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Features of Bio Energetic Metabolism in Children Born after Assisted Reproductive Technologies

Synenko V.V[1]*, Stoieva T.V[2], Bratkova L.B[1], Prokhorova S.V[2] and Fedin M.V[1]

Department of Pediatrics, Odessa National Medical University, Odessa, Ukraine.

[1]*Assistant of the Department of Pediatrics, Odessa National Medical University.*

[2]*Dr of the Department of Pediatrics, Odessa National Medical University.*

*Correspondence:
Synenko V.V, Assistant of the Department of Pediatrics, Odessa National Medical University, Tel: +380969111646.

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ABSTRACT

The features of the functioning of key enzymes of bio energetic metabolism in children born with the application of ART at different age periods. A cytochemical analysis of the activity of key mitochondrial enzymes was performed: succinate dehydrogenase (SDH), α-glycerophosphate dehydrogenase and α-GPDH. The material for the analysis was the buccal epithelium. The material was collected by scraping the epithelium from the inner surface of the cheek.

The examined children were representatively distributed into age groups: 1st group - children of the first year old (38 children of the main and 20 children of the control group), 2nd group - from 1 to 3 years old (52 children of the main group and 20 children of the control group), 3rd group - from 4 to 7 years old (46 children of the main group and 20 children of the control group). The average age was 2.7 ± 1.9 years.

Conclusion: The study of the activity of mitochondrial enzymes SDH and α-GPDH revealed the most pronounced deviations in the functioning of SDH in the group of children from 1 to 3 years old, which was associated with delayed physical development, allergic diseases, prematurity and diseases of the cardiovascular system. A decrease in the concentration of the enzyme GPDH was most expressed in the older group of children from 4 to 7 years old, and was associated with delayed physical development, Broncho-pulmonary diseases, prematurity, and diseases of the digestive system.

Keywords

Assisted reproductive technologies (ART), Children, Succinate dehydrogenase (SDH), α-glycerophosphate dehydrogenase (α-GPDH), Mitochondrial enzymes.

Introduction

At the moment, the medical scientific society is paying increasing interest to assisted reproductive technologies (ART). A wide range of methods that make it possible to get pregnant and give birth to a child helps millions of couples to successfully fight infertility. The number of children born with the help of ART is increasing daily. But the main goal of a reproductive specialist is not just to get a pregnancy and give birth to a child, but to make sure that preconception pathological conditions do not affect the health of children. Infertility and the problem of children born as a result of ART requires careful analysis. It has been established that many health problems of future parents become the causes of infertility. Among the factors leading to infertility are female and male infertility, anatomical and genetic abnormalities and various somatic and endocrine diseases. A special place takes the infertility of unknown origin, in the emergence of which the features of energy exchange play a certain role. A decrease in the activity of energy processes is observed even at the stage of gametogenesis and embryogenesis.

In a number of works by U.F. Nasirov et al. the role of insufficiency of energy processes in impaired implantation, non-gestation and obviously subsequently affects the energy potential of a born child, impaired placental nutrition and oxygenation, and a decrease in the energy potential of a born child has been proven [1-3]. In the work of L.A. Pestryaeva et al. [4] the consequences of impaired energy metabolism can be a violation of adaptation, which is indicated in works. Physical Development Disorder by Chugunova O.L. [5], the Development of Multiple Organ Failure by Shurupiy D.A., as well as the impact on cognitive and adaptive capabilities [6]. The condition of the bioenergetic link can be assessed by a number of key enzymes SDH, α-GPDH. The most studied among the enzymes of energy exchange is SDH [7], it reflects the state of tissue respiration, and failure leads to hypoxic conditions.

Objective

To study the features of the functioning of key enzymes of bioenergetic metabolism in children born with the application of ART at different age periods.

Materials and Methods

We examined 136 children born as a result of induced pregnancy (IP), as well as 60 children born as a result of spontaneous pregnancy (SB). Inclusion criteria were: age from 0 months to 7 years, birth with ART (AI). This age group was divided into 3 groups under 1 year old, from 1 to 3 years old and from 4 to 7 years old. All children provided anamnestic data, assessed psychophysical development and somatic health.

A cytochemical analysis of the activity of key mitochondrial enzymes was performed: succinate dehydrogenase (SDH), α-glycerophosphate dehydrogenase, α-GPDH. The material for the analysis was the buccal epithelium. The material was collected by scraping the epithelium from the inner surface of the cheek. The following reagents were used for the analysis: kits for the cytochemical determination of SDH, α-GPDH. Staining of smears was carried out according to Pierce method 1957, modified by R.P. Nartsisova 1886. The exposition of the material was carried out by the V.S. Sukhorukov method, in the author's modification. Microscopy was carried out under a light microscope with a resolution of 40, 100.

Statistical processing of the research results was carried out using the methods of parametric and nonparametric statistics using the computer program Statistika 12, Microsoft Excel.

Results

The examined children were representatively distributed into age groups: 1st group - children of the first year old (38 children of the main and 20 children of the control group), 2nd group - from 1 to 3 years old (52 children of the main group and 20 children of the control group), 3rd group - from 4 to 7 years old (46 children of the main group and 20 children of the control group). The average age was 2.7 ± 1.9 years. No significant gender differences were found – p> 0.05 prevailed. At the time of the examination, no acute inflammatory and infectious diseases were recorded.

During the study, the data of the pregravid period were analyzed, taking into account the state of health of the mothers, as well as the duration and causes of infertility. The main preconception factors that influenced fertility and subsequent health of children: age of mothers over 35 years old, extragenital pathology, chronic diseases of the urinary system, inflammatory diseases of the pelvic organs, endocrine diseases. When studying the characteristics of the vital history of children, it was found that 67.6 ± 4.0 % were born on time, 32.4 ± 4.0 % of children were born before the term, this group of children had such deviations as delayed physical development (prematurity, decreased body weight, body length), mental development 8.8 ± 2.4 %, the presence of congenital malformations 24.3 ± 3.7 % (mainly of the cardiovascular and digestive systems), diseases of the perinatal period 20.6 ± 3.5 % (IUGR, intrauterine pneumonia, hypoxic-ischemic encephalopathy).

The study of bio energetic metabolism revealed changes in key enzymes. One of the most important enzymes of bioenergetic metabolism is succinate dehydrogenase (SDH), which simultaneously participates in the tricarboxylic acid cycle and the respiratory electron transport chain.

In the examined children, the content of the SDH enzyme corresponded to and exceeded the norm in $81.6 \pm 6.3\%$ in the group of induced pregnancy in children of the 1st group. In group 2, this indicator was $44.2 \pm 6.9\%$. In group 3 - 52.2 ± 7.4 %.

The most expressed changes were observed in children of group 2, where a decrease in SDH was determined in 55.8% of children x^2 12,34 (p=0,001) OR 11,4 [2,5-51,9, CI 95%], RR 5,6. At the same time, an increased content of the enzyme was observed in children of the 1st group $31.6 \pm 7.5\%$, $x^2 = 5.32$ (p = 0.05), OR 8,77 [1,1-71,4, CI 95%], RR 6,3.

A taken comparative analysis of the concentration of the SDH enzyme in the groups of induced pregnancy and spontaneous pregnancy (Figure 1).

Table 1: Indicators of the cytochemical activity of SDH in children of different age groups.

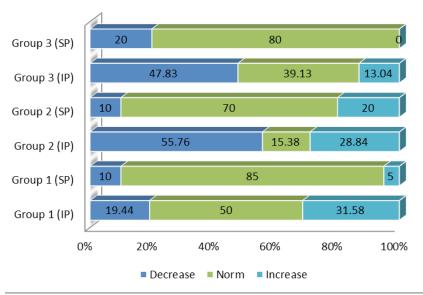| Indicators	Group 1		Group 2		Group 3	
	Decrease	Increase	Decrease	Increase	Decrease	Increase
Induced pregnancy	$19,4 \pm 6,3\%$	$31,6 \pm 7,5\%$	$55.8 \pm 6,9\%$	$28.8 \pm 6,3\%$	$47,8 \pm 7,4\%$	$13,0 \pm 5,0\%$
Spontaneous pregnancy	$10,0 \pm 6,7\%$	$5,0 \pm 4,9\%$	$10,0 \pm 6,7\%$	$20,0 \pm 8,9\%$	$20,0 \pm 8,9\%$	0
x^2	0,71	5,32	12,34	0,58	4,52	2,87
p	0,65	0,048	0,001	0,64	0,064	0,22

Figure 1: Comparative characteristics of the activity of the SDH enzyme in children, the main and control groups.
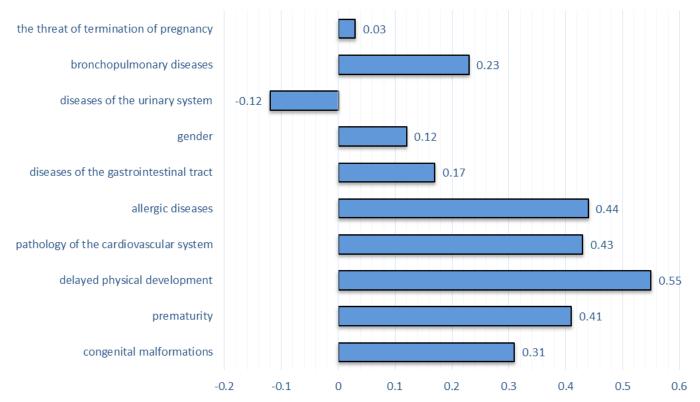

Figure 2: Association of a decrease of cytochemical activity of SDH with the revealed clinical and anamnestic data.

Table 2: Indicators of cytochemical activity of α-GPDH in children of different age groups.

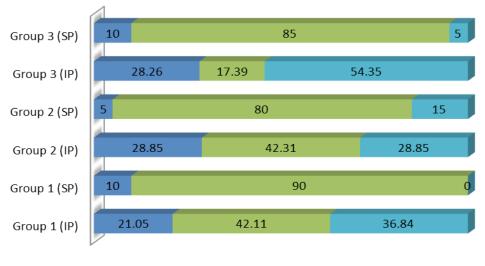| Indicators	Group 1		Group 2		Group 3	
	Decrease	Increase	Decrease	Increase	Decrease	Increase
Induced pregnancy	$21,1 \pm 6,6\%$	$36,8 \pm 7,8\%$	$28,9 \pm 6,3\%$	$28,9 \pm 6,3\%$	$28,3 \pm 6,6\%$	$54,4 \pm 7,3\%$
Spontaneous pregnancy	$10,0 \pm 6,7\%$	0	$5,0 \pm 4,9\%$	$15,0 \pm 8,0\%$	$10,0 \pm 6,7\%$	$5,0 \pm 4,9\%$
x^2	1,12	9,71	4,72	1,48	2,65	14,22
p	0,49	0,005	0,006	0,362	0,19	0,0001

Figure 3: Comparative characteristics of the activity of the enzyme α-GPDH in children, the main and control groups.
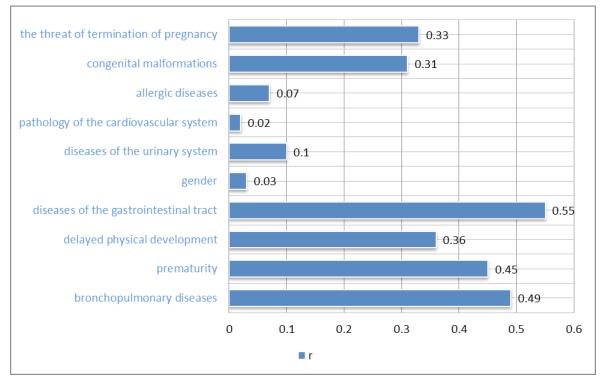

Figure 4: Association of a decrease in the cytochemical activity of α-GPDH with the revealed clinical and anamnestic data.

As you can see in the presented diagram, the normative indicators differed in the main and control groups, the most pronounced difference was noted in the 2nd group $x^2 = 20.3$ (p = 0.0001).

The study established the effect of a decrease in the SDH enzyme on the occurrence of pathology (Figure 2).

Characterized by the presence of correlations between a decrease in the concentration of succinate dehydrogenase in cells and a number of pathological conditions, such as delayed physical development r = 0.55 p < 0.03, allergic diseases r = 0.44 p < 0.05, diseases of the cardiovascular system r = 0.43 p < 0.05.

The next enzyme that has been studied is α-GPDH. This enzyme is responsible for the transport of electron equivalents from the cytoplasm to mitochondria, and the exchange of phospholipids.

In the examined children with IP, the content of the α-GPDH enzyme corresponded to and exceeded the norm in $78.9 \pm 6.6\%$ in group 1, $71.1 \pm 6.3\%$ in group 2 and $71.7 \pm 6.6\%$ in group 3.

The most pronounced changes with an increased concentration of granules in the concentration of α-GPDH granules were observed in children of group 3 (54.4 ± 7.3%), and in children of group 1 in 36.8% ± 7.8. At the same time, a decrease in enzyme indices was observed in group 2 (28.9% ± 6.3) (Table 2).

In a comparative analysis of the normal concentration of the enzyme α-GPDH in the main and control groups, significant differences were observed: in group 1 - x^2= 12.4 (p = 0.001); in group 2 - x^2= 13.3 (p = 0.001), in the group 3 - x^2= 27.1 (p = 0.0001) (Figure 3).

The study revealed the presence of correlations between a decrease in the concentration of the enzyme α-glycerophosphate dehydrogenase and the following pathological conditions: delayed physical development r = 0.36 (p < 0.05), broncho-pulmonary diseases r = 0.49 (p < 0.03), diseases of the gastrointestinal system r = 0.55 (p < 0.02) (Figure 4).

Thus, the dependence of various pathological conditions on the efficiency of energy exchange in ART children was revealed. And age-related features with gradual optimization of indicators are due to the adaptation of energy metabolism.
Clinical example: Child A. 5 years old, boy.

The boy was conceived by ICSI, after the 2nd attempt, was born from a three fetal pregnancy at 37 weeks, by caesarean section. It is important to note that the first fetus died soon after birth from multiple organ failure of unknown origin, the third child from triplets, a girl, develops in accordance with age norms.

According to the anamnesis, child A., birth weight – 1765 g, was diagnosed with Cardiovascular Development Abnormalities, IUGR, an anomaly in the development of the cochlear nerve, and autism spectrum disorders. Cytochemical analysis showed a decrease in the concentration of SDH and GPDH enzymes in child A (Figure 5, 6).
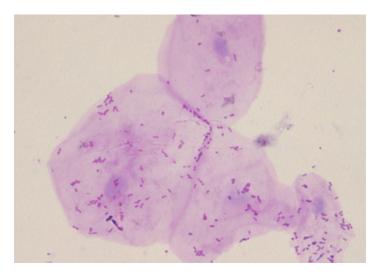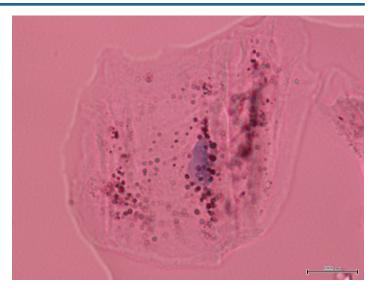

Figure 6: Buccal epithelium preparation with colored granules of α-GPDH enzyme in a 5-year-old IP child.

Conclusion

The study of the activity of mitochondrial enzymes SDH and α-GPDH revealed the most pronounced deviations in the functioning of SDH in the group of children from 1 to 3 years old, which was associated with delayed physical development, allergic diseases, prematurity and diseases of the cardiovascular system. A decrease in the concentration of the enzyme GPDH was most expressed in the older group of children from 4 to 7 years old, and was associated with delayed physical development, broncho-pulmonary diseases, prematurity, and diseases of the digestive system.

A simultaneous decrease in the concentration of the enzymes SDH and α-GPDH affects the indicators of physical development and also worsens the development of the prognosis of somatic p = 0,01 and mental health.

Further research is required on the energy metabolism in children born after ART, the study of age aspects in larger cohorts, in order to address the issues of appropriate correction, as well as to prevent the development of possible energy deficiency states.

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Figure 5: Buccal epithelium preparation with colored granules of SDH enzyme in a 5-year-old IP child.

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