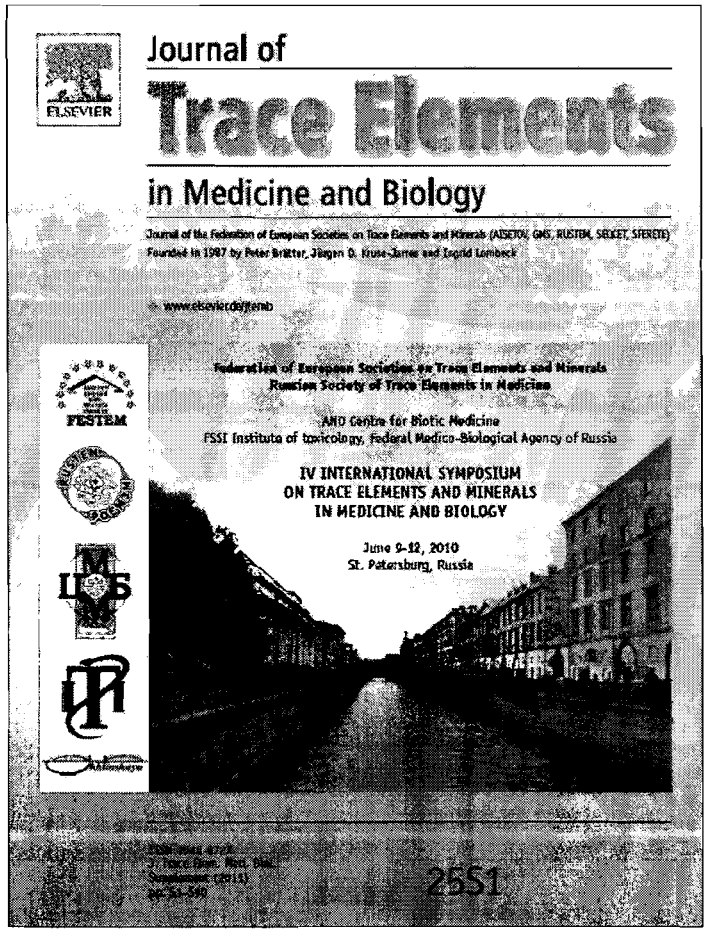

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FOURTH INTERNATIONAL FESTEM SYMPOSIUM

Indispensable and replaceable amino acids in the blood serum and their relationship with macro- and microelements in the newborns of Fe-deficient anemic mothers (in conditions of an industrial city)

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ABSTRACT

Anemia of the newborn is undoubtedly an actual problem in pediatrics. The imbalance between amino acids and biologically active macro- and microelements participating in hematopoiesis and Fe metabolism play an important role in its pathogenesis. Therefore knowledge of amino acid metabolism in the newborn helps to gain insight into pathogenetic mechanisms and to choose the right therapy. A complex inspection of 169 newborns of 18–34-year-old women was done. The control group consisted of 42 newborns of women with normal pregnancy and parturition. The case group consisted of 127 newborns of women with Fe-deficit anemia. Unquestionably one of the factors of Fe-deficit anemia of women aggravates the gestation period, delivery and after-birth period, and has an injurious effect on the newborn. Changes in the trace element and free amino acid metabolism were interconnected in the "mother–newborn" system as evidenced from correlations between the levels of some amino acids, trace element metabolism and erythropoiesis. The pathogenetic importance of the disturbance of the trace element and amino acid metabolism dictates the choice of the correct therapy of Fe-deficit anemia of pregnant women. The experience and results of our investigations support the necessity of preventive estimation of the content of macro- and microelements and amino acids in the blood serum of newborn to correct metabolic disturbances.

Introduction

The World Health Organisation reports that in all countries despite their economic development the number of pregnant women with iron-deficiency anemia has increased from 21% to 80% (hemoglobin level) and from 50% to 90%, respectively (serum Fe) [1,2]. The Ministry of Health of the Russian Federation reports that during the last ten years such cases have increased by 6.3 times [3,4]. In the Sverdlovsk region every second woman suffers from Fe-deficiency, during pregnancy; in Yekaterinburg – every third [5].

The unfavourable effect of a pregnancy with of Fe-deficit on the newborn's health is known [6,7]. According to official statistics, a threatening number of Fe-deficit anemic (FDA) children have been observed in Russia during the last 10 years. Among children under 1 year the cases have increased to 58.3% and account for 112.6‰. In some regions the number of FDA-children reaches 82% [8–10]. The high prenatal and infant morbidity and newborn mortality of anemic women suggests that the solution of this problem goes hand in hand with an actual medico-social trend towards prophylaxis and treatment of women to decrease infant morbidity and mortality [11–15].

Anemia of the newborn is undoubtedly an actual problem in pediatrics [7,9,13,16]. An important role in its pathogenesis is played by the imbalance between amino acids and biologically active macro- and microelements participating in hemopoiesis and Fe metabolism; therefore knowledge of amino acid metabolism in the newborn helps to gain insight into pathogenetic mechanisms and to choose the right therapy [17–21].

Cases and methods

The research was done in the Maternity Hospital № 1 in Yekaterinburg. 169 newborns (mothers were pregnant at the age of 18–34) were inspected. The control group was 42 newborns whose mothers had a physiological pregnancy and normal parturition. In accordance with the recommendations of the World Health Organisation the criterion for defining pregnant women

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and newborns as anemic was a hemoglobin level of 110 g/L or lower. Fe-deficit anemia of the average degree was found in 127 women (70 > Hb < 90 g/L). In the newborns an average magnitude of 6.0 ± 0.44 on Apgar scale was found.

Blood indices and ferrokinetics were investigated in all women in the third trimester of pregnancy and their neonate. The blood composition was estimated on the automatic blood analyzer "Micro SX." For the spectrophotometric estimation of Fe and Fe-bonding ability of the blood TIBS sets were used ("HUMAN", Poland). Fe-deposition ability was estimated from the concentration of the serum ferritine using the set produced by "Hoechst", Germany.

We estimated the contents of macro- and microelements and amino acids in the blood serum of somatically healthy and anemic pregnant women and their newborns.

The content of the trace minerals Cu, Zn, Fe, Mg, Ca, Pb, Cd, Co, and Sr in the blood serum was analyzed in triplicate by atomic absorption spectrophotometry (PerkinElmer Analyst 1000, USA) and by atomic absorption (spectrophotometer by "AAS", Germany). Separate and disposable sterilized plastic syringes were used for blood collection. The blood sample was left standing for 1 h to coagulate, and serum was separated at 2000 rpm centrifugation for 10 min, transferred to a 5 mL polystyrene tube and stored at −18 °C to 20 °C until the analysis was done.

The amino acid pool of the blood serum was estimated by ion-exchange chromatography on the Automatic Amino Acid Analyzer ("AAA-339M", Czechia). The women's blood was taken from the vein during delivery, and the newborns' blood was taken from the umbilical cord vein. Protein precipitation of the suspension was done immediately using 10% sulfosalicilic acid (SSA). A standard solution containing all amino acids was analyzed for quality control after every five samples.

Statistical analysis was carried out with the program "Statistica & Microsoft Excel." Results were expressed as mean ± standard error (SEM). Parameters showing a Gaussian distribution were analyzed by Student's *t*-test. The Mann–Whitney *U*-test was used for the parameters with non-Gaussian distribution. The correlation between variables was evaluated by Pearson's correlation coefficients, or Spearman's rank correlation coefficients were used to relate trace elements concentration, amino acids activities and medical data. The distinctions between the samples were considered to be statistically significant at $p < 0.05$.

Results and discussion

During the first hours after the delivery the healthy newborn of the control mother group exhibited 180.0–214 g/L of hemoglobin and a high syderemia level (serum ferritine: SF = 165.0 ± 1.7 ng/mL, serum Fe: 26.8 ± 0.4 mkmol/L; transferrine saturation with Fe: 66.8%) against the background of a very low total iron binding capacity of the serum: 40.12 ± 0.9 mkmol/L ($p < 0.05$). The newborns' syderemia levels were significantly higher than those of the mothers. The data give evidence of functional possibilities of liaison and neutralization mechanisms in the excess of organic iron in the bloodstream of the system mother–newborn.

The children born by the anemic women exhibited microcytosis or accelerated formations of erythrocytes – an early sign of anemia. This was evidenced by the leftwards-shifted Price–John's curve. The number of erythrocytes and hematocrit was significantly lower ($p < 0.001$). The lower average erythrocytes volume (MCV = 71.2 ± 0.7 mkm^3) and hemoglobinopenia were marked: Hb < 101 g/L ($p < 0.05$).

The anemic newborn exhibited lower contents of ferritin (26.0 ± 3.1 ng/mL) and ferrum (11.8 ± 3.1 mkmol/mL) in the serum, transferrine saturation with ferrum was below 28% – an evidence of lower erythropoiesis effectiveness ($p < 0.05$). The arising fetal hyposyderemia added to the pathogenesis of the prenatal hypotrophy. A direct correlation in the serum Fe content was revealed between mothers and their newborn's body mass ($r = 074$, $p < 0.05$). The stock of iron in a newborn's organism was dependent on that in the mother. This was supported by the direct correlation of the ferritine levels in the serum blood between the mothers and the newborns ($r = 0.61$, $p < 0.05$).

It is known that in the embryonic and fetal pathological development the microelement metabolism plays a great role, often influencing the whole metabolic processes. In anemic mothers a placenta with a high Cd and Pb level promotes the penetration of the toxic metals into the organism of the newborn, breaking early adaptation and disturbing infant health. In our preceding research anemic women exhibited placenta failure accompanied by a deficiency in essential Fe, Cu, Ca, Zn, Mg in their newborn's blood during the first hours of birth [20,22]. The Cd level in the blood of such children increased 5 times (0.02 ± 0.001 mkg/mL), the Pb level increased 1.9 times (0.29 ± 0.07 mkg/mL) compared to the children born by somatically healthy mothers. The essential microelements were measured at low levels: Cu – 0.68 ± 0.085 mkg/mL; Zn – 1.4 ± 0.95 mkg/mL; Fe – 0.81 ± 0.05 mkg/mL; Mg – 14.5 ± 0.06 mkg/mL (Fig. 1).

Thus, the combined effect of metals through the system mother–placenta–newborn was unfavourable for the fetus, as oxygen entry was disturbed. A strong direct correlation was observed between the anemic newborn's body mass and microelements: Mn ($r = 0.87$, $p = 0.02$), Fe ($r = 0.81$, $p = 0.04$). These newborns were a group of high risk of the development of pathologies provoked by the transplacental entry of toxic microelements.

The amino acid spectrum of the pregnant women's blood serum and their newborns in both groups was constant and consisted of 23 amino acids. The total concentration of amino acids (3226.9 ± 88.7 mkmol/L) in anemic pregnant women was by 19.5% ($p < 0.05$) lower compared to the women with a physiological pregnancy. The newborns (anemic mothers) exhibited total concentrations of free amino acids in the blood serum that were 27.3% $p < 0.05$ lower (2714.7 ± 77.0 mkmol/L) [22].

The pool of free amino acids in the blood serum of these newborns (anemic mothers) was lower than that of their mothers (15.9%, $p < 0.05$). The analysis of the blood serum amino acid spectrum showed that in a physiological pregnancy the ratio between indispensable and replaceable amino acids in the system "mother–newborn" was 0.8 and 0.82 accordingly [22]. The genesis of anemia during the gestation period was based on the disturbance of amino acid metabolism accompanied by the imbalance of amino acids in the blood serum, the ratio between indispensable and replaceable acids being reduced down 0.63 (mother) and 0.62 (newborn). The pool of indispensable amino acids in the blood serum of anemic pregnant women correlated with the low fetal mass at birth ($r = 0.83$, $p = 0.004$) [22].

The impoverishment of the free amino acid pool in the anemic newborn was accompanied by the 26% reduction of the indispensable acid levels ($p < 0.05$). Concentrations of the indispensable amino acids were also significantly lower due to their intensive consumption by the blood-forming tissue: methionine – 75.6% lower, histidine – 32.7%, leucine – 30.7%, isoleucine – 65% (the latter is intensively used in the hemoglobin formation ($p < 0.05$)), and valine – 40.5%. This amino acid is responsible for the formation of the fetal blood-forming system (Fig. 2). We also observed decreased levels of low-hydrophobic amino acids participating in the cell proliferation stimulation and necessary for the fetal growth and development (lysine – 14.7% lower, arginine – 63.0%, $p < 0.05$), as well as reduced numbers of erytrocytes and hemoglobin in the blood serum ($r = 0.71$, $r = 0.63$, accordingly, $p < 0.05$). It is important that fetuses used both pools of the pregnant women – Fe and amino acid – through the placenta membrane.

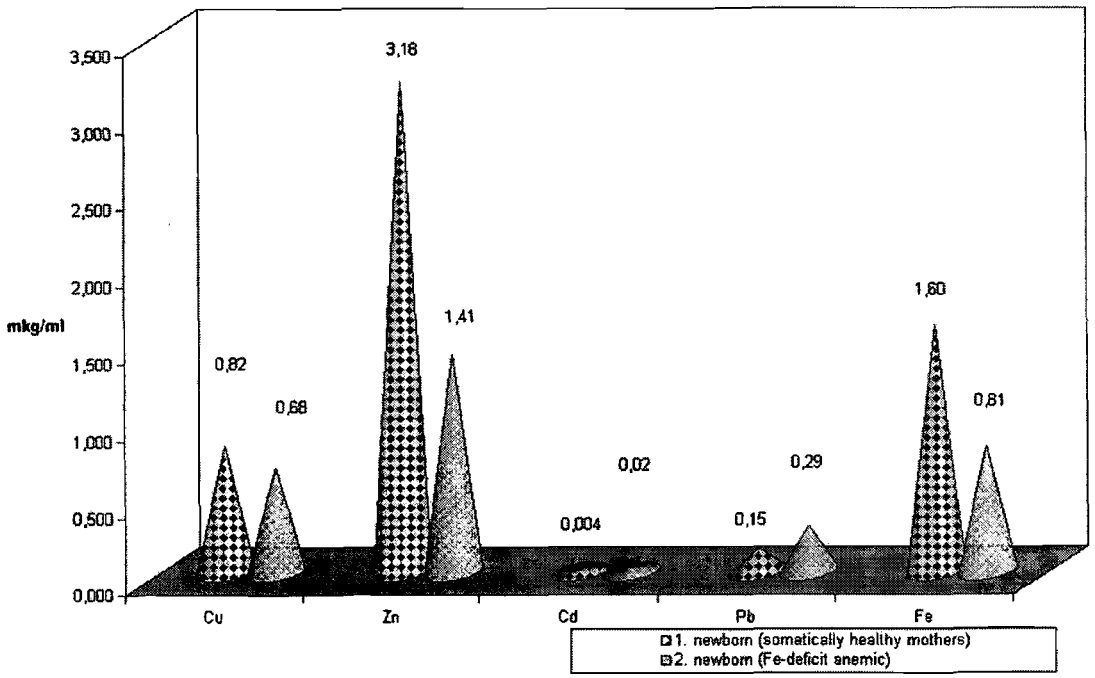

Fig. 1. Microelements in the umbilical cord blood of the newborn. (1. – somatically healthy mothers.) (2. – anemic mothers.)

In anemic newborns a significant correlation was observed between hemoglobin and histidine levels ($r = 0.51$, $p < 0.05$), between the number of eritrocytes and the lysine level ($r = 0.67$, $p < 0.05$). Correlations between the levels of indispensable amino acids (arginine, lysine, methionine, histidine), erytrocytes and hemoglobin evidenced of a connection between amino acids and the biogenic trace elements metabolism.

The revealed Ca concentrations in the blood serum of the healthy newborns stimulated the synthesis of amino acids participating in the plastic processes: replaceable asparagine ($R = 0.82$, $p = 0.041$), cysteine ($R = 0.88$, $p = 0.018$), indispensable leucine ($R = 0.88$, $p = 0.018$). Mg stimulated replaceable glutamine ($R = 0.82$, $p = 0.041$), Fe stimulated cysteine ($R = 0.82$, $p = 0.04$).

Reverse correlations were between Fe and aspartic acid ($R = -0.82$, $p = 0.04$), Fe and tryptophan ($R = -0.82$, $p = 0.04$) in the blood serum of children. Reverse correlations were marked between xenobiotic Cd and cysteine ($R = -0.92$, $p = 0.008$) leucine ($R = -0.92$, $p = 0.008$), lysine ($R = -0.92$, $p = 0.008$) (Table 1). Reverse correlations were marked between xenobiotic Pb and alanine ($R = -0.81$, $p = 0.049$).

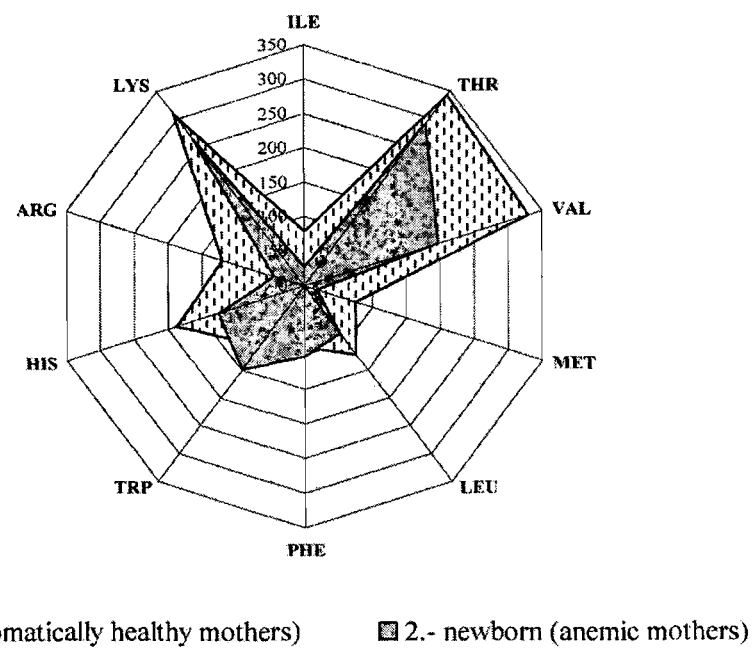

Fig. 2. Indispensable amino acids in the blood serum of the newborn. (1. – somatically healthy mothers.) (2. – anemic mothers.)

Table 1
Correlations between the levels of amino acids and trace elements in the newborn's blood serum (somatically healthy mothers).

Correlation pairs	R (Spearman)	p-level
Cystein acid Mg	−0.94286	0.004805
Taurine Zn	−0.94286	0.004805
Aspartic acid Fe	−0.82857	0.041563
Asparagine Ca	0.82857	0.041563
Asparagine Co	−0.83324	0.039396
Glutamine Mg	0.82857	0.041563
Proline Cu	−0.88571	0.018845
Alanine Pb	−0.81168	0.049858
Cysteine Fe	0.82857	0.041563
Cysteine Ca	0.88571	0.018845
Cysteine Cd	−0.92582	0.008050
Methionine Sr	−0.88273	0.019820
Isoleucine Co	−0.92582	0.008050
Isoleucine Sr	−0.97101	0.001249
Leucine Ca	0.88571	0.018845
Leucine Cd	−0.92582	0.008050
Tryptophan Fe	−0.82857	0.041563
Lysine Cd	−0.92582	0.008050

Table 2
Correlations between the levels of amino acids and trace elements in the newborns's blood serum (Fe-deficit anemic mothers).

Correlation pairs	R (Spearman)	p-level
Cystein acid Cd	0.89443	0.040519
Serine Fe	−0.90000	0.037386
Valine Fe	0.90000	0.037386
Leucine Cd	−0.89443	0.040519
Phenylalanine Cd	−0.89443	0.040519
Histidine Cd	−0.89443	0.040519
Arginine Fe	0.90000	0.037386
Arginine Ca	−0.90000	0.037386

In the blood serum of the anemic newborn direct correlations were marked between the levels of trace elements and indispensable amino acids: between Fe and valine ($R = 0.9$, $p = 0.037$), Fe and arginine ($R = 0.9$, $p = 0.037$), reverse correlations were marked between Cd and histidine ($R = -0.89$, $p = 0.04$), Cd and phenylalanine ($R = -0.89$, $p = 0.04$), Cd and leucine ($R = -0.89$, $p = 0.04$). A significant reverse connection was between arginine and Ca ($R = -0.9$, $p = 0.037$) (Table 2). A reverse correlation was between Fe and serine in the blood serum of ill children ($R = -0.9$, $p = 0.037$).

The revealed correlations between the levels in the blood of some amino acids, protein fractions, macro- and microelements, hemoglobin and erythrocytes supported the conclusion that metabolic changes in indispensable amino acids, proteins and microelements were interrelated in the anemic newborn.

Conclusions

It was revealed that Fe-deficit anemia (average degree) in pregnant women caused a secondary metabolic disturbance of trace elements and amino acids in their newborn, thus increasing the risk of perinatal fetal sufferings. One of the factors of anemia pathogenesis in the newborn was a change in the structure of the blood serum amino acid pool towards lower total contents of indispensable amino acids and higher contents of some replaceable amino acids. Changes in the trace element and free amino acid metabolism were interconnected in the "mother–newborn" system as evidenced from correlation between the levels of some amino acids, trace element metabolism and erythropoiesis.

The pathogenetic importance of the disturbance of trace element and amino acid metabolism dictates the choice of correct therapy of Fe-deficit anemia of pregnant women. The results of the study support the necessity of preventive estimation of the content of macro- and microelements, indispensable and replaceable amino acids in the blood serum of newborns and can be used for the prenatal diagnosis of iron deficiency and targeted correction of the metabolic disturbances.

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