Ante and Postnatal Ultrasound Contribution and Near-infrared Spectroscopy (NIRS) Monitoring in Preterm Newborns with Intrauterine Growth Restriction Under 32 Weeks of Gestation

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IUGR remains an important health problem in developing countries around the world, being one of the major obstetrical syndromes associated with placental defects, but also one of the topical issues of neonatology, and in particular the association between IUGR and prematurity under 32 weeks of gestation. Neonatal morbidity and mortality remain significant and has an important economic impact. The need for more stringent diagnostic criteria remains a problem. The study proposes to follow the time of extraction of a premature pregnancy IUGR with gestation age ≤32 weeks, taking into account the centralization of bloodflow as well as IH (hypoxic index) during observation, following the immediate consequences on this new category - as well as their prognosis depending on the associated pathology using cerebral serial Doppler ultrasounds and near-infrared spectroscopy (NIRS).

Keywords: prematurity, intrauterine growth restriction, neonatal Doppler ultrasounds , near-infrared spectroscopy

Fetal growth restriction (FGR) is a common and complex clinical problem which confers a considerable risk of morbidity. In addition to infectious causes and congenital malformations, FGR has been identified as a major contributor to perinatal mortality. Intrauterine growth restriction (IUGR) is a pathologically small fetus (ie EFW < 10th centile, oligohydramnios, abnormal UA Doppler AND/ OR poor interval growth velocity AND/ OR EFW < 3rd centile)[1,2].

Intrauterine growth failure affects up to 10% of pregnancies and is often referred to as small-for gestational age (SGA), intrauterine growth restriction (IUGR) or fetal growth restriction (FGR) in an inconsistent and confusing manner. Traditionally, an estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th centile raises concerns over suboptimal intrauterine growth, however the distinction between normal and pathologic growth often cannot reliably be made at this arbitrary cut-off. This was also described as a deviation or reduction from the expected growth pattern and is usually the result of a reduced hereditary growth potential or multiple adverse effects on the fetus. The normal newborn is the one whose birth weight is between the 10th and 90th percentiles for gestational age, sex, and race without any malnutrition and growth restriction characteristics. The terms IUGR and SGA have been used as synonyms in medical literature, although there are differences between the two. The definition of SGA is based on cross-sectional evaluation (either prenatal or postnatal) and this term has been used for those newborns whose birth weight is less than the 10th percentile for gestational age or two standard deviations below the population norms represented on the growth charts, and the definition only considers birth weight without any specification of intrauterine growth or other physical characteristics at birth [2-6]. Extensive antenatal Doppler ultrasound allows assessment of well-fetal status and detection of IUGR and Doppler on uterine arteries, umbilical arteries, and on middle cerebral arteries. Although almost all veins and large arteries have been studied through Doppler in the case of IUGR neonates, however, in practical management is used Doppler velocytometry on the umbilical arteries and middle cerebral artery. Umbilical arteries were the first Doppler evaluated. Doppler waves at their level have a characteristic appearance of *saw teeth*. In the case of fetuses suspected of having IUGR, if the Doppler waves in the umbilical arteries look normal and the intrauterine growth curve ascends over a period of two weeks, the fetus may be considered to be healthy, small constitutional. The abnormal appearance of Doppler wavelengths of the umbilical arteries is an early sign of fetal suffering. The average time interval between the absence of enddiastolic flow in the umbilical arteries and the onset of delayed deceleration was estimated at about 12 days (0-49 days). Also, studies have demonstrated a progressive increase in velocimetric flow velocity in the umbilical arteries to extreme cases of inverted enddiastolic flow. Increasing diastole at the MCA level is a fetal compensatory mechanism that is reactive to uteroplacentral failure (*brainstorming* mechanism). If compensatory mechanisms are overcome, fetal damage occurs rapidly. Therefore, the serial Doppler ultrasounds will estimate the duration of use of fetal compensatory mechanisms, the abnormal venous Doppler appearance indicating fetal deterioration and the need for emergency cesarean section [7-10]. After birth the association of cerebral ultrasound in sagittal and coronal section with Doppler being performed on the anterior cerebral artery and pericallosal artery following the value of RI after birth to monitored *the brain sparing* effect (BS) with near-infrared spectroscopy (NIRS) to assess oxygenation status of the brain and of splanchnic

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organs allows an assessment of subsequent complications of this particular category – premature with IUGR[11-12].

Experimental part

Study population and methods

The study proposes to follow the time of extraction of a premature pregnancy IUGR with gestation age ≤ 32 weeks, taking into account the centralization of bloodflow as well as IH (hypoxic index) during observation, following the immediate consequences on this new category - as well as their prognosis depending on the associated pathology. Dates were collected from the National Registry of Respiratory Distress in Romania, the included period was between 2015-2017 (01.06.2017), the study was retrospective, the category included preterm with IUGR with GA under 32 weeks and preterm with GA under 32 weeks born or transferred in the NICU of Municipal Clinical Hospital - Odobescu Maternity Hospital - Timisoara. The variables were immediate clinical comparisons of preterm with IUGR with centralization of bloodflow and without it, respectively: perinatal asphyxia, persistent pulmonary hypertension, necrotizing enterocolitis, sepsis, pulmonary haemorrhage. Were recorded using duplex pulsed color Doppler ultrasound (Philips, Affiniti 50G) with a convex C 8-5 MHz transducer. Splanchnic and cerebral regional oxygen saturations were monitored via NIRS [Somanetics 5100 INVOS System, Troy,MI]. NIRS sensors were placed over the abdomen [splanchnic bed] and on the fore head (cerebral bed) to measure cerebral regional saturations (rScO2) and infra-umbilical abdomen splanchnic regional saturations (rSsO2). The optical sensor measures the quantity of reflected ligh tphotons as a function of 2 wave lengths (730 and 805 nm) and determines the spectral absorption of the underlying tissue 14,22.

Results and discussions

During this period, a total of 6301 births were 190 preterm with GA <32 weeks (3.01%), of which SGA (1.02%) and 114 AGA (1.8%, table 1). Significantly more SGA pregnancies were complicated by hypertension and eclampsia.

Pregnancy complications such as infection and PPROM did not differ significantly in SGA, when compared with AGA premies.

Interestingly, multiple pregnancies ended in AGA premies (21.05% vs 7.89%, p= 0.01). Multiple pregnancy carries a higher risk of prematurity, intrauterine growth restriction, and prenatal death, as well as elevated risks to the mother including preeclampsia, diabetes, and hemorrhage during delivery. Multiple pregnancies have become more common in the industrialized world due to advances in reproductive medicine. As a result, obstetric care for women with multiple pregnancies and neonatal care for multiple babies have become more intense and challenging[14]. Premies born from mothers with diabetes were more often AGA (7.01% vs 0%).In literatures early IUGR is associated with hypertensive disorders of the pregnancy and preeclampsia in up to 73 and 52% of the cases respectively [12-13]. It is hypothesized that the syndrome of pre-eclampsia stems from a failure of placental implantation and development [14-16] which leads to a failure in physiologic increase of uterine perfusion during pregnancy.

Apgar scores at one and five minutes of life, respectively, were similar (table 2).

After birth, IH was calculated, as suggested by Arbeille, by adding the daily reductions of the C / O ratio (in percent below the limit value of 1) during the observation period.

IH was calculated based on the last 7 C / O ratios measured over the last 7 days before birth. On days out of the study, the C / O value was determined as the mean value of the two closest values measured over a 48h interval.

Ultrasound discoveries: in newborn with centralization (HI- Arbeille over 165) the complications was IVH grade 2/3- 76% and periventricular hyperechogenities 23,7%. In newborn without centralization (HI-Arbeille under 100) the complications was IVH Grade and white matter damage (table 3).

The C/U ratio must be calculated continuously during the prenatal monitoring of pregnancies complicated by IUGR and hypoxia, and its variation over time should be assessed. Whether blood flow redistribution (C/U ratio < 1) can be considered as a beneficial physiological adaptation depends on both the degree of reduction in pO_2 and the duration of exposure to hypoxia. There may be harmful effects on the brain tissue if blood flow redistribution is too prolonged or too severe. The introduction of the new vascular score, HI, which takes into account both the duration and the intensity of fetal flow redistribution, could improve considerably the prevention of hypoxic brain lesions, which are one of the most common causes of perinatal morbidity and mortality [15]. NIRS monitoring on this category of newborns was started immediately after birth. From the 38 newborns who were born after observation of phenomenon of centralized circulation, NIRS monitoring revealed an cerebral oxygenation index >50

	Premies≤ 32 weeks		p
	SGA (n= 76)	AGA (n= 114)	
Infection	26 (34.21%)	42 (36.84%)	0.26
PPROM	36 (47.36%)	50(43.85%)	0.6
Hypertension	18 (23.68%)	0	<0.05
Eclampsia	12 (15.78%)	4 (3.5%)	<0.05
Mutiple pregnancy	6 (7.89%)	24 (21.05%)	0.01
Diabetes	0	8 (7.01%)	0.01

Table 1
MATERNAL IUGR ETIOLOGY

		Premies≤ 32 weeks		p
		SGA (n= 76)	AGA (n= 114)	
Apgar scores in the first minute of life	1-4	5 (6.57%)	17 (14.91%)	0.26
	5-7	37 (48.68%)	56 (49.12%)	
	8-10	34 (44.75%)	41 (35.96%)	
Apgar scores in the first five minutes of life	1-4	1 (3.1%)	4 (6%)	0.82
	5-7	8 (25%)	16 (23%)	
	8-10	23 (71.9%)	47 (70.1%)	

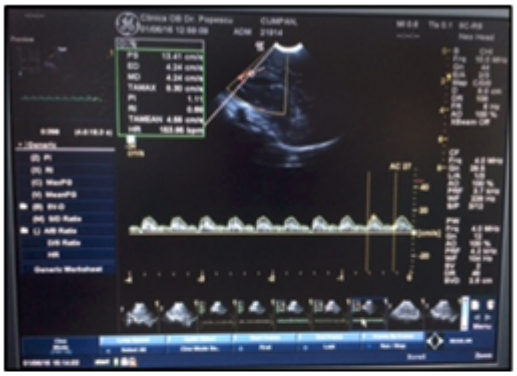
Table 2
APGAR SCORES

PREMATURE and SGA	TOTAL 76	ICP- 5 days	COMPLICATIONS
WITH CENTRALIZATION	38	0,56-0,70/ HI-ARBEILLE- OVER 165	-IVH GR.2-3 – 29/ 76,3% - PERIVENTRICULAR HYPERECHOGENITIES 23,7%
WITHOUT CENTRALIZATION	38	HI-ARBEILLE UNDER 100	- IVH GRD.1/ - WHITE MATTER DAMAGE

Table 3
ULTRASOUND DISCOVERIES

Premature and SGA	TOTAL 76	COMPLICATIONS
WITH CENTRALIZATION	IO CEREBRAL OVER 50- 27 CASES	IVH GRD. 1/ IVH GRD. 2
38	IO CEREBRAL UNDER 50- 11 CASES	IVH GRD. 2-3
	IO MESENTERIC UNDER 50 - 38	PHARALYTIC ILEUS (NEC GR.I/II - BELL)
WITHOUT CENTRALIZATION 38	IO CEREBRAL OVER 50- 33	NO COMPLICATIONS
	IO CEREBRAL UNDER 50- 5	IVH GRD. 2/ IVH GRD. 2
	IO MESENTERIC UNDER 50 -11	PHARALYTIC ILEUS (NEC GR.I/II - BELL

Table 4
NIRS



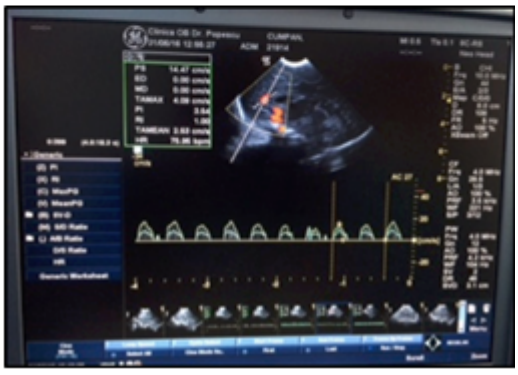
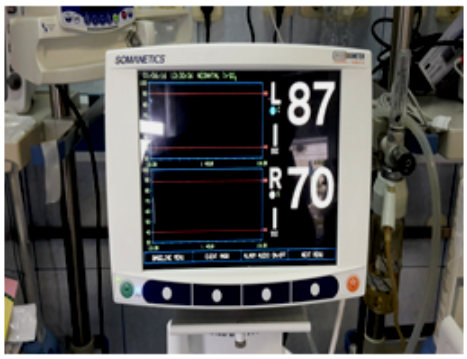


Fig. 1.RI to anterior cerebral artery/pericalosal artery using cerebral ultrasound in the first 7 days of life



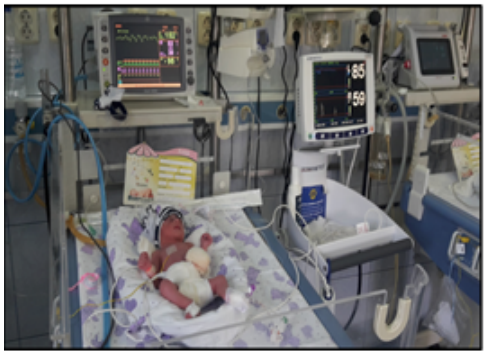


Fig. 2. Oxygenation index detected by INVOS

		Premies≤ 32 weeks		p
		SGA (n= 76)	AGA (n= 114)	
Gestational age (weeks)		30.4±1.6	29.5±2.2	<0.0001
Gender	Girls	48 (63.15%)	59 (51.75%)	0.05
	Boys	28 (36.84%	55 (48.24%)	
Birth weight (g)		1152.27±353.15	1458.25±412.35	0.03
Birth delivery mode	Vaginal	11 (14.47%)	37 (32.45%)	0.01
	C-section	65 (85.52%)	77 (67.54%)	
Mother's age	<18	6 (7.89%)	10 (8.77%)	0.51
	18-30	28 (36.84%)	60 (52.63%)	
	30-40	33 (43.42%)	37 (32.45%)	
	>40	9 (11.84%)	7 (6.14%)	
Apnoea		48 (63.15%)	84 (73.68%)	0.32
Mechanical ventilation		20 (26.31%)	40 (35.08%)	0.28
Pneumonia		4 (5.26)	0	0.01
EUN		47 (61.84%)	7 (6.14%)	<0.0001
Pulmonary chronic disease	O2 > 28 days	18 (23.68%)		
	O2n > 36 weeks	12 (15.78)		
Death		2 (2.63%)	5 (4.38%)	0.82

Table 5

at 27 newborns(although there were alterations on the Doppler performed on the anterior cerebral artery and pericallosal artery); short term complication observed was IVH gr. I.

Value of cerebral oxygenation index <50 determined IVH gr. II and III and white matter damage.Mesentery-association between centralized circulation and mesenteric oxygenation index below 50 caused paralytic ileus and NEC stage 1-2 (BELL).

The cases (38) without phenomenon of centralized circulation even if presented cerebral oxygenation index <50 did not developed severe IVH or white matter damage. In exchange, those with mesenteric oxygenation index <50 developed paralytic ileus / NEC stage 1-2 (BELL).

At 6301 births were 190 preterm with GA <32 weeks (3.01%), of which SGA (1.02%) and 114 AGA (1.8%). Significantly more SGA than AGA premies were born via C-section (85.52% vs 67.54%, p=0.01).

We did not find any significant differences between SGA and AGA premies across mother's age categories.

There was an increase NEC rate, pulmonary chronic lung disease and sepsis (Pneumonia) in preterm with growth restriction compared to preterm infants with the same age of gestation.

The restriction of growth in premature neonates was not found to protect against other neonatal outcomes associated with prematurity (table 5).

Conclusions

The clinical and paraclinical management of premature with IUGR remains a challenge compared to premature without IUGR. There was an increase in mortality and NEC rate, pulmonary haemorrhage and sepsis in preterm with growth restriction compared to preterm infants with the same age of gestation. The restriction of growth in premature neonates was not found to protect against other neonatal outcomes associated with prematurity. Cerebral hemodynamics changes can persist after birth which involves a different attitude on the monitoring and clinical management of brain PM with IUGR compared to premature without IUGR. Correlation of antenatal and postanatal ultrasound indices as well as NIRS monitoring represents an important step in following the clinically and paraclinically evolution of this population of newborns-the IUGR newborns remains the most vulnerable population of newborns. The cerebral and mesenteric oxygenation index obtained by NIRS monitoring was proposed to be used in the routine clinical management of IUGR newborns. Due to the fact that IUGR newborns have different cerebral and mesenteric hemodynamics comparing to AGA, they represent a special category between the prematures admitted in NICU. They need a different approach regarding the interpretation of cerebral and mesenteric oxygenation and correlation with the appropriate charts.

-IUGR associated with prematurity under the 32nd week of gestation remains a great challenge for the neonatologist and obstetrician.

-Other causes of small gestational age (SGA) fetuses, such as chromosomal abnormalities and intrauterine infections, should be considered before the diagnosis of RCIU is pronounced.

-SGA is a different pathological entity with potential for great outcome and prognostic.

-Fetal Doppler ultrasound ant postnatal Doppler ultrasoud and NIRS is the most accurate and non-invasive method of evaluating placental performance.

-Combined Doppler analysis performed at the umbilical artery and the middle cerebral artery can show the degree of placental damage, the redistribution pattern and the degree of cardiac damage respectively.

-Management of a fetus with growth restriction and prematurity should reach a balance between the risks of pre-term intrauterine chronic hypoxia with preterm delivery and its associated risks.

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