Neonatal short-term outcomes in infants with intrauterine growth restriction

Monica G. Hasmasanu, MD, Sorana D. Bolboaca, PhD, Melinda I. Baizat, MD, Tudor C. Drugan, PhD, Gabriela C. Zaharie, PhD.

ABSTRACT

الأهداف: تقييم نتائج المواليد حديثاً والمصابين بنقص النمو داخل الرحم لدى عينة من الرضع الرومانيين في وحدة الولادة.

الطريقة: أُجريت هذه الدراسة من نوع دراسة الحالات المقرنة بحالات الشاهد في جناح المواليد حديثاً، عيادة النساء والولادة الأولى، مستشفى كلوج نابوكا، كلوج نابوكا، رومانيا وذلك خلال الفترة من يناير 2012م إلى يونيو 2014م حيث قمنا بتقسيم الأطفال إلى قسمين وهما مجموعة الحالات (مجموعة المواليد حديثاً والمصابين بنقص النمو داخل الرحم)، ومجموعة الشاهد التي كانت تحمل نفس الصفات من حيث العمر الحملي. ولقد شملت مجموعة الدراسة المواليد حديثاً الذي كان وزنهم وطولهم عند الولادة أقل 10 بالمئة من العمر الحملي. وتم اختيار كافة المواليد في المجموعتين من نفس جناح المواليد في المستشفى.

النتائج: شملت الدراسة 142 طفلاً تضمنهم عينة الدراسة في كافة المجموعتين. وأشارت نتائج الدراسة بأن العمليات القيصرية قد كانت منتشرة بشكل كبير من الناحية الإحصائية لدى مجموعة المواليد حديثاً والمصابين بنقص النمو داخل الرحم (66.9%) مقارنة بمجموعة الشاهد (46.5%; p=0.0006). ولقد كان مقياس أبجار خلال دقيقة واحدة لدى غالبية الرضع في كلي المجموعتين أكثر من أو يساوي 7 (77.9% لدى مجموعة الحالات مقارنة مع 77.5% لدى مجموعة الشاهد) حيث لم يكن هنالك اختلافات واضحة إحصائياً بين المجموعتين. بالإضافة إلى ذلك فقد كانت نسبة المواليد في مجموعة الحالات والمصابة بنقص السكر في الدم والنزيف داخل البطين أعلى بصورة كبيرة من الناحية الإحصائية من مجموعة الشاهد (p<0.05). ولقد كان نقص السكر في الدم من العوامل المرتبطة بصورة واضحة من الناحية الإحصائية مع نقص النمو داخل الرحم (OR=4.763, 95% CI: 1.711-13.255).

الخاتمة: أظهرت هذه الدراسة بأن كلاً من نقص السكر في الدم والنزيف داخل البطين قد كانت من الصفات التي تميزت بها مجموعة المواليد المصابين بنقص النمو داخل الرحم.

Objectives: To assess the neonatal outcomes in newborns with intrauterine growth restriction (IUGR) in a Romanian population in a 3 level maternity unit.

Methods: A matched case-control design, with one control for each patient was used. The case group comprised neonates with birth weight and birth length below the 10th percentile for the gestational age. Individual matching by gender and age of gestation was used to identify the control group. Both cases and controls were selected from the infants admitted to and discharged from the Neonatal Ward, at the First Gynecology Clinic, of the County Emergency Hospital Cluj-Napoca, Cluj-Napoca, Romania, between January 2012 and June 2014.

Results: One hundred and forty-two subjects were included in each group. The cesarean delivery was significantly more frequent in the IUGR group (66.9%) compared with controls (46.5%; p=0.0006). The Apgar score at one minute was ≥7 for most infants in both groups (77.9% IUGR group versus 77.5% control group), with no significant differences between the groups. A significantly higher percentage of infants in the IUGR group had hypoglycemia or intraventricular hemorrhage compared with the controls (p<0.05). Hypoglycemia proved a significant factor for IUGR (odds ratio = 4.763, 95% confidence interval: 1.711-13.255).

Conclusion: Hypoglycemia and intraventricular hemorrhage characterized the IUGR newborns.

Saudi Med J 2015; Vol. 36 (8): 947-953
doi: 10.15537/smj.2015.8.11533

From the Department of Neonatology (Hasmasanu, Zaharie), the Department of Medical Informatics and Biostatistics (Bolboaca, Drugan), Iuliu Hatieganu University of Medicine and Pharmacy, and the Department of Neonatology (Baizat), Gynecology Clinic, Emergency County Hospital, Cluj-Napoca, Romania.

Received 3rd March 2015. Accepted 22nd June 2015.

Address correspondence and reprint request to: Dr. Sorana D. Bolboaca, Department of Medical Informatics and Biostatistics, No. 6, Louis Pasteur Street, Cluj-Napoca 400349, Romania. E-mail: sbolboaca@umfcluj.ro

Disclosure. This study was supported by the European Social Fund, Human Resources Development Operational Programme 2007-2003, project no. POSDRU/159/1.5/S/138776.

Fetal growth restriction (FGR) or intrauterine growth restriction (IUGR) is a multifactorial disorder affecting the fetal development rate that often results in multiple adverse peri- and postnatal morbidities and mortality.[1] Birth weight and/or birth length below the 10th percentile for gender and gestational age are characteristics of small-for-gestation newborns and these babies are constitutionally small.[2] A birth weight <10th percentile that appeared due to a pathological process, which did not allow attaining the personal biological growth potential identifies an infant with IUGR.[3] Intrauterine growth restriction occurs due to fetal factors (for example, congenital anomalies, chromosomal disorders, toxoplasmosis, other infections [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus, and herpes simplex),[4] placental factors (for example, placental insufficiency, abnormal implantation, anomalies, infarction, and so forth),[5] or maternal factors (for example, poor nutrition,[6] maternal smoking,[4] gestational hypertension,[4] history of previous IUGR birth/delivery).[7] Two main growth patterns are known in IUGR, namely symmetrical and asymmetrical, with differences in etiology, clinical aspect and prognosis. The main short-term neonatal complications of IUGR include metabolic, thermal, and hematological disturbances leading to morbidities such as low Apgar score, hypoxia and the need for respiratory support, hypoglycemia, hypothermia, necrotizing enterocolitis (NEC), sepsis, hyperbilirubinemia, prolonged neonatal intensive care unit admission.[8,9] Limited data related to IUGR in Romanian neonates is available in the specialty literature. The latest study on this was reported by Sbârcea and Râcă[10] and aimed to investigate demographic, anthropometric, and early morbidities in IUGR infants in a level 3 maternity ward from Bucharest. They identified an incidence of 4.68%, almost twice smaller than the incidence identified in our study, and showed that maternal factors (such as low socio-economic status, extreme age, and constitutional factors) are the main factors associated with IUGR.[10] The objective of our study was to assess the short-term outcomes and to identify the factors associated with IUGR in a North-West Romanian population referred to a tertiary teaching hospital.

Methods. A matched one:one case-control study was the design used to reach the proposed objectives. The study was retrospectively conducted at the Neonatal Ward of the First Gynecology Clinic, County Emergency Hospital Cluj-Napoca, Cluj-Napoca, Romania in neonates with parents residing in Romania who were discharged in the period from January 2012 to June 2014. The First Gynecology Clinic is a tertiary teaching hospital in the North-West of Romania and serves as referral center for Cluj, Sălaj, Bistrița-Năsăud, and Maramureş counties. The North-West region covers an area of almost 34,000 km^2 (~15% from the total area of Romania) and has a stable population of around 2,500,000 citizens (~12% of the total population of Romania). All subjects with birth weight and birth length below the 10th percentile for the gestational age[2] were included in the IUGR group (case group). An individual matching method was applied to identify each subject who met the inclusion criteria in the IUGR group one control. The controls were chosen to be matched by gender and gestational age from the infants born in the same Neonatal Ward and in the same period (same year). The exclusion criteria were as follows: insufficient details in the medical charts regarding gender and gestational age, twins, and newborn with genetic disorders.

The medical charts were reviewed and the following data was collected on a Microsoft Excel database for each subject included in the study: demographics (gender), anthropometric data (weight [g], length [cm], head circumference [cm]), delivery data (gestational age, type of delivery [vaginal/cesarean]), clinical data, para-clinical data (see **Table 1**, reference values in the same table)[11] and mother's age. The collected clinical data were as follows: Apgar score at one minute after

Table 1 - Reference value for Astrup and biochemical parameters among newborns.

Name	Reference value
Astrup	
pH	7.30 - 7.40
pCO_2 (mm Hg)	35 - 50
pO_2 (mm Hg)	30 - 40
Base Excess (mmol/L)	-4 - (+4)
HCO_3 (mmol/L)	19 - 22
Aspartate aminotransferase (IU/L)	18 - 74
Alanin aminotransferase (IU/L)	8 - 78
Lactate dehydrogenase (U/L)	290 - 501
Creatinine (mg/dL)	≤0.6
Urea (mg/dL)	4 - 15
Blood glucose (mg/dL)	30 - 90
Creatine kinase (U/L)	20 - 200
Creatine kinase-MB (U/L)	<24
Hemoleucogram	
Hemoglobin (g/dL)	15 - 20
Hematocrit (%)	45 - 61
White blood cells (/mm^3)	5,000 - 35,000
Platelets (/mm^3)	250,000 - 450,000

pCO_2 - partial pressure of carbon dioxide in arterial blood, pO_2 - partial pressure of oxygen, HCO_3 - bicarbonate

birth, birth injuries, respiratory distress, heart failure, hyperbilirubinemia, hypocalcemia, hypoglycemia, NEC, intraventricular hemorrhage, number of days for weight recovery, total enteral nutritional days, hospitalization stay. Neonatal hypoglycemia is defined as blood sugar levels under 40mg/dl (lower than 2.2mmol/l).[12] The value of blood sugar is measured using the glucometer and is monitored at one hour, 2 hours, 4 hours, and 6 hours after birth. Whenever low values of blood sugar were identified the confirmation was made by the central laboratory, but the treatment was not delayed.[13] The NEC was defined using the modified Bell's criteria; clinical and radiological information staging of stage IIA, IIB, or IIIA (proven with no surgery including distension and/or signs of peritonitis, with x-ray evidence of pneumatosis intestinalis) or stage IIIB (NEC confirmed at surgery).[14] In term infants, hypocalcemia was defined as total serum calcium concentration less than 2mmol/L (8mg/dL) or ionized fraction of less than 1.1mmol/L (4.4mg/dL) in term infants and as total serum calcium concentration less than 1.75mmol/L (7mg/dL) in preterm infants. Neonatal thrombocytopenia is defined as a platelet count less than 150,000/microL.[15] Biochemical parameters (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase [LDH], urea, creatinine, blood glucose) were determined on a Konelab apparatus (Thermo Scientific™, Vantaa, Finland) by the spectrophotometer method. Abacus Junior 5 (Diatron GmbH, Vienna, Austria) with Coulter method was used for counting cells passing through a small aperture and for measuring the hemoglobin content of red blood cells. A Nova Biomedical Critical Care Xpress Blood Gas Analyzer (Billerica, USA) was used to determine Astrup parameters.The study was conducted according to the principles of Helsinki Declaration, and was approved by the Ethical Committee of Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Cluj-Napoca, Romania.

According to the Romanian guidelines for the evaluation of newborns with risks (such as preterm, small newborn gestational age, newborns with neurological abnormalities, menigitis) a transfontanelar ultrasound is performed on the first day of life and it is repeated on the third, seventh, and on a weekly follow-up or any time when the symptoms require it.[16] The grading system of the intraventricular hemorrhage was as follows[17]: grade 1 = bleeding confined to the periventricular area, grade 2 = intraventricular bleeding (10-50% of the ventricular area on sagittal view), and grade 3 = intraventricular bleeding (>50% of the ventricular area or distends the ventricle). The data was primarily included in the electronic data collection file of one of the authors and double-checked by another author. Furthermore, the screening for errors was carried out using the validation rules, based on the extreme possible values for each quantitative variable and on a list of possible values for qualitative variables. The identified errors were corrected before the statistical analysis was carried out. The missing values were left as missing and the sample size, on which the results were obtained, was provided, whenever different, with the eligible sample size.

Statistical analysis. Qualitative variables were summarized as percentages and associated 95% confidence interval (CI) (values presented in squared brackets along the manuscript) calculated with an exact formula.[18] Quantitative variables were expressed as mean±standard deviation for data that proved normally distributed; otherwise median and (Q1-Q3), where Q1=first quartile and Q3=third quartile, was used. Comparisons between groups were made with paired t-test for normally distributed data; otherwise, Sign test was applied. Association of anthropometric and/or co-morbidity factors with the IUGR was analyzed using binary logistic regression, main effect model. Variables (excepting derived variables) that proved significantly different between the groups were used as independent variables. Statistical analysis was carried out using Statistica software version 8 (StatSoft Inc., Tulsa, OK, USA) at a significance level of 5%.

Results. A total number of 150 infants with IUGR (cases) out of 4,790 newborn babies admitted in the Neonate Ward were identified during the study period, leading to an incidence of 3.1% in the studied Neonatal Ward. Matched controls were identified just for 142 of IUGR infants (95% CI: 90.00-98.00), so 142 cases and an equal number of controls were included in the study. No individual matched controls could be found for 2 baby girls with gestational age of 28 weeks, one baby boy of 29 weeks, one baby girl with gestational age of 30 weeks, 2 baby girls with gestational age of 31 weeks, one baby boy of 38 weeks, and one baby boy of 39 weeks. The majority of the infants included in each group were girls, with a girl:boy ratio equal to 1.68 (girls: 62.7%; 95% CI: 54.23-70.42 versus boys: 37.3%; 95% CI: 29.58-45.77). The gestational age of the infants included in each group varied from 28 weeks (4 infants) to 41 weeks (5 infants) with a maximum number of infants with the gestational age of 38 weeks for boys and 39 weeks for girls. The age of mothers varied from 15-years-old to 44-years-old, with a median

and an interquartile range of 30 (26-33) years-old for included cases and 31 (27-34) years-old for controls. No significant difference regarding the age of the mothers was identified when cases were compared with controls (Sign statistics=1.55, p=0.1213).

A significantly higher percent of infants in the IUGR group (66.9%; 95% CI: 58.46-74.64) were born by cesarean section compared with controls (46.5%; 95% CI: 38.03-54.92; Z-statistics=-5.171, p=0.0006). The Apgar score at one minute was higher than or equal to 7 for most of the infants in both groups (case group: 77.9%; control group: 77.5%) with no significant differences between groups (p>0.05). Birth weight (g) of the IUGR infants varied from 740-2940g with significantly lower values compared with controls (**Table 2**). Other investigated anthropometric characteristics and comparisons between the case and control groups are presented in **Table 2**.

Intraventricular hemorrhage of grade one was seen in 9 cases (7 infants on IUGR group and 2 infants in control group) while one infant in the IUGR group presented an intraventricular hemorrhage of grade 3. Percentages of investigated co-morbidities are presented in **Table 3**. Note that in all cases the hypoglycemia was transient with normalization after providing optimal intake of carbohydrates. One case of cerebral ischemia was identified in the IUGR group. The infant was a boy with gestational age of 31 weeks, birth weight of 1170g, length of 36cm and resulting from a pregnancy with hypertension diagnosed in the first trimester, which was hard to control with drugs. He was born by cesarean section with severe asphyxia at birth, (Apgar score 2 at one minute, metabolic acidosis, hypocalcemia and multi-organ dysfunction: renal impairment, cerebral impairment and increased cytolysis enzymes) requiring intubation in the delivery room (synchronized intermittent mechanical ventilation [SIMV]), administration of surfactant 200mg/kg/dose 20 minutes after birth, the nasal continuous positive airway pressure (CPAP), and oxygen for a total of 288 hours. On the third day of life rating, transfontanelar ultrasonography revealed intraventricular hemorrhage grade 3 and elements of cerebral ischemia.

Necrotizing enterocolitis was observed only in the IUGR group (3 infants). All the cases of NEC were girls with the following characteristics:- Infant one: Twenty-nine weeks gestational age, 900g birth weight, Apgar score at one min equal to 2, respiratory distress, needed administration of Curosurf 200mg/kg/dose and SIMV ventilation for 96 hours and after nasal CPAP

Table 2 - Anthropometric characteristics and comparisons between groups of newborns with IUGR and matched controls.

Characteristic	Case group (n=142)	Control group (n=142)	Sign statistics (p-value)
	Median (range)		
Birth weight (g)	2,195 (1,665-2,475)	2,850 (2,450-3,238)	11.45 ($2.26 \cdot 10^{-30}$)
Length (cm)	48 (43.25-50.00)	51 (48-53)	6.24 ($2.39 \cdot 10^{-20}$)
Cranial perimeter (cm)	31 (29-33)	33 (32-34)	7.70 ($1.41 \cdot 10^{-14}$)
Days for weight recovery	7 (4-8)[a]	8 (6-10)[a]	3.12 (0.0018)
Total enteral nutrition (days)	1 (1-5)[a]	1 (1-2)[a]	2.34 (0.0191)

[a]valid data = 141, IUGR - intrauterine growth restriction,

Table 3 - Presence of co-morbidities according to group and differences between groups of newborns with IUGR and matched controls.

Co-morbidity	(%)		Z-statistics (p-value)	
	Case	Control		
Intraventricular hemorrhage (n=138)	7.3	2.1	1.99	(0.0464)
Baby resuscitation (n=141)	14.9	17.0	-0.49	(0.6253)
Birth injuries* (n=140)	14.3	37.1	-4.37	(<0.0001)
Respiratory distress (n=140)	15.0	15.0	0.00	(0.9999)
Hyperbilirubinemia (n=140)	72.1	65.0	1.29	(0.1982)
Hypoglycemia (n=139)	27.3	4.3	5.26	(<0.0001)
Hypocalcemia (n=139)	6.5	3.6	1.09	(0.2739)
Heart failure (n=139)	4.3	2.2	1.02	(0.3091)

* caput succedaneum (11 cases), ecchymosis (8 cases), or cephalohematoma (2 cases), IUGR - intrauterine growth restriction, n = number of non-missing data

and with early and late sepsis and NEC Bell stage 2 with abdominal radiography showing pneumatosis intestinalis. Infant 2: Gestational age of 34 weeks, 1350g birth weight, intraventricular hemorrhage grade one, with mother with gestational hypertension from 28 gestation weeks, cesarean section delivery, with respiratory distress and mechanical ventilation, nose CPAP, early sepsis, NEC Bell stage one. The abdominal radiography identified abnormal gas pattern, dilated loops, and thickened bowel walls. Infant 3: A girl, 35 weeks gestational age, 1550g with Dexametasone prophilaxy, mode of birth cesarean section, with Apgar score one at one minute, severe acidosis (pH 6.8 from umbilical cord) with respiratory distress, SIMV ventilation for 24 hours, curosurf 200mg/kg/dose, early sepsis, heart failure and NEC Bell stage 2. Respiratory support was given to 13.5%, 95% CI: 8.52-19.85 of the infants in the IUGR group, and to 16.3%, 95% CI: 10.64-23.40 of control infants.

Significantly smaller numbers of platelets were identified in infants with IUGR (205.169±89.490) compared with controls (251.162±85.630; t-statistics=-4.11, *p*-value=0.0002). Furthermore, significantly higher values of pO_2 in infants with IUGR (63.32±31.16) compared with controls (51.61±18.07) (n=49) were identified (t-statistics=2.29, *p*=0.0312). The percentage of IUGR infants with abnormal values of lactate dehydrogenase smaller than 290 UL or higher than 501 U/L (70.7%) proved significantly smaller (Z-statistics=-2.5906, *p*=0.0096) compared with the percentage of controls with abnormal values of LDH (89.8%). No significant differences between groups were observed regarding all the other investigated para-clinical parameters ($p>0.05$). The hospitalization stay proved significantly higher for the IUGR infants compared with controls (case: median=9, quartile range [5-16.75]; control: median=5, quartile range [4-8]; $p<0.0001$). Binary logistic regression analysis, with dependent variable as group (case versus control) and the independent variables as infants characteristics that proved significantly different between groups, was conducted and the identified model (Likelihood Ratio: statistics=125.64, $p<0.0001$) is presented in **Table** 4.

Discussion. In our retrospective study, the risk factors in the IUGR neonates hospitalized in a tertiary teaching hospital in the North-West of Romania during a period of 2 and a half years were successfully assessed. The IUGR was found to have an incidence of 3.1% in our sample, the result being similar to the previous study conducted in Romania[10] (4.68%) and to the results reported by Romo et al[19] (3% and 7%). The proportions of baby girls proved significantly higher compared with the proportion of baby-boys ($p<0.0001$). This result is opposite to the girls:boys proportion in the Neonatal Ward during the study period (46.1% girls versus 53.9% boys; Z-statistics=10.83, $p<0.0001$).

Despite the fact that maternal age over 35 or 40-years-old was identified as risk factor for IUGR,[20] no significant difference regarding the mothers' age in the IUGR and control groups was identified in our study ($p>0.05$). Contrarily, other studies[21] showed that the younger age of mothers[7] along with other factors, such as hypertensive disorderes, pregestational diabetes, and autoimmune disease[21] are risk factors for IUGR. However, our results are similar to the results reported by Benavides-Serralde et al.[22] As expected, a significantly higher percentage of IUGR infants were born by cesarean section compared with the controls ($p<0.0001$), similar result being obtained in other studies.[23,24] In the Neonate Ward where the present study was conducted, 1583 out of 4790 babies were born by cesarean section (33.05%, 95% CI: 32.37-65.42%) during the investigated time-frame.

In our study, the Apgar score at one minute was not significantly different among IUGR and controls as fetal monitoring was rigorous and the birth occurred before the onset of the severe fetal distress. The Apgar score at 5 minutes is predictive of asphyxia but needs to be contextualized within the contemporary perinatal and neonatal care framework in different settings.[25] The Apgar score at 5 minutes was not assessed in our study

Table 4 - Results of binary logistic regression analysis of newborns with IUGR and matched controls.

Variable	Coefficient	Standard error	Statistics (*p*-value)		OR [95% CI]
Birth weight (g)	-0.004	0.001	-6.07	($1.29 \cdot 10^{-9}$)	0.996 [0.994-0.997]
Length (cm)	0.250	0.073	3.41	($6.48 \cdot 10^{-4}$)	1.284 [1.112-1.483]
Cranial perimeter (cm)	0.199	0.108	1.84	(0.0651)	1.221 [0.988-1.509]
Birth injuries (yes)	0.756	0.370	-2.05	(0.0408)	0.470 [0.228-0.969]
Hypoglycemia (yes)	-1.561	0.522	2.99	(0.0028)	4.763 [1.711-13.255]
Constant	-7.651	3.133	-2.73	(0.0064)	

OR - odds ratio, [95% CI] - lower and upper bound of 95% confidence interval, IUGR - intrauterine growth restriction

because all the values at one minute were ≥7, without significant differences between the groups (p>0.05). The obtained values of Apgar score were similar to those reported by Sbârcea and Râcă.[10]

As expected, birth weight, length, ponderal index, and cranial perimeter proved significantly lower in the IUGR group compared with the group in the controls (p<0.001, **Table 2**). Birth weight is an indicator of fetal growth and low birth weight predicts short-term survival of the newborn better than any other characteristic.[26] Small body size at birth also appears to be an important predictor for long-term health whereas fetal under-nutrition may increase susceptibility to diseases that occur later in life, especially cardiovascular diseases.[27] The number of days of weight recovery was more homogenous in the IUGR group compared with that of controls (**Table 2**) and the value proved significantly lower compared with that of controls (p<0.01). The median number of days of total enteral nutrition was equal to one in both groups but the values were heterogenous in the IUGR group compared with the controls (**Table 2**, p=0.0191).

Three out of 8 investigated co-morbidities proved different in the IUGR group compared with that of controls. Intraventricular hemorrhage (p<0.05) and hypoglycemia (p<0.001) proved significantly higher in the IUGR group compared with that of controls while birth injuries were significantly more frequent in controls (p<0.001) (**Table 3**). A significantly higher percent of subjects with hypoglycemia and intraventricular hemorrhage was reported by Ortigosa Rocha et al[28] in late-preterm IUGR infants. Two co-morbidities represented by cerebral ischemia (one subject) and NEC (3 subjects) were observed exclusively in IUGR group. Early complications common in infants with IUGR reported in specialty literature are low Apgar score, hypoxia, hypoglycemia, hypothermia, NEC, sepsis, and hyperbilirubinemia.[8,9] In our study, only hypoglycemia proved significantly higher in the IUGR infants (p<0.0001), the percentage of hypoglycemia in the IUGR infants being similar to that reported by Sehested and Pedersen[23] (31%). The incidence of intraventricular hemorrhage (7.25%) was higher in our group compared with previously published results (2%),[23] and the difference could be explained by the differences between populations and/or the difference between health care systems. The presence of birth injuries such as ecchymosis (8 cases), caput succedaneum (11 cases), cephalohaematoma 2 cases was significantly higher in the control group compared with the IUGR group and this result could be explained by the type of delivery; a significantly higher percentage of IUGR infants (66.9% IUGR versus 46.5% control) being born by cesarean section. The IUGR infants stay longer in hospital compared with controls (p<0.001), which is a similar result to the results reported by Olusanya.[8]

The logistic regression analysis conducted to investigate the relation between the presence of IUGR and infants' characteristics that proved significantly different in the IUGR group compared with that of controls identified 2 risk factors for this pathology: length and hypoglycemia (**Table 4**). According to the results presented in **Table 4**, hypoglycemia is expected to be almost 5 times more frequent in the IUGR group compared with the controls while length is expected to be 1.3 times smaller in the IUGR group compared with controls. Apgar scores lower than 7 were identified in almost 19% of IUGR infants, the hypoglycemia was reported in 15.7%, while the hyperbilirubinemia was reported in 14.6% of the cases. The differences between our results and the results previously published by Sbârcea and Râcă[10] could be summarized as higher incidence of hypoglycemia and hyperbilirubinemia. These differences could be explained by different investigated periods (2005-2010 in the study conducted in Bucharest and 2012-2014 in our study), differences between populations, and between the applied guidelines (mention must be made that the clinical guidelines for neonatology were introduce in Romania no earlier than 2008).

Our study conducted in the North-West of Romania characterizes the infants with IUGR, and has several limitations. The main limitation relates to the type of study; since the design was retrospective, it is susceptible to information bias, the data collected reflecting what was recorded in the medical charts. Furthermore, the retrospective design did not allow the assessment of late morbidities in the IUGR infants while the assessment of long-term effects of IUGR could be of clinical interest. In the same view, parental factors were not investigated since in the medical charts just the mother's age is registered. The absence of an individual matched control for each eligible case could not be seen as a limitation since only 5.33% of eligible cases were lost from the analysis and this did not affect the overall results. During the investigated period, the number of IUGR cases closely reflected the expected number of cases according to other similar publications.[10] The small sample size could reflect in the low incidence of co-morbidities in the investigated groups. The differences between co-morbidities in the investigated groups, compared with what scientific literature reports, could be explained by the differences that existed in the implemented protocols during pregnancy and/or delivery. Based on the design of the study our study bear evidence of level III with grade B for healthcare recommendation.[29]

In conclusion, our study shows that hypoglycemia and intraventricular hemorrhage characterized the IUGR group. Within our study, infants with IUGR, were found to be lower in length and have hypoglycemia. Our findings highlight the need to give special attention to hypoglycemia and intraventricular hemorrhage in infants with IUGR. Nevertheless, the assessment of the co-morbidities in infants with IUGR in a more complex frame, such as parents' characteristics (diseases, nutrition, and pregnancy history), immunological or genetic characteristics of infants, could provide relevant information to clinical practice.

References

1. Demicheva E, Crispi F. Long-term follow-up of intrauterine growth restriction: cardiovascular disorders. ***Fetal Diagn Ther*** 2014; 36: 143-153.
2. Lausman A, Kingdom J; Maternal Fetal Medicine Committee, Gagnon R, Basso M, Bos H, et al. Intrauterine growth restriction: screening, diagnosis, and management. ***J Obstet Gynaecol Can*** 2013; 35: 741-757. English/French
3. Rizzo G, Arduini D. Intrauterine growth restriction: diagnosis and management. ***A review. Minerva Ginecol*** 2009; 61: 411-420.
4. Mayer C, Joseph KS. Fetal growth: a review of terms, concepts and issues relevant to obstetrics. ***Ultrasound Obstet Gynecol*** 2013; 41: 136-145.
5. Sato Y, Benirschke K, Marutsuka K, Yano Y, Hatakeyama K, Iwakiri T, et al. Associations of intrauterine growth restriction with placental pathological factors, maternal factors and fetal factors; clinicopathological findings of 257 Japanese cases. ***Histol Histopathol*** 2013; 28: 127-132.
6. Hovdenak N, Haram K. Influence of mineral and vitamin supplements on pregnancy outcome. ***Eur J Obstet Gynecol Reprod Biol*** 2012; 164: 127-132.
7. Muhammad T, Khattak AA, Shafiq-ur-Rehman, Khan MA, Khan A, Khan MA. Maternal factors associated with intrauterine growth restriction. ***J Ayub Med Coll Abbottabad*** 2010; 22: 64-69.
8. Olusanya BO. Intrauterine growth restriction in a low-income country: Risk factors, adverse perinatal outcomes and correlation with current WHO Multicenter Growth Reference. ***Early Hum Dev*** 2010; 86: 439-444.
9. Aucott SW, Donohue PK, Northington FJ. Increased morbidity in severe early intrauterine growth restriction. ***J Perinatol*** 2004; 24: 435-440.
10. Sbârcea A, Râcă N. Evaluation of Risk Factors Involved in Intrauterine Growth Restriction. ***Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţi*** 2012; 22: 225-233.
11. Taketomo CK, Hodding JH, Kraus DM, editors. Pediatric Dosage Handbook. 14th ed. Hudson (OH): Lexi-Comp; 2007.
12. Ogata ES. Carbohydrate homeostasis. In: MacDonald MG, Mullett MD, Seshia MMK, editors. Avery's Neonatology: Pathophysiology and Management of the Newborn. 6th ed. Philadelphia (PA): Lippincott Williams & Wilkins 2005; 876-891.
13. Ognean ML, editor. Diagnosis and treatment of hypoglycemia newborn. Clinical guidelines in Neonatology. Guideline 14/ Revision 0 [Internet] 2010 [Romanian; Accessed 2014 Dec 2]. Available from: http://www.ms.ro/documente/14%20diagnosticul%20si%20tratamentul%20hipoglicemiei%20neonatale_9180_7493.pdf
14. Gregory KE, Deforge CE, Natale KM, Phillips M, Van Marter LJ. Necrotizing enterocolitis in the premature infant: neonatal nursing assessment, disease pathogenesis, and clinical presentation. ***Adv Neonatal Care*** 2011; 11: 155-164; quiz 165-166.
15. Wiedmeier SE, Henry E, Sola-Visner MC, Christensen RD. Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system. ***J Perinatol*** 2009; 29: 130-136.
16. Ognean ML, editor. Follow the newborn at risk for neurological sequelae and development. Practical Guidelines for Neonatology. Guideline 13/Revision 1 [Internet] 2010. [Romanian; Accessed 2014 Dec 2]. Available from: http://www.ms.ro/documente/13%20urmarirea%20nou%20nascutului%20cu%20risc%20pentru%20sechele%20neurologice%20si%20de%20dezvoltare_9180_7492.pdf
17. Volpe JJ. Intracranial Hemorrhage: Germinal Matrix-Intraventricular Hemorrhage in the Premature Infant. In: Volpe JJ, editor. Neurology of the Newborn. 5th ed. Philadelphia (PA): Saunders Elsevier; 2008. p. 517-588.
18. Jäntschi L, Bolboacă SD. Exact probabilities and confidence limits for binomial samples: applied to the difference between two proportions. ***ScientificWorldJournal*** 2010; 10: 865-878.
19. Romo A, Carceller R, Tobajas J. Intrauterine growth retardation (IUGR): epidemiology and etiology. ***Pediatr Endocrinol Rev*** 2009; 6 Suppl 3: S332-S336.
20. Motghare DD, Vaz FS, Pawaskar AM, Kulkarni MS. Maternal determinants of intrauterine growth restriction in Goa, India: a case-control study. ***Global Journal of Medicine and Public Health*** 2014; 3: O8.
21. Hendrix N, Berghella V. Non-placental causes of intrauterine growth restriction. ***Semin Perinatol*** 2008; 32: 161-165.
22. Benavides-Serralde A, Hernández-Andrade E, Fernández-Delgado J, Plasencia W, Scheier M, Crispi F, et al. Three-dimensional sonographic calculation of the volume of intracranial structures in growth-restricted and appropriate-for-gestational age fetuses. ***Ultrasound Obstet Gynecol*** 2009; 33: 530-537.
23. Sehested LT, Pedersen P. Prognosis and risk factors for intrauterine growth retardation. ***Dan Med J*** 2014; 61: A4826.
24. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). ***Ultrasound Obstet Gynecol*** 2013; 42: 400-408.
25. Bharti B, Bharti S. A review of the Apgar score indicated that contextualization was required within the contemporary perinatal and neonatal care framework in different settings. ***J Clin Epidemiol*** 2005; 58: 121-129.
26. Wilcox AJ. On the importance--and the unimportance--of birthweight. ***Int J Epidemiol*** 2001; 30: 1233-1241.
27. Salam RA, Das JK, Bhutta ZA. Impact of intrauterine growth restriction on long-term health. ***Curr Opin Clin Nutr Metab Care*** 2014; 17: 249-254.
28. Ortigosa Rocha C, Bittar RE, Zugaib M. Neonatal outcomes of late-preterm birth associated or not with intrauterine growth restriction. ***Obstet Gynecol Int*** 2010; 2010: 231842.
29. Chung KC, Swanson JA, Schmitz D, Sullivan D, Rohrich RJ. Introducing evidence-based medicine to plastic and reconstructive surgery. ***Plast Reconstr Surg*** 2009; 123: 1385-1389.