Morbidity in Prematurity Associated with Fetal Growth Restriction: Experience of a Tertiary Care Center

Morbilidade na Prematuridade Associada a Restrição do Crescimento Fetal e nos Prematuros Leves para a Idade Gestacional: Experiência de um Centro de Referência

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ABSTRACT

Introduction: Prematurity and low birth weight have been associated with increased neonatal morbidity and mortality. This study aimed to evaluate possible risk factors for prematurity associated with fetal growth restriction and being small for gestational age and to determine the incidence of morbidity in these two groups of infants.

Material and Methods: Retrospective case-control study of newborns with gestational age of less than 32 weeks, with obstetric diagnosis of fetal growth restriction and with the clinical diagnosis of small for gestational age, admitted to the Neonatal Intensive Care Unit of a tertiary hospital for a period of six years.

Results: A total of 356 newborns were studied, with an incidence of 11% of fetal growth restriction and 18% of small for gestational age. Pre-eclampsia was the risk factor for gestation with higher statistical significance (47% *vs* 16%, *p* < 0.001) in small for gestational age newborns. There was also a higher incidence of mild bronchopulmonary dysplasia (66% *vs* 38%, *p* = 0.005), late sepsis (59% *vs* 37%, *p* = 0.003), retinopathy of prematurity (58% *vs* 26%, *p* = 0.003) and necrotizing enterocolitis (20% *vs* 9%, *p* = 0.005). Mortality was similar in all three groups.

Discussion: There were fewer newborn males diagnosed with fetal growth restriction during pregnancy compared to women. Significant differences were observed in the group of these infants regarding the occurrence of chorioamnionitis and pre-eclampsia in comparison to the control group. Newborns with fetal growth restriction and small for age had higher scores on clinical risk indices compared to the control group. In general, small for gestational age newborns had a higher incidence of morbidity than infants with fetal growth restriction and the control group.

Conclusion: Advances in neonatal intensive care decreased mortality in preterm infants. However, there are still significant differences in the incidence of morbidity in newborns with growth compromise. The collaboration between obstetricians and neonatologists provides the basis for a correct clinical evaluation, early signaling and global intervention on these newborns, with a significant impact on short and long-term prognosis.

Keywords: Fetal Development; Fetal Growth Retardation; Infant, Premature; Infant, Small for Gestational Age; Morbidity

RESUMO

Introdução: A prematuridade e o baixo peso ao nascer têm sido associados a maior morbilidade e mortalidade neonatais. Este estudo teve como objetivo avaliar possíveis fatores de risco para a prematuridade associada a restrição do crescimento fetal e a recém--nascidos leves para a idade gestacional e determinar a incidência da morbilidade nestes dois grupos de recém-nascidos.

Material e Métodos: Estudo caso-controlo retrospetivo dos recém-nascidos com idade gestacional inferior a 32 semanas, com o diagnóstico obstétrico de restrição do crescimento fetal e com o diagnóstico clínico de leves para a idade gestacional, internados na Unidade de Cuidados Intensivos Neonatais de um hospital terciário, durante um período de seis anos.

Resultados: Foram estudados 356 recém-nascidos, observando-se uma incidência de 11% de restrição do crescimento fetal e 18% de leves para a idade gestacional. A pré-eclâmpsia foi o fator de risco da gestação com maior significado estatístico (47% *vs* 16%, *p* < 0,001) nos recém-nascidos leves para a idade gestacional. Observou-se também, nestes recém-nascidos, maior incidência de displasia broncopulmonar ligeira (66% *vs* 38%, *p* = 0,005), de sépsis tardia (59% *vs* 37%, *p* = 0,003), de retinopatia da prematuridade (58% *vs* 26%, *p* = 0,003) e de enterocolite necrotizante (20% *vs* 9%, *p* = 0,005). A mortalidade foi idêntica nos três grupos.

Discussão: Encontraram-se menos recém-nascidos do sexo masculino diagnosticados com restrição do crescimento fetal durante a gravidez comparativamente ao sexo feminino. Observaram-se diferenças significativas no grupo destes recém-nascidos, quanto à ocorrência de corioamnionite e de pré-eclâmpsia, face ao grupo controlo. Tanto os recém-nascidos com restrição do crescimento fetal como os leves para a idade gestacional apresentaram uma pontuação mais elevada nos índices de risco clínico comparativamente ao grupo controlo. De forma global, os recém-nascidos leves para a idade gestacional tiveram maior incidência de morbilidade que os recém-nascidos com restrição do crescimento fetal e que o grupo controlo.

Conclusão: Os avanços nos cuidados intensivos neonatais diminuíram a mortalidade nos recém-nascidos prematuros. Contudo, observam-se ainda diferenças significativas na incidência da morbilidade nos recém-nascidos com compromisso do crescimento. A colaboração entre obstetras e neonatalogistas constitui a base para uma correta avaliação clínica, sinalização precoce e intervenção global sobre estes recém-nascidos, com impacto significativo no prognóstico a curto e longo prazo.

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ARTIGO ORIGINAL

INTRODUCTION

An increased prevalence of caesarean section births and induction of labour with a medical indication have been found, with an impact on prematurity rates.[1]

Prematurity is a consequence of foetal growth restriction (FGR) and an increase in the incidence of small for gestational age (SGA) newborns (NB) has been found with a lower gestational age (GA).[2] Preterm birth and growth restriction represent an increased risk for NB as both are associated with neonatal complications.[3]

FGR (or intrauterine growth restriction) refers to a condition in which NB failed to reach genetic growth potential,[4,5] even though there is no international consensus on its definition.[6] Diagnosis is established by foetal growth rate obtained through serial obstetric examinations[7] and 5-7% of pregnancies are estimated to be affected.[8] Placental insufficiency is the major cause of this pathology.[8] In addition, the diagnosis of SGA NB is a clinical diagnosis and is defined as growth below the 10th percentile for GA. However, after birth, a birth weight below the 10th percentile for GA is widely used as a measure of growth restriction.[9] Therefore, the strengths and weaknesses of both measures, as well as the selection of patterns and percentiles are under continuous debate.[9] It is known that not every SGA NB present with FGR and can only be constitutionally small.[10] In addition, not all the foetuses having failed to reach genetic growth potential are below the 10th percentile for the expected weight.[2,4] The causes may be maternal, placental or foetal and FGR severity and SGA NB outcome depend on the aetiology.[11] Secular trends in birth weight mediated by inter-generational factors have also been described by some authors.[12]

Advanced maternal age, maternal pre-pregnancy overweight or low weight, maternal toxic habits, occupational, social and economic level and medically-assisted reproduction have been described as maternal risk factors associated with FGR.[6,13-15] Other conditions, including pre-eclampsia, pregnancy-induced hypertension, autoimmune diseases, diabetes mellitus and essential hypertension have been considered.[13,16] The prevalence of SGA NB is a good indicator of maternal health and nutritional status, according to some authors.[17]

As regards placental factors, placental size and function abnormalities have been described, producing dysfunctional maternal-foetal nutrient exchange, endocrine and growth factors, as well as cytokines.[18] As regards foetal factors, birth defects, TORCH group (toxoplasmosis, rubella, syphilis, cytomegalovirus and herpes) congenital infections and genetic disorders have been identified.[11]

Together with prematurity, FGR and/or SGA NB have been associated with higher morbidity and mortality throughout the first year of life[8,19] and with an increased risk of different pathologies in adulthood.[1,20] A higher incidence of neonatal asphyxia, hypothermia, metabolic acidosis, polycythaemia, hypoglycaemia and hypocalcaemia has been found.[11] Psychomotor developmental disorders in the first year of live[8,15] and impaired somatometric recovery have also been described.[21] Higher predisposition to metabolic syndrome, stroke and recurrence of low birth weight in the offspring have also been found in adulthood.[1,22-24]

Even though preterm births represent only 5-10% of births, these correspond to over two-thirds of neonatal deaths (35% - 60% with gestational age less than 32 weeks) and are an important challenge to healthcare systems due to the need for highly specialised medical-surgical care.[19]

This study aimed at the assessment of the incidence of preterm births with antenatal diagnosis of FGR as well SGA preterm births in our unit, the assessment of pregnancy and delivery-related risk factors and the characterisation of neonatal morbidity associated with these situations, namely regarding the incidence of patent arterial duct, necrotising enterocolitis, late-onset sepsis, retinopathy of prematurity, neurological complications and bronchopulmonary dysplasia.

MATERIAL AND METHODS
Study type

This was a retrospective case-control study with data from the *Registo Nacional de RN de Muito Baixo Peso* national database (National Registry of Very Low Birth Weight Newborns).

Participants

NB admitted to the Neonatal Intensive Care Unit (NICU) of the *Hospital de Santa Maria* with a diagnosis of preterm, FGR and SGA NB, throughout a six-year period between 1 Jan 2010 and 31 Dec 2015 were included in the study.

Study inclusion criteria included GA of less than 31 weeks and six days, with an obstetric diagnosis of FGR (birth weight below the 10th percentile and abnormal umbilical artery Doppler)[25] and/or clinical diagnosis of SGA (birth weight below the 10th percentile for GA according to 2013 gender-specific Fenton charts).[26]

Data collection

Data regarding our unit and from the *Registo Nacional de RN de Muito Baixo Peso* database were analysed.

The presence of the following pregnancy-related risk factors was assessed: pre-eclampsia, diabetes mellitus, chorioamnionitis and early-onset intraventricular haemorrhage. The following gestation characteristics were also considered - spontaneous pregnancy or in-vitro fertilisation (IVF), singleton or twin pregnancy and vaginal or caesarean-section delivery.

As regards NB, the following parameters were assessed: GA, gender, birth weight (BW), induction of foetal lung maturity, Apgar score, CRIB (clinical risk index for babies), SNAPPE (score for neonatal acute physiology – perinatal extension), need for endotracheal intubation (ETI),

need for invasive (IV) or non-invasive ventilation (NIV), patent arterial duct (PAD) with an indication for medical or surgical treatment, late-onset sepsis, necrotizing enterocolitis, need for supplemental oxygen at 28 days and at 26 weeks of life,[27] retinopathy of prematurity (ROP), length of stay in hospital and abnormal transfontanellar ultrasound [periventricular leukomalacia, peri/intraventricular haemorrhage (P/IVH) and periventricular haemorrhagic infarction (PVHI)]. The following medical complications were also assessed: hydrocephalus with the need for ventriculoperitoneal (VP) shunt and for supplemental oxygen at discharge. NB presenting with birth defects were excluded from the study.

Data analysis

Both groups of patients (NB antenatally diagnosed with FGR and SGA NB) were compared to a control group including NB with the same GA, although with a somatometry adequate to the gestational age and not diagnosed with FGR, admitted to the same NICU over the study period.

Microsoft Excel® 2013 and SPSS® 20 software were used for data analysis. Mann-Whitney's test was used for mean comparison; chi-square test and Fisher's exact test were used for the comparison of dichotomous variables; median value was used as measure of central tendency of GA and BW variables and interquartile range as measure of dispersion. A 5% significance level was considered.

RESULTS

A total of 356 NB at less than 32 weeks' GA (median GA of 29 weeks) admitted to the NICU over the 2010-2015 period. From these, 40 NB diagnosed with FGR were included, corresponding to an 11% incidence and 63 as SGA (51 with BW below P10 and 12 with BW below P3), corresponding to an 18% incidence. A median BW of 900 g was found in NB with FGR, 1,150 g in SGA NB and 1,155 g in the control group. Only 22 SGA NB were diagnosed with FGR.

Mortality distribution per gestational age and birth weight in the group of FGR/SGA NB and in the control group is shown in Table 1.

A slight female predominance regarding the diagnoses of FGR (52%) and SGA (57%) compared to the control group (44%) was found.

Pathology was presented by 44% of the mothers of NB with FGR and by 67% of the mothers of SGA NB, in contrast with 51% in the control group. Pre-eclampsia was found in 47% of the mothers of SGA NB *vs.* 16% in the control group, corresponding to a significant difference ($p < 0.001$). Twin pregnancy was found in around 30% of the FGR/SGA NB. Spontaneous pregnancy was mostly found in SGA NB group (75%) *vs.* only 50% in the group of NB with FGR. C-section delivery was mostly found in both groups (>80%). These numbers were not significantly different when compared to the control group and GA, maternal pathology and delivery type comparisons are shown in Tables 1, 2 and 3.

Table 1 – Mortality per gestational age and birth weight in the group of FGR/SGA NB and in the control group

GA (weeks)	FGR/SGA (n)	BW (g) Min - Max	Deaths (n)	Control (n)	BW (g) Mín - Máx	Deaths (n)
23	0	NA	NA	2	545 - 550	2
24	4	470 - 500	3	9	510 - 799	8
25	4	430 - 560	3	16	600 - 930	6
26	14	530 - 649	1	22	639 - 1100	4
27	12	300 - 680	2	28	720 - 1230	2
28	25	549 - 810	2	43	750 - 1409	5
29	7	568 - 924	0	48	950 - 1640	4
30	21	640 - 1043	0	47	930 - 1790	2
31	16	909 - 1200	0	60	1110 - 2240	2
Total	103		11 (11%)	275		35 (13%)

GA: gestational age; FGR: foetal growth restriction; SGA: small for gestational age; BW: birth weight; Min: minimum; Max: maximum; NA: not applicable

Table 2 – Pregnancy and delivery-related risk factors – comparison between SGA NB and the control group

Variable	SGA (n)	%	Control (n)	%	p
Gestational age (weeks), mean (min - max)	27.9		28.6		< 0.01
Spontaneous	47	75	213	77	NS
IVF	16	25	62	23	NS
Caesarean section	37	93	204	65	< 0.001
Twin pregnancy	20	31	109	39	NS
Pre-eclampsia	30	47	45	16	< 0.001
Diabetes mellitus	3	5	26	9	NS
Early-onset intraventricular haemorrhage	8	12	29	10	NS
Chorioamnionitis	2	3	46	16	NS

SGA: small for gestational age; IVF: in vitro fertilization; NS: non-significant

Table 3 – Pregnancy and delivery-related risk factors – comparison between NB with FGR and the control group

Variable	FGR (n)	%	Control (n)	%	p
Gestational age (weeks), mean (min - max)	28.9		28.4		NS
Spontaneous	20	50	213	77	NS
IVF	20	50	62	23	NS
Caesarean section	53	84	188	64	< 0.005
Twin pregnancy	13	32	109	39	NS
Pre-eclampsia	13	32	45	16	NS
Diabetes mellitus	2	5	26	9	NS
Early-onset intraventricular haemorrhage	2	5	29	10	NS
Chorioamnionitis	1	2	46	16	< 0.005

FGR: foetal growth restriction. IVF: in vitro fertilization; NS: non-significant

The need for IV was required by 60% of SGA NB and by 50% of NB with FGR, compared to 47% in the control group while NIV was required by 84% of SGA NB and by 87% of NB with FGR, compared to 53% in controls. The need for supplemental oxygen at 28 days was required by 66% of SGA NB and by 55% of NB with FGR *vs.* 38% in the control group (significant difference *vs.* SGA NB, *p* = 0.005). Other variables with significant differences in SGA NB group *vs.* control group included: late-onset sepsis (59% *vs.* 37%, *p* = 0.003), ROP (58% *vs.* 26%, *p* = 0.003) and necrotizing enterocolitis (20% *vs.* 9%, *p* = 0.005). Late-onset sepsis was the only pathology with a statistical significance (*p* = 0.04) in NB with FGR.

The need for supplemental oxygen at discharge was the major complication found in SGA NB (27%). Data regarding morbidity are shown in Tables 4 and 5.

DISCUSSION

The presence of possible pregnancy or delivery-related risk factors for prematurity associated with FGR and/or SGA NB was assessed in this study, in addition to the assessment of morbidity and mortality. Birth weight estimate

Table 4 – Neonatal Morbidity – comparison between SGA NB and the control group

Variable	SGA (n)	%	Control (n)	%	p
Induction of foetal lung maturity	44	70	191	69	NS[a]
Length of stay in hospital (mean, in days)	86	NA	53	NA	< 0.001[b]
1 min Apgar score (mean score)	7	NA	7	NA	NA
5 min Apgar score (mean score)	9	NA	9	NA	NA
Resuscitation with intubation	44	70	174	63	NS[a]
CRIB (mean score)	5.3	NA	2.5	NA	< 0.001[b]
SNAPPE (mean score)	31.7	NA	17.2	NA	< 0.01[b]
Invasive ventilation	38	60	129	47	NS[a]
Non-invasive ventilation	53	84	146	53	NS[a]
Necrotizing enterocolitis	13	20	24	9	< 0.01[a]
PAD, medical treatment	17	27	52	19	NS[a]
PAD, surgical treatment	6	9	12	4	NS[a]
Oxygen at 28 days	34	66	105	38	< 0.01[a]
Oxygen at 36 weeks	17	34	41	15	NS[a]
Late-onset sepsis	37	59	103	37	< 0.005[a]
ROP	27	58	73	26	< 0.005[a]
Peri/intraventricular haemorrhage	10	16	63	23	NS[a]
Periventricular haemorrhagic infarction	3	5	9	3	NS[c]
Cystic periventricular leukomalacia	4	9	22	8	NS[c]
Complications	**LIG (n)**	**%**	**Control (n)**	**%**	**p**
Hydrocephalus with the need for VP shunt	1	4	14	5	NS[c]
Oxygen at discharge	7	27	16	6	NS[c]

SGA: small for gestational age; CRIB: clinical risk index for babies; SNAPPE: score for neonatal acute physiology perinatal extension; PAD: Patent arterial duct; ROP: retinopathy of prematurity; VP: ventriculoperitoneal; NS: non-significant; NA: not applicable; [a] chi-square test; [b] Mann-Whitney U test; [c] Fisher's exact test; *p* < 0.05.

and antenatal detection of FGR play an important role in obstetric decisions regarding the indications for induction of labour and parental counselling. In contrast, NB growth percentile, calculated by birth weight, is the key information used by paediatricians for decision making at the neonatal unit.[9] An 11% incidence of FGR and 18% of SGA NB has been found in our group of preterm NB, probably due to the fact that the hospital is a neonatal and obstetric national reference centre. Two thirds of the SGA NB in our study were not diagnosed with FGR during pregnancy. Even though ultrasound imaging is the gold standard test for the diagnosis of FGR, a 20% error associated to the weight estimate has been usually described by different authors.[28,29] The use of growth curves in clinical practice not adapted to severe prematurity has been described as one of the reasons for this result.[30,31]

Pregnancy and delivery-related risk factors

A strong association between birth weight and pregnancy complications associated with prematurity has been described by Zeitlin et al.[32] Some of the risk factors probably responsible by low birth weight, that were described in literature, were assessed in our study within the retrospective analysis of pregnancy and delivery.[6] No differences between the groups regarding the type of gestation (spontaneous or with IVF) were found in our group of patients. In addition, a

third of FGR/SGA NB have resulted from a twin gestation, in line with the control group and that is why this variable was not considered as a significant factor. Significant differences regarding the presence of pregnancy pathology were found in FGR NB, namely regarding the presence of chorioamnionitis. A high percentage of patients with pre-eclampsia has also been found in the SGA NB group, when compared to the control group (47% vs. 16%, p < 0.001), clearly corresponding to the pregnancy pathology more closely associated with neonatal morbidity.

Gender differences

Less male than female NB diagnosed with FGR during pregnancy were found in our group of patients, in line with Monier et al. and Magalhães et al., probably explained by the use of NB growth references non-adjusted to gender, which can also be adapted to what was found in SGA NB.[30,33]

The absence of a template of somatometry at birth in the Portuguese population is worth mentioning and therefore leading to the use of international graphic patterns, with subsequent non-adjustment between these and the characteristics of each population. The population in our hospital usually shows a great socio-cultural heterogeneity, including European immigrants, as well as of African and Asian origin, which is worth mentioning. This mismatch in

Table 5 – Neonatal morbidity – comparison between FGR NB and the control group

Variable	FGR (n)	%	Control (n)	%	p
Induction of foetal lung maturity	36	90	191	69	< 0.01[a]
Length of stay in hospital (mean, in days)	72	NA	53	NA	NS[b]
1 min Apgar score (mean score)	8	NA	7	NA	NA
5 min Apgar score (mean score)	10	NA	9	NA	NA
Resuscitation with intubation	21	52	174	63	NS[a]
CRIB (mean score)	3.9	NA	2.5	NA	< 0.01
SNAPPE (mean score)	21.8	NA	17.2	NA	< 0.05
Invasive ventilation	20	50	129	47	NS[a]
Non-invasive ventilation	35	87	146	53	NS[a]
Necrotizing enterocolitis	5	12	24	9	NS[a]
PAD, medical treatment	8	20	52	19	NS[a]
PAD, surgical treatment	3	7	12	4	NS[c]
Oxygen at 28 days	22	55	105	38	NS[a]
Oxygen at 36 weeks	8	20	41	15	NS[a]
Late-onset sepsis	23	57	103	37	< 0.05[a]
ROP	15	37	73	26	NS[a]
Peri/intraventricular haemorrhage	5	12	63	23	NS[a]
Periventricular haemorrhagic infarction	4	10	9	3	NS[c]
Cystic periventricular leukomalacia	3	7	22	8	NS[c]
Complications	**FGR (n)**	**%**	**Control (n)**	**%**	**p**
Hydrocephalus with the need for VP shunt	1	16	14	5	NS[c]
Oxygen at discharge	0	0	16	6	NS[c]

SGA: small for gestational age; CRIB: clinical risk index for babies; SNAPPE: score for neonatal acute physiology perinatal extension; PAD: Patent arterial duct; ROP: retinopathy of prematurity; VP: ventriculoperitoneal; NS: non-significant; NA: not applicable [a] chi-square test; [b] Mann-Whitney U test; [c] Fisher's exact test; p < 0.05.

the classification of NB also has an impact on the assessment of the individual diagnosis and subsequently on any subsequent medical approach.[34]

The fact that the height of the parents of SGA NB was not obtained is a limitation of the study that is worth mentioning.

CRIB and SNAPPE score assessment

The initial clinical severity in preterm NB is assessed by CRIB (clinical risk index for babies) score based on birth weight, gestational age, presence of birth defect, base excess and fraction of inspired oxygen, which was developed in the United Kingdom by the International Neonatal Network in 1993 and is used for the measurement of the risk of hospital death.[35] A 5.3 average maximum score in SGA NB ($p < 0.001$) and 3.9 in NB with FGR ($p < 0.01$) have been found in our study. A significantly lower score of severity was found in the control group, with a 2.5 average score. Even though the three groups correspond to a CRIB level I in medical practice, differences are significant, showing a trend towards a higher clinical risk in both groups, mostly in SGA NB.

The SNAPPE (score for neonatal acute physiology – perinatal extension) score is an extension of the SNAP (score for neonatal acute physiology) scale, which was developed by Richardson et al.[36] aimed at the assessment of the clinical severity in NB at admission to a NICU, including all the physiological parameters of the SNAP, in addition to the assessment of birth weight, perinatal history including the Apgar score and the classification of SGA NB.[37,38] A higher score in the SNAP-PE when compared to the control group has been found in NB with FGR/SGA, in line with was found when the CRIB application was used (31.7 in SGA and 21.8 in FGR vs. 17.2 in the control group). Again, significantly different scores were found in both groups and a higher risk of a poorer outcome in these NB was confirmed.

Bronchopulmonary dysplasia

An increased prevalence of bronchopulmonary dysplasia (BPD) was found in SGA NB in a recent study, regardless of an antenatal diagnosis of FGR.[30] The risk of BPD was also strongly associated with SGA NB in another study, with a decline in prevalence as birth weight increased.[32] The need for supplemental oxygen at 28 days of life was found in 66% of SGA NB ($p = 0.005$) and the double of what was found in the control group at 36 weeks (34% vs. 15%), even though this was not a significant difference. The dependence on supplemental oxygen was also the main complication in SGA NB at discharge (27%), which was not found in NB with FGR in our study, in line with literature, even though it can be due to the presence of lung maturity in only 70% of the SGA NB, compared to 90% in NB with FGR.

Neurological outcomes

Brain volume abnormalities that are sensitive to multiple perinatal risk factors and neonatal morbidities/interventions have been found in extreme preterm NB.[39,40] An association between smaller regional brain volume and neurological impairment in prematurity has been found in different studies,[39-41] including one study developed by our group.[40] These large volume decline was associated with an increased cerebrospinal fluid (CSF) volume and smaller total brain size, suggesting cerebral atrophy.[39,40]

Significantly reduced thalamus and basal ganglia volumes have been found in another study with NB with FGR when compared to NB with an appropriate weight for gestational age.[42] These abnormalities have probably induced clinical outcomes regarding learning and memory, language function and visuospatial function.[42]

Periventricular haemorrhage (PVH > 2) in preterm NB is an acquired injury with a direct impact on morbidity, mortality and long-term neurodevelopment.[43] However, SGA was not associated with PVH or cystic periventricular leukomalacia in the study by Zeitlin et al.[32] A 16% and 12% rates of PVH were found in SGA NB and NB with FGR in our study, respectively, while a 9% rate of cystic periventricular leukomalacia was found in SGA NB and 7% in NB with FGR, with no significant differences when compared to the control group.

Mortality and morbidity

A higher risk of mortality and morbidity associated with birth weight below the 10th percentile was found in the Models of organising access to intensive care for very preterm births in Europe (MOSAIC Research Group study),[44] which was a population cohort study in children born before the 32 weeks of gestation. Nevertheless, other studies have found a significant decline (around 20%) in perinatal morbidity and mortality with the early detection and orientation of foetuses with FGR.[45] An adequate obstetric and perinatal approach can explain the absence of a significant difference in mortality between NB with FGR and the control group.

A higher prevalence of late-onset sepsis has been found in NB with FGR ($p < 0.05$) and in SGA NB ($p < 0.005$) in our study, regarding the analysis of the incidence of morbidity, when compared to the control group. The rate of late-onset sepsis in these NB can be explained by a delayed enteral feeding, which is associated with an increased duration of parenteral nutrition and the need for central catheter. Higher incidence of ROP (58% vs. 26%, $p < 0.005$) and necrotizing enterocolitis (20% vs. 9%, $p < 0.01$) has been found in SGA NB when compared to the control group, with significant differences.

Globally, a higher morbidity has been found in SGA NB when compared to both the NB with FGR and the control group in our study, giving support to the hypothesis that low weight percentile at birth reflects a real deficit in organ growth and development.

Limitations of the study

1. Less male than female NB antenatally diagnosed with FGR were found, probably explained by the use of growth references non-adjusted to gender, which may have also regarded SGA NB.

2. A great social and cultural heterogeneity has been found in the population attended by our hospital, with a possible mismatch regarding the classification of NB, with an impact on the assessment of the individual outcome and on the subsequent medical approaches.

3. The height of the parents of SGA NB was not obtained.

Strengths:

1. This study was developed based on the experience of a reference centre in Neonatal Intensive Care and including a group of 356 NB with GA less than 32 weeks.

2. Seventeen clinical parameters for the assessment of morbidity were analysed, as well as the characteristics of gestation and the major pregnancy-related risk factors described in literature.

What does this study add to national medical literature?

This study was aimed at the re-assessment of the possible pregnancy and delivery-related risk factors of prematurity associated with FGR and/or SGA NB and found that pre-eclampsia was the pathology most strongly associated with neonatal morbidity.

A higher incidence of morbidity has been found in SGA NB when compared to NB with FGR and the control group, giving support to the hypothesis that low weight percentile at birth reflects a real deficit in organ growth and development.

CONCLUSIONS

Significantly increased survival and reduced morbidity and mortality in preterm NB have been produced by the advances in neonatal intensive care. However, significant differences have still been found as regards the prevalence of BPD, necrotizing enterocolitis, late-onset sepsis and retinopathy of prematurity in SGA NB and late-onset sepsis in NB with FGR. A strong association between SGA NB and maternal pre-eclampsia has also been found in our study.

An impaired foetal growth corresponding to low birth weight for GA and gender has shown higher impact on NB morbidity when compared to patients antenatally diagnosed with FGR and no impaired growth.

Active communication and collaboration between obstetricians and neonatologists are crucial for a correct clinical assessment, signalling and global action on these NB, reducing early morbidity and late outcomes.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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