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World Kidney Day 2023 – Kidney Health for All

Preparing for the unexpected, supporting the vulnerable!

Respecting the kidney of the premature, the low birth weight newborn (LBW) and the intrauterine growth compromised newborn (IUGR)

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Introduction

Every year, the second Thursday of March is dedicated to World Kidney Day around the world. This campaign, created in 2006 by the International Society of Nephrology (ISN) together with the International Federation of Kidney Foundations (IFKF), aims to disseminate information about kidney diseases, focusing on prevention, early diagnosis and adequate treatment for all, in all nations.

This year, the campaign brings as a sub-theme 'caring for the vulnerable' which in the pediatric context requires alerting to the premature kidney, the risks of acute kidney injury (AKI) in Neonatal Intensive Care Units (NICU) and the predisposition to chronic kidney disease (CKD) throughout life. For those with congenital anomalies of the kidney and urinary tract (CAKUT) and who represent the main cause of CKD in childhood, a line of care, in specialized centers, with correct diagnoses and effective treatments can prevent the loss of kidney function by delaying the need for a kidney transplant or dialysis treatment.

In Brazil, the Departments of Pediatrics of the Brazilian Society of Nephrology (SBN) and of Neonatology and Nephrology of the Brazilian Society of Pediatrics (SBP) joined forces to launch this document. They have graciously translated this to English and have shared it with the Neonatal Kidney Collaborative – for dissemination to our members across the world.

Prematurity, Fetal and Epigenetic Programming and its consequences

Premature birth is an important public health problem, due to its implications for neonatal morbidity and mortality; reducing its prevalence is a global priority in order to achieve target 3 of the Sustainable Development Goal (SDG), which aims to end all preventable deaths in newborns and children under 5 years of age by 2030.[1]

Prematurity has a complex etiology, which makes it difficult to establish the prevention and treatment of its complications. [2] The main maternal causes include pregnancy

complications, such as pre-eclampsia/eclampsia, maternal hemorrhage, placental abruption and placenta previa, in addition to morbidities, such as diabetes and other chronic diseases that precede pregnancy, such as kidney or heart morbidities. [3]

In addition to these, the environmental factors considered in changing the programming of disease development are exposure to pollution, stress, drugs, toxic agents, and nutrition.[4]

Advances in medical care and technology have resulted in improved survival for extremely premature babies. Prevalence rates of preterm births are increasing due to advanced maternal age, increased use of reproductive technology, and multiple pregnancies.[5]

Exposure to various conditions that lead to premature birth, prematurity itself and the management of these fragile neonates in the NICU can lead to permanent changes in the function and structure of several organs.[6,7]

A 2009 systematic review of more than 2 million low birth weight (LBW) babies concluded that there is a 1.73 chance (95% CI: 1.44 - 2.08) for developing CKD.7 Studies in humans and in animals strengthened the association between prematurity, low birth weight, small for gestational age, delayed intrauterine growth and CKD.[8,9]

The National Institute of Child Health and Human Development described the concept of Developmental Origins of Health and Disease (DOHaD), based on Barker's hypothesis.[10,11] This concept is related to the fetal and postnatal programming of the development of chronic diseases in adults and proposes that the pathophysiology of chronic noncommunicable diseases would be related to events that occur during the prenatal period and in early childhood.[11-13] This means that an adverse environment in fetal life and during early childhood would imply an increased risk of chronic diseases in adult life.[14] Therefore, this programming is a process through which a stimulus or insult establishes a response that is permanent. The critical periods for this programming are fetal life and early childhood. Exposure during a critical period of an individual's development can influence the structure and/or physiological function of any organ throughout life.[15-18]

Studies have shown that an unfavorable childhood psychosocial environment was associated with higher blood pressure, greater anthropometric risk, and higher cardiovascular risk biomarkers.[19] This is believed to be caused by epigenetics, when genes can undergo environmental and intrinsic influences that alter the phenotype without altering the DNA sequence, they are perpetuated in cell divisions and are transmitted to future generations.[20] This set of environmental and intrinsic marks is called the Epigenome.[20]

This fetal programming is associated with maternal, placental, and fetal factors; thus, an unfavorable intrauterine environment provides inhospitable experiences that are experienced by the embryo. This embryo undergoes adaptations (epigenetic phenomena) and consequently there will be compromised renal maturation. This is what we call the Fetal Programming of Adult Kidney Diseases. And this programming is perpetuated during the first year of life.[15-18]

The main mechanisms of fetal and postnatal programming of kidney diseases are: the number and size of nephrons, the integrity of telomeres, genetic and hormonal factors and epigenetics.[18] The main molecular mechanisms of reduction in the number of nephrons are: oxidative stress, changes in the renin-angiotensin system, changes in

sodium transporters, altered renal sympathetic activity, effect of glucocorticoids, epigenetic regulation, and the difference between the sexes, being worse in males.[18]

We know that nephrogenesis begins in the 6th week of gestation, continues until the 36th week of gestation and 60% of nephrons are formed in the third trimester. Nephron development continues up to 40 days after birth; however, with the formation of abnormal nephrons that age rapidly.[21,22] For these reasons, prematurity culminates in a reduction in nephron mass and this lower number of nephrons favors hypertension and compensatory hyperfiltration in the remaining units, a hypothesis that has been coined the Brenner hypothesis.[23,24]

Brenner extended the principle of the DOHaD theory to kidney development, pointing out that fetal stress factors, including prematurity, can lead to a reduction in the number of nephrons at birth, predisposing to CKD in adolescence and adulthood. [25] This association between prematurity, LBW and increased risk of CKD affects individuals throughout their life, as noted by Gjerde et.al to extent for at least 50 years after birth. [26]

What we've learned over time

Studies have shown strong associations between smaller number and size of glomeruli and higher risk of proteinuria, arterial hypertension (AH) and progressive CKD.[27,28] A meta-analysis carried out in Australia with more than 2 million individuals from 31 studies showed that LBW was associated with an 80% increase in the odds of albuminuria and sustained low glomerular filtration rate (GFR), and a 60% increase in the odds of end-stage chronic kidney disease (ESRD) in adults, compared with those with normal weight at birth birth.[7] Vikse et al., studied more than two million births in Norway and demonstrated that of these, 526 had ESKD. The authors found that the RNBP was 1.7 times more likely to evolve to ESKD and the small for gestational age (SGA) was 1.5 times more likely.[29] In Finland, a study with more than 20,000 people born from 1924 to 1944 and that were followed until death showed that prematurity and LBW were associated with an increased risk of CKD.[30] Babies born at less than 34 weeks had a 2.6 times greater risk of developing CKD, babies with LBW had 1.4 times more those with intrauterine growth retardation (IUGR) were 2.4 times more likely to have microalbuminuria and reduced GFR, and those with IUGR were 2.4 times more likely to have albuminuria.[30] A case-control study of Japanese children with childhood-onset CKD showed a 21% prevalence of LBW and a strong correlation between prematurity and CKD.[31] The CKiD Study with 489 children showed that 17% were LBW, 13% premature, 15% IUGR, and 41% admitted to the NICU. The authors concluded that prematurity and IUGR are new risk factors for short stature and lower weight percentiles in children with mild to moderate CKD, regardless of renal function.[32] Another study conducted in Norway with nearly 2,700,000 subjects showed that 1181 developed ESKD. The authors concluded that compared to those who were not LBW, those born LBW had an adjusted hazard ratio for ESKD of 1.61 (1.38-1.98). Similarly, compared to those who did not have SGA, those with SGA had an adjusted hazards ratio for ESKD of 1.44 (1.22 – 1.70) at 50 years of life.[9] They found an additive effect, whereby those that had all 3 characteristics (premature, LBW and SGA) had an adjusted hazard ratio of ESKD of 2.96 (1.84 – 4.76) compared to those without these risk factors.[9]

Long term consequences

A large Swedish study assessed the risk of CKD and its consequences from childhood to mid-adulthood in 4.2 million individuals by birth status, according to groups a) extremely preterm: 22-27 weeks; b) very premature: 28–33 weeks; c) late preterm: 34–

36 weeks; d) early term: 37–38 weeks; e) term: 39–41 weeks; f) post-term: ≥ 42 weeks.6,33 The authors found:

1. CKD developed in 4305 (0.1%) individuals during follow-up of 87 million people per year.

2. CKD incidence rates were 9.2 per 100,000 person-years for all preterm births combined with other risk factors, 5.9 for preterm births, and 4.5 for term births.

3. Individuals born extremely premature had a three times greater risk of developing CKD compared to those born at term.

4. Among individuals with neonatal AKI, 24% developed CKD.

5. Prematurity was associated with a five-fold increased risk of CKD before age 10 compared with full-term birth.

6. Presence of congenital anomalies was associated with a 20-fold higher incidence of CKD. Other risk factors were male gender, maternal obesity and maternal pre-eclampsia.

7. Among siblings, the association between prematurity and CKD risk was maintained, suggesting that the association was not genetically or environmentally determined.[33]

Other studies have evaluated long-term renal consequences in extremely preterm infants. The risk of nephrocalcinosis was 14% and survivors with nephrocalcinosis at two years had impaired tubular function. AH persisted for up to seven years in 25%.34-37 When extreme prematurity and LBW survivors were compared with term neonates, the following was observed: a reduced renal volume, increased cystatin C and urea until the age of 7 to 11 years, and presence of microalbuminuria. Those who had additional AKI had a lower GFR than those without AKI.[38,39] The following changes were also observed in these same patients: reduced tubular bicarbonate and phosphate reabsorption, decreased urinary osmolality up to seven years of age, higher baseline BP higher levels, lower GFR, higher salt sensitivity, microvascular endothelial dysfunction with increased vascular resistance, reduced vascular diameter that exacerbates the effects of nephron deficit in the premature kidney, increased glomerular capillary pressure distributed over fewer glomeruli and with lower compensatory capacity of arterioles afferent kidneys in the adjustment of inlet pressure, glomerulomegaly, hyperfiltration, proteinuria via activation of the renin-angiotensin system, glomerulosclerosis, and progressive CKD.[40-42]

It is important to emphasize that premature infants are prone to neonatal AKI, and this favors the reduction in the number of nephrons and enhances the progression to CKD. Studies have shown that AKI has an incidence of 48% in newborns < 29 weeks. It is multifactorial and is related to: vasomotor nephropathy, lower GFR during the first weeks of life, tubular immaturity, exposure to nephrotoxins, increased risk of renal vascular thrombosis, perinatal asphyxia, and sepsis. Animal models, critically ill children and surviving adults with AKI were at high risk of developing CKD.[43-45]

In April 2016, a Workshop was held with the aim of highlighting the association between fetal and child development and the increased risk of diseases in adulthood, focusing on AH and CKD, suggesting possible practical solutions for the future. The need for early action to prevent CKD and other noncommunicable diseases was highlighted. Out of this event came a consensus for action.[46]

Crump et al., (2019)[6] suggest that premature infants may need early preventive evaluation and long-term clinical follow-up for timely detection and treatment of hypertension, in addition to monitoring proteinuria and renal function. They also suggest preventive actions aimed at reducing modifiable maternal risk factors, such as obesity, sedentary lifestyle, smoking and alcohol use.

In this context, Luyckx and Brenner (2005)[47] suggested that birth weight should also be used as a surrogate marker for the future risk of adult disease, especially in underdeveloped communities.

Despite the importance of detecting changes in newborns' renal function to determine preventive actions throughout life, and even with the latest advances in science in neonatology, the assessment of renal function in premature newborns remains challenging. [48] Glomerular filtration rate (GFR), insignificant during intrauterine life, when the kidneys still do not function primarily as water and fluid regulatory organs, is represented by the GFR or plasma volume of a substance that can be completely filtered by the kidneys in a given unit of time, without undergoing reabsorption or tubular secretion. [49]

GFR is considered the most sensitive and specific laboratory marker for changes in kidney function, being essential in the detection and diagnosis of kidney diseases and in monitoring their treatment.[49] It can be estimated using predictive formulas, based on endogenous or exogenous serum markers. and clinical variables such as height, weight, and gender. [50]

Among the markers that help estimate GFR, the most commonly used is serum creatinine, an endogenous marker, produced from non-enzymatic dehydration of muscle creatine, which makes it dependent on muscle mass; it is predominantly eliminated by glomerular filtration, but is also influenced by various factors such as diet, growth and disease, muscle mass, and medications making it a sub-optimal biomarker. [51]

At birth, serum creatinine is high, as it reflects the mother's renal function, while the GFR is physiologically low, around 20 mL/min/1.73 m2 for a full-term newborn, it decreases over the first few weeks for reflect the kidney function of the newborn, while GFR increases progressively after birth until adult levels are reached by approximately 1.5-2 years of age. The serum creatinine level remains relatively stable in the first two years and increases as the child accumulates muscle mass, proportionally to the increase in GFR. [51]

Another important marker is urinary output, whose threshold for diagnosing AKI is 1 mL/kg per hour or less, on average over 24 hours on days 2 to 7 after birth. Diaper weighing every 3 hours or passing a urinary catheter are acceptable for monitoring.[45]

Another biomarker, cystatin C, can better estimate GFR in neonates due to its minimal placental transfer, relatively constant production rate and independence of inflammatory conditions, muscle mass, gender, body composition and age, but its high cost and lack of a standardized measurement method preclude its widespread clinical use so far. [52]

Recommendations present in the KDIGO (Kidney Disease Improving Global Outcomes) guidelines, aiming to improve the overall results of renal disease management, suggest the use of the Schwartz equation (2009) because it is easy to apply, using serum creatinine and height (in centimeters). [53]

Evaluation of the glomerular filtration rate

$$ClCre\ (mL/min/1.73\ m2) = \frac{K \times height\ (cm)}{SCr\ (mg/dL)}$$

K = constant

0.31 (premature)

0.33 (malnourished infant up to 12 months old)

0.45 (eutrophic infants up to 12 months old)

0.55 (> one year)

Methods: colorimetric, Jaffé, alkaline picrate, kinetic

Enzymatic method: the constant will be 0.413

In addition to GFR, alterations in renal function in children who were born prematurely can be detected in childhood, through a decrease in renal volume, increase in blood pressure (BP) or microalbuminuria. [54]

Several studies with follow-up of individuals who were born with low weight, identified renal deficit in later age groups, with prevalence that varied from 8% in Australia, 16.1% in Norway and 23.2% in the USA. [26, 55, 56] Another study carried out in Japan to estimate the prevalence of pediatric CKD recruited individuals between 3 months and 15 years of age born between 1993 and 2010 and identified a prevalence of 27.8% of CKD. [57]

Importance of the Neonatal Unit

The importance of the Neonatal Unit for the future of these children is enormous. Neonatology is the newest medical specialty and the one that has undergone the most changes due to the learning curve of the health team and technological advances. Looking at the timeline of the daily life of neonatal units, we have the dimension of changes in the routine care of these newborns who need special care. These changes are decisive for health in adult life and especially for the prevention of progressive CKD.

In the past, all newborns admitted to the Neonatal Unit were placed in Radiant Heat Cradles – this type of bed facilitated the handling of the baby, in general with many devices. However, the heating modality causes a great loss of water, making it difficult to handle water and may lead to hypovolemia and, consequently, low renal flow. Currently, the more immature the newborn is, the greater the indication of placing it in a Humidified Incubator (an advance in the strategy of reducing liquid loss due to the low-keratinized skin of preterm infants).

In addition to the type of bed to be chosen for the newborn born before term, there is the importance of fluid handling – a perennial challenge for the neonatologist – what is the appropriate water quota in different clinical situations, what parameters to use to guide the therapeutic plan. In this topic, we remember the difficulty in sharing the handling of patent ductus arteriosus. The behavior of performing water restriction and using high doses of furosemide (despite discussions about the origin of this strategy)[58] combined with stealing blood flow from the systemic to the pulmonary circulation culminated in AKI. In the past, many of these children were referred for peritoneal dialysis, often with a negative outcome. Currently, even with the survival of increasingly immature children, these indications are rare due to better understanding of physiology and better care planning.

In the care plan, the role of the multidisciplinary team is vital. The water balance is a consecrated tool for anticipating needs. Control of what is administered and losses guides the therapeutic plan for the water part. The propaedeutics also incorporated other tools that help in the analysis of the patient's volemic condition, among them, the functional echo (evaluation of vena cava volume and ejection fraction).

As already mentioned, epigenetics has had many studies and we have advanced in its understanding. Once again the Neonatal Unit is crucial. A genuine effort by the entire team to guarantee breast milk guarantees the offer of microRNA present in the fat vesicles of breast milk, which is different from the mother's milk of the preterm baby. Elegant studies have provided us with this knowledge. [59-61]

A prospective cohort study conducted in the Netherlands to assess the impact of infant feeding on the kidney function of 5,043 children with a mean age of 6 years, found that those who were never breastfed had lower renal volume and lower estimated GFR, while breastfed children had the shortest duration of breastfeeding associated with lower renal volume suggesting that breastfeeding is associated with subclinical changes in renal outcomes in childhood.[62]

The Kangaroo Mother Care and all its care logic, with increasingly early skin-to-skin contact, guarantees the construction of a robust microbiome that will provide this child with a better condition to overcome adversities in the neonatal period and in future life.[63,64] Carpeting with the home microbiota will make a difference in the risk of infection. Colostrotherapy (immunotherapy), early diet, breast milk and skin-to-skin contact – care plans designed in the Neonatal Unit and that allow better care for the kidney – in the present, in the unit and in adult life.

Regarding the management of newborns, especially neonates born premature, LBW and those with IUGR it is extremely important that health professionals are more rigorous in terms of preventing AKI due to nephrotoxicity. Exposure to nephrotoxins is high and can be reduced through the rational use of antimicrobials, antifungals and the management of other nephrotoxic drugs according to GFR estimates. Systematic supervision programs existing in some centers give warning signs about the number of concomitant nephrotoxic drugs and the need for dose adjustments according to serum creatinine and GFR contributing to reduce the risk of AKI. (Baby NINJA-Nephrotoxic Injury Negated by Just-in-Time Action).[65]

Considering that postnatal factors can increase vulnerability to kidney diseases among these children, especially those from populations living under unfavorable conditions from a socioeconomic point of view, it is opportune to recommend the establishment of care protocols for outpatient follow-up with a focus on the early identification of CKD, including serum creatinine and GFR measurements, urinary protein/creatinine ratio in morning sample, blood pressure measurements during the first years of life, in addition to timely referrals, focusing on the prevention of CKD and its complications.

A very long journey begins with a small step. On the path of life, special attention must be given to those who started with a very small step, so that we can help them to take a healthier path.

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