

Parental Factors Associated with Intrauterine Growth Restriction

Monica G. Hășmășanu^{1,2}, Sorana D. Bolboacă³, Tudor C. Drugan³, Melinda Matyas^{1,2}, Gabriela C. Zaharie^{1,2}

¹Iuliu Hațieganu University of Medicine and Pharmacy, Department of Neonatology, Cluj-Napoca, Romania;

²Emergency Clinical County Hospital, Department of Neonatology, Cluj-Napoca, Romania;

³Iuliu Hațieganu University of Medicine and Pharmacy, Department of Medical Informatics and Biostatistics, Cluj-Napoca, Romania

SUMMARY

Introduction Linear growth failure is caused by multiple factors including parental factors.

Objective The aim of this study was to evaluate parental risk factors for intrauterine growth restriction (IUGR) on a population of Romanian newborn infants in a tertiary level maternity facility for a period of 2.5 years.

Methods A retrospective matched case-control study was conducted in the Emergency County Hospital of Cluj-Napoca, a university hospital in North-Western Romania. The sample was selected from 4,790 infants admitted to the Neonatal Ward at 1st Gynecology Clinic between January 2012 and June 2014.

Results The age of mothers was significantly lower in the IUGR group compared to controls ($p=0.041$). A significantly higher percentage of mothers had hypertension in the IUGR group compared to those in the control group ($p<0.05$). No other significant differences were identified with regard to the investigated characteristics of mothers between IUGR infants compared to controls ($p>0.13$). The age of fathers of infants with IUGR proved significantly lower compared to controls ($p=0.0278$). The analysis of infants' comorbidities revealed no significant difference between groups for respiratory distress, hyperbilirubinemia, hypocalcaemia, and heart failure ($p>0.27$). Intracranial hemorrhage, necrotizing enterocolitis and hypoglycemia were significantly higher in the IUGR group compared to controls. The logistic regression identified hypertension as a significant risk factor for IUGR (OR=2.4, 95% CI [1.3–4.5]).

Conclusion Although the age of the mothers and fathers proved significantly lower in the IUGR group compared to controls, only hypertension in the mothers proved significant risk factors for IUGR.

Keywords: intrauterine growth restriction; parental characteristics; risk factor

INTRODUCTION

Infants with intrauterine growth restriction (IUGR) are defined as those with birth weight below the 10th percentile for its gestational age and it is a consequence of several factors [1]. Genetic and environmental factors influence the development throughout the growth period. Linear growth failure is largely confined to the intrauterine period and the first few years of life, and it is caused by multiple factors like inadequate diets, infections, maternal chronic diseases [2, 3]. Few studies have examined the effect of parental factors on postnatal growth of infants with IUGR. Short stature of the mother and poor maternal nutrition stores are associated with an increased risk of intrauterine growth retardation [4]. Maternal weight was found to be a stronger predictor of offspring birth weight than maternal height [5, 6]. Geographical differences in newborn phenotype showed to be related to the differences in maternal size and body composition [4]. The same study suggests that the mother's skeletal size and soft tissue mass have independent effects on birth weight. Maternal birth weight proved to be one of the strongest pre-

dictors of neonatal size and is associated with offspring birth length, head circumference and mid-upper arm circumference as well as with infant birth weight [4]. A positive association between increasing maternal age and increasing risk for IUGR was also demonstrated with an odd ratio of 3.2 (95% CI [1.9–5.4]) for maternal age ≥ 40 years [7]. Another study identified that advanced maternal age (≥ 35 years old) is an independent risk factor for IUGR [6]. A different factor that has been shown to influence the fetal development is maternal smoking behavior due to epigenetic change on human placental genes observed on mothers who smoked [8]. In a pregnancy with hypertension and preeclampsia the risk for IUGR is higher, and the risk increases with the severity of preeclampsia [9, 10].

The fathers of infants with IUGR showed more likely to be insulin resistant (log insulin resistance: OR=5.99, 95% CI [2.25–15.91]), hypertensive (OR=1.09, 95% CI [1.02–1.16], $p=0.006$ for diastolic blood pressure; OR=1.08, 95% CI [1.02–1.14], $p=0.007$ for systolic blood pressure), and to smoke cigarettes (OR=3.09, 95% CI [1.10–8.22], $p=0.01$) compared with fathers of normally grown offspring [11].

Correspondence to:

Sorana D. BOLBOACĂ
Iuliu Hațieganu University of
Medicine and Pharmacy
Department of Medical
Informatics and Biostatistics
6 Louis Pasteur
400349 Cluj-Napoca
Cluj
Romania
sbolboaca@umfcluj.ro

OBJECTIVE

The main objective of our study was to identify and to quantify parental risk factors for IUGR of a Romanian population in a tertiary level maternity facility for a period of 2.5 years and to compare them to newborns without IUGR.

METHODS

A matched case-control study was conducted in the Emergency County Hospital of Cluj-Napoca, a university hospital in North-Western Romania. The hospital serves as a referral center for the Cluj, Sălaj, Bistrița-Năsăud, and Maramureș counties. Subjects for this study were selected from 4,790 infants admitted to the Neonatal Ward at 1st Gynecology Clinic, Emergency County Hospital Cluj-Napoca, and discharged in the period from January 2012 to June 2014. The inclusion criteria for the IUGR group were as follows: IUGR diagnosis (defined as birth weight below the 10th percentile), and availability of the following data on medical records [12]:

- Infant sex (F/M) and gestational age (weeks);
- Infant anthropometric measurements: weight (kg), height (cm), head circumference (cm);
- Infant co-morbidities (yes/no): birth injuries, respiratory distress, hyperbilirubinemia, hypoglycemia, hypocalcaemia, necrotizing enterocolitis, heart-failure, intracranial hemorrhage;
- Maternal data: maternal age, ethnicity, number of pregnancies, number of deliveries, medical history (especially hypertension).

Whenever possible, data related to age, ethnicity and health history of father were also collected.

A matched control in terms of gender and gestational age was chosen in a 1:1 ratio for each IUGR infant. A total number of 150 infants with IUGR were admitted to the Neonatal Ward at 1st Gynecology Clinic during the study period, and 142 of them met the eligibility requirements. A total of 140 matched controls were identified, resulting in an investigated sample of 280 subjects (140 with IUGR and 140 controls).

Ethical approval was obtained from the Iuliu Hațieganu University of Medicine and Pharmacy Ethics Committee.

Statistical analysis

Neonatal ponderal index (NPI), a derivate index calculated based on collected data, was computed for each infant included in the study using the following formula [13, 14]: $NPI = 100 \times \text{weight (g)} / \text{height (cm}^3\text{)}$.

Variables were analyzed as collected and/or as derived variables:

- Infants with the number of weeks of gestation smaller than 37 were considered preterm, while infants with 37 to 41 weeks of gestation were considered term.
- Birth weight (classification regardless of the gestational age – according to International Classification

of Diseases version 10 [15]): LBW = low birth weight, defined as birth weight < 2.5kg (ICD-10: P07.1); VLBW = very low birth weight, defined as birth weight < 1.5kg (ICD-10: P07.1); and ELBW = extremely low birth weight, defined as birth weight < 1.0kg (ICD-10: P07.0).

- Maternal age: 15–19 years old, 20–34 years old, ≥35 years old.

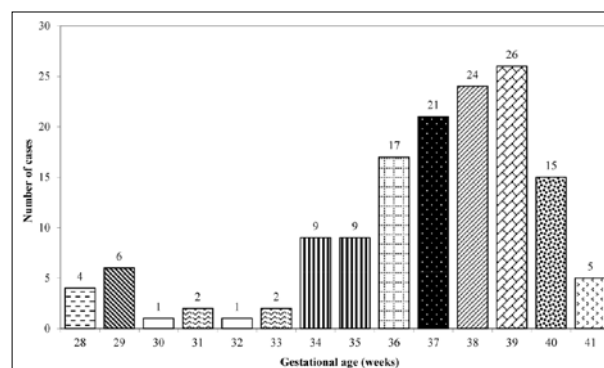
Descriptive statistical analysis of data as percentages and associated 95% confidence interval (values presented in square brackets throughout the manuscript, calculated with an exact formula) were used for qualitative variables and mean \pm standard deviation for normally distributed data or median and 1st and 3rd quartiles (values provided in round brackets) [16, 17]. Cross tabulations with cases in rows and controls in columns were used to assess the association between the groups. The McNemar's test was used in cross tabulations, while paired Student's t-test for quantitative normally distributed data and the Wilcoxon test for not-normally distributed quantitative variables were applied to compare the groups. Uni- and multivariate logistic regression was used to investigate the association of parental factors with intrauterine growth restriction. Parental variables with a p-value lower than or equal to 0.25 in the univariate analysis were the input data for the multivariate logistic regression. Statistical analysis was done with Statistica (v. 8.1) at a significance level of 5%.

RESULTS

Infants with and without IUGR were similar regarding birth as preterm vs. term, with a 1:1 ratio. The majority of infants included in the study were female (62.9%) [54.9–70.7], their percentage being significantly higher compared to male ($p < 0.0001$). No significant difference in terms of living place defined as rural or urban was identified between IUGR group and control group (IUGR 64.8% from urban vs. controls 70.4%; $p = 0.3107$).

The gestational age of most infants included in the study was from 36 to 40 weeks (Graph 1).

The infants with IUGR proved to have significantly lower anthropometric characteristics compared to controls (Table 1). Median for weight recovery was of eight days (interquartile range [5–12]) for IUGR group and of



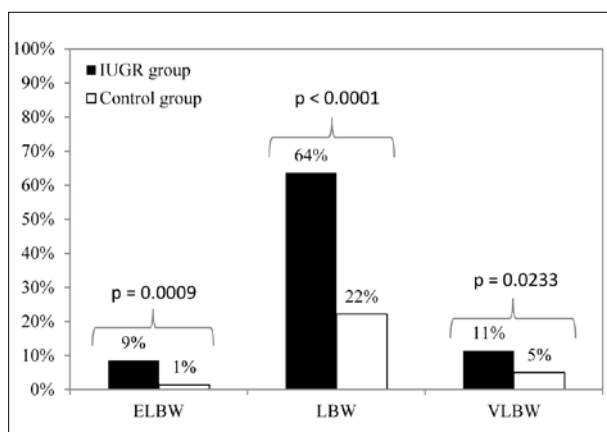
Graph 1. Distribution of gestational age

Table 1. Anthropometric characteristics of infants

Characteristic	IUGR	Control	p-value
Birth weight (kg)	2.2 (1.7–2.5)	2.9 (2.5–3.3)	<0.0001
Height (cm)	48 (44–50)	51 (48–53)	<0.0001
Neonatal ponderal index (g/cm ³)	2.0 (1.8–2.2)	2.1 (2.0–2.4)	<0.0001
Head circumference (cm)	31 (29–33)	33 (32–34)	<0.0001

The values are median and Q1–Q3, where Q1 = 1st quartile (25th percentile) and Q3 = 3rd quartile (75th percentile).

IUGR – intrauterine growth restriction

**Graph 2.** Differences on classes of birth weight according to group

ELBW – extremely low birth weight; LBW – low birth weight; VLBW – very low birth weight

12 days (interquartile range [7–13]) for controls, the difference being significant ($p=0.0010$).

The percentage of infants with LBW, VLBW, or ELBW proved significantly higher compared to controls (Graph 2), the groups being identified as significantly different by the McNemar's test ($p=0.0376$).

Birth injuries, necrotizing enterocolitis, and hypoglycemia co-morbidities proved significantly different between groups. A higher percentage of trauma in the control group and higher percentage for necrotizing enterocolitis and hypoglycemia in the IUGR group (Table 2).

Distribution of maternal age on classes was homogeneous between groups (three mothers younger than 20 years, 107 with an age between 20 and 34 years, and 30 with an age of 35 years or older). The summary and comparison of parental characteristics are presented in Table 3.

In the IUGR group, 37 mothers were hypertensive (26.4%) [CI 19–34] while in the control group just 19 mothers had hypertension (13.6%) [8.6–20.0]. In the majority of cases, mother's hypertension was diagnosed during pregnancy (IUGR group: 91.9% [78.5–97.2] vs. control group: 84.2% [58.2–94.5]). A significantly higher percentage of mothers with hypertension in the IUGR group was diagnosed during pregnancy ($p=0.0082$).

The logistic regression analysis was conducted to identify significant parental factors related to IUGR. Hypertension in mothers proved a significant factor for IUGR (Table 4).

The power of the study calculated for a sample size of 140 and a significance level of 5%, taking into consider-

Table 2. Co-morbidities (summary and comparison)

Characteristic	IUGR		Control		p-value
	N (%)	95% CI	N (%)	95% CI	
Intracranial hemorrhage	9 (6.4)	2.9–12.1	3 (2.1)	0.7–6.4	0.0518
Birth injuries	20 (14.3)	8.6–21.4	52 (37.1)	29.3–45.7	<0.0001
Respiratory distress	21 (15.0)	9.3–22.1	22 (15.7)	10.0–22.9	0.9062
Hyperbilirubinemia	99 (70.7)	62.2–77.9	91 (65.0)	56.4–72.9	0.2790
Necrotizing enterocolitis	3 (2.1)	0.7–6.4	0 (0.0)		<0.0001
Hypoglycemia	39 (27.9)	20.7–35.7	6 (4.3)	1.4–9.3	<0.0001
Hypocalcaemia	9 (6.4)	2.9–12.1	5 (3.6)	1.4–7.9	0.3123
Heart failure	6 (4.3)	1.4–9.3	3 (2.1)	0.7–6.4	0.4047

N – number of subjects; 95% CI – 95% confidence interval; IUGR – intrauterine growth restriction

Table 3. Parental characteristics by groups: summary and comparisons

Characteristic		IUGR	Control	p-value
Mother	Age (years) ^a	29.2±5.2	30.5±5.3	0.0415
	Romanian ^b	137 (97.9)	133 (95.0)	0.1336
	Number of children ^b	85 (60.7)	79 (56.4)	0.5048
	Positive medical history ^b	29 (20.7)	26 (18.6)	0.6811
	Hypertension ^b	37 (26.4)	19 (13.6)	0.0119
	Double test positive (n=51) ^b	1 (0.7)	0 (0.0)	n.a.
	Triple test positive (n=53) ^b	2 (1.4)	1 (0.7)	0.7728
	Torch Rubella (n=65) ^b	1 (0.7)	0 (0.0)	n.a.
	Torch CMV (n=65) ^c	1 (0.7)	1 (0.7)	0.7237
Father	Age (years) ^c	32 (28–35)	33 (30–36)	0.0278
	Romanian ^b	135 (96.4)	131 (93.6)	0.2684
	Positive medical history ^b	3 (2.1)	4 (2.9)	0.8501

a: mean value ± standard deviation; paired t-test

b: number (%); McNemar's test

c: median (Q1–Q3), where Q1 = 1st quartile (25th percentile), Q3 = 3rd quartile (75th percentile); Wilcoxon test

n – number of subjects; CMV – cytomegalovirus; n.a. – not available

Table 4. Results of logistic regression on paternal factors

Characteristic	OR	95%CI	Coefficient±SE	p-value
Mother age (years)	0.96	0.90–1.02	-0.04±0.03	0.1885
Father age (years)	0.98	0.91–1.04	-0.02±0.03	0.4901
Mother hypertension	2.48	1.2–4.52	0.88±0.32	0.0060
Mother ethnicity	0.42	0.10–1.73	-0.87±0.73	0.2280
Constant			1.85±0.86	0.0319

SE – standard error

ation a percentage of 13.6 of hypertension in mothers of infants without IUGR for our matched case-control design, is equal to 0.98.

DISCUSSION

The investigated sample of newborns proved homogenous in terms of number of preterm and term infants in both IUGR and control groups. A significant proportion of newborns were female, reflecting the distribution of gender in the Romanian newborn population during the investigated period.

The gestational age of the investigated sample varied from 28 weeks to 41 weeks, with the majority of cases between 36 and 40 weeks. In our sample, most of the newborns were born at term, which explains why incidence of respiratory distress was equal in the two groups.

IUGR is a frequent complication in preterm infants and is the cause of most elective late-preterm (birth between 34 weeks and 36 6/7 weeks of gestation) deliveries [18]. In our sample we had 35 late-preterm infants, which represents 70% of preterm infants and is similar to the previously published data (63–70% of all preterm births [19, 20]).

The analysis of the anthropometric characteristics (birth weight, height, NPI and head circumference) proved significantly lower in the IUGR infants compared to controls (see Table 1). The number of days needed to recover the weight proved significantly lower in the IUGR group compared to controls (IUGR group = eight days, control group = 12 days, $p < 0.05$) since parenteral nutrition support associated with enteral nutrition was required in the first days.

As expected, the majority of infants in the control group had normal weight at birth. The number of infants with low, very low, and extremely low birth weight proved significantly higher in the IUGR group compared to controls (Graph 2), with the highest proportion of LBW in infants with IUGR (64%).

Infants with IUGR and prematurity had risk for hypoglycemia, intraventricular hemorrhage, prolonged hospital stay and increased need for neonatal intensive care unit treatment when compared to appropriate for gestation age infants, thus demonstrating the severity of these cases [20, 21].

The analysis of co-morbidities as presented in Table 2 revealed several findings.

No significant difference in respiratory distress, hyperbilirubinemia, hypocalcaemia and heart failure ($p > 0.27$) was obtained between groups.

Intracranial hemorrhage was more frequent in the IUGR group compared to the control group (Table 2).

Identification of a significantly higher proportion of hemorrhage in the IUGR group compared to controls is expected if a larger sample size is investigated.

Compared to controls, a significantly lower proportion of IUGR infants had birth injuries ($p < 0.0001$). This result could be explained by the type of delivery, most of the infants in the IUGR group being delivered through caesarean section [22].

Necrotizing enterocolitis was observed in the IUGR group only, as necrotizing enterocolitis is morbidity characteristic to the infants with IUGR that have intestinal ischemia, and is significantly more frequent in comparison with the appropriate age for gestation in the population [20].

A significantly higher percentage of infants in the IUGR group had hypoglycemia, compared to controls ($p < 0.0001$). It is known that hypoglycemia is significantly more frequent in newborns with IUGR in comparison with the appropriate age for gestation in the population [23, 24].

The analysis of parental characteristics on the investigated sample revealed the following (Table 3):

- The age of the mothers proved significantly lower in the IUGR group compared to controls ($p = 0.041$), but was not identified as a risk factor for IUGR. Other studies showed that maternal age equal to or greater than 35–40 years is a risk factor for IUGR [5, 6].
- A significantly higher percentage of the mothers had hypertension in the IUGR group compared to controls ($p < 0.05$).
- No other significant differences were identified with regard to the investigated mothers' characteristics between the IUGR infants and those in the control group ($p > 0.13$).
- Similar with maternal age, the age of the fathers of infants with IUGR proved significantly lower compared to controls ($p = 0.0278$).

Multivariate logistic regression analysis was conducted using those predictors that showed in univariate analysis p -values equal to or greater than 0.25. The following four predictors accomplished the criterion and were included in multivariate logistic regression: maternal and paternal age, presence of hypertension in mother and mother's ethnicity. The logistic regression conducted on our sample identified neither maternal nor the paternal age as risk factors for IUGR (Table 4). Just one predictor, namely mother's hypertension, proved a significant risk factor for IUGR (OR=2.41, 95% CI [1.29–4.52]).

Preeclampsia, gestational hypertension and unexplained intrauterine growth restriction may have similar determinants and consequences [25]. Hypertensive disorders in pregnancy determine vascular abnormalities of the placenta, fetal hypoxia, malnutrition and IUGR [26]. In our study, the presence of hypertension in the mother in the IUGR group especially diagnosed during pregnancy has been identified. Hypertension in the mother has been identified in the majority of the cases during pregnancy (IUGR group: 91.9% [78.5–97.2] vs. control group: 84.2% [58.2–94.5]). A significantly higher proportion of mothers with hypertension in the IUGR group was proved when

hypertension diagnosed during pregnancy was considered. Furthermore, the single significant risk factor for IUGR identified by logistic regression analysis was also hypertension in mothers.

The power of our study (0.98) sustains that the results obtained in it are true for the North-Western Romanian population. Despite reasonable power of the study, several limitations could be listed. The first one is related to the absence of an appropriate growth reference chart – growth charts adapted from Fenton were used in this study as recommended by the Nutrition Guide for preterm infants from Romania [27, 28]. The second limitation of the study is determined by the restricted access to other parental characteristics (such as mother's weight and height, father's weight and height, maternal pre-pregnancy weight, maternal diet, lifestyle) due to retrospective collection of data.

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CONCLUSION

The maternal and paternal age was significantly lower in the IUGR group compared to controls. Despite this fact, neither was identified as a risk factor for IUGR. A significantly higher percentage of mothers in the IUGR group had hypertension, compared to the control group, while logistic regression analysis identified the mother hypertension as a significant risk factor for IUGR.

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Карактеристике родитеља повезане с интраутерусним заостајањем у расту

Моника Г. Хашмашану^{1,2}, Сорана Д. Болбоака³, Тудор Ц. Друган³, Мелинда Маћаш^{1,2}, Габријела Ц. Захарије^{1,2}

¹Универзитет медицине и фармације „Јулију Хаџијегану“, Катедра за неонатологију, Клуж-Напока, Румунија;

²Ургентна окружна клиничка болница, Одељење неонатологије, Клуж-Напока, Румунија;

³Универзитет медицине и фармације „Јулију Хаџијегану“, Катедра за медицинску информатику и биостатистику, Клуж-Напока, Румунија

КРАТАК САДРЖАЈ

Увод Недостатак линеарног раста узрокује неколико чинилаца, укључујући карактеристике родитеља.

Циљ рада Циљ ове студије била је процена карактеристика родитеља као фактора ризика за интраутерусно заостајање у расту (ИУЗР) новорођенчади у румунској гинеколошко-акушерској здравственој установи терцијарног нивоа током две и по године.

Методе рада Ретроспективна анамнестичка студија упарених случајева изведена је у Ургентној окружној болници у Клужу, универзитетској болници на северозападу Румуније. Узорак је одабран међу 4.790 новорођенчади примљених на Неонатално одељење Прве гинеколошке клинике између јануара 2012. и јуна 2014. године.

Резултати Мајке чија су деца заостјала у расту (ИУЗР група) биле су статистички значајно млађе од мајки деце контролне групе ($p=0,041$). Хипертензија је утврђена у значајно већем проценту код мајки у ИУЗР групи него код мајки у

контролној групи ($p<0,05$). Нису установљене друге значајне разлике у погледу истраживаних карактеристика новорођенчади из ИУЗР групе наспрам оних из контролне групе ($p>0,13$). Очеви новорођенчади са ИУЗР били су такође статистички значајно млађи у поређењу с очевима деце из контролне групе ($p=0,0278$). Анализа коморбидитета новорођенчади није показала значајне разлике између група у погледу дисајних сметњи, хипербилирубинемije, хипокалцемије и слабости срца ($p>0,27$). Интракранијална крварења, некротизирајући ентероколитис и хипогликемија значајно су били чешћи у ИУЗР него у контролној групи. Логистичка регресија је препознала хипертензију као значајан фактор ризика за ИУЗР ($OR=2,4$; $95\%CI=1,3-4,5$).

Закључак Иако се старосна доб мајки и очева показала знатно нижом у ИУЗР него у контролној групи, само се хипертензија мајки показала значајним фактором ризика за ИУЗР.

Кључне речи: интраутерусно заостајање у расту; карактеристике родитеља; фактори ризика

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