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ORIGINAL ARTICLE

Preventive care and follow-up of preterm infants: the point of view of a pediatric nephrologist

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Abstract

Objective: Review renal and cardiovascular complications derived from premature births, to warn the pediatrician about preventive care and to recommend an approach toward the follow-up. **Metodology:** non-systematic review of literature which based its data on: National Library of Medicine, US National Library of Medicine, Latin American and Caribbean Literature on Health Sciences and Scientific Electronic Library Online, ranging from 2010 to 2021. The articles were delved into the issues of prematurity, low birth weight, restricted intrauterine growth and its relation with cardiovascular and renal diseases; and proposed follow-up strategies. **Results:** The incidence of premature births has increased in the last few decades, with a variation between 5% to 14%, and, consequently, the rate of chronic-related diseases related to this situation has increased as well. The number of incomplete and immature nephrons in premature babies derives from the lack of completeness of nephrogenesis, which takes place at around 36 weeks of pregnancy. This nephron deficit necessitates a hemodynamic adaptation to meet the demands of urinary excretion. This process may be responsible for glomerular hypertension, the hypertrophy of remaining nephrons and resulting renal injuries. Factors such as low birth weight, restricted intrauterine growth and premature birth all contribute towards the global increase of the prevalence of renal disease, systemic arterial hypertension and metabolic syndrome. **Conclusion:** Children born premature, with low birth weight and restricted intrauterine growth must have their arterial pressure and kidney functions monitored throughout the paediatric follow-up, and sent to a paediatric nephrologist whenever any abnormalities are detected.

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INTRODUCTION

Epidemiology studies have associated gestational and perinatal factors, such as prematurity, intrauterine growth restriction (IUGR), and low birth weight, with the onset of chronic diseases throughout life. The remarkable increase in the survival of preterm infants seen in recent decades shed light onto the broad spectrum of comorbid conditions to which they are exposed. Besides the known sequelae of preterm birth, which include altered psychomotor development and respiratory diseases, preterm infants are at risk of developing cardiovascular disease, kidney disease, systemic hypertension, and metabolic syndrome, to name a few.

Preterm infants must be followed closely via preventive care measures to allow the early detection and treatment of possible conditions. Studies show that few pediatricians adequately monitor preterm infants after discharge from a neonatal ICU[1]. This review is meant to inform pediatricians of the systemic complications of prematurity, guide preventive care, and recommend a follow-up approach.

Data source

This non-systematic review of biomedical literature presents a collection of historical and updated references about the subject of interest. Searches were conducted in the National Library of Medicine (MEDLINE), the US National Library of Medicine (PubMed), the Latin American and Caribbean Literature on Health Sciences (LILACS) and the Scientific Electronic Library Online (SciELO) databases covering the period from 2010 to 2021. The review included articles written in English based on the following search parameters: ("Premature birth" OR "Intrauterine growth restriction" OR "low birth weight" OR "small for gestational age") AND ("renal disease" OR "kidney disease" OR "Albuminuria" OR "proteinuria" OR "Hypertension") AND "follow-up". Editorials and letters to the editor on the subject were excluded, as were articles not available in full and duplicates.

Origin of adult chronic diseases

Chronic kidney disease (CKD) and cardiovascular disease are chronic noncommunicable diseases and important causes of early death worldwide. Their origins are believed to involve "developmental programming" related to unfavorable intrauterine and postnatal growth conditions. Prematurity and low birth weight are some of these conditions.

DOHaD (Developmental Origins of Health and Disease) brings together information from various fields of knowledge to propose new methods for investigating the mechanisms involved in and the influence of adverse events occurring in the early stages of human development on the patterns of occurrence of health and disease throughout life[2].

Developmental programming refers to a process in which the exposure to and stimuli from the environment (intrauterine, environmental, and maternal) during pregnancy and in early postnatal life may induce structural and developmental changes in the developing being.

The concept of fetal origins of adult disease, also known as the Barker Hypothesis, states that adverse events in the early periods of development, especially during gestation, may cause permanent changes in physiology and metabolism, resulting in increased risk of developing certain diseases[3]. Barker and colleagues have correlated birth weight and environmental conditions during childhood to the cardiovascular health of adult individuals born in the early 20th century in Hertfordshire, England. Their studies showed that people with low weight at birth (<2500g) remained biologically different in adulthood from individuals born with adequate weight. Individuals born with low weight had higher blood pressure and a greater propensity to develop type 2 diabetes. Moreover, low birth weight was associated with altered pattern of plasma lipids, decreased bone density, different responses to stress, less elastic arteries, and specific hormone secretion patterns. These observations gave rise to the thrifty phenotype hypothesis, which postulates that the fetus is able to adapt to an adverse intrauterine environment, optimizing the use of energy supplies in order to ensure its survival[3,4]. Thus, the development and severity of various comorbid conditions depend on the individual's genetic vulnerability, exposure to adverse environmental factors, and the period in which these stressful events transpired.

Predisposing factors

Prematurity

The WHO defines prematurity as infants born with a gestational age (GA) of less than 37 weeks or 259 days, counted from the first day of the mother's last menses.[5] The worldwide incidence of preterm births has increased in recent decades, ranging from 5% to 14%, with an annual occurrence of approximately 14.9 million cases[6].

The Committee on Obstetric Practice, together with the American Institute of Ultrasound in Medicine and the Society for Maternal-Fetal Medicine (2017), consider early obstetric ultrasound examination (before 14 weeks of gestation) to be the gold standard for estimating gestational age. In situations where the date of the last menses is unknown or early ultrasound examination has not been performed, it is possible to calculate the gestational age of the newborn through tests such as Capurro and New Ballard scores. The latter provides a more accurate assessment of preterm infants, since it uses data from physical and neurological examination. Depending on the GA, infants can be described as extremely (GA less than 28 weeks), very (GA 28 to 32 weeks), or moderately preterm (GA 32 to < 37 weeks). Moderately preterm infants can be further described as late preterm when GA resides between 34 to < 37 weeks.

Despite recent advances in the care of preterm newborns, prematurity is still one of the leading causes of death

in the neonatal period. An increasing number of neonatal ICU survivors are reaching adult age and, consequently, the number of cases of chronic disease related to prematurity is increasing.

Intrauterine growth restriction and low birth weight

Intrauterine growth restriction (IUGR) affects 3 to 7% of newborns. IUGR is detected in ultrasound examination. It occurs as a consequence of maternal, fetal, or placental dysfunction, and results in growth failure. Placental insufficiency is the main cause, evidenced by anomalous blood flow in the uterine artery, umbilical cord, or middle cerebral artery of the fetus. Utero-placental blood flow is consequently compromised, reducing the supply of nutrients and oxygen to the fetus[7]. The negative effect of hypoxia and early malnutrition on kidney development is greater in IUGR when compared to prematurity alone[8].

Birth weight has been related to disease, nutritional status and maternal habits, and may predict neonatal risk of mortality, infection, and prolonged hospitalization. The category low birth weight is assigned to infants born weighing between 1500 and 2500g; very low weight to infants weighing between 1000 and 1500g; and extreme low weight to infants born weighing less than 1000g. The term small for gestational age (SGA) refers to infants born with a weight below the 10th percentile (p10) according to Lubchenco's growth curve[9].

Low weight may be associated with prematurity and/or intrauterine growth restriction. Main causes include drug abuse, smoking, malnutrition, infections, and maternal diseases, such as hypertension.

Nephrogenesis

The kidneys begin to develop during the third week of gestation, with an exponential increase in the number of nephrons occurring between the 19th and 28th weeks, and are completely developed around the 36th week. This process results in the formation of approximately 1,000,000 nephrons in each kidney, and explains the potential deleterious effects of births occurred before the 28th week of gestation. When nephrogenesis ceases, only tubular, vascular, and interstitial tissue continue to grow. Epithelial cells decrease in density as the nephrons expand, with the inner glomeruli becoming more mature; nephrons in the outer cortex are the last to expand, making them more vulnerable to an unfavorable extrauterine environment[10].

Preterm infants start life with few and immature nephrons. Exposure to external stressors – hemodynamic changes, nephrotoxic drugs, infection, inadequate nutrition – may cause further reductions in the number of nephrons, as shown in animal studies, and increase the risk of development of kidney disease[11,12].

The mechanisms involved in the cessation of nephrogenesis in preterm infants are not entirely known. Hyperoxia negatively impacts kidney development, as do nephrotoxic drugs, increasing the risk of acute kidney injury (AKI)[13].

The glomerular filtration rate (GFR) is decreased in newborns and grows proportionately to the number of nephrons formed and as the glomeruli become mature. After the process is complete, an increase in the GFR occurs secondary to increased renal blood flow and changes within the glomeruli[10].

A deficit in the number of nephrons causes increases in the individual glomerular filtration rate, so that urinary excretion demands are met. Blood pressure also increases to ensure sufficient natriuresis. These hemodynamic adaptations cause glomerular hypertension, glomerular and tubular growth, hypertrophy of the remaining nephrons, and kidney injury[14].

A low number of nephrons is a determining factor in the onset of chronic kidney disease and systemic hypertension. The smaller number of glomeruli seen in preterm newborns decreases the effective glomerular filtration area. Thus, hyperfiltration, proteinuria, and glomerular sclerosis may occur[15]. However, not all infants born with a reduced number of nephrons (single kidney, for example) develop CKD. This suggests that risk factors added during the development of the kidneys may contribute to a gradual loss of kidney function[16].

Late complications

Hypertension, chronic kidney disease and metabolic disease

Hypertension and CKD have a significant impact on mortality and morbidity. Systemic hypertension affects 25% to 35% of adults worldwide[17] and related comorbid conditions are directly linked to some of the leading causes of death, such as acute myocardial infarction (AMI) and stroke.

Extremely low birth weight due to IUGR is associated with systemic hypertension in several stages of life. However, it is still unclear whether this link extends to other categories of preterm infants[18]. Ferdous et al. described the occurrence of hypertension at 16 years of age in 13.5% of the individuals born weighing 600 to 1,250 grams versus only 4% among individuals born full-term with adequate weight[19]. Higher frequency of systemic hypertension in adults with a history of prematurity has also been described in population studies, such as the Dutch POPs[20].

CKD decreases life expectancy and quality of life and generates substantial costs on public healthcare systems, particularly with renal replacement therapy in adults. The death rate of children with CKD is 1,000 times greater than that of healthy children. Delays in diagnosis occur primarily due to the nonspecific nature or inexistence of early symptoms, which favors accelerated disease progression and higher mortality[21].

Low birth weight, IUGR, and prematurity contribute to an overall increase in the prevalence of kidney disease. Risk triples when these three factors are combined[22]. A British cohort study found that low birth weight contributed to 70% of the risk of CKD in adulthood and that for each 1 kg reduction

in birth weight, there was a 2.13 ml/min/1.73m² decrease in the GFR[23]. Although the authors of the British study found no association with proteinuria, a Japanese study described an inversely proportional correlation between prevalence of proteinuria in adolescents and birth weight[24]. Other anomalies associated with CKD (microalbuminuria, hypertension and/or low kidney volume) were described by Sanderson et al. in 50% of adolescents born extreme preterm and Harer et al. in 25% of children born with very low weight[25,16].

Heidemann et al. found 15% of children at two years of corrected age with metabolic syndrome, another comorbid condition described in very low birth weight preterm infants. The proportion was four times higher than that of a Brazilian school population from the interior of São Paulo (six to 16 years, 3.6%) and an American adolescent population (4.2%). Prematurity, regardless of IUGR, was associated with hypertension and dyslipidemia. The authors hypothesized that very preterm birth or nutrient deprivation during intrauterine life induces epigenetic changes that result in dyslipidemia, hypertension, obesity, and insulin resistance, the main components of the metabolic syndrome[26].

Adequate nutrition and growth during childhood are key determinants of health in adulthood. Catch up growth, especially after growth restriction in early developmental stages (including intrauterine life), may be deleterious in the long term and have consequences on cardiovascular, metabolic, and kidney function and structures[3].

Recommendations for the follow-up of at-risk patients

Populations with a history of prematurity, low birth weight, or IUGR are at risk of developing chronic disease. American, European, and Brazilian consensus statements stipulate that populations at risk should have their blood pressure measured before the age of three years in routine visits[27].

Medical history must include data about gestation, maternal diseases, birth weight, GA, length of stay in the neonatal ICU, and complications during this period. Use of nephrotoxic drugs, placement of a catheter in the umbilical artery, or AKI during hospitalization must also be considered.

Microalbumin and creatinine levels to calculate the GFR and ultrasound examination with measurement of the kidneys to follow the growth of the kidneys are indicated annually for individuals at higher risk (birth weight < 1500g and GA < 28 weeks) and every five years for others (Table 1).

It is recommended that the GFR be estimated based on mathematical equations that minimize the biological variability of serum creatinine, considering items such as height, age, sex, and laboratory test results. In 1976, Schwartz described the simplified equation [K * height (cm)] / SCr (mg per dL) to estimate the GFR in children based on serum creatinine level and height. In 2009, the constant "k" was updated (k = 0.413) in accordance with the international standardization of IDMS (Isotope Dilution Mass Spectrometry)-traceable creatinine (Table 2)[28].

Table 1. Preterm infant follow-up recommendations.

Recommendation	Preterm < 37 weeks Birth weight < 2500g	Preterm < 28 weeks Birth weight < 1500g
Blood pressure measurement	Every visit	Every visit
Microalbuminuria	Every 5 years	Yearly
Creatinine and estimated GFR	Every 5 years	Yearly
Kidney echography	Every 5 years	Yearly
Advice about nephroprotection	Every visit	Every visit

GFR: glomerular filtration rate.
FSource: adapted from Crump[28].

Table 2. Schwartz equation for estimating the glomerular filtration rate.

GFR (ml/min/ 1.73 m2) = k* x height (in cm) / serum creatinine (in mg/dl) ** k varies depending on the method used to measure creatinine*			
Jaffe method (alkaline picrate)			
Preterm Infants (1st year of life)	**Full-term infants** (1st year of life)	**Children**	**Male adolescents**
K = 0.33	k = 0.45	k = 0.55	K = 0.70
Calibration to IDMS-traceable creatinine:			
Preterm Infants (1st year of life)	**Full-term infants*** (1st year of life)	**Children and adolescents**	
k = 0.25	k = 0.34	k = 0.413	

Source: Modified from Schwartz et al. and Mian et al.[28]
* The K coefficient for infants in methods calibrated to IDMS-traceable creatinine was suggested by Schwartz from unpublished and yet unvalidated observations[28].

Pediatricians must be encouraged to advice this group of patients about nephroprotective care, including matters such as avoiding the use of nephrotoxic drugs (especially non-steroid anti-inflammatory drugs); drinking; smoking; a sedentary lifestyle; obesity; and excess sodium in the diet, often present in ultra-processed foods. Patients with high blood pressure and/or changes in kidney function tests must be referred to a pediatric nephrologist for evaluation[29].

CONCLUSION

Children born prematurely, with low birth weight, or with IUGR are at risk for chronic kidney disease, hypertension, and metabolic disease. Pediatricians must be aware of the systemic complications of prematurity, and provide every patient in this population with individualized follow-up.

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