Low birth weight, nephron number and chronic kidney disease

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ABSTRACT

Chronic kidney diseases have a significant impact on morbidity and mortality worldwide. Low birth weight, fetal growth restriction and prematurity are indicators of fetal growth and development disorders associated with a congenital reduction in nephron number, which predisposes to an increased risk for chronic kidney disease. On an individual basis, a small nephron number at birth is not always enough to determine the onset of chronic kidney disease, but it decreases the ability of the kidneys to resist any insults to renal tissue that may occur later in life, such as exposure to nephrotoxic drugs or episodes of acute kidney injury. The high incidence of low birth weight and preterm birth globally suggests that, at the population level, the impact of alterations in fetal development on the subsequent onset of chronic kidney disease could be significant. The implementation of strategies aimed at reducing the incidence of prematurity, fetal growth restriction, as well as other conditions that lead to low birth weight and a reduced nephron number at birth, provides an opportunity to prevent the development of chronic kidney disease in adulthood. For these purposes the coordinated intervention of several specialists, including obstetricians, gynecologists, neonatologists, nephrologists, and family doctors, is necessary. Such strategies can be particularly useful in resource-poor countries, which are simultaneously burdened by maternal, fetal and child malnutrition; poor health; epidemics caused by communicable diseases; and little access to screening and primary care.

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Introduction

Cardiovascular diseases, hypertension, type 2 diabetes mellitus and chronic kidney diseases are now the leading cause of morbidity and mortality worldwide.[1] Genetic and environmental factors contribute to their pathogenesis, while fetal development influences their risk of onset. In the mid-80s the English epidemiologist David Barker first demonstrated a relationship between low birth weight, defined as weight less than 2.5 kg, and increased risk of death from cardiovascular diseases in adulthood,[2,3] and suggested that adverse conditions during gestation in the critical period of fetal life could cause the non-optimal development of certain organs (fetal programming hypothesis).

Subsequently, the association between fetal growth and developmental disorders, expressed by low birth weight, small for gestational age (birth weight below the 10th percentile for reference gestational age) or prematurity (birth before the 37th week of gestation) (Table 1), and the onset of diseases in adulthood was extended to other non-communicable diseases.[4-8] Since globally the incidence of low birth weight and preterm birth is respectively 15% and 10%,[9,10] every year millions of children are born with the risk of developing non-communicable diseases in adulthood, including hypertension and chronic kidney disease. In this regard, a recent study showed that SARS-CoV-2 infection during the third trimester of pregnancy

increases by almost three times the risk of preterm birth.[11] Therefore, the current COVID-19 pandemic, by increasing the risk of prematurity in neonates, could predispose them to the development of non-communicable diseases throughout their lives.

Fetal programming of nephron number and birth weight

In humans, nephrogenesis begins at the ninth week of gestation and ends at the 34-36th week. After birth, the ability to form new nephrons is lost. Since about 60% of nephrons is formed during the third trimester of pregnancy, preterm birth and kidney damage experienced during this period of gestation (*e.g.*, exposure to nephrotoxic drugs) may impair nephrogenesis and reduce the number of nephrons.

Autopsy studies have shown that the average number of nephrons in humans is 1 million per kidney, ranging between 210,000 and 2.7 million.[12] Despite this variability, the available evidence supports the existence of a direct relationship between the number of nephrons and birth weight. An increase of 257,426 nephrons in each kidney is estimated for every kg of body weight gain at birth.[13] Premature infants with fetal growth restriction have fewer nephrons than those with adequate weight for gestational age,[14] suggesting further inhibition of nephrogenesis by fetal growth restriction.

In 1988 Barry Brenner, a Harvard nephrologist, suggested that low birth weight neonates had a reduced nephron endowment along with a predisposition to increased risk of hypertension and chronic kidney disease if, during their lives, a further decrease in nephron number, due to episodes of acute kidney injury or the onset of diseases, such as diabetes mellitus (Figure 1), would have occurred.[15] The congenital reduction in the number of nephrons translates, according to Brenner's hypothesis, into a compensatory hyperfiltration of the glomeruli - the filtering units - to maintain the homeostasis of the organism. In the long term, this mechanism becomes detrimental to the glomeruli, resulting in the development of hypertension and proteinuria which, in turn, can progressively damage the renal parenchyma up to end-stage kidney disease.[15]

Several studies have shown that unfavorable prenatal conditions (induced by maternal exposure to dexamethasone, diets with reduced protein or caloric content) lead to reduced nephron endowment. For example, in rats, exposure to a low-protein diet during gestation was associated with a decrease in nephron number (by about 30%) and birth weight of 'new-borns' compared to controls, with subsequent development of hypertension.[16] Another study showed that fetal exposure to dexamethasone was also associated with reduced nephron number and birth weight compared to controls. In adult life, renal function (glomerular filtration rate) was significantly lower, and albuminuria was higher, in animals exposed to dexamethasone during gestation.[17]

This evidence supports the hypothesis that fetal growth and development disorders, which manifest as low birth weight or preterm birth, are associated with a congenital reduction in nephron number, thus resulting in an increased risk of hypertension and chronic kidney disease later in life.

Table 1. Definitions of birth weight categories and preterm birth.

Category	Definition
Birth weight categories	
Normal birth weight	From 2500 to 4000 g
Low birth weight	<2500 g
Very low birth weight	<1500 g
Extremely low birth weight	<1000 g
Appropriate for gestational age	Birth weight between the 10th and 90th percentile for gestational age
Small for gestational age	Birth weight below the 10th percentile for gestational age
Large for gestational age	Birth weight above the 90th percentile for gestational age
Gestational categories	
Extremely preterm	<28 weeks' gestation
Very preterm	<32 and >28 weeks' gestation
Moderately preterm	<34 and >32 weeks' gestation
Late preterm	<37 and >34 weeks' gestation
Full term	>37 weeks' gestation

Birth weight, prematurity, blood pressure

Low birth weight and prematurity are associated with increased blood pressure in adulthood. Two meta-analyses showed that systolic blood pressure values were higher in adolescents born with very low birth weight (defined as weight less than 1.5 kg) or preterm compared to controls born at term (mean increase in systolic blood pressure of 2.5 mmHg), as well as in subjects in different age groups with low birth weight compared to those with birth weight greater than 2.5 kg (mean increase in systolic blood pressure of 2.28 mmHg).[18,19]

These differences are relevant because, at the population level, it is estimated that a decrease in systolic blood pressure of 2 mmHg reduces the risk of mortality from stroke by 10% and the risk of mortality from ischemic heart disease in middle age by 7%.[20] It is important to emphasize that blood pressure may be higher, although still within the normal range, in children and adolescents born with low body weight or prematurely compared to their peers born with adequate weight or full-term. However, since it is known that blood pressure tends to increase with advancing age, it is likely that these differences in pressure are accentuated with aging. In addition, in those born with low body weight or preterm, even a rapid and excessive weight gain during infancy increases the risk of hypertension.[21,22] This evidence suggests that the impact of fetal programming on the onset of hypertension can be modulated by growth in the first years of life.

Nephron number, blood pressure and renal function

In Caucasian adults who died from road accidents, significantly lower nephron numbers were observed in hypertensive subjects compared to normotensive controls matched for gender, age, height and weight.[23] This important study demonstrated the potential causal relationship between nephron deficit and the development of hypertension. However, evaluation of the contribution of fetal programming to the onset of hypertension in adulthood was not possible due to the lack of information on birth weight. The association between reduced nephron number and hypertension

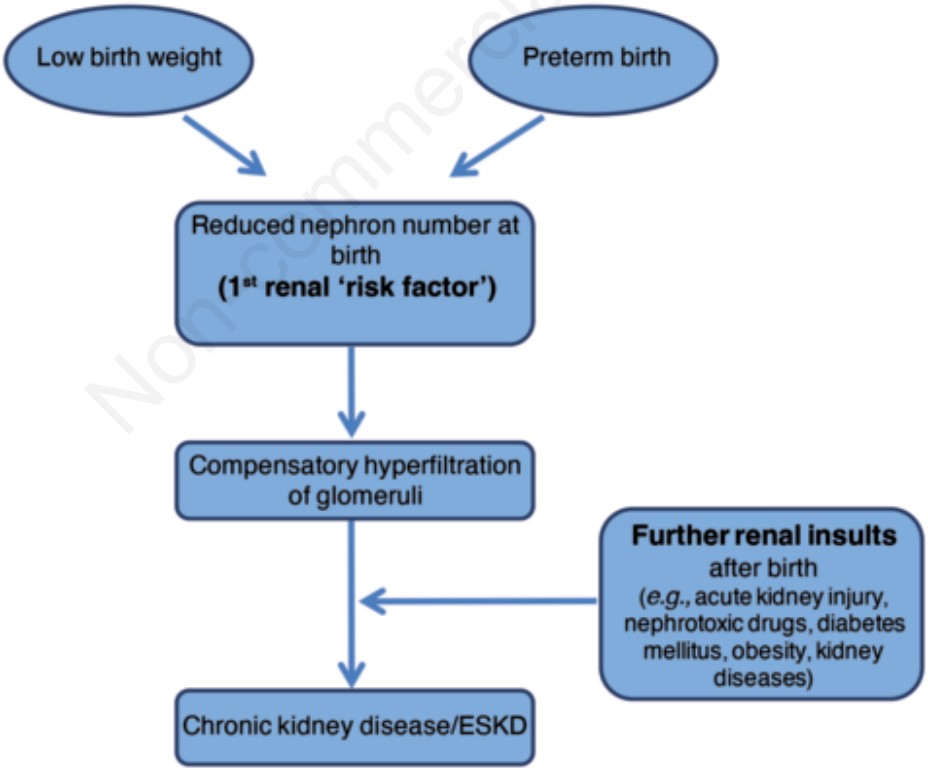

Figure 1. Effects of fetal programming on the risk of chronic kidney disease development. Fetal growth and development disorders, which manifest as low birth weight and preterm birth, are associated with a congenital reduction in nephron number (first renal 'risk factor'). Kidneys with low nephron endowment have a lower ability to compensate for any further insults that may occur throughout life, including episodes of acute kidney injury, exposure to nephrotoxic drugs, and diseases, such as diabetes mellitus, obesity, or kidney diseases. The result is a predisposition to a greater risk of chronic kidney disease and progression to end-stage kidney disease (ESKD).

was also found in African American, Australian aboriginal and Japanese populations. However, in individuals of African descent, the relationship does not appear to be as linear as that observed in other populations.[24-27]

In kidney donors, a direct correlation between glomerular filtration rate and number of non-sclerotic nephrons, estimated by morphometric analysis of the kidney biopsy in combination with computed tomography, both performed at the time of donation, was found.[28,29]

An autopsy study also showed that nephron number was significantly lower in patients with chronic kidney disease or hypertension than in age-matched normotensive controls.[27] Since the number of sclerotic glomeruli was similar in these three groups, it was hypothesized that a congenital reduction in nephron number may have contributed to the onset of hypertension and chronic kidney disease.[27,30]

Birth weight, prematurity, and renal function

Low birth weight and prematurity increase the risk of neonatal acute kidney injury. Similarly to the evidence collected about blood pressure, glomerular filtration rate may be significantly lower, albeit within the normal range, in low birth weight or preterm children and adolescents compared to their peers born at term or with adequate weight. However, with time and exposure to further renal injuries over the course of life, these differences may be accentuated, increasing the risk of chronic kidney disease.

Neonatal acute kidney injury

The incidence of acute kidney injury in the neonatal population ranges from 16% to 71%. Part of this variability derives from the lack, until recently, of a uniform definition of acute kidney injury in neonatology. To overcome this limit the classification system developed by the KDIGO organization (Kidney Disease: Improving Global Outcomes) (based on serum creatinine and diuresis) and adapted to the neonatal age was proposed (Table 2).[31-33] Premature neonates admitted to intensive care units are particularly susceptible to acute kidney injury, not only due to the possible congenital reduction in nephron number associated with preterm birth, but also due to frequent exposure to nephrotoxic drugs, such as aminoglycoside antibiotics and non-steroidal anti-inflammatory drugs. Evidence that in pediatric and adult patients exposure to nephrotoxic drugs constitutes a modifiable risk factor for the onset of acute kidney injury[34] provided the rationale for extending interest in the consequences of using these drugs also in the neonatal population. Specifically, a study conducted in a cohort of 107 very low birth weight infants showed that 87% were treated with at least one nephrotoxic drug, including gentamicin (86%), indomethacin (43%) and vancomycin (25%). Birth weight was inversely proportional to the number of nephrotoxic drugs administered. Furthermore, the treatment course with these drugs was longer in patients with acute kidney injury than in those with normal kidney function.[35] More recently, in a study involving 8283 infants admitted to intensive care units and treated with different combinations of nephrotoxic drugs, the incidence of acute kidney damage was 17%.[36] The fact that, out of the 23,399 infants exposed to nephrotoxic drugs during the period under investigation, 15,113 were excluded from the analysis due to the lack of at least two measurements of serum creatinine, as required by the KDIGO criteria, is of relevance.[36] These findings underline the need to minimize and monitor the use of nephrotoxic drugs in the neonatal population by implementing screening programs. In particular, Baby NINJA (Nephrotoxic Injury Negated by Just-in-time Action), a protocol designed to mitigate acute kidney injury associated with nephrotoxic drug exposure in infants admitted to intensive care units,[37] is based on the identification of patients receiving treatment with at least three nephrotoxic drugs within 24 hours or with aminoglycoside antibiotics for at least four days, and subsequent daily monitoring of serum creatinine until two days after the end of treatment or at resolution of the acute kidney injury episode.[37] The implementation of this program has resulted in a reduction in exposure to nephrotoxic drugs as well as in the incidence and duration of acute kidney injury episodes in the neonatal intensive care unit context.[37]

Table 2. Classification of neonatal acute kidney injury proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) organization.

Stage	SCr	Urine output
0	No change in SCr or rise <0.3 mg/dL	≥0.5 mL/kg/h
1	SCr rise ≥0.3 mg/dL within 48 h or SCr rise ≥1.5-1.9 × reference SCr* within 7 days	<0.5 mL/kg/h for 6-12 h
2	SCr rise ≥2.0-2.9 × reference SCr*	<0.5 mL/kg/h for ≥12 h
3	SCr rise ≥3.0 × reference SCr* or SCr ≥2.5 mg/dL** or receipt of dialysis	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

*Defined as the lowest previous SCr value; **SCr value ≥2.5 mg/dL (221 µmol/L) represents glomerular filtration rate <10 mL/min/1.73 m^2. SCr, serum creatinine.

In low birth weight or preterm infants, episodes of acute kidney injury in neonatal age are associated with an increased risk of mortality and a prolongation of length of stay in the neonatal intensive care unit.[38,39] Evidence from studies in preterm or full-term infants suggests that 31% (range, 9-83%) of those who survive episodes of acute kidney injury later develop chronic kidney disease.[40] Therefore, in these infants kidney function should be periodically monitored until adulthood.[40]

Glomerular filtration rate and albuminuria

Numerous studies involving subjects in different age groups have reported a reduction in glomerular filtration rate in those born with low birth weight or preterm.[41-44] In particular, in neonates on the first day of life it was observed that the clearance of amikacin, used as a marker of glomerular filtration rate, was significantly lower in those born with low birth weight or preterm compared to controls born at term.[42] In a cohort of infants born prematurely (less than 30 weeks of gestation and/or birth weight less than 1 kg), at the mean age of 7.6 years the glomerular filtration rate was significantly lower, although within the normal range, in those with perinatal growth restriction versus those with adequate growth.[43] Similarly, significantly lower mean glomerular filtration rates were reported in prematurely born adolescents than their term-born peers (126.2 mL/min/1.73 m^2 and 134.3 mL/min/1.73 m^2, respectively).[41] At a population level, it is estimated that among adolescents, one of 13 born with low birth weight, and one of five born with very low birth weight, has a glomerular filtration rate lower than 90 mL/min/1.73 m^2 and/or elevated systolic blood pressure.[45] A meta-analysis of 36 studies involving both pediatric and adult patients estimated an increase in glomerular filtration rate of 2.09 mL/min/1.73 m^2 for each kg of birth weight gain.[46] In addition, a recent study conducted in a cohort of Australian Aborigines aged 5 to 40 who underwent assessment of renal function at baseline and after a median of 11.6 years, reported that birth weight correlated directly with glomerular filtration rate and inversely with albuminuria. The increase in urinary albumin excretion between the two visits was more marked in subjects with low birth weight.[47] Furthermore, the association between low birth weight and albuminuria was amplified in the presence of high body mass index and history of post-streptococcal glomerulonephritis.[47]

The 'Dutch famine', a terrible famine that struck the Netherlands between 1944 and 1945, provided an opportunity to study the relationships between insufficient nutrition during gestation and health in adulthood. In particular, in a cohort of adults aged between 48 and 53, exposure to famine in the second trimester of pregnancy, a period of active nephrogenesis, was associated with a higher prevalence of microalbuminuria. Anthropometric measurements (weight or length) at the time of birth were not associated with the presence of microalbuminuria, suggesting the need to characterize further markers of fetal growth and development disorders capable of identifying subjects at risk of developing alterations in the permeability of the glomerular capillary wall to proteins (albeit of minor entity) in adulthood.[48]

Chronic kidney disease and end-stage kidney disease

Various case series have reported the occurrence of secondary forms of focal segmental glomerulosclerosis in adolescents or adults with very low birth weight.[49-51] Low birth weight and prematurity significantly increase the risk of chronic kidney disease in childhood.[52,53] In addition, a Japanese study estimated that about 20% of pediatric-onset chronic kidney disease appears to be attributable to low birth weight and prematurity.[52] The relationship between low birth weight and the development of chronic kidney disease has also been confirmed in studies involving adults. A meta-analysis of 31 studies that included more than 2 millions of subjects reported that being born underweight increased by 70% the risk of chronic kidney disease, defined by the combination of albuminuria, decreased glomerular filtration rate, or end-stage kidney disease.[54] In addition, a recent study reported that among people with normal birth weight, having siblings with low birth weight increases by 33% the risk of developing chronic kidney disease in adulthood.[55] These findings suggest a possible contribution of family history to the risk of developing chronic kidney disease, which could be ascribable to sharing genetic and/or environmental factors.[55] Two population-based studies have reported that prematurity also increases the risk of developing chronic kidney disease in adulthood. In particular, in a Swedish cohort the risk of chronic kidney disease among young adults (maximum age of 43 years) was almost double in those born preterm compared to full-term, and was inversely proportional to gestational age at birth.[6] In a Finnish cohort with a median age of 65 years, the risk of chronic kidney disease was significantly higher in those born before the 34th week of gestation. However, when stratified by gender, the relationship remained significant only in women.[56] These data suggest that there may be gender differences in the kidney's adaptation mechanisms to the congenital reduction in nephron number. Recently, a registry study showed that low birth weight (defined as birth weight below the 10th percentile of reference with respect to gender: 2.94 kg in males and 2.85 kg in females), reduced weight in relation to gestational age (birth weight below the 10th percentile reference

for gestational age and gender) and prematurity (birth before 37 weeks of gestation) increased the risk of developing end-stage kidney disease during the first 50 years of life by 61%, 44% and 54%, respectively. The risk was even higher in case of concomitance of the three markers of fetal growth and development disturbance.[57] Alterations in the fetal programming of the number of nephrons, which are associated with low birth weight or prematurity, are not always sufficient to cause the onset of kidney disease, on an individual level. However, it is possible that kidneys with a reduced nephron number have a lower ability to compensate for any insults to kidney tissue that may occur over the course of life, including exposure to nephrotoxic drugs, episodes of acute kidney injury, and diseases such as diabetes mellitus, obesity or renal diseases.[58] In support of this hypothesis, low birth weight has been associated with faster progression of several primary kidney diseases, including IgA nephropathy, minimal change glomerulopathy, chronic pyelonephritis, Alport's syndrome, and autosomal dominant polycystic kidney disease.[59-63] In particular, low birth weight and small size for gestational age, especially in combination, were associated with an increased risk of progression to end-stage kidney disease in young adults with IgA nephropathy.[60] Finally, it has been suggested that, regardless of weight and gestational age at birth, conditions that may lead to a congenital decrease in nephron number, such as prenatal exposure to environmental toxins (especially pesticides and heavy metals), could underlie a new form of nephropathy found in the Mexican state of Aguascalientes, common mainly in young adults aged 20 to 40 years, and characterized by glomerulomegaly and focal segmental glomerulosclerosis.[64]

Low Birth Weight and Nephron Number Working Group recommendations

The 'Low Birth Weight and Nephron Number Working Group', a multidisciplinary working group consisting in internationally renowned experts in the fields of obstetrics, neonatology and nephrology, investigated the issues related to the impact of fetal growth disorders on the development of hypertension and chronic kidney disease, with the aim of suggesting prevention strategies.[58,65] The proposed recommendations aim to improve maternal and child health and underline the importance of the collaboration of different specialists in intervening not only on strictly clinical risk factors, but more generally on people's lifestyle.[58,65]

To optimize the fetal health, maternal health before and during pregnancy must be safeguarded, paying close attention to prevention and treatment of diabetes, obesity, hypertension, and preeclampsia, according to available guidelines. Nutrition during pregnancy must ensure adequate intake of macro- and micronutrients, while harmful substances such as alcohol and tobacco must be avoided.[58,65] The growth of the fetus must be monitored and, in case of fetal growth restriction, the most appropriate time for childbirth must be established.

As also recommended by the World Health Organization, weight and gestational age at birth should be recorded. Conditions such as low birth weight, fetal growth restriction and prematurity should be part of personal health data and considered as risk factors for hypertension and chronic kidney disease.

The nutritional recommendations in pediatric age underline the importance of exclusive breastfeeding until the sixth month of life and prudent introduction of new foods to allow regular and balanced growth.[66] It is important to avoid too rapid and excessive growth to prevent renal risk associated with overweight and obesity.[9]

Children born preterm, with a low birth weight and fetal growth restriction, as well as those exposed to preeclampsia or gestational diabetes, should be followed over time in order to promptly detect first signs of renal function impairment, carrying out an annual check of blood pressure and urinalysis from the age of three years.[65] This screening can be anticipated to the first year of life in severely premature infants (born before the 32nd week of gestation), in those with very low birth weight (less than 1500 grams), and in those who developed acute kidney injury in the neonatal period.[65,67]

If other risk factors coexist (such as high blood pressure, previous episodes of acute kidney injury, proteinuria, cardiovascular disease, renal abnormalities, obesity, or diabetes), assessment of renal function - including proteinuria - should be performed at least every two years.[31,67] During childhood, screening of low birth weight, growth-restricted and preterm individuals should be carried out at medical check-ups, or at two-year intervals during school age. In low-resource settings, simplified screening could coincide with public health interventions - such as vaccination campaigns - or be conducted by community health workers. If possible, screening should be integrated with other health activities, to avoid labelling children as 'sick'. Signs of impaired renal function or structural abnormalities in the kidneys found on ultrasound examination should be followed up by a pediatrician or a pediatric nephrologist, where possible. From the age of 18 onwards, blood pressure, body mass index and urinalysis should be monitored at least every two years until the age of 40 years, and thereafter annually. All low birth weight or preterm women should be

carefully monitored during pregnancy for gestational weight gain, fetal growth, and the possible development of preeclampsia. It is important to educate families of low birth weight or preterm children to a healthy lifestyle as well as to avoid exposure to nephrotoxic drugs.[58,65]

Conclusions

Chronic kidney disease has a significant impact in terms of morbidity and mortality worldwide. Although it is not possible to quantify the impact of fetal programming on the onset of these diseases, numerous lines of evidence associate low birth weight with impaired nephrogenesis, with the consequent reduction in nephron number and an increased risk of developing chronic kidney diseases in adulthood. Implementing strategies aimed at reducing the incidence of prematurity, fetal growth restriction, as well as other conditions that lead to low birth weight and reduced nephron number at birth, offers the opportunity to prevent the onset of chronic kidney disease in adulthood. A coordinated intervention by various specialists, including obstetricians, gynecologists, neonatologists, nephrologists, and family doctors, is therefore required. Such strategies can prove particularly useful in resource-poor countries, which simultaneously bear the burdens of maternal, fetal and child malnutrition; poor health; epidemics caused by communicable diseases; and limited access to screening and primary care.

It is also mandatory to develop accurate and non-invasive methods to measure nephron number in vivo, in order to promptly identify and follow over time children predisposed to a greater risk of chronic kidney damage due to congenital decreased nephron endowment.

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