Unfavorable influence of prematurity on the neonatal prognostic of small for gestational age fetuses

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Abstract. Vascular stress at the level of the uterus-placental unit, with chronic placental ischemia, results in intrauterine growth restriction. Expectation management can be used, when the situation allows, in cases of compensated intrauterine growth restriction. The aim of the present study was to evaluate the neonatal prognosis of preterm births with and without growth restriction and term births with growth restriction in order to improve decisional accuracy regarding the termination of pregnancy. The frequency of term birth infants with low birth weight for gestational age was ~2%. The male sex, predominated only in the group of premature infants with normal weight for the gestational age. The highest frequency of neonatal complications studied occurred in the group of preterm neonates small for gestational age (SGA) with statistical significance obtained for cardiovascular arrest acute respiratory failure, ulcer-necrotic enterocolitis, respiratory distress, cerebral edema, intraventricular hemorrhage, cerebral hemorrhage, pulmonary hemorrhage, neonatal infection, hypoglycemia, retinopathy, anemia, hemorrhagic disease, disseminated intravascular coagulation, disease of hyaline membranes, neonatal sepsis, need for intensive neonatal therapy and death. In conclusion, immediate neonatal adaptation of SGA preterm neonates is more deficient than for preterm neonates with appropriate weight for gestational age; the adaptation of preterm neonates, in turn, is more deficient than term newborns with intrauterine growth restriction. The term newborns with intrauterine growth restriction have a neonatal adaptation comparable to that of the term newborns with weight corresponding to the gestational age.

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Introduction

Fetal consequences of defective placentation with poor vascular flow secondary to abnormal physiological transformation of the spiral arteries are intrauterine growth restriction, oligohydramnios, abruptio placentae, and adverse fetal biophysical score. In this context, the fetuses resulting from pre-eclampsia pregnancies have an increased risk of preterm birth and unfavorable perinatal and neonatal prognosis.

In order to reduce these complications, expectation management can be used, when the situation allows. The conditions that impose emergency therapeutic behavior are divided into maternal and fetal conditions. The maternal conditions include high blood pressure values resistant to antihypertensive treatment (>160/110 mmHg); persistent, treatment-resistant headache; epigastralgia or pain in the right shoulder resistant to anti-algic treatment; visual disorders, motor deficits or sensory disorders; stroke; myocardial infarction; HELLP syndrome; newly developed renal failure or worsening of renal function; pulmonary edema; eclampsia; and suspected abruptio placentae or vaginal bleeding in the context of the placenta previa (1-3).

Fetal conditions that require emergency therapeutic action include a biophysical score of 4 or less; intrauterine fetal death; minimal chances of fetal survival in the context of fetal

malformation incompatible with life or extreme prematurity; changes in Doppler velocimetry with inverted end-diastolic flow of the umbilical artery (4).

The decision to implement therapeutic intervention is made after the complete clinical and paraclinical evaluation and the determination of the risk/benefit ratio, both maternal and fetal. More specifically, the biological evaluation should be performed prior to obstetrical decision and should include: Hemoleucogram; biochemical evaluation of renal function, liver function, and markers of hemolysis; and urinary test for evaluation of proteinuria. The fetal evaluation is based on the complete obstetrical ultrasound examination, with assessment of fetal growth and weight, respectively, as well as assessment of the volume of the amniotic fluid and the fetal biophysical score along with the Doppler velocimetry of the umbilical arteries, the mean cerebral artery and the cerebroplacental ratio (5). Both prematurity and intrauterine growth restriction are the fetal complications most often associated with preeclampsia. Intrauterine growth restriction is a marker of fetal distress and an important risk factor for fetal intrauterine degradation, and the onset of complications of prematurity further contribute to a less favorable prognosis (6).

The aim of the present study was to evaluate the neonatal prognosis of preterm births with and without growth restriction and term births with growth restriction in order to improve decisional accuracy regarding the termination of pregnancy.

Patients and methods

The purpose of this study was to comparatively evaluate the neonatal evolution and the rate of short-term neonatal complications of the preterm infants with normal weight for the gestational age and of the preterm infants with low weight for the gestational age, as well as of the term infants small for gestational age (SGA). We carried out a retrospective study using the database of the neonates of the Neonatology Clinic of the Emergency University Hospital of Bucharest with a third degree maternity ward, for a period of 3 years. The cases of preterm birth were selected according to the World Health Organization (WHO) definition of birth before 37 full weeks of gestation. Only live newborn cases were selected and analyzed. The cases of premature newborns were classified in two categories according to the birth weight, namely with appropriate weight for the gestational age, named group 1, including 78 cases with low weight according to the gestational age corresponding to the international growth curves, named group 2, including 1,121 cases. Therefore, the low weight cases selected were those in which the weight at birth was below the two standard deviations of the growth curves corresponding to the gestational age. There were also cases of babies with low birth weight born at term who were selected for the purpose of comparative analysis of their neonatal prognosis (group 3 including 206 cases). The parameters analyzed were gestational weight and age as directional criteria, fetal sex, mode of birth (cesarean or spontaneous birth), and Apgar index at 1 min as a marker of immediate postnatal fetal status. The obstetric features analyzed included fetal presentation, the spectrum of hypertensive disorders of pregnancy, fetal malformations, nuchal cord and true umbilical cord knot. The immediate neonatal complications and neonatal markers analyzed were: Cardiovascular arrest, acute respiratory failure, ulcer-necrotic enterocolitis, hypoxia, respiratory distress, cerebral edema, intraventricular hemorrhage, cerebral hemorrhage, pulmonary hemorrhage, patent ductus arteriosus, neonatal hypoglycemia, retinopathy, anemia, hemorrhagic disease, disseminated vascular coagulation, hyaline membrane disease, neonatal sepsis, need for neonatal intensive care and death. A total of 1,405 subjects were analyzed and were divided into 3 study groups: group 1 representing live, preterm infants with low weight for gestational age; group 2 representing living newborns, premature but with weight corresponding to the gestational age; and group representing term newborns with low birth weight. The cumulative and comparative analysis by frequency and sex were analyzed in the first phase, following the cumulative and comparative analysis of all the neonatal and obstetrical parameters of the cases in the 3 group sand the statistical analysis regarding the significant difference, or the frequency of the complications analyzed, in the 3 study groups through the chi-square test. The results were analyzed and interpreted according to the obtained P-value; $P<0.05$ was considered to be statistically significant.

The data collected retrospectively did not contain personal information and only the ethics committee agreement of the University Emergency Hospital of Bucharest was required and obtained without the need of informed consent or the consent of the patient/legal representative in the case of minors.

Results

Our study group included a total of 1,405 newborns with a minimum gestational age of 23 weeks and a maximum of 41 weeks. Regarding the correspondent birth weight, the minimum value recorded in the total study group was 240 grams and the maximum 4,260 grams. Fig. 1 shows the division into groups, according to the working method. During the duration of the study (3 years), a total of 1,199 premature infants were registered and the majority (1,121 cases, 93.5%) had appropriate weight for gestational age, and only 6.5% of the preterm cases were classified as presenting reduced weight for the gestational age. The frequency of term birth infants with low birth weight for gestational age was ~2% of all births registered during the three years of study. In the study group, the highest proportion, group 2 (79.8%) had premature infants with normal weight for the gestational age followed by group 3 with term infants with low weight for the gestational age (14.7%), and group 1 with preterm infants with low weight for gestational age (5.6%) (Table I). Regarding the frequency per sex, the male sex, noted with 1 in Table II, predominated only in study group 2, the group of premature infants with normal weight for the gestational age. The other two study groups were characterized by low weight for gestational age with predominantly female infants.

For each study group, the Apgar index was analyzed in terms of median, maximum, and minimum. Thus, for all 3 study groups, the following results were obtained for a 95% confidence interval. Group 1 had a median Apgar index of 7, with a minimum value of 1 and a maximum value of 9.

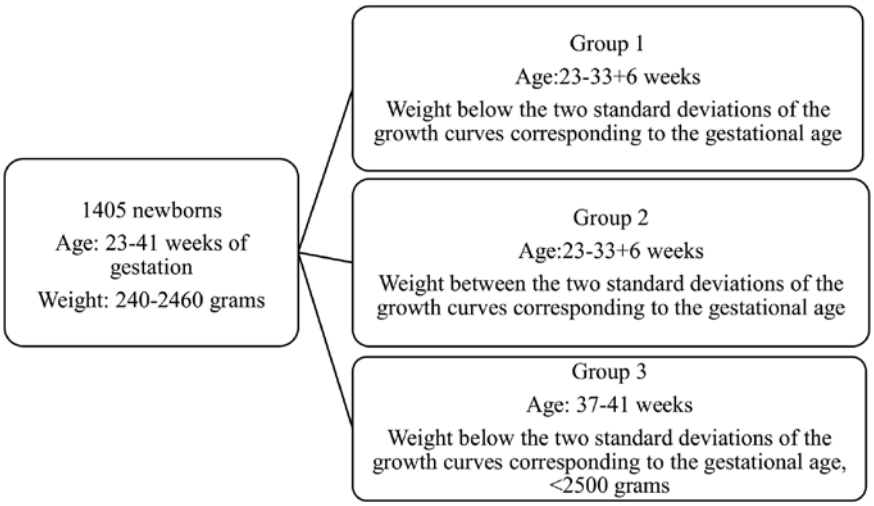

Figure 1. The division into groups of the studied population.

Table I. Frequency by study groups.

Study groups	Frequency	%
Valid		
1	78	5.6
2	1,121	79.8
3	206	14.7
Total	1,405	100

Table II. Frequency by sex in the study groups.

	Sex		
Group	Male	Female	Total
1	37	41	78
2	573	548	1,121
3	85	121	206
Total	695	710	1,405

Group 2 was characterized by a median of the Apgar index of 8, a minimum value of 0, and a maximum value of 10. Study group 3 was characterized by a median Apgar index of 9, a minimum value of 1 and a maximum value of 10.

Regarding the mode of birth, for all the 3 study groups, birth through cesarean section predominated (Table III). The greatest difference in percentage was in the group of premature infants with low birth weight for the gestational age, with a difference of more than 3 times the percentage (23%) for the spontaneous birth and for the cesarean birth (77%).

The smallest difference was obtained for the term low birth cases with low weight for the gestational age, with a difference of 16%, favoring birth through caesarean section. For the entire study group, birth by cesarean section predominated, and there was also a statistical significant difference between the 3 study groups, P=0.004.

As indicated in the working methods, obstetric and neonatal parameters were independently analyzed both from a descriptive point of view and based on the statistical differences that exist between the three study groups.

The incidence of obstetric aspects, namely fetal presentation, obstetric pathology in the spectrum of hypertensive pregnancy disorders, fetal malformations, multiple nuchal cord, or true umbilical cord knot is summarized in Fig. 2.

The incidence of pelvic presentation predominates in pregnancies with low gestational age, that is, in both normal and low-weight premature pregnancies, and hypertensive pregnancy pathology predominated in study groups characterized by low weight; however, there was no statistical difference for the low birth weight group in this study.

All the neonatal complications, including the incidence of the complications within each study group, and the existence or not of statistical significance for the study groups are shown in Table IV.

Analyzing each parameter separately, we obtained a statistically significant difference, predominantly in preterm infants with low weight for the gestational age, for the following complications: Cardiovascular arrest occurred in 6% of the subjects in group 1, with a significant difference of 1% in the incidence of complications between groups 2 and 3; for acute respiratory insufficiency, the difference in incidence was even greater, the premature infants with low weight for the gestational age (24% compared to 8 and 2% corresponding to the other groups); a difference in the incidence for ulcer-necrotic enterocolitis (group 1, 13%; group 2, 1%; and group 3, 0%), having statistical significance was otherwise obtained according to the collected data; hypoxia also predominated among preterm infants: 58% of infants with low weight for gestational age, 23% for premature infants with weight corresponding to gestational age, and 9% for term infants with low weight for gestational age.

Respiratory distress had an incidence of 29% in group 1, significantly higher than group 2 (13%) and group 3 (0%), and cerebral edema occurred only in premature cases, with an incidence of 6% for those with low weight for gestational age and 2% for those with appropriate weight.

Table III. Manner of birth in the three study groups.

	1		2		3		Total		
Group	No.	%	No.	%	No.	%	No.	%	P-value
Spontaneous birth	18	23	370	33	87	42	475	34	0.004
Cesarean birth	60	77	751	67	119	58	930	66	

Table IV. Frequency of neonatal complications in the three study groups and their comparative statistical analysis.

	1		2		3		Total		
Neonatal characteristic	No.	%	No.	%	No.	%	No.	%	P-value
Total	78	6	1,121	80	206	15	1,405	100	NA
Cardiovascular arrest	5	6	13	1	1	0	19	1	<0.001
Acute respiratory failure	19	24	87	8	5	2	111	8	<0.001
Ulcer-necrotic enterocolitis	10	13	10	1	0	0	20	1	<0.001
Hypoxia	45	58	260	23	18	9	323	23	<0.001
Respiratory distress	23	29	147	13	0	0	170	12	<0.001
Cerebral edema	5	6	27	2	0	0	32	2	0.004
Intraventricular hemorrhage	22	28	114	10	3	1	139	10	<0.001
Pulmonary hemorrhage	9	12	38	3	0	0	47	3	<0.001
Patent ductus arteriosus	0	0	12	1	1	0	13	1	0.491
Cerebral hemorrhage	7	9	49	4	1	0	57	4	0.003
Neonatal hypoglycemia	21	27	157	14	9	4	187	13	<0.001
Retinopathy	15	19	47	4	1	0	63	4	<0.001
Anemia	25	32	101	9	5	2	131	9	<0.001
Hemorrhagic disease	6	8	28	2	1	0	35	2	0.002
Disseminated vascular coagulation	2	3	1	0	0	0	3	0	<0.001
Neonatal sepsis	12	15	63	6	16	8	91	6	0.002
Need for neonatal intensive care	24	31	94	8	4	2	122	9	<0.001
Death	14	18	51	5	2	1	67	5	<0.001
Hyaline membrane disease	6	8	21	2	0	0	27	2	<0.001

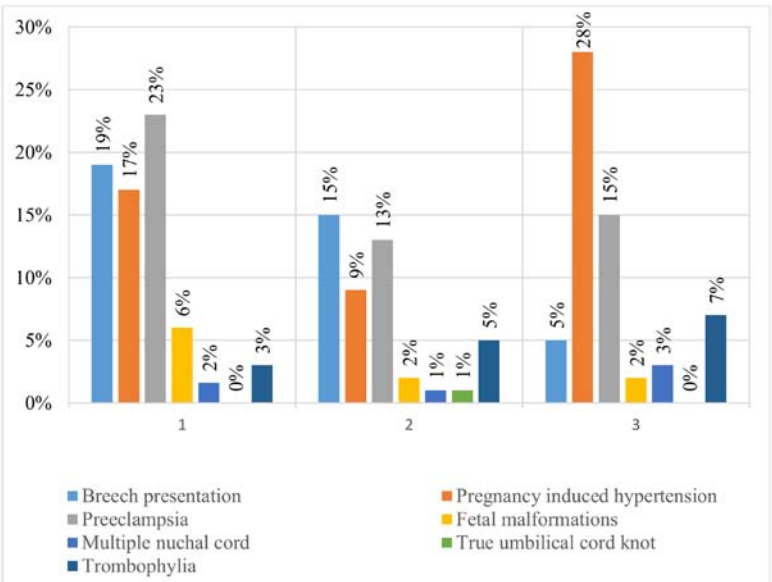

Figure 2. Comparative incidence of obstetric aspects studied in the three groups.

Neonatal complications, such as cerebral edema, pulmonary hemorrhage, neonatal seizures and disseminated intravascular coagulation, persistence of the arterial canal, cerebral hemorrhage, hyaline membrane disease, and retinopathy had a 0% incidence in the term neonatal group with low birth weight. Each of these complications predominated in the group of preterm newborns with intrauterine growth restriction, with the exception of the persistence of the arterial canal, which predominated in study group 2, with an incidence of 1%, and was absent in group 1. For cerebral edema, pulmonary edema and disseminated intravascular coagulation, the difference in incidence was statistically significant. For group 3, complications such as intraventricular hemorrhage and neonatal anemia presented minimum incidences of 1 and 2%, respectively. For these complications, the predominance was also the highest in group 1 (premature infants with low weight for the gestational age), namely 28 and 32%, respectively, which are significantly higher percentages than those obtained in the other study groups.

Regarding the incidence of neonatal infections, a significant incidence was noted in all 3 study groups, with a significant predominance among the group of premature infants with low-weight for the gestational age (38%); whereas, for the premature infants with the weight corresponding to the gestational age, the incidence was 19%, similar to that of term newborns with low weight for gestational age (16%). Regarding neonatal sepsis, a higher incidence was obtained of infants with low birth weight for gestational age (15%) and significant but smaller incidence was obtained for the other 2 study groups (6 and 8%, respectively).

Regarding the need for neonatal intensive care, it was 18% for group 1, 5% for group 2, and 1% for group 3, with a statistically significant difference between the three groups. Additionally, a statistically significant difference was obtained for the rate of neonatal death, which predominated by 8% in preterm infants with low weight for gestational age and was absent in term infants with low weight for gestational age.

Discussion

Prematurity remains the leading cause of neonatal morbidity and mortality. Intrauterine growth restriction is another first-line cause of the adverse neonatal prognosis, both as a single pathology or in association with prematurity. According to previous studies, there is a concordant relationship between preterm birth and intrauterine growth restriction (7). Intrauterine growth restriction shows chronic fetal distress based on placental dysfunction, with placental abnormal vascularization leading to hypoperfusion, ischemia, and release of reactive oxygen species in the context of oxidative stress.

Both prematurity and intrauterine growth restriction have an increased incidence among pregnancies complicated with preeclampsia (8), results that are consistent with the data in the literature. In this context, we decided to highlight the unfavorable short-term prognosis of prematurity, as well as intrauterine growth restriction, in both preterm and term infants with low birth weight.

According to the results obtained, the frequency of premature births in the Emergency University Hospital of Bucharest, a multidisciplinary hospital in which multiple complex cases are addressed, was ~13%. The cases of complicated preterm infants with intrauterine growth restriction accounted for 6.5% of all premature births recorded in the clinic during the 3 years of study and ~1% of all births. The cases of newborns with low birth weight for the gestational age accounted for ~2% of all births recorded during the study period. Thus, the data obtained are consistent with reports in the literature; the proportion of intrauterine growth restriction among preterm births is higher than that among term births (7).

Another parameter that was consistent with the published reports is the predominance of female fetal sex in cases of intrauterine growth restriction (9,10) and the predominance of male sex among premature births. However, the difference was not significant; therefore, according to the results, we can consider the following conclusions of the study by Quiñones *et al* (11), focusing mainly on the influence of fetal sex on the perinatal prognosis of cases of intrauterine growth restriction: Fetal sex is not associated with unfavorable perinatal prognosis in cases of intrauterine growth restriction.

The purpose of the analysis of the values of the Apgar index as a marker of the immediate neonatal adaptation was to objectively highlight the difference of adaptation, especially in the case of premature infants with low weight for gestational age and those infants with weight corresponding to their gestational age. The values obtained were not different from expectations, more specifically, the adaptation of preterm infants with low weight for the gestational age was the most deficient, with a median value of 7. Fig. 1 shows that there were no values that deviated significantly from the value of the median, with the distribution being proportional. However, the degree of adaptation was higher in the group of premature infants with weight corresponding to the gestational age, as expected. It appears that the values of the Apgar index were higher in this group. However, in the single cases of small Apgar index, the median assigned to group 2 was 8. The most favorable adaptation was noted in the newborns in group 3. Maximum values of the Apgar score were noted in groups 2 and 3.

Birth by caesarean section predominated in all study groups, with a statistically significant difference noted among the 3 groups. This is justified by the fact that birth by cesarean section of premature infants is associated with lower neonatal mortality (12), which is explained by the possibility of early and promising neonatal intensive care (13). Additionally, in this context, it is worth mentioning that the birth weight is inversely proportional to the rate of neonatal complications, in which the impact of the vaginal birth decreases with increasing fetal weight (14). Even though premature birth is not an absolute indication of cesarean delivery, this mode of birth provides a better prognosis for preterm infants by avoiding prolonged labor and allowing for a less traumatic birth (14).

Regarding obstetric factors, it is not surprising that we obtained a higher incidence of pelvic presentation among preterm infants; however, the incidence of pelvic presentation among low-weight newborns for gestational age was slightly higher than that in the general population. The data at the general population level show an incidence of caesarean

section of 4-40% among term births an 25-60% among premature births, which is inversely proportional to the gestational age. As seen in Fig. 2, the incidence of pregnancy-induced hypertension predominates in cases of growth restriction, both in premature newborns and particularly in newborns with term growth restriction. This situation is also characteristic of preeclampsia, except that it prevails in preterm infants with intrauterine growth restriction and low weight for gestational age. These results confirm previous results of other studies, namely that placental functional disorders belong to the group of progressive multifactorial pathologies that present deteriorating signs and symptoms over time.

Fetal malformations predominated in the group of premature newborns with growth restriction, which is consistent with published reports on the association of fetal malformations with intrauterine growth restriction (15,16) and prematurity (17). The umbilical cord pathology, mainly the true cord knot, did not have a significant association with intrauterine growth restriction, which is consistent with the data in the literature; however, this association has not been fully established and is still being studied (18-20). Regarding the multiple nuchal cord, a statistically significant association has not yet been evidenced between these condition and adverse neonatal prognosis (21). According to the results obtained in this study, the incidence of multiple nuchal cord was higher in the groups with growth restriction.

Essentially, the purpose of the present study is to show that intrauterine growth restriction, a condition closely related to placental dysfunction, is a common diagnosis that is associated with an increased risk of perinatal mortality and morbidity. The fetal response consists in circulatory adaptations, respectively brain-sparing reflected by the value of cerebroplacental ratio, which has a better predictability index of adverse outcomes especially in fetuses with intrauterine growth restriction (22). The meta-analysis published in 2016, aiming to evaluate the perinatal predictability value of cerebroplacental ratio concluded that abnormal cerebroplacental ratio is associated with increased rates of unfavorable perinatal outcome, having a moderate-high specificity and sensitivity (23). An abnormal cerebroplacental ratio was associated with higher rates of need of neonatal intensive care and neonatal complications and suggest a poorer perinatal outcome of fetuses with intrauterine growth restriction (23). Regarding the normalization of the cerebroplacental ratio, the results of a recent sub-analysis which started from the hypothesis that normalization of this ratio associates with a poorer perinatal outcome due to the loss of the compensatory mechanism of brain sparing, showed that there is no additional worsening of the perinatal prognosis given by this normalization (24). Recent studies have analyzed the impact of the abnormal cerebroplacental ratio on neurodevelopmental outcome in fetuses with intrauterine growth restriction. Meher *et al* in their review suggested that the brain sparing phenomenon has not only a protective benefit but is associated with a poorer psychomotor development at one and two years caused by implied cerebral hypoxia (25).

In the context of the results obtained, as well as of the discussions regarding the advantages of the expectant management for both short- and long-term outcomes, the decision regarding choosing the most appropriate time for termination of the pregnancy becomes even more difficult. Thus, each case should be treated individually with a therapeutic behavior guided by the main pathology but also the associated one in order to reduce the rate of iatrogenic prematurity among the fetuses with intrauterine growth restriction but also to offer them the best prognosis.

Further, with reference to Table IV, which contains the frequency and comparative analysis of all the neonatal complications studied for the 3 groups, one can observe the objective impact of intrauterine growth restriction during the immediate neonatal period.

Thus, as discussed in the results, the highest frequency of neonatal complications occurred in study group 1. Statistical significance was obtained for the following complications: Cardiovascular arrest ($P<0.001$), acute respiratory failure ($P<0.001$), ulcer-necrotic enterocolitis ($P<0.001$), hypoxia present in 58% of premature cases with growth restriction and in 23% of cases of gestational age weight ($P<0.001$), respiratory distress ($P<0.001$), cerebral edema ($P=0.004$), intraventricular hemorrhage ($P<0.001$), cerebral hemorrhage ($P=0.003$), pulmonary hemorrhage ($P<0.001$), neonatal infection ($P<0.001$), hypoglycemia ($P<0.001$), retinopathy ($P<0.001$), anemia ($P<0.001$), hemorrhagic disease ($P=0.002$), disseminated intravascular coagulation ($P<0.001$), disease of hyaline membranes ($P<0.001$), neonatal sepsis ($P=0.002$), need for intensive neonatal therapy ($P<0.001$), and death ($P<0.001$).

Intrauterine growth restriction is associated with an increased risk of both antenatal and neonatal complications. There is an increased negative impact on prognosis when fetuses with intrauterine growth restriction are born premature. In this study, newborns with low weight for gestational age had an increased incidence in complications in comparison to newborns with adequate weight, specifically: cardiovascular arrest, 0.1% in the general population and 1% in the present study; acute respiratory failure, 0.45% in the general population and 2% in the present study (14); however, respiratory distress, cerebral edema, ulcer-necrotic enterocolitis, pulmonary hemorrhage, persistence of the arterial canal, cerebral hemorrhage, seizures, retinopathy, hemorrhagic disease, disseminated intravascular disease, and hyaline membrane disease were absent in term infants with low birth weight for gestational age, indicating that these newborns have a good neonatal adaptation by leaving an environment already unfit for their well-being, i.e. intrauterine.

In conclusion, intrauterine growth restriction can occur both in the context of pre-existing chronic hypertension and in the context of severe preeclampsia. In principle, preeclampsia is so frequently associated with intrauterine growth restriction that the latter has traditionally been included as a feature of preeclampsia, regardless of any additional diagnostic criteria. During the study, it was shown that preeclampsia is the main condition that leads to the most severe cases of intrauterine growth restriction. Immediate neonatal adaptation of preterm neonate small for gestational age is more deficient (indicated by lower Apgar index values) than for preterm neonates with appropriate weight for gestational age; the adaptation of preterm neonates, in turn, is more deficient than term newborns with intrauterine growth restriction. The term newborns with intrauterine growth restriction have a neonatal adaptation comparable to that of the term newborns with weight corresponding to the gestational age. Birth by caesarean section

had an increased incidence both in the cases of premature newborns with weight corresponding to the gestational age and in the cases with premature or term growth restriction. Gestational hypertension is a major risk factor for intrauterine growth restriction without a statistically significant difference between premature and term births. Preeclampsia, on the other hand, is significantly associated with prematurity and intrauterine growth restriction and especially in cases presenting both conditions simultaneously. Fetal malformations are a determinant factor of growth restriction, but also of prematurity.

After analyzing the neonatal parameters of the 3 study groups, which included premature infants with low weight for gestational age, preterm infants with weight corresponding to the gestational age and term newborns with low weight for gestational age, we can conclude that the growth restriction superimposed on prematurity is associated the most unfavorable prognosis among all the parameters.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FIR, DNa, CB and DNe collected, analyzed and interpreted the patient data regarding the main neonatal complications associated with prematurity and intrauterine growth restriction. FF substantially contributed to the conception of the study and the statistical analysis of the data. MMC contributed to the interpretation of the results. NT and REB were involved in the conception of the study, collected and interpreted the patient data, and were major contributors in the writing of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The data collected retrospectively did not contain personal information and only the Ethics Committee agreement of the University Emergency Hospital of Bucharest was required and obtained without the need of informed consent or the consent of the patient/legal representative in the case of minors.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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