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Long-term anthropometric and metabolic evaluation of healthy newborns with intrauterine growth restriction

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ABSTRACT

Introduction. Birth weight is the most significant anthropometric indicator of the clinical status of neonates. Intrauterine growth restriction (IUGR) is the cause of increasing death rate in neonates and is associated with adult cardiovascular disease and metabolic syndrome. The purpose of our study is to evaluate the relationship between IUGR, the development of children and metabolic complications in children up to the age of five.
Material and methods. We performed a prospective study over a period of 4 years (2010-2013) on a group of 622 newborns with IUGR without any reported conditions during the neonatal period. The nutritional status assessment was performed by determining the weight, length, body mass index and their integration according to age and sex, on the growth curves proposed by the World Health Organization and was compared to that of 627 IUGR infants admitted to the Neonatal Intensive Care Unit. The triglyceride, cholesterol and glucose levels were evaluated and compared with normal values for age.
Results. The obesity incidence (16.1%) is significant higher ($\chi 2=32.23$, $p<<0.01$, 95%CI). 57.6% of cases with BMI above the normal range, and overweight increases with age (29% in 2-year-olds, vs. 56.7% in 5-year-olds). The obesity incidence decreases with age (32.9% in 2-year-old, vs. 9.1% in 5-year-olds). The evaluation of the metabolic syndrome: 18% of the investigated children had hyperglycemia, and cholesterol and triglycerides levels ($f=10.34$, $p=0.00001$, 95%CI) increase with age. 32.8% of the evaluated children had cholesterol levels above 170 mg/dl.
Conclusions. Overweight and obesity incidence among children born with IUGR are increased compared to the general population. It is necessary to establish the relationship between the eating habits and the studied parameters, that could elucidate the relationship of the increasing weight and the biochemical parameters (triglycerides and cholesterol).

Keywords: intrauterine growth restriction, obesity, overweight, metabolic syndrome, newborn

INTRODUCTION

Birth weight is an essential indicator of the clinical status of neonates. *Both length* and *weight* express the intrauterine development of the fetus, as a result of three major factors: maternal, fetal and placental. These two parameters have always been used in order to identify infants with a potential risk for the occurrence of complications in the neonatal period.

Intrauterine malnutrition is the cause of low birth size – both in terms of length and weight, it influences further development during childhood and has long term consequences on adult health (1).

If intrauterine malnutrition is associated with aggressive postnatal feeding, impaired postnatal

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growth can sometimes lead to childhood obesity and adult cardiovascular disease and metabolic syndrome. This is known as the hypothesis of fetal programming of adult disease (1-3).

The hypothesis, developed by Barker in 1988, states that there is a significant association between low birth weight and increased prevalence of obesity, hypertension, type II diabetes and cardiovascular disease among adults born with intrauterine growth restriction (IUGR). It shows the importance of postnatal growth and development of infants with IUGR, and helps to establish a care strategy in order to prevent and reduce risks by identifying and influencing the onset of these diseases during adulthood.

The purpose of our study is to evaluate the relationship between IUGR and the development of children up to the age of five, by assessing the anthropometric and metabolic complications in newborns with IUGR, with no neonatal conditions.

MATERIAL AND METHODS

We performed a prospective study over a period of 4 years (2010-2013) in "Cuza-Voda" Clinical Hospital of Obstetrics and Gynecology, in Iasi, Romania, on a group of 622 newborns with IUGR, but without any reported conditions during the neonatal period and a group of 627 IUGR infants that were admitted to the Neonatal Intensive Care Unit due to various neonatal conditions, used for comparison of nutritional dynamics.

We excluded from our study infants with severe congenital malformations and infants from twin pregnancies.

The following parameters were evaluated in both groups: gestational age, birth weight and length, gender, body mass index. In the first group we further assessed: blood glucose, triglycerides and cholesterol levels, between the ages of two and five.

IUGR was defined as a birth weight below the 3rd percentile (on the fetal growth charts) (4).

The nutritional status assessment was performed by determining the weight and height/length and calculating the body mass index (BMI) = Weight (kg)/Height (m), and their integration, according to age and sex, on the growth curves proposed by the World Health Organization (5) (Table 1).

The metabolic profile was assessed by measuring plasmatic levels of glucose, triglycerides and cholesterol, using wet chemistry on a RX Daytona+® analyzer (Randox Laboratories Ltd., Crumlin, County Antrim, UK).

Postprandial triglyceride and glucose levels were compared to the values published in the International Diabetes Federation workshop in 2007, and defined as triglyceride levels above 150 mg/dl and blood glucose level higher than 110 mg/dl (6).

The statistical analysis *was performed* through *SPSS* 20 software, using parametric tests. The reference parameter p represents the significance level of the test that was compared with the critical threshold value of p=0.05, corresponding to a 95% confidence level. The results were considered significantly modified *statistically* for $p<0.05$.

RESULTS

During 4 years, 24007 infants were born in "Cuza-Voda" Hospital and 1249 (5.2%) of these were diagnosed with IUGR.

The study group included term infants, with birth weights between 2100 to 2950 grams and birth lengths between 45 to 52 cm (Table 2). The results showed a higher frequency (62.38%) of healthy female newborns with IUGR ($\chi^2=9.55$, p=0.002, 95%CI).

The evaluation of the children nutritional status at 2-5 years of age showed that obesity prevalence in the group of former healthy IUGR newborns (16.1%) was significantly higher compared to sick IUGR infants – 4.8% ($\chi^2=32.23$, $p<<0.01$, 95%CI). There is a high proportion of cases (57.6%) with BMI above the normal range in healthy newborn infants with IUGR. The analysis of children that were born with IUGR, but without any reported conditions during the neonatal period, showed that the prevalence of overweight increases with age: from 16% at the age of 2 to 56.7% at the age of 5, but the prevalence of obesity decreases with age (32.9% t the age of 2 vs. 9.1% at the age of 5) (Fig. 1). Regarding IUGR infants that were admit-

TABLE 1. *Definition of obesity and overweight by age and gender*

	Gender	Age 2 years	Age 3 years	Age 4 years
Overweight	F	BMI=18-18.6	BMI=17.1-18.3	BMI=16.8-18.4
	M	BMI=18.1-18.7	BMI=17.4-18.4	BMI=17-18.1
Obesity	F	BMI > 18.7	BMI > 18.4	BMI > 18.5
	M	BMI > 18.8	BMI > 18.5	BMI > 18.2

TABLE 2. *Statistical indicators of anthropometrical parameters at birth*

	Mean	Mean		SD	SE	Min	Max	Q25	Median	Q75
		-95%	+95%							
GA (wks)	39.3	39.2	39.4	1.0	0.1	37	42	39	39	40.0
BW (g)	2614.8	2605.4	2624.3	120.4	4.8	2100	2950	2550	2600	2700
L (cm)	48.60	48.50	48.71	1.33	0.05	45	52	48	49	50

FIGURE 1. *Assessment of nutritional status according to the age at the time of evaluation*

ted to the Neonatal Intensive Care Unit, the percent of those with high BMI is 18.1%, as both incidence of obesity and overweight decrease over time (7.6% at the age of two to 1.7% at the age of 5, and 20.9% to 14.5%, respectively).

Analysis of the BMI values in former healthy IUGR newborns shows that 43.4% of them have a BMI above normal values. The average value was 16.8±1.54 SD, minimum and maximum values are 11.1 and 25 (Table 3).

At the age of 2 the BMI values were between 13.5 to 25, with a mean of 17.7. During the next two years BMI decreases, but increases again by the age of 5. In the study group, the overweight prevalence doubles between the ages of 2 and 5, even though obesity decreases.

BMI values were significantly higher at the age of 3, showing a significant decrease with age ($F=14.52$, $p<<0.01$, 95%CI) (Fig. 2).

Triglyceride levels increase significantly in former healthy newborns with IUGR. Also, cholesterol levels increase significantly after the age of 3; the average values are higher the maximum limit of the normal range (170 mg/dl).

Most of the investigated children had blood glucose levels situated in the normal range (80-100 mg/dl). 18% of the children born IUGR, without neonatal conditions, had hyperglycemia, and 2.5% of the cases were at the lower limit of the normal blood sugar range (70 mg/dl). The highest values of the blood sugar levels, but within the normal range,

TABLE 3. *Statistical indicators of BMI in children born with IUGR and no neonatal condition*

Mean BMI	Mean		SD	SE	Min	Max	Q25	Median	Q75
	-95%	+95%							
16.82	16.63	17.01	1.54	0.10	11.10	25.00	15.80	16.80	17.60

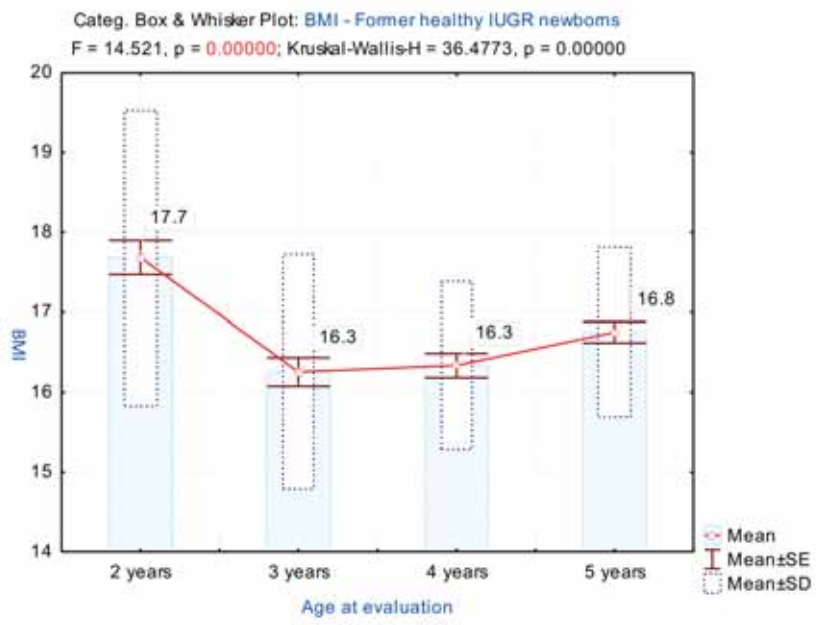

FIGURE 2. *BMI distribution by age*

TABLE 4. *Statistical indicators of biochemical parameters in former healthy IUGR newborns*

	Mean	Mean		SD	SE	Min	Max	Q25	Median	Q75
		-95%	*-95%*							
Blood glucose	87.3	84.9	89.7	10.6	1.2	70.0	123.0	79.5	88.0	92.0
Triglycerides	59.5	53.5	65.5	25.9	3.0	29.0	150.0	43.0	48.0	67.0
Cholesterol	144.5	136.9	152.1	32.6	3.8	100.0	197.0	110.0	144.0	178.0

were detected in 3-year-olds and decreased by the age of five (Fig. 3).

The ranges of triglyceride levels with the highest incidence in the study group were included in the range of 40-80 mg/dl. 13.8% of the children born IUGR, without neonatal conditions, presented triglyceride levels higher than 80 mg/dl.

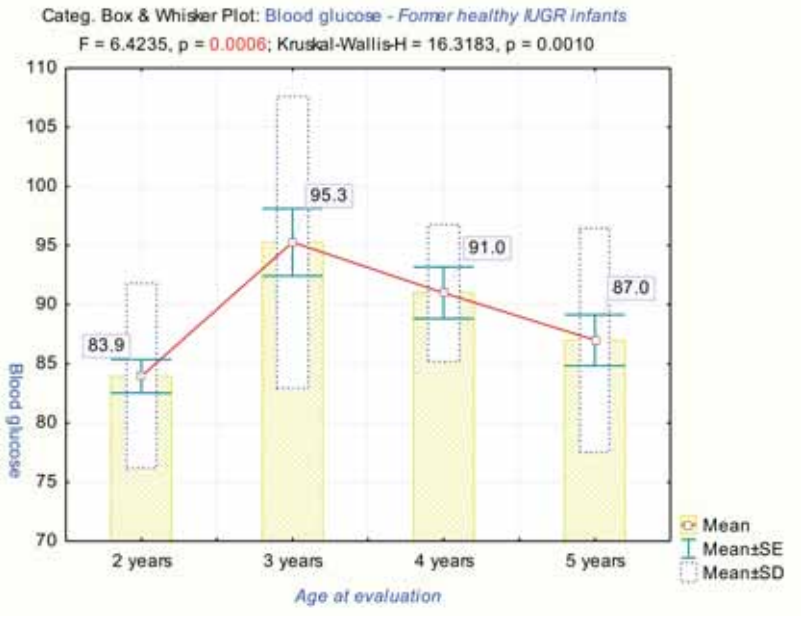

FIGURE 3. *Average blood glucose levels in children born IUGR, without neonatal conditions*

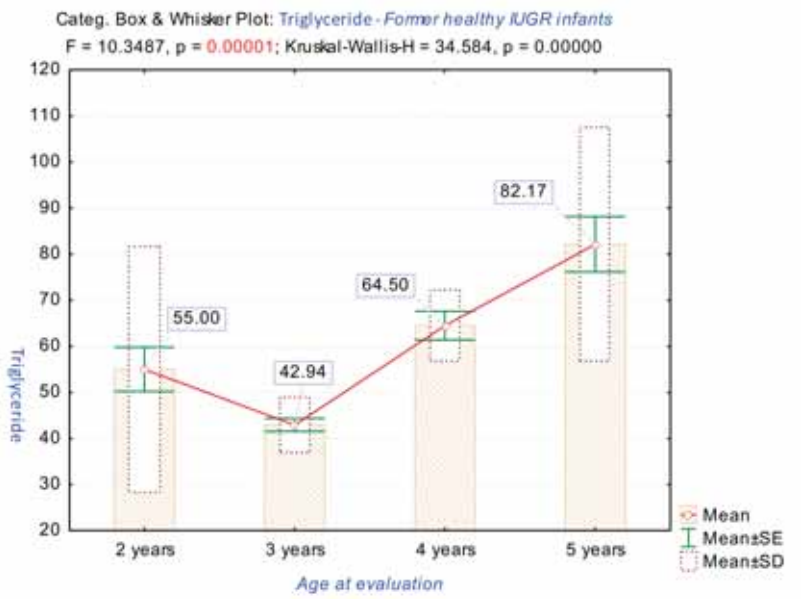

FIGURE 4. *Average triglycerides levels in children born IUGR, with no neonatal condition*

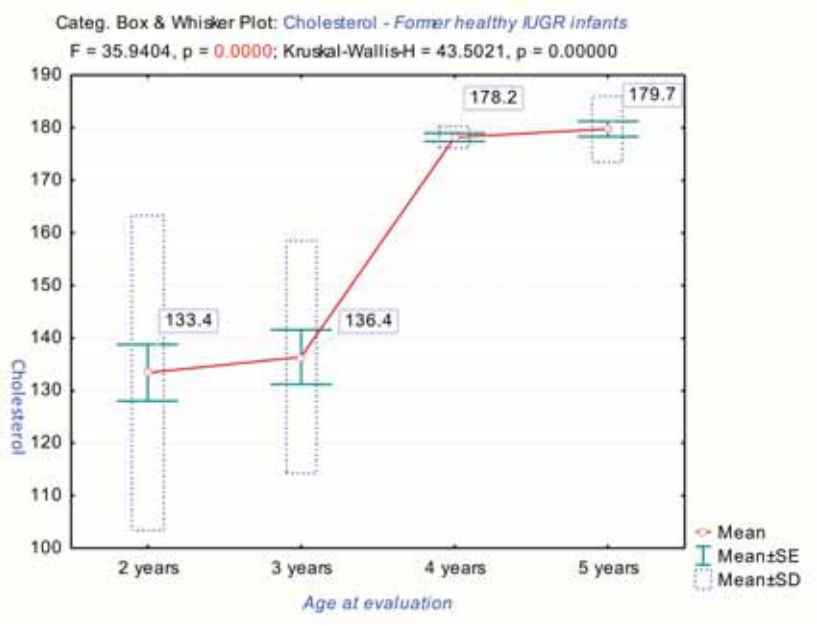

FIGURE 5. *Average cholesterol levels in children born IUGR, without neonatal conditions*

The lowest values are recorded in 3-year-olds (43 mg/dl), but tend to double by the time the infants reach the age of 5 (82 mg/dl). This increase is statistically significant (F =10.34, p=0.00001, 95%CI) (Fig. 4).

The analysis of cholesterol levels reveals that 32.8% of the children born IUGR, without neonatal conditions, had cholesterol levels higher than 170 mg/dl. The mean cholesterol values were lower at the ages of 2 and 3, but rose dramatically (F=35.94, p<<0.001), by more than 40 mg/dl, at the ages of 4 and 5 (Fig. 5).

DISCUSSIONS

The incidence of cases with IUGR in our study group was 5.2%, which is within the European standard range (between 4.6% and 15.3%) (7-12). Risk factors for IUGR are sometimes preventable and include: genetic predisposition, preconceptional maternal nutritional status, maternal weight gain during pregnancy, social and economic status, maternal tobacco and alcohol use, pollution (13). Despite prophylaxis, IUGR has a constant incidence and long-term consequences can be serious.

The percentage of overweight children increases with age, ranging from 29% at 2 years of age to 56.7% at 5 years of age. In this particular study group, however, the incidence of obese children decreases with ageing (32.9% at 2 years of age versus 9.1% at 5 years of age). The increase is probably gradual later, as ascertained by a study conducted in 2013 in Romania on 8-year-old children, in which the prevalence of obesity and overweight was 27.75% (14).

Therefore, a high proportion of overweight and obese children probably come from infants born with IUGR. In children 2 to 5 years of age, the incidence of overweight in this population is almost double, compared to non-IUGR infants (7). Because in this particular study group, the percentage of obese children decreases with age, we can suggest that obesity is also influenced by other factors, such as lifestyle choices and eating habits, which are not covered in our study. As a characteristic of our country, it should be mentioned that Romania is the only European Union country whose overweight population does not become obese after 64 years of age; in all the other EU countries, the obese population increases with age (6). Various studies delineate the association between overweight/obesity in children younger than 5 years and overweight/obesity in adults, underlining the negative influence of the raised anthropometric indices at the age of 2 and the direct causal relationship with obesity in adults (15,16).

18% of the subjects presented blood sugar levels that were at the upper limit of normal, while 2.5% of the subjects were recorded at the lower limit value. During the study, none of the subjects was diagnosed with type 1 diabetes.

Hyperglycemia during childhood is one of the most important comorbidities, and, if it is associated with obesity, increases the risk of mortality in early adulthood (6).

Serum cholesterol and triglycerides were within normal limits in our study, but showed an increase with age. Studies on adolescent and adult populations do not demonstrate a direct correlation between the increased values of these two parameters and early mortality, but their key role in increasing the incidence and severity of cardiac disease (17-19).

CONCLUSIONS

Overweight and obesity incidence among children born with IUGR are increased compared to the incidence found in general population, and the increase is more pronounced with age.

In the 2 to 5-year-old population, blood glucose values do not increase with age. Both triglycerides and cholesterol show increase with age, but maintain within normal ranges.

The study period should be extended at least until adolescence, in order to follow the evolution of these subjects and to detect the early complications of the metabolic syndrome.

Obesity and metabolic syndrome are regulated epigenetically, starting from in utero nutrition and continuing with postnatal feeding of infants and toddlers. It is therefore necessary to further study the relationship among eating habits, increasing weight, and biochemical parameters.

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