In the standard diet group, there was also a statistically significant increase in free carnitine levels at baseline and at the end of the study. This is due to the intake of carnitine with breast milk.

Weight gain showed significant differences between the two groups (Figure 2). As can be seen in this figure, although the birth weight was higher in the group that received more protein, it was not statistically significant. Subsequently, at the end of the first week of life, the weight gain curve was downward in the standard diet group due to a greater initial weight loss. In contrast, the FG group showed an upward weight gain due to early protein supplementation. Thus, the mean weight on day 7 in the SN group was 3224.00 ± 419.64 g, while in the FG group it was 3545.83 ± 405.39 g (p = 0.004). Subsequently, the growth of the infants in both groups was accompanied by a steady increase in weight, the corresponding growth curves were ascending, parallel to the 50 % percentile, until the moment of discharge from the hospital. On the 21st day of life, the statistical difference in body weight between the groups was maintained: 3554.62 ± 452.28 g for the SN group (n = 26) versus 3966.90 ± 439.08 g for the FG group (n = 20), at p = 0.003.

The generalized data (without taking gender into account) showed that the infants in the SN group initially lost more weight and recovered it more slowly than the infants in the FG group. Thus, the mean weight recovery in the protein supplementation group was almost twice as fast as in the standard diet group: 5.0 days (1.0; 8.0) versus 10.0 days (8.0; 16.0), with U = 173.00; p = 0.0002. It is noteworthy that this was achieved with the same dietary intake. The children in the enrichment group also showed a statistically greater daily weight gain: 24.76 g/kg/day (14.2; 30.36) versus 18.62 g/kg/day (12.5; 24.3), with U = 263.00; p = 0.02.

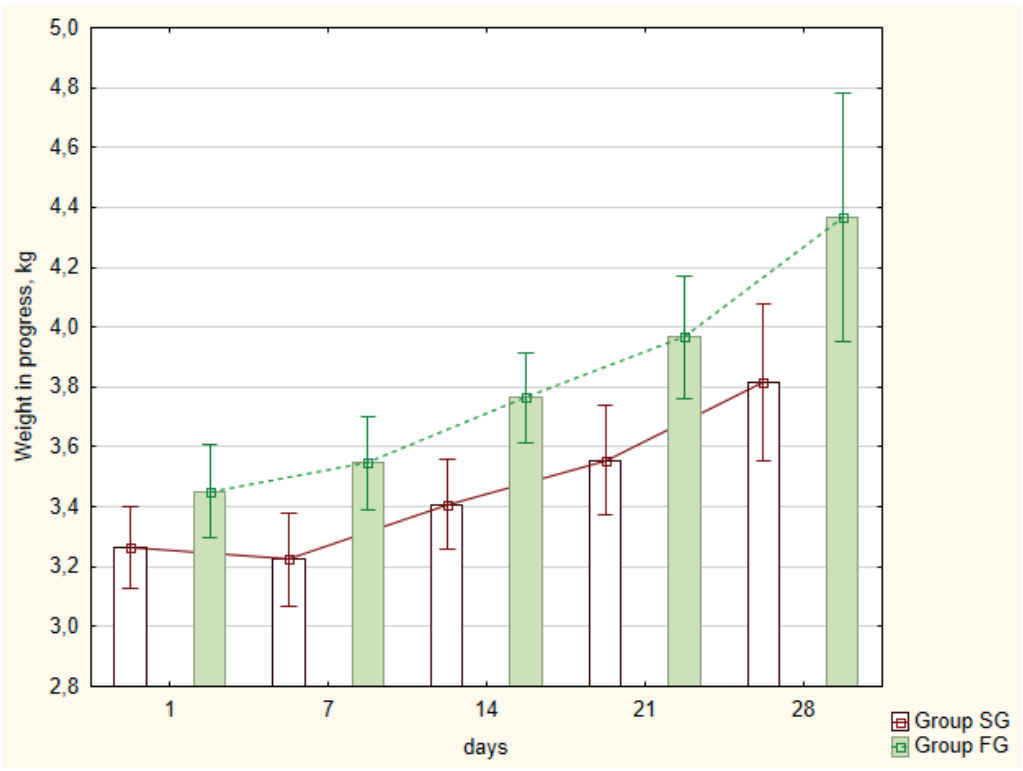

Fig. 2. Weight dynamics between groups

*Note * – statistically significant differences between groups*

As for the dynamics of changes in body length among infants, it was similar to weight (Fig. 3). The analysis revealed that the growth of babies began to increase already in the first week of life up to the 28th day, statistically significant differences began to appear as early as the 7th day. On the 21st day of observation, when most children in the enrichment group were ready for discharge, the body length indicators for the SN and FG groups were respectively: 53.52 ± 2.04 cm, versus 55.83 ± 1.43 cm, at p = 0.0001. Indicators of physical development of infants when assessed using Fenton diagrams adapted to the 50th week of adjusted age demonstrated a parallel increase in body length in infants of both groups from the first week of life.

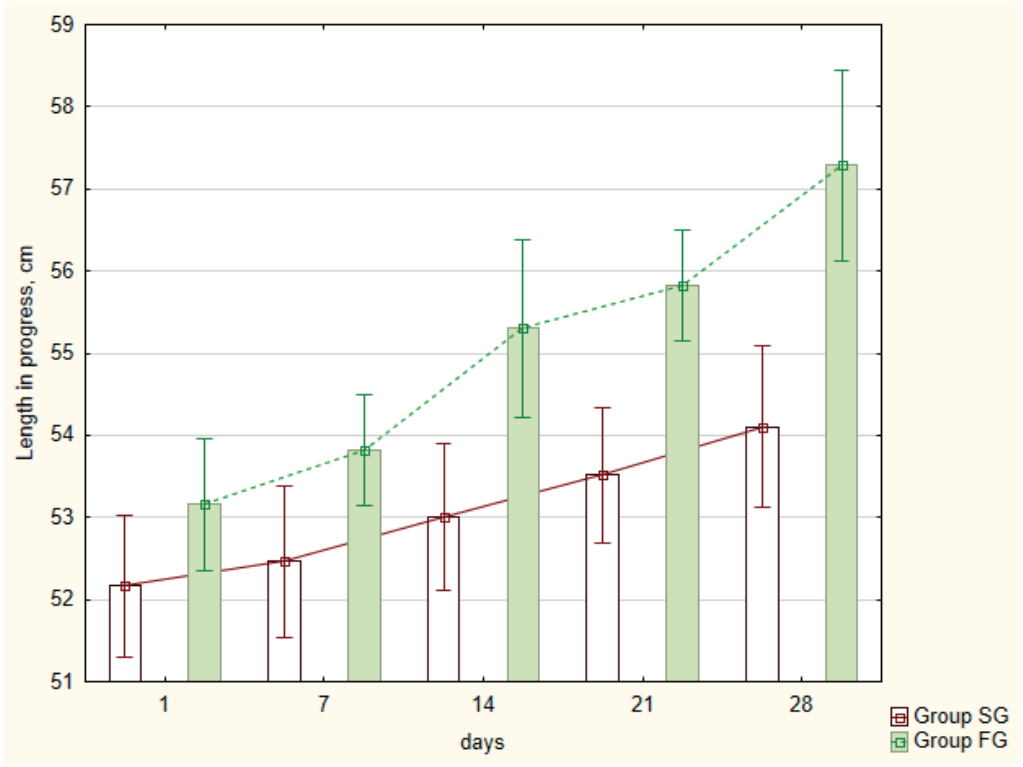

Fig. 3. Dynamics of body length growth

*Note * – statistically significant differences between groups*

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As shown in Figures 2 and 3, the differences in physical development were mainly related to body weight and length. The increase in head circumference was similar in both groups, with no statistical difference, and corresponded to an ascending curve parallel to the 50 % percentile. Accordingly, neonates of the FG spent less time in the NICU and hospital. Thus, after 23 days, only 7 (24.14 %) infants remained in the high protein group and 15 (50 %) in the standard nutrition group. Therefore, a comparative analysis of physical development after 21 days of life was not important.

The results of the BIA measurements during the study and the indicators calculated taking into account the body weight of the girls in both groups are summarized in Table 2.

Table 2

Dynamics of changes in BIA and «dry weight» among female newborns

Indicator, units of measurement	SN (n=9)#	FG (n=11)#	p-level	U
Bioelectric Impedance, ohm, Me (Q1; Q3)				
At birth	698.0 (603.0; 756.0)	740.0 (705.0; 789.0)	0.15	30.00
21st day or discharge†	562.0 (533.0; 588.0)	646.0 (634.0; 655.0)	0.003	10.00
Impedance index, cm2/Ω, Me (Q1; Q3)				
At birth	3.37 (2.49; 3.44)	3.12 (2.76; 3.17)	0.7	44.00
21st day or discharge†	3.91 (3.56; 4.42)	3.95 (3.51; 4.10)	0.82	46.00
Fat-free body mass (FFM), kg, Me (Q1; Q3)				
At birth	2.51 (2.47; 2.90)	2.86 (2.69; 3.29)	0.11	28.00
21st day or discharge†	2.83 (2.74; 2.9)	3.27 (3.00; 3.54)	0.03	15.00
Fat-free body mass (FFM), %, Me (Q1; Q3)				
At birth	84.58 (83.35; 85.42)	82.99 (81.57; 83.40)	0.07	25.00
21st day or discharge†	84.71 (83.65; 85.30)	82.21 (81.55; 83.10)	0.0051	8.00

 # – number of children from 1 to 14 days of observation; † – number of observations for girls on day 21 was in the SN group n = 8, in the FG group n = 10;

It is noteworthy that statistically significant differences in tissue impedance and FFM were obtained at day 21. The latter was higher in absolute numbers in the girls of the protein-supplemented group: 3.27 (3.00, 3.54) in the FG group versus 2.83 (2.74, 2.9) in the SN group, with U = 15.0; p = 0.03. It should be noted that the total body weight at 21 days was significantly higher in the fortified group, and in general the girls in this group grew better. Thus, in the third week, the body weight of girls in the FG group was 3982.50 (3610.00; 4340.00) g, while in the SN group it was 3320.00 (3235.00; 3460.00) g, with U = 7.5; p = 0.004. However, when the percentage of «dry» body weight relative to total weight was calculated, the opposite result was obtained: in women in the FG group, the percentage was 82.21 (81.55; 83.10) %, versus 84.71 (83.65; 85.30) % in the SN group, with U = 8.0; p = 0.0051. Thus, increased protein supplementation in term girls, even with short-term supplementation, was associated with greater accumulation of fat mass.

The analysis of the growth pattern in males showed no differences found in girls (Table 3).

When analyzing the dynamics of weight gain, it was found that boys of both groups grew approximately equally, and on the 21st day of life, the indicators did not have a statistical difference, for the CN group 3675.00 (3295.00, 4050.00) g (n = 18), against the average body weight in the FG group 3960.00 (3721.00, 4340.00) g (n = 10), with U = 50.0; p = 0.06, although half of the boys were discharged home by the third week of life.

Table 3

Dynamics of changes in BIA and «dry weight» among male newborns

Indicator, units of measurement	SN (n=21)#	FG (n=18)#	p-level	U
Bioelectric Impedance, ohm, Me (Q1; Q3)				
At birth	684.0 (614.0; 698.0)	643.5 (592.0; 688.0)	0.27	149.50
21st day or discharge†	594.0 (541.0; 623.0)	569.0 (548.0; 594.0)	0.41	159.50
Impedance index, cm2/Ω, Me (Q1; Q3)				
At birth	3.06 (3.01; 3.40)	3.42 (3.10; 3.74)	0.17	139.50
21st day or discharge†	4.01 (3.61; 4.22)	4.06 (3.92; 4.70)	0.41	150.00
Fat-free body mass (FFM), kg, Me (Q1; Q3)				
At birth	2.81 (2.69; 2.97)	2.83 (2.73; 3.15)	0.37	157.00
21st day or discharge†	3.10 (2.81; 3.36)	3.11 (2.91; 3.33)	0.04	47.00
Fat-free body mass (FFM), %, Me (Q1; Q3)				
At birth	85.15 (85.00; 84.38)	84.78 (84.75; 83.77)	0.49	164.00
21st day or discharge†	84.61 (84.85; 83.22)	83.68 (83.84; 82.55)	0.19	62.00

 # – number of children from 1 to 14 days of observation; † – number of observations for boys on day 21 was in the SN group n = 18, in the FG group n = 10;

Accordingly, there were no statistically significant differences for impedance and body composition indicators. The nature of the sex differences in body composition and growth influenced the results generalized to the entire cohort of children studied (Table 4).

Obviously, the nature of the differences is influenced by the difference found in female neonates. The absolute value of «lean» body weight increased in proportion to the increase in body weight and was significantly higher in the FG group at 21 days of age. The total weight in the FG group was 3960.00 (3691.00; 4340.00) g, versus 3460.00 (3240.00; 3980.00) g in the SN group, at U = 131.5 p = 0.005, and for FFM –3.12 (2.98; 3.30) g, versus 2.87 (2.68; 3.09) g, at U = 137.0; p = 0.01. The analysis of body composition in percentages showed an increase in the formation of more dry mass in the children who ate normally, without protein fortification and carnitine supplementation. Thus, the percentage of FFM was 84.71 (83.27; 85.47) % in the children on the standard diet, compared to 83.09 (81.93; 83.96) % in the FG group, U = 117.00; p = 0.002.

Table 4

Dynamics of changes in BIA and «dry weight» in newborns without regard to sex

Indicator, units of measurement	SN (n=30)#	FG (n=29)#	p-level	U
Bioelectric Impedance, ohm, Me (Q1; Q3)				
At birth	686.0 (613.00; 702.0)	680.0 (622.0; 740.0)	0.57	397.50
21st day or discharge†	586.0 (540.00; 623.0)	597.0 (563.0; 650.0)	0.22	353.50
Impedance index, cm2/Ω, Me (Q1; Q3)				
At birth	3.08 (2.94; 3.44)	3.20 (3.09; 3.70)	0.42	381.50
21st day or discharge†	3.96 (3.56; 4.28)	4.01 (3.68; 4.37)	0.73	397.00
Fat-free body mass (FFM), kg, Me (Q1; Q3)				
At birth	2.75 (2.51; 2.96)	2.85 (2.70; 3.15)	0.13	334.00
21st day or discharge†	2.87 (2.68; 3.09)	3.12 (2.98; 3.30)	0.01	137.00
Fat-free body mass (FFM), %, Me (Q1; Q3)				
At birth	84.96 (83.79; 85.45)	84.00 (83.03; 85.01)	0.06	308.00
21st day or discharge†	84.71 (83.27; 85.47)	83.09 (81.93; 83.96)	0.002	117.00

 # – number of children from 1 to 14 days of observation; † – number of observations for the 21st day was in the SN group n = 26, in the FG group n = 20;

To determine whether the body composition of neonates in each group changed from birth to discharge, we compared the percentage of FFM, and the results are shown in Table 5.

Table 5

Comparison of FFM, %, in neonates at baseline and end of study within groups

Indicator, units of measurement	At birth	21st day or discharge†	p-level	T
Girls, SN	84.58 (83.35; 85.42) (n=9)	84.71 (83.65; 85.30) (n=8)	0.66	-0.46
Boys, SN	85.00 (84.38; 85.45) (n=21)	84.85 (83.22; 85.96) (n=18)	0.01	2.74
Total, SN	84.96 (83.79; 85.45) (n=30)	84.71 (83.27; 85.47) (n=26)	0.05	2.02
Girls, FG	82.99 (81.57; 83.40) (n=11)	82.21 (81.55; 83.10) (n=10)	0.03	2.62
Boys, FG	84.75 (83.77; 86.01) (n=18)	83.84 (82.55; 84.05) (n=10)	0.01	3.17
Total, FG	84.00 (83.03; 85.01) (n=29)	83.09 (81.93; 83.96) (n=20)	0.0009	3.92

As can be seen from the data presented here, the growth of the children fed the standard program was not accompanied by changes in body composition, as evidenced by the absence of a significant difference in lean mass at birth and at the end of treatment. In contrast, increased protein intake resulted in a decrease in lean body mass as a percentage of actual body weight, as evidenced by the performance of the fortified group. Of particular note, the reduction in FFM in neonates receiving more protein did not differ by gender.

In general, children who consumed more protein were transferred from the ICU sooner – 10.00 (8.00, 12.00) days versus 12.00 (11.00, 16.00) days, U = 235.00; p = 0.0024; discharged from the hospital sooner – 21.00 (19.00, 27.00) days versus 26.50 (22.00, 31.00) days, U = 267.00, p = 0.0109.

Discussion. We present the results of a study of a group of term infants who showed very early differences in body structure at the end of hospitalization. The children required treatment in intensive care units for perinatal conditions. As a result of the study, we found that full-term infants who were fed mostly breast milk according to the standard approach had less fat mass at the end of the treatment than the group of children who received increased protein intake throughout the nursing period. The latter

was achieved by fortifying the breast milk with a protein supplement and adding carnitine to the treatment program. The decrease in lean body mass occurred against a background of better physical development in the fortified group, as evidenced by significantly higher anthropometric development indicators in infants in the fortified group. Our study is one of the few to evaluate body composition in term infants requiring treatment in the NICU.

In recent years, many researchers have investigated the hypothesis that increased protein intake in sick and healthy children of various ages promotes better physical development, accompanied by the formation of a body structure predominantly free of fat mass. Most of the studies have been conducted in premature infants, who are more likely to have physical developmental delays. Amesz E. M. hypothesized that formulas enriched in energy and protein, with an increased protein-to-energy ratio, improve lean mass gain in preterm infants [27]. The authors conducted a randomized controlled trial in which preterm infants were fed fortified milk or formula until 40 weeks' gestation, at which time they were randomized to receive a protein-enriched preterm formula or a term formula. Feeding was continued for up to 6 months, after which anthropometric and body composition assessments were performed using dual-energy X-ray absorptiometry (DEXA). Infants fed the lower-protein formula had lower fat mass, especially boys, but the differences were not significant. The results of this study are similar to ours.

Recently, differences in body composition in healthy full-term infants fed a protein-enriched diet for one year were studied to determine the effects on future body composition [12]. This multicenter study compared groups of infants fed breastmilk or a formula with increased protein (relative to the reference) and a balanced formula for full-term infants during the first months of life. Body mass index and anthropometric parameters were assessed at 1, 2 and 6 years of age. It was found that increased protein intake led to an increase in body mass index at 2 and 6 years of age in the children who received more protein, and increased the risk of obesity by a factor of 2.6. This is known to influence the development of the so-called «metabolic syndrome» and has negative consequences [28]. The main goal of our study was to improve hospital outcomes by reducing the time spent in bed and the need for mechanical ventilation, which was demonstrated, but better physical growth with a higher percentage of body fat may be a limitation for the implementation of this practice. Recently, many studies conducted in preterm infants have shown that increased protein intake allows for better growth in this group, which still differs from the development of full-term infants without disease [4]. Historically, preterm infants have been found to have lower height and weight, more adipose tissue, and a correspondingly higher body mass index. However, there are few studies in cohorts of term infants, although certain subpopulations of term infants with impaired nutritional tolerance may have additional nutritional needs [29,30]. At the same time, studies have been published demonstrating the benefits of increased protein intake in the context of breast milk fortification. Mariani E. et al. demonstrated that higher protein in the diet of preterm infants contributes to better physical development and neurological outcomes in the future, but the body composition of the children was not assessed in this work [31].

The study of body composition in healthy, term-born infants using DEXA is almost a reference method for determining body composition, but recently there have been many publications pointing to the possibilities of bioelectrical impedance [23]. A comparison of BIA and DEXA was performed by N. Q. Dung et al. The randomized study included 118 children (51 boys, 67 girls), all born preterm at a mean age of 30.1 ± 3.1 weeks and a birth weight of 1.26 ± 0.47 kg. Body composition was measured at a postmenstrual age of 38.6 ± 3.8 weeks and an actual body weight of 2.6 ± 0.54 kg using dual-energy X-ray absorptiometry [24, 29]. Weight and height were collected along with bioelectrical resistance measurements for further mathematical calculation of FFM. Multiple regression analysis was performed to evaluate the prediction of FFM using impedance index (Ht2/I, cm2/Ω) and body weight. Stronger correlations demonstrated that body weight was a more effective predictor of FFM than impedance index. However, as a bedside monitoring, FFM has been proposed to rely more on weight variability than BIA, but in general the accuracy of the calculation of dry mass was almost equal to the reference (DEXA), which led us to choose this technique. In addition, other authors have successfully used this simple and inexpensive method of determining body composition in their studies [19, 23].

In conclusion, feeding full-term infants in the NICU with artificially high-protein breast milk contributes to a better hospital stay, which may have some economic impact, and to better physical development, but this practice contributes to an increase in the fat content of infants at the expense of females, which affects the overall group index. The results may have implications for future metabolic programming. This may be due to certain limitations of our study: small sample size, use of bioimpedance analysis instead of dual-energy X-ray absorptiometry, and lack of follow-up of children.

Conclusions

1. Consumption of more protein relative to the reference requirement and carnitine supplementation in term neonates in the intensive care unit promotes better growth and is associated with a shorter hospital stay.

2. The increase in body weight in children receiving protein supplementation above the standard intake was accompanied by an increase in adipose tissue content in females compared with the group fed breast milk without fortification, which may have implications for metabolic programming in the future.

3. Bioimpedance analysis is a simple, non-invasive method for determining fat-free mass in term infants, which should be a useful tool for assessing changes in body composition in the neonatal unit.

4. Studies with a larger number of observations and a more comprehensive examination of infants are needed. At present, we cannot recommend increasing the protein intake of term infants in the NICU.

Prospects for further research: To examine the full implications, it is advisable to conduct a study that includes a catamnestic analysis of children's physical development,

neurological development, body composition, and overall morbidity in infancy. Studies should determine whether changes in body composition are the result of diet alone, or whether genetic and other environmental factors have an impact.

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СКЛАД ТІЛА ДОНОШЕНИХ НОВОНАРОДЖЕНИХ НА ТЛІ ПІДВИЩЕНОГО СПОЖИВАННЯ БІЛКА У ВІДДІЛЕННІ ІНТЕНСИВНОЇ ТЕРАПІЇ

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Резюме.

У дослідженні вивчали результати впливу підвищеної дотації протеїнів та L-карнітину в програмі харчування доношених новонароджених із захворюваннями перинатального періоду на покращення результатів фізичного розвитку, зміни складу тіла та на показники лікування у стаціонарі.

Мета – оцінити вплив короткотривалого підвищеного споживання білка доношеними новонародженими та дотації L-карнітину на формування складу тіла та основні показники фізичного розвитку дітей.

Матеріал і методи дослідження. Для перевірки запропонованої гіпотези харчування новонароджених досліджено показники життя 59 доношених дітей, яких рандомізовано на дві групи. Перша група (n = 30) отримувала стандартне харчування молоком матері (СХ) або формулою, друга група (n = 29) отримувала фортифікований білковою добавкою харчовий продукт (ГЗ) та дотацію L-карнітину протягом перебування у лікарні. На початку і в кінці лікування вивчали фізичний розвиток дітей та склад тіла за допомогою біоелектричного імпедансу.

Протокол дослідження узгоджено та схвалено регіональною Комісією з питань біоетики Запорізького державного медико-фармацевтичного університету. Дослідження виконано із дотриманням морально-етичних норм згідно правил IGH/GCP, Гельсінської декларації (1964 з доповненнями 1975, 1983, 1989, 1996, 2000 р.р.), Конвенції Ради Європи про права людини і біомедицини та законодавства України. Інформована письмова згода була отримана від батьків пацієнтів перед початком дослідження.

Всі статистичні аналізи проводилися з використанням програмного забезпечення Statistica 13.0, TIBCO SoftwareInc. (№ ліцензії JPZ804I382130ARCN10-J) та Microsoft Excel 2013 (№ ліцензії 00331-10000-00001-AA404). Визначення вірогідності різниці абсолютних значень середніх величин проводили, використовуючи непараметричні методи статистичного аналізу: критерій Манна – Вітні (U) для непов'язаних груп і критерій знаків Вілкоксона (Т) для пов'язаних груп. Статистична значущість визначалася, як $p < 0,05$.

Дослідження виконано в рамках науково–дослідницької роботи кафедри анестезіології та інтенсивної терапії ДЗ «Запорізький державний медико-фармацевтичний університет МОЗ України» – «Оптимізація діагностики та інтенсивної терапії поліетіологічних уражень головного мозку, кишково-шлункового тракту, нирок у новонароджених та дітей старшого віку», № держреєстрації 0118U007142.

Результати дослідження. Немовлята обох груп мали рівнозначні характеристики маси, довжини та обводу голови на початку дослідження. Пропорції немовлят обох статей відповідали межам 50 %-го перцентилю. В цілому, запропонована стратегія харчування сприяла кращим показникам фізичного розвитку малюків та статистично вірогідним, більш швидким відновленням маси тіла в групі фортифікації. Так, узагальнений показник маси тіла дітей групи ГЗ склав 3966,90 ± 439,08 г, порівняно з групою СХ 3554,62 ± 452,28 г, при $p = 0,0033$. В цілому, діти, які споживали більше білка, раніше переводилися з відділення інтенсивної терапії –10,00 (8,00; 12,00) днів проти 12,00 (11,00; 16,00) днів, при $U = 235,00$; $p = 0,0024$; раніше виписувались зі стаціонару – 21,00 (19,00; 27,00) днів проти 26,50 (22,00; 31,00) днів, при $U = 267,00$, $p = 0,0109$. Дана стратегія виявилася безпечною, що підтверджено нормальними рівнями фенілаланіну та сечовини на всіх етапах обстеження дітей. Аналіз складу тіла у відсотках виявив зростання з формуванням більшої кількості сухої маси у малюків, які харчувалися звичайно, без білкової фортифікації та додавання карнітину. Так, відсоток FFM у дітей при стандартному харчуванні складав в фіналі 84,71(83,27;85,47) %, проти FFM 83,09 (81,93;83,96) % в групі ГЗ, при $U = 117,00$; $p = 0,0020$. На показник загальної когорти впливали зміни складу тіла, виявлені серед осіб жіночої статі: в ГЗ відсоток склав 82,21 (81,55;83,10) % проти 84,71 (83,65;85,30) % в групі СХ, при $U = 8,0$; $p = 0,0051$. Отже, підвищена дотація протеїну у доношених дівчат, навіть при короткотривалій дотації, супроводжувалась більшим накопиченням жирової маси.

Висновки. Споживання більшої кількості протеїну та дотація карнітину у доношених новонароджених, які перебували у відділенні інтенсивної терапії, сприяє кращому зростанню на тлі формування складу тіла з більшим вмістом жиру серед осіб жіночої статі, що є фактом обмеження застосування даної стратегії без більших, за кількістю спостережень, досліджень.

Ключові слова: склад тіла; гіпоксично-ішемічна енцефалопатія; новонароджений; діти; фізичний розвиток; біоелектричний імпеданс; грудне молоко.

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