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BIOCHEMICAL AND PHYSIOLOGICAL CHARACTERISTICS OF NEONATES BORN TO MOTHERS WITH DIABETES DURING GESTATION

BIOHEMIJSKE I FIZIOLOŠKE KARAKTERISTIKE NOVOROĐENČADI IZ DIJABETIČNIH TRUDNOĆA

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Summary: The aim of this study was to investigate how glucose homeostasis disorders influence biochemical homeostasis and fetal maturation. A prospective randomized study included 102 infants: 31 newborns of mothers with glucose homeostasis disorders (Group I) and 71 newborns of healthy mothers (Group II). In the pregnant women, the mean age, body weight and height, BMI, parity, duration of the disease and the mode of labor were estimated. The following procedures were performed in each newborn infant: physical examination, determination of Apgar score, measurements of birth weight and length, estimation of neurological status, clinical estimation of gestational age, ECG and ultrasonography of the brain, as well as the basic hematologic, biochemical and microbiological analyses. Newborn infants of diabetic pregnancies were small for gestational age and of high birth weight. The levels of Na^+, K^+ and Cl^- ions did not show significant differences between the investigated groups, whereas the levels of total Ca and Mg were significantly decreased (2.18±0.59 and 0.65±0.17 mmol/L) ($p<0.001$) in the investigated group relative to the control group (2.42±0.53 and 0.81±0.09 mmol/L). The newborn infants of diabetic pregnancies presented with significantly decreased values of phosphates, bicarbonates and pH, whereas the difference in total osmolality was not statistically significant. The level of glucose at birth in the infants of diabetic mothers was lower (2.91±0.51 mmol/L) ($p<0.001$) than in the infants of healthy pregnancies (3.94±0.29 mmol/L). Glycemia lower than 2 mmol/L was recorded in 6.5% of infants of the investigated group. The level of bilirubin was significantly increased (209.71±56.66 mmol/L) ($p<0.001$) in infants of diabetic mothers compared to those of the healthy ones (155.70± 61.14 mmol/L), like the incidence of clinically manifested hyperbilirubinemia. Disorders of maternal glucose homeostasis cause biochemical disorders such as hypoglycemia, hypocalcemia, hyperbilirubinemia, hypomagnesemia and are associated with impaired maturation and congenital malformations of the fetus.

Keywords: biochemical analyses, neonates, diabetes, pregnancy

Kratak sadržaj: Cilj rada je utvrditi kako poremećaj homeostaze glukoze utiče na biohemijsku homeostazu i maturaciju ploda. Prospektivnim i randomiziranim ispitivanjem obuhvaćena su 102 novorođenčeta, 31 novorođenče majki sa poremećajem homeostaze glukoze (I grupa) i 71 novorođenče zdravih majki (II grupa). Trudnicama je određena prosečna starost, telesna visina, telesna težina, BMI, paritet, dužina trajanja bolesti i praćen je način porođaja. Svakom novorođenčetu urađen je fizikalni pregled, određen Apgar skor, neurološki status, izmerena telesna težina i dužina, obavljena klinička procena gestacijske starosti, EKG i ultrazvučni pregled mozga kao i osnovne hematološke, biohemijske i mikrobiološke analize. Novorođenčad iz dijabetičnih trudnoća manje su gestacijske starosti i veće telesne težine. Nivo jona Na^+, K^+ i Cl^- ne pokazuje značajne razlike između ispitivanih grupa, dok je nivo ukupnog Ca i Mg značajno ($p<0,001$) niži (2,18±0,59 i 0,65±0,17 mmol/L) u ispitivanoj u odnosu na kontrolnu grupu (2,42±0,53 i 0,81± 0,09 mmol/L). Kod novorođenčadi iz dijabetičnih trudnoća nalazimo i značajno niže vrednosti fosfata, bikarbonata i pH, dok razlika u ukupnom osmolalitetu nije značajna. Nivo glukoze po rođenju je niži ($p<0,001$) kod novorođenčadi iz dijabetičnih (2,91±0,51 mmol/L) nego zdravih (3,94±0,29 mmol/L) trudnoća. U ispitivanoj grupi 6,5% novorođenčadi imalo je glikemiju manju od 2 mmol/L. Nivo bilirubina značajno je ($p<0,001$) veći kod dijabetične (209,71± 56,66 mmol/L) nego zdrave (155,70±61,14 mmol/L) novorođenčadi, kao i incidenca klinički manifestne hiperbilirubinemije. Poremećaj homeostaze glukoze majke uzrok je biohemijskih poremećaja: hipoglikemije, hipokalcemije, hiperbilirubinemije, hipomagnezijemije, a povezan je i sa usporenom maturacijom i kongenitalnim malformacijama ploda.

Ključne reči: biohemijske analize, novorođenčad, dijabetes, trudnoća

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Introduction

Today, 3–10% of pregnancies are affected by abnormal glucose regulation. Of these cases, 80% are related to gestational diabetes (1). Major causes of morbidity in the newborns of mothers with diabetes – gestational or preexisting – include the following: fetal macrosomia, growth small for gestational age, metabolic abnormalities, hematologic disorders, congenital malformations and cardiorespiratory anomalies. Fetal macrosomia is a consequence of the increased transfer of glucose, amino acids and fats through the fetoplacental membrane causing accelerated fetal growth (2). It is defined by body weight above the 90th percentile on a standard growth curve (or body mass above 4500 g at term) (3, 4).

Early prenatal recognition of macrosomia is of high importance for the prevention of birth complications such as shoulder dystocia, clavicle fracture and injury of the brachial plexus, cephalhematoma and asphyxia. Small growth for gestational age occurs in pregnant women with chronic disorders of the blood vessels (vasculopathy), causing impaired nutrition of the fetus. It may occur in 20% of diabetic pregnancies. The newborns are hypotrophic, the birth weight is below the 10th percentile, the body mass 2500 g at term (5).

Metabolic abnormalities include:

a) hypoglycemia–caused by hyperinsulinemia due to hyperplasia of fetal pancreatic beta-cells consequent to maternal glucose transfer through the placenta (6);

b) hypocalcemia,

c) hypomagnesemia.

Newborn infants of diabetic mothers present with 15–30% deceased values of calcium and magnesium in the first 24 hours after birth. Hematologic disorders include:

a) polycythemia caused by increased erythropoiesis due to fetal hypoxia. It occurs in 15–30% of newborn infants of diabetic mothers;

b) hyperbilirubinemia due to asphyxia, increased erythropoiesis and functional immaturity of the liver occurring in 20–40% of newborns of diabetic mothers.

Congenital malformations:

a) CNS (anencephaly, spina bifida)

b) cardiovascular system (VSD, transposition of great blood vessels, Fallot's tetralogy and cardiomyopathy)

c) urogenital tract (renal agenesis, ureteral duplication, hydronephrosis)

d) gastrointestinal tract (duodenal atresia, small left colon syndrome).

Malformations are 3–4 times more frequent in the newborn infants of diabetic mothers. They are the most frequent sign of perinatal mortality. High levels of HbA1C>8.5 in the first trimester are associated with macrosomia and an increased incidence of fetal malformations. Diabetes with vascular disorders can indirectly influence the incidence of malformations (asphyxia and toxemia due to decreased kidney clearance) (7). Respiratory disorders are recorded in 40% of diabetic mothers' newborn infants. The most frequent are transient tachypnea (TTN) and respiratory distress syndrome (RS) type II. The central role in the formation of TTN and RS is played by a less severe degree of immaturity marked by lecithin/sphingomyelin ratio in the amniotic fluid characteristic for mature lungs (L/S>2.0), and a negative finding of phosphatidylglycerol. Respiratory distress syndrome (RDS) is the most severe disease in newborn infants caused by the lack of surfactant in the alveoli. Almost every disease or pathological condition may lead to RDS (immaturity, hypoxemia, acidemia, asphyxia, maternal diabetes etc).

The aim of this study was to investigate how the disorder of glucose homeostasis influences the biochemical homeostasis and maturation of the fetus.

Material and Methods

A prospective and randomized study included 102 newborn infants of mothers with regular menstrual cycles, known date of the last period and gestational age determined by ultrasonographic biometry in the first trimester of pregnancy. The newborns were distributed in 2 groups based on perinatal pathology. The first–investigated group (n=31) included the infants of mothers presenting with glucose intolerance or manifest diabetes – either preexisting or gestational diabetes mellitus (8), estimated by the criteria of the WHO Expert Committee for Diabetes Mellitus. The second–control group comprised the newborn infants (n=71) of healthy mothers who satisfied the criteria of the WHO for normal singleton pregnancies, born at term (266–287 days of gestation) (9). In the pregnant women the mean age, body height, body weight, body mass index (BMI), parity, duration of the disease and the mode of labor were determined.

In each newborn infant the Apgar score, gestational age body weight, body height and ECG were determined and ultrasonography of the brain was done. Hematologic and biochemical analyses included complete blood count, glucose level, ALT, AST, bilirubin, pH, acid-base status, electrolytes and the marker of infection (CRP). Microbiological analyses were also performed (throat, nose and skin smears). The newborns underwent physical, internal and neurological examinations associated with the pediatric estimation of gestational age. Blood for

analyses was obtained from the umbilical artery immediately after delivery. Blood for the liver function control was taken from the newborn infant's heel, 24–48 h post delivery.

Hematological parameters were determined on an automatic hematologic analyzer (Nikon Kohden MEC 6138, Japan). Electrolyte values – Na^+, K^+, Cl^- and bicarbonates as well as the pH values, BE, pCO_2, pO_2 and O_2 saturations were determined on a GEM 3000 apparatus, by an ion selective electrode. Concentrations of the total Mg were estimated by a colorimetric XYLIDYL BLUE analysis with standard values on a PRIME filter photometer. Concentrations of the total Ca were estimated by the use of the ortho-cresolphthalein method on a PRIME filter photometer apparatus. Concentrations of inorganic phosphates were determined using a phosphomolibden procedure on a PRIME filter photometer. Bilirubin concentrations were estimated by the optic procedure using a Reichart-Unistat (Germany) bilirubinometer. The activity of AST and ALT enzymes was determined by the use of a kinetic optimized procedure with TRIS buffer, without PP (IFCC) on a PRIME filter photometer. Glucose concentration was estimated by the glucose oxidase procedure (GOD/PAP) using a PRIME filters photometer. Concentrations of total proteins were estimated by BIURET procedure. Total osmolality was determined by the osmometric method of freezing-point depression measurement using a Halbmicroosmometer. The value of CRP was estimated by a nephelometer – the MICROS CRP (ABX).

Statistical analysis

Data are expressed as mean ± standard deviation and number (%). T-test was applied to compare the distribution of the newborns in the investigated group (I) and control group (II). The p value was regarded as significant if it did not exceed 0.05. All analyses were performed using the statistical package SPSS for Windows (Version 15.0).

Results

Neonates of healthy mothers present with statistically significantly higher gestational age (279±4.76) than the infants of diabetic mothers (252±7.24) ($p<0.05$). 81.7% of newborns of healthy mothers were born at 38–40 gestational weeks, versus 64.5% infants of diabetic mothers. Body weight above 4000 g was recorded in 64.7% of infants of diabetic mothers relative to 35.3% of cases in healthy mothers. Infants of diabetic mothers experience an increased number of red blood cells, platelets, higher levels of hemoglobin and hematocrit than the newborns of healthy mothers ($p<0.05$) (*Table I*). There was no statistically significant difference in the levels of K^+, Na^+ and Cl^- ions between the investigated groups

Table I Values of investigated parameters in the serum of newborn infants of the investigated (I) and control group (II).

Parameters	Group	($\bar{x}$±SD)
	I (n=31)	II (n=71)
Rbc ($x10^{12}$/L)	5.2±0.65	4.9±0.55
Hct (%)	0.57±0.08	0.56±0.07
Hgb (g/L)	200.71±6.75	191.29±2.68
Wbc ($x10^9$/L)	14.29±3.51	15.69±4.25
Pl ($x10^9$/L)	225.29±22.83	196.34±21.18
Na^+ (mmol/L)	137.71±5.13	139.41±3.93
K^+ (mmol/L)	4.19±0.69	4.24±0.66
Cl^- (mmol/L)	101.32±10.89	102.34±9.73
Total Mg (mmol/L)	0.65±0.17	0.81±0.09
Total Ca (mmol/L)	2.18±0.59	2.42±0.53
pH	7.25±0.08	7.33±0.06
Phosphate (mmol/L)	1.71±0.45	1.85±0.39
HCO^{3-} (mmol/L)	22.90±2.43	22.0±1.51
Osmolality (mmol/kg)	267.70±3.48	269.0±2.98
BE (mmol/L)	–5.48±2.13	–4.68±1.37
pO_2 (kPa)	6.3±0.99	8.30±1.59
pCO_2 (kPa)	6.74±1.36	5.76±0.51
Saturation O_2 (%)	82.06±10.74	87.52±7.32
Bilirubin (μmol/L)	209.71±56.66	155.70±61.14
ALT (U/L)	20.0±7.23	18.23±6.05
AST (U/L)	45.77±16.77	49.32±4.89
Glucose (mmol/L)	2.91±0.51	3.94±0.29
Total proteins (g/L)	59.70±5.68	56.40±6.40

(*Table I*). Concentrations of the total Ca and Mg were statistically significantly decreased ($p<0.001$) in the serum of diabetic mothers' infants than in the infants of healthy mothers. The value of Ca^{2+} ion of less than 1 mmol/L was recorded in 6.5% of newborns of diabetic mothers, which was clinically very significant. The investigated group also presented with lower levels of inorganic phosphates and bicarbonates than the control group. The mean values of pH were significantly lower ($p<0.01$) in the investigated than in the control group. The difference in total osmolality was not statistically significant.

The newborn infants of diabetic mothers experienced increased values of BE, in comparison to the infants of healthy mothers, which was statistically significant ($p<0.05$). Infants of healthy mothers experienced significantly lower values of the partial pressure of carbon dioxide-pCO_2 relative to the infants of diabetic mothers, and this difference was

also statistically significant. Respiratory acidosis occurred in 45.2% of diabetic mothers' infants versus 5.6% of cases in the infants of healthy mothers.

Infants of healthy mothers had increased values of partial pressure pO_2 when compared with diabetic mothers' infants, and the difference was statistically significant ($p<0.01$). 74.2% of the newborn infants of diabetic mothers presented with hypoxemia versus 28.2% of infants of healthy mothers. The healthy mothers' infants had increased O_2 saturation relative to the infants of diabetic mothers. The difference was statistically significant ($p<0.01$). The values of saturation were decreased below the normal level in 19.4% of infants of diabetic mothers, relative to the 4.2% of cases in healthy mothers.

The values of bilirubin in the infants of diabetic mothers were increased in relation to the values in the infants of healthy mothers – the difference was statistically significant ($p<0.05$).

The serum glucose levels in the infants of diabetic mothers were significantly lower ($p<0.01$) when compared with those in the infants of healthy pregnant women. A glucose level of less than 2 mmol/L was recorded in 6.5% of the newborns of diabetic mothers. Infants of diabetic mothers presented with an increased level of total proteins when compared with the infants of healthy pregnant women. A CRP value >5 μmol/L was found in 12.9% of infants of diabetic mothers versus 16.9% in healthy mothers' infants. The difference was not statistically significant ($p>0.05$).

Impaired maturation of organic systems and increased incidence of congenital malformations are the basic physiological characteristic of infants in diabetic mothers. Clinical manifestations of the immaturity of cardiorespiratory system (tachypnea, respiratory distress syndrome, tachycardia and bradycardia) were recorded in 23 (74.19%) infants of diabetic mothers and 17 (23.94%) infants of healthy mothers. Congenital cardiovascular anomalies (ASD, VSD and transpositions) were diagnosed in 5 (16.2%) newborns in the investigated group and 1 (1.4%) newborn infant in the control group ($p<0.01$). There were no registered neonatal deaths in the perinatal period.

Discussion

The composition of the fetal extracellular environment changes during the embryo-fetal development, parallel to its growth and maturation. Glucose is a basic source of energy. During the third trimester, beside glucose, the fetus also uses amino acids (20–30% of energy requirements). Fats are building components which the fetus uses only for energetic requirements under the conditions of hypoxia. It is essential to point out the very important role of glucose in maintaining the acid-base status and osmotic balance, i.e. the total homeostasis of the fetal organism (10). Maternal hyperglycemia and hyperlipidemia are the initiators of pathological processes, resulting in metabolic disorders of glucose, protein and fats, fetal hypoxia and acidosis, impairment of fetal growth, maturation and ontogenesis (11). The risk of perinatal pathology is proportional to the severity of metabolic processes, duration, degree and intensity of pathological changes in the maternal organism, which substantially affect the fetoplacental transfer of information and substances. Increase in peripheral resistance to insulin induces and/or intensifies the disorders of glucose homeostasis in pregnancy. Beside hyperglycemia, the serum of the pregnant women with glucose intolerance is characterized by an increased concentration of lipids (10). The values of calcium and magnesium may be decreased, and the decreased bicarbonates point to the development of ketoacidosis. The increased need for insulin can lead to hyperglycemic coma. Infants of diabetic mothers are most often hypoglycemic, hypertrophic (and/or less frequently hypotrophic) and immature (and/or less frequently dysmature) with a very high incidence of congenital malformations (most often CVS) and pathologic hyperbilirubinemia, which makes the decision on the time and mode of delivery still more complex. Fetal maturity may outgrow gestational age (the state of hypoxia) or fall behind the gestational age (diabetes and pregnancy). Gestational age is only the first step in clinical orientation leading to a decision on the completion of pregnancy. The most precise estimation of gestational age and fetal maturity is obtained by postnatal methods, but even two parameters may not coincide in all cases (12). Our results showed that the neonates of diabetic mothers were born with decreased gestational age when compared to the infants of healthy mothers. 64.5% of infants of diabetic and 81.7% of infants of healthy pregnant women were born in the period between 38–40 weeks of gestation. Infants of diabetic mothers are affected by macrosomia. Fetal macrosomia is a consequence of maternal hyperglycemia and hyperlipidemia which lead to an increase in the transport of glucose and lipids through the fetoplacental membrane and accelerate the synthesis of insulin in fetal pancreas. Regardless of the improvement of perinatal control and good regulation of glycemia in pregnant women, macrosomia still remains a significant complication in newborn infants. Coetze and Levitt (7) found that 40% of infants of diabetic mothers experienced macrosomia. Similar data were also reported by Pildes (13). The body weight above 4000 g was recorded in 64.7% of infants of diabetic and 35.3% of infants of healthy mothers, whereas, according to the standard values of fetal maturity, 35.5% of newborns of diabetic pregnancies were estimated as hypertrophic, which is in agreement with the results reported by American authors. Matthew et al. (14) followed-up 465 pregnant women with diabetes and recorded 30% of

hypertrophic newborn infants. The growth small for gestational age occurs in pregnant women who suffer from chronic changes of blood vessels (vasculopathies), hypertensive syndrome and nephropathy during pregnancy. It is the result of reduction of fetal uteroplacental blood flow and hypoinsulinemia, which was proved by the investigations of Kainualinen et al. (15) and Morris (16). A group of authors from Austria (17) investigated 30 diabetic pregnant women presenting with chronic changes in blood vessels. The investigation showed that 20% of newborns experienced a small body mass (2250±496 g) and impaired growth. In our investigation 22.6% of infants of mothers with glucose intolerance were found hypertrophic. The newborns of diabetic mothers more frequently experience hematologic disorders. The increased mass of red blood cells and hematocrit causes the aggregation of platelets increasing the risk for vein thrombosis in the infants of diabetic mothers. Blood viscosity is also increased as well as the level of erythropoietin resulting from a chronic intrauterine hypoxia. The increased HbA_{1C} in diabetic mothers represents an increased affinity for oxygen, impairing the transfer of oxygen to the fetus. Polycythemia with a vein hematocrit above 65% may cause ischemia and damage to fetal organs resulting from the decelerated blood flow. Hyperbilirubinemia in these infants is caused by asphyxia, increased erythropoiesis and functionally immature liver. Also, the newborn infants of diabetic mothers experience metabolic abnormalities. The most important are hypoglycemia, hypocalcemia and hypomagnesemia. Hypoglycemia may present within the first few hours of life, and it affects about 50% of infants (10). Symptoms may include tremor, apnea, lethargy, hypotonia, high pitched cry, poor feeding, cyanosis and convulsions. Decreased levels of calcium are caused by the decreased response of parathyroid hormone and decreased accumulation of calcium during the last trimester of pregnancy, significantly increasing the risk of hypocalcemia in the infants of diabetic mothers (18). Our results showed a significant polycythemia in 13.3% of cases. The values of calcium lower than 1 mmol/L were found in 6.5% of infants of diabetic pregnancies. The newborns of mothers presenting with the disorders of glucose homeostasis experience lower levels of bicarbonates and pH, which is manifested by an increased incidence of hypoxia in the early neonatal period and increased values of lipids and proteins in the serum. Our results once again proved that hyperglycemia was associated with the impaired maturation and congenital malformations of the fetus (19, 20). Infants of diabetic mothers more frequently experience impaired breathing, whereas 48.4% of infants in our sample had respiratory disorders resulting from an antagonistic effect of insulin on the stimulation of surfactant synthesis, i.e. the impaired maturation of type II alveoli cells (21). Hypoglycemia, hypothermia, polycytemia, cardiac insufficiency and cerebral edema caused by birth trauma and asphyxia may also induce impaired breathing (22). Functional abnormalities of the heart were recorded in 30% of infants including interventricular septal hypertrophy and cardiomyopathy, whereas cardiac insufficiency occurred in 50–10% of infants of diabetic mothers (19, 21).

Neurological disorders may be caused by perinatal asphyxia, glucose and electrolyte abnormalities, polycythemia and birth trauma. The consequences of hypoglycemia and perinatal depression may present within the first 24 hours of life, whereas the consequences of hypocalcemia and hypomagnesemia most frequently manifest between 24 and 72 hours after birth (23). The incidence of congenital malformations has been 3–5 times increased in the infants of diabetic mothers (24, 25). In our sample, 16.22% of newborn infants presented with a heart defect. The most frequent cardiovascular anomalies were as follows: VSD, ASD, transposition of great blood vessels etc. Of the other malformations, lumbosacral agenesia was the most frequent one.

The newborn infants of diabetic pregnancies are heavier and longer, presenting with significantly decreased values of glucose, calcium, magnesium, bicarbonates and pH at birth, and significantly increased levels of lipids, proteins and hematologic disorders. Maternal hypoglycemia is associated with impaired maturation and an increased incidence of congenital malformations of the fetus.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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