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ORIGINAL ARTICLE

Cardiovascular risk factors and hypertension at 5-6 years in children born with a gestational age ≤ 32 weeks

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Abstract

Prematurity, low birth weight, being small for gestational age (SGA), fetal growth restriction (FGR), and admission on a neonatal intensive care unit are cardiovascular risk factors. The objective of this study was to analyze the proportion of patients with cardiovascular risk factors and hypertension at 5-6 years of age, in a cohort of children born very preterm (PTN). Observational, retrospective and cross-sectional study of children born with a gestational age ≤ 32 weeks, hospitalized in a level III neonatal unit, in Portugal, in 2015-2016, currently aged 5-6 years. FGR was identified by the obstetric team. SGA neonates were classified according to Fenton 2013 growth charts. Body mass index (BMI) was classified according to the World Health Organization charts for its z-score and blood pressure (BP) according to the European Society of Hypertension (2016). Thirty patients were included, with a mean age of 5.4 ± 0.6 years, 57% female. The mean gestational age was 29.2 ± 1.9 weeks, the proportion of FGR was 20% and of SGA 20%. At 5-6 years old, 20% presented an increased BMI, 60% an increased BP, and 17% an increased BMI and BP. BMI at 5-6 years was higher in females (U = 33,000; p = 0.02) and had an inverse correlation with birth weight percentile (r = 0.382; p = 0.04) and a positive correlation with BMI percentile at discharge from neonatology (r = 0.414; p = 0.02). No significant correlations for BP were found. In a population at risk, it is essential to promote cardiovascular health, allowing early interventions and prevention.

Keywords: Prematurity. Fetal growth restriction. Low birth weight. Small for gestational age. Metabolic syndrome.

Fatores de risco cardiovascular e hipertensão aos 5-6 anos em crianças nascidas com idade gestacional ≤ 32 semanas

Resumo

São fatores de risco cardiovasculares a prematuridade, o baixo peso ao nascer, ser leve para a idade gestacional (LIG), a restrição do crescimento fetal (RCF) e o internamento numa unidade de cuidados intensivos neonatais. O objetivo do estudo foi analisar a proporção de doentes com fatores de risco cardiovasculares e hipertensão arterial aos 5-6 anos de idade, numa coorte de crianças muito prematuras. Estudo observacional, retrospectivo e transversal de crianças nascidas com idade

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gestacional ≤ 32 semanas, hospitalizadas numa unidade neonatal nível III, em Portugal, em 2015-2016, atualmente com 5-6 anos. A RCF foi identificada pela equipa de obstetrícia. Os recém nascidos foram classificados como LIG conforme as curvas de Fenton (2013). O índice de massa corporal (IMC) foi classificado segundo as curvas da Organização Mundial de Saúde para o seu z-score e a pressão arterial (PA) segundo a European Society of Hypertension (2016). Incluíram-se 30 participantes, com idade média de 5,4 ± 0.6 anos, 57% do sexo feminino. A idade gestacional média foi de 29,2 ± 1.9 semanas, a proporção de RCF de 20% e a de LIG 20%. Aos 5-6 anos de vida, 20% apresentava aumento do IMC, 60% aumento da PA e 17% aumento do IMC e da PA. O IMC aos 5-6 anos foi superior no sexo feminino (U = 33,000; p = 0.02), apresentando uma correlação inversa com o percentil do peso ao nascer (r = 0.382; p = 0.04) e uma correlação positiva com o percentil do IMC à data da alta da neonatologia (r = 0.414; p = 0.02). Não se verificaram correlações com significado estatístico para a PA. Numa população de risco, é fundamental promover a saúde cardiovascular, permitindo a intervenção precoce e prevenção.

Palavras chave: Prematuridade. Restrição do crescimento fetal. Baixo peso ao nascer. Leve para a idade gestacional. Síndrome metabólica.

Keypoints

What is known
- Prematurity, low birth weight, being small for 60.0%, higher than that reported for children with vascular risk factors.
- Newborns under these conditions have an in associated conditions are risk factors for cardiovascular disease that should be identified early.

What is added
- The prevalence of a high pressure profile gestational age, and fetal growth restriction are cardio the same age.
- This study reinforces that prematurity and its creased risk of future cardiovascular disease.

Introduction

The increasing complexity of neonatal intensive care units over the years have allowed the survival of newborns with lower gestational ages and birth weights. Their survival is associated with some risks, namely the development of metabolic syndrome (MS), which increases the risk of developing other cardiovascular diseases[1]. MS is defined as the combination of central adiposity, hypertension (HTN), dyslipidemia, and abnormal glucose regulation[1].

In preterm newborns (PTN), there is premature exposure to adverse conditions of extra uterine life in organs that are immature[2]. The glomerular and endothelial damages lead to structural alterations, increasing the risk of developing HTN[2]. Prematurity may also be associated with the development of insulin resistance, as the largest expansion of the beta cell mass has been shown to take place in the second half of prenatal development[3]. Overall, there is an increased risk of developing MS in PTN and up to one-half may be attributed to an adverse intra-uterine environment[4].

In the 90's, Barker's work revealed that small for gestational age (SGA) neonates had also an increased risk to develop MS[5]. Barker's hypothesis of the fetal origins of disease describes a mechanism through which a fetus adapts to an adverse prenatal environment[3,4]. This adaptation is crucial for short-term survival, but results in specific fetal gene expression changes that persist after birth, when the fetus is no longer in a hostile environment, and an interplay between genetic and environmental factors influence *in utero* programming of adult diseases in these patients[3,4]. Multiple studies have corroborated Barker's findings with either an inverse relationship or a U-shaped relationship between birth weight and cardiovascular disease[4]. Nowadays, it is known that children born SGA are more likely to develop central adiposity, HTN, insulin and leptin resistance, diabetes, dyslipidemia, MS, and other cardiovascular diseases, compared to children born with a normal weight[2-4]. Fetal growth restriction (FGR) also exposes the neonate to a higher risk of MS in adult life and the mechanism may be related to a reprogramming in mitochondrial function, an abnormal accumulation of lipids in nonphysiologic storage depots, a lower number of nephrons, and the impact of growth restriction on pancreatic function[3-6]. It is well-known that individuals who display poor growth *in utero* have also an increased risk of obesity, decreased lean muscle mass, HTN, insulin resistance, type 2 diabetes mellitus, dyslipidemia, MS, and premature development of cardiovascular diseases[4,6].

The development of these cardiovascular risk factors and diseases is more evident in those PTN who were

born SGA as a consequence of FGR and not just because of these conditions individually[2]. In fact, the increased risk of cardiovascular diseases seems to be due to failure to achieve growth potential[4]. Furthermore, the risk seems to be independent of socioeconomic status, confirming intra uterine growth as a marker of life-long cardiovascular health[4].

Postnatal growth also seems to have an influence on the development of these complications. Although exposure to an improved nutrition may cause children who born SGA to achieve a catch-up growth, rapid childhood growth aggravates the risk of developing cardiovascular disease[3].

The main objective of this study was to analyze a cohort of children born very PTN, with gestational age ≤ 32 weeks, and to verify the proportion of cardiovascular risk factors and diseases at 5-6 years of age.

Methods

Study design

Observational, retrospective, and crosssectional study, in a cohort of children born very PTN, at 5-6 years old. Data collection were performed during 6 months (from January 1 to June 30, 2021).

Inclusion and exclusion criteria

We included children born very PTN, with gestational age ≤ 32 weeks and neonatal hospitalization in a level III neonatal intensive care unit, in Lisbon (Portugal), born between January 2015 and December 2016, aged 5-6 years in 2021. Children without computerized weight, height or blood pressure (BP) records in 2021 were excluded from the study.

Objectives

The main objective was to analyze the proportion of cardiovascular risk factors and diseases (high BMI, increased abdominal circumference, high pressure profile, insulin resistance, or dyslipidemia) in this cohort of children born very PTN and currently with 5-6 years.

The secondary objective was to assess the association of obstetric (maternal age, obstetric pathology, FGR, fetal lung maturation, twin pregnancy) and neonatal (gender, gestational age, birth weight, neonatal nutrition, days of life and weight at discharge) factors on cardiovascular disease at 5-6 years old.

Data collection

In the national prematurity database, we identified the newborns born in 2015-2016 with a gestational age ≤ 32 weeks and neonatal hospitalization in our neonatal intensive care unit. The variables of interest for the study (clinical, anthropometric, and analytical data) were collected from the computerized clinical process of each patient, always maintaining their confidentiality.

The presence of FGR was identified by the obstetric team. SGA neonates were classified according to Fenton 2013 growth charts, taking for threshold the 10th percentile for weight. BMI was classified according to the World Health Organization (WHO) charts for its z-score (underweight for z-score < –1, normal weigh for z-score between –1 and +0.99, overweight for z-score between +1 and +1.99, and obesity for z-score ≥ +2) and BP according to the 2016 European Society of Hypertension tables (normal for BP percentile < 90th, high-normal for BP percentile between 90th and 95th, and hypertension for BP percentile ≥ 95th).

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics version 24. Data were summarized using descriptive statistics (frequency/percentage, mean ± standard deviation, and intervals). The normality of the variables was determined using the asymmetry test and confirmed with the Shapiro Wilk test. To verify whether two groups differed significantly, it was used Student's t test for samples with normal and homogeneous distribution and Mann Whitney test for the others. Pearson's and Spearman's correlation coefficient was used to assess correlation between numerical variables. Significance level was set at *P*-value ≤ 0.05.

Results

General characteristics

Of the 98 children in the cohort, 30 had computerized weight, height and BP records and were therefore included. It corresponded to 23 pregnancies, with a mean age of 5.4 ± 0.6 years, mostly females (*f* = 17; 56.7%).

Regarding the obstetric history, there was evidence of cardiovascular pathology in 7 (23.3%) cases (hypertension in 6, gestational diabetes in 1 and dyslipidemia in 1), of FGR in 6 (20.0%) cases, and of twin pregnancy

in 14 (46.7%) cases. Induction of fetal lung maturity was done in 26 (86.7%) cases. The mean maternal age was 35.0 ± 6.1 years.

Regarding neonatal hospitalization, the mean gestational age was 29.2 ± 1.9 weeks, and the mean birth weight was 1101.5 ± 371.2g (mean weight percentile: 32.5 ± 22.8). Six (20.0%) newborns were SGA. Twenty seven (90.0%) patients needed parenteral nutrition, with a mean length of 14.8 ± 10.9 days. The mean age of exclusive enteral feeding was 17.2 ± 13.7 days. The mean length of stay on the intensive care unit was 71.1 ± 41.8 days, corresponding to a mean post menstrual age of 38.8 ± 4.8 weeks. At the time of hospital discharge, the patients had a mean weight of 2498.4 ± 559.6g (mean weight percentile: 9.0 ± 10.7) and a mean weight gain of 1397.0 ± 663.6g.

At 5-6 years old, 6 (20.0%) children had an increased weight (overweight in 33.3% and obesity in 66.7%), 18 (60.0%) had a high pressure profile (high BP in 55.5%, stage 1 HTN in 33.3% and stage 2 HTN in 11.1%), and 5 (16.7%) had concomitant high BMI and high pressure profile. The increase in BP was mainly due to the increase in systolic BP. Two (11.1%) patients with increased BP were being followed up at the pediatric HTN clinic and were under pharmacological therapy. No patient was being followed up for other cardiovascular risk factors or diseases, and none had undergone analytical assessment for dyslipidemia or blood glucose at our hospital.

Cardiovascular risk factors and diseases at 5-6 years old

Regarding BMI, it was significantly higher in females (only female children in the increased BMI group *versus* 45.8% in the normal BMI group; U = 33,000; p = 0.02) and presented a statistically significant inverse correlation with birth weight percentile (r = 0.382; p = 0.04) and a statistically significant positive correlation with the BMI percentile at discharge from neonatology (r = 0.414; p = 0.02). In a non-statistically significant way, it was found that obstetric pathology, twinning, FGR, fetal lung maturation, and concomitant increased BP value at 5-6 years were risk factors for increased BMI at 5-6 years. On the other hand, shorter length of parenteral nutrition, earlier introduction of exclusive enteral feeding, shorter length of hospital stay, shorter post menstrual age at discharge, and lower weight gain were protective factors for it.

Regarding BP, there were no statistically significant correlations. Nevertheless, in a non-statistically significant way, fetal lung maturation, female gender, longer length of parenteral nutrition, longer length of hospital stay, higher post menstrual age at discharge, higher weight at discharge, higher weight gain during hospital stay, and concomitant increased BMI at 5-6 years were risk factors for increased BP at 5-6 years.

It was not possible to identify other cardiovascular risk factors or diseases, like central adiposity, dyslipidemia or insulin resistance.

The results are summarized in Table 1.

Discussion

Prematurity is associated with several risk factors for cardiovascular diseases, namely FGR, low birth weight, and being SGA. In this study, we were able to study the prevalence of overweight/obesity and of high pressure profile in our cohort, but not other clinical or analytical MS parameters, as there was no reference to them in the computerizes records and this was an observational study.

Prevalence of overweight/obesity and high pressure profile at 5-6 years

In our sample, the prevalence of overweight/obesity was 20.0%, of high pressure profile 60.0%, and of concomitant overweight/obesity and high pressure profile 16.7%. Comparing these prevalences with those reported in the literature for healthy children, it was found that the prevalence of overweight/obesity was identical to that reported by the WHO for children with the same age, around 20%[7], but the prevalence of high pressure profile was higher than the overall pediatric prevalence, estimated to be around 4-5%[8,9]. Thus, prematurity, in our sample, seems to be a more important risk factor for BP than for BMI, although, taking into account the sample selection, the comparison with the healthy population is imprecise.

Neonatal cardiovascular risk factors

One of the most recognized neonatal cardiovascular risk factors is birth weight and, in our sample, we found a significant inverse correlation between birth weight and BMI at 5-6 years. Furthermore, we found that the BMI at discharge from neonatology, which may indicate a tendency for a too rapid weight catch-up, also identified as a neonatal cardiovascular risk factor, had a significant positive correlation with BMI at 5-6 years as well (although the growth after this period has not been

Table 1. Sample characteristics

Total (*f* = 30)					
Maternal age (years)	35.0 ± 6.1 [17.0-42.0]	Newborn gender – Female (*f*; %) – Male (*f*; %)	 17 (56.7%) 13 (43.3%)	Discharge – Days of life	 71.1 ± 41.8 [30.0-246.0]
Obstetric pathology – Yes (*f*; %) – No (*f*; %)	 12 (40.0%) 18 (60.0%)	Gestational age (weeks)	29.2 ± 1.9 [25.0-32.0]	– Post menstrual age (weeks)	38.8 ± 4.8 [34.0-61.0]
Intrauterine growth restriction – Yes (*f*; %) – No (*f*; %) – Unknown (*f*; %)	 6 (20.0%) 23 (76.7%) 1 (3.3%)	Birth weight – Grams – Percentile – Small for gestational age • Yes (*f*; %) • No (*f*; %)	 1101.5 ± 371.2 [520.0-2350.0] 32.5 ± 22.8 [4.0-98.0] 6 (20.0%) 24 (80.0%)	– Weight in grams – Weight percentile – Weight gain (grams)	 2498.4 ± 559.6 [1960.0-4780.0] 9.0 ± 10.7 [0.0-40.0] 1397.0 ± 663.6 [528.0-4080.0]
Induction of fetal lung maturation – Yes (*f*; %) – No or incomplete (*f*; %)	 26 (86.7%) 4 (13.3%)	Nutrition – Length of parenteral nutrition (days)	14.8 ± 10.9 [0.0-47.0]	Body mass index at 5-6 years – Normal (*f*; %) – Overweight (*f*; %) – Obesity (*f*; %)	 24 (80.0%) 2 (6.7%) 4 (13.3%)
Twin pregnancy – Yes (*f*; %) – No (*f*; %)	 14 (46.7%) 16 (53.3%)	– Introduction of exclusive enteral feeding (day of life)	17.2 ± 13.7 [1.0-64.0]	Blood pressure at 5-6 years – Normal (*f*; %) – Normal-high (*f*; %) – Stage 1 hypertension (*f*; %) – Stage 2 hypertension (*f*; %)	 12 (40.0%) 10 (33.3%) 6 (20.0%) 2 (6.7%)

evaluated, therefore the too rapid catch up hypothesis corroborated). There was no statistically significant correlation between birth weight or too rapid weight catch-up and BP in our sample.

Another neonatal cardiovascular risk factor described is FGR. Although not statistically significant, we found that there were a higher proportion of participants with FGR in the increased BMI group compared to the normal BMI group (33.3% *versus* 16.7%), appearing to be a risk factor for high BMI, but not for high pressure profile.

Regarding gender, male fetus have an increased risk of cardiovascular disease, because they grow at a faster rate and this accelerated growth trajectory makes them more vulnerable[2]. Nevertheless, in our sample, BMI at 5-6 years was significantly higher in females. These differences may be explained by the lower birth weight (997.3 ± 260.7g *versus* 1264.0 ± 438.1g in the male group) and the higher proportion of SGA (23.5% *versus* 6.7%) and FGR (35.3% *versus* 0.0%) in the female group.

It is worth mentioning the high proportion of maternal cardiovascular pathology in our sample (30.4%), which reinforces the importance of the preconception and during pregnancy care, one of the points mentioned by the WHO for pediatric obesity prevention[10].

Prematurity versus term

When preterm birth occurs, it is often because the benefits of ending the pregnancy outweigh the risks of maintaining it and, although it is associated with short, medium and long-term consequences, namely cardiovascular diseases, it may be a life saving condition.

Cardiovascular diseases remain one of the leading causes of mortality in the world and the risk of developing it increases with the increasing number of cardiovascular risk factors[4]. The main therapeutic weapon in cardiovascular diseases is prevention.

Growth, BMI, BP, and healthy lifestyles should be regularly assessed in the pediatric appointments of these risk patients, strengthening family health literacy. History of acute kidney injury in the neonatal period or during infancy, HTN, obesity and other cardiovascular risk factors and diseases require annual clinical and laboratory evaluations, beginning at 6 months after discharge and including microalbuminuria, serum creatinine and/or cystatin C[2].

This study has some limitations:

– It is an observational and retrospective study, with the limitations underlying these types of studies.
– The following variables were not included: nutrition in the first 4-6 months of life (namely breastfeeding versus high caloric formulas), weight gain in the first 2-3 years of life, abdominal/hip/waist perimeter, percentage of fat/lean mass, and analytical study of lipid and glucose metabolism at 5-6 years. Thus, it was not possible to identify other cardiovascular risk factors or diseases.
– The prevalence of cardiovascular diseases in a sample born at term and of the same age was not studied.
– The reduced size of the sample may limit the assessment of conclusions.

Conclusions

Preterm birth and its short, medium and long-term consequences are associated with an increased metabolic risk. Thus, the main therapeutic weapon is prevention and we must provide strategies to maximize the cardiometabolic health of these risk children. The early diagnosis and treatment may reduce the morbidity and mortality of these diseases, with an important health impact, especially in developed countries.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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