Alterations in fetal kidney development and increased risk for adult diseases

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ABSTRACT

A low birth weight (LBW, < 2500 g), intrauterine growth restriction (IUGR), and preterm birth (PB, < 37 weeks of gestational age) are the most common clinical factors for an altered programming of nephron number and are associated with a greater risk for hypertension, proteinuria, and kidney disease later in life. At present, an indirect assessment of total nephron number based on postnatal markers is the most important approach to evaluate the risk for future kidney disorders in newborn infants with a LBW, IUGR or PB.

Here we describe advances made in animal experiments and biochemical markers in humans, and the recommendations for the prevention of preconception kidney injury, including social factors and chronic diseases. According to the evidence, IUGR and prematurity alone can modulate nephrogenesis and kidney function, and, if occurring simultaneously, their effects tend to be cumulative.

Key words: nephrons, kidney diseases, low birth weight infant, intrauterine growth restriction, preterm birth.

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INTRODUCTION

A life course approach is in line with the United Nations 2030 Agenda for Sustainable Development, the World Health Organization recommendations in the Minsk Declaration, and the Global Action Plan for the Prevention and Control of Noncommunicable Diseases (NCDs).

A much broader approach is suggested for health maintenance, including kidney development and the prevention of kidney disease.^{1,2}

ENVIRONMENTAL IMPACT

Epidemiological studies have demonstrated that the preconception, fetal, and perinatal stages may have an effect on the development of adult kidney disease (*Figure*).

According to a meta-analysis of 31 studies encompassing more than 2 million subjects, infants with a LBW had a 70 % risk for chronic kidney disease (CKD) in adulthood, defined as albuminuria, reduced glomerular filtration rate or kidney failure.³ Although changes in kidney function are generally mild and may even be within normal ranges in children and adolescents, they may progress to renal dysfunction that manifests with age or overlapping kidney injuries.

Exposure to diabetes, gestational overweight and obesity, and a suboptimal maternal nutrition are more commonly recognized as risk factors for an early programming of kidney development in the offspring. Such data are based on the finding that the renal functional reserve is lower in young adult children of mothers with diabetes during gestation than in those whose fathers had diabetes.^{4,5}

Such relation is magnified by the development of acute kidney injury among preterm newborn infants,

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Medications given to the mother before delivery were also associated with an effect on neonatal kidney function. Antenatal administration of tocolytic agents was significantly associated with a lower glomerular filtration rate (GFR) in the newborn infant at 7 days.⁶ Other reports have suggested that the administration of the selective COX-2 inhibitor nimesulide as tocolytic induces kidney failure and chronic kidney disease in newborn infants.⁷

Recent studies have identified mutations in the *APOL1* gene associated with a higher risk for focal segmental glomerulosclerosis among subjects of African descent; however, largescale genome studies have failed to identify dominant genes or polymorphisms associated with most kidney diseases.⁸ In contrast to the genetic and lifestyle paradigms as determinants of NCDs, the Developmental Origins of Health and Disease (DOHaD) approach has emerged as a complementary and more comprehensive pathophysiological model of the risk for NCDs.

DEVELOPMENTAL PROGRAMMING OF NEPHRON NUMBER

In normal developmental conditions, nephrogenesis continues until the 36th week of gestation and new nephrons are not developed following a term birth.⁹ Among preterm newborn infants, nephrogenesis may occur until 40 days after birth, but it may be abnormal in extremely preterm infants.^{10,11}

An altered programming of nephron number





LBW: low birth weight (< 2500 g); PB: preterm birth (< 37 weeks of gestational age); STDs: sexually transmitted diseases. Modified from Luyckx et al.¹²

is an important liaison between the exposure to developmental stressors and the subsequent risk for hypertension and kidney disease.^{12,13} LBW, IUGR, and PB are the most common clinical factors for a low nephron number and are associated with a higher risk for hypertension, proteinuria, and kidney disease in adulthood.¹²

Data obtained in human kidneys examined post mortem showed a direct correlation between the number of nephrons and birth weight across the patient age spectrum. Based on these data, an increase of 257 426 glomeruli per kilogram increase in birth weight has been inferred.¹⁴

The general consensus is that there are approximately 1 million nephrons per kidney; however, current data indicate that the number of nephrons varies remarkably from subject to subject, up to 13 times in some populations. A large variability in the number of nephrons is already evident at birth, suggesting a strong effect on development.¹⁴ Individuals born with a total number of nephrons towards the lower end of the range may be more prone to developing hypertension and renal dysfunction, especially after exposure to renal stress, such as an additional nephron loss, hypertension or diabetes.¹⁵

Based on the early epidemiological evidence relating LBW and cardiovascular disease in adults, Brenner et al.¹⁶ proposed the hypothesis that kidney development programming may result in a reduced number of nephrons, which may in turn be a factor contributing to a higher blood pressure and a higher risk for CKD.

INDIRECT ASSESSMENT OF THE TOTAL NUMBER OF NEPHRONS

To date, an indirect assessment of total nephron number based on clinical, imaging, biochemical, and molecular markers in the postnatal period is the most important approach to evaluate the risk for future kidney disorders in newborn infants with a LBW.¹⁷

Nephron number is a critical variable in defective renal maturation and progression to kidney disease. Therefore, it is an important indicator of kidney functional capacity, and a low nephron number is considered a significant risk factor for kidney disease.¹⁸⁻²⁰

A reduced nephrogenesis may be associated with hyperfiltration, hypertension, glomerular damage, and proteinuria, which, in turn, initiate a vicious cycle leading to the loss of functional units and long-term kidney failure.²¹ Kidney disease is therefore a global public health priority. Given the high cost of treatment, both for patients and society, prevention is the most effective strategy to address the increasing global burden of kidney disease in a sustainable manner.

ANIMAL RESEARCH AND BIOCHEMICAL MARKERS IN HUMANS

Advances in animal research and biochemical markers in humans have encouraged the consensus that it is necessary to intercede early to prevent CKD and other related NCDs later in life, associated with a low number of nephrons in infants with a LBW, born small for gestational age (SGA), and with prematurity, and to design coordinated interventions.²² These strategies will allow to optimize interventions aimed at limiting or interrupting the programming cycle of CKD throughout the course of life, especially in the most underdeveloped regions.

ANIMAL EXPERIMENTS

The objective of the study by Myrie et al.,²³ a novel model of spontaneous IUGR in Yucatan miniature swine, allowed to assess the association between fetal growth impairment and rapid postnatal growth and the programming of hypertension and metabolic syndrome in adulthood. At 9 months of age, blood pressure (BP) telemetry devices were implanted to assess BP before (0.5 % NaCl) and after (4.5 % NaCl) a 7-day salt-loading period. At 10 months of age, the number of nephrons was determined. Swine with IUGR showed a relatively higher NaCl intake (p < 0.05) and experienced significant catch-up growth. Adult swine with IUGR also showed a higher BP and a 43 % reduction in the number of nephrons per kidney (p < 0.05). Nephron number evidenced a positive association with birth weight and a negative correlation with BP (p < 0.05).

The study by Boubred et al.,²⁴ demonstrated that hypertension and CKD induced by IUGR are related to the magnitude of nephron number reduction, regardless of the cause. Systolic BP, GFR, proteinuria, nephron number, and glomerulosclerosis were compared among the offspring of rats with IUGR prenatally exposed to a maternal low-protein diet (9 % of casein; LPD offspring) or maternal administration of betamethasone (BET offspring). Both antenatal interventions led to IUGR and a similar reduction in birth weight. Compared to normal controls, BET offspring showed a severe nephron deficit

(-50 %, p < 0.01), an impaired GFR (-33 %, p < 0.01)p < 0.05), and systolic hypertension (+17 mmHg, p < 0.05). The presence of glomerulosclerosis was twice as high in BET offspring than in the controls (p < 0.05). Kidney function and structure were unchanged in LPD offspring in the long term, although they showed a moderate nephron deficit compared to BET offspring. The mechanisms proposed to account for the effects of diet manipulation on the number of nephrons include epigenetic modification, global modulation of gene expression, a higher fetal exposure to glucocorticoids due to a reduced expression in placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11\beta HSD2) that metabolizes maternal glucocorticoids and prevents them from reaching the fetus and decrease renal angiogenesis.^{25,26}

Studies using rat models demonstrated that the number of nephrons decreases in the offspring proportionately to maternal vitamin A levels. A reduction in nephron number may be mediated by the effects of all-trans retinoic acid in ureteric bud branching and vascular growth in the developing kidney.²⁷ The supply of an optimal postnatal diet to rats with a LBW, when nephrogenesis is still continuing, led to the restoration of the nephron number and the prevention of subsequent hypertension.²⁸ A systematic review confirmed that deficiencies in maternal folate, vitamin A, and total energy intake during pregnancy are associated with harmful effects on kidney function and structure.⁵

Recent studies using magnetic resonance imaging with ferritin are capable of accurately measuring the number of glomeruli in mice and have been used *ex vivo* in human kidneys; however, these techniques are far from being clinically applicable in a non-invasive manner.^{22,29}

These findings underscore the importance of developing early markers of nephron number and the need for a long-term follow-up of adults born prematurely and exposed to glucocorticoids in the prenatal or postnatal period.

SUBSTITUTE MARKERS OF NEPHRON NUMBER

Both prematurity and IUGR are associated with a higher risk for kidney injuries in adulthood. According to the evidence, once renal impairment starts, it is often hard to prevent its progression to renal disease.³⁰ Therefore, it is critical to identify, as soon as possible, infants born preterm and those with IUGR at risk for kidney disease in order to initiate preventive measures before the onset of renal dysfunction.³¹

At present, an indirect assessment of total nephron number based on postnatal markers is the most important approach to evaluate the risk for future kidney disorders in newborn infants born preterm.³² Actually, it is believed that a reduction in the number of nephrons, due to a decreased nephrogenesis, is an important cause of adverse renal course in this group.¹⁸

The study by Aisa et al.,³³ showed the potential early onset of renal damage in infants with IUGR and preterm newborn infants at 30-40 days of corrected postnatal age by measuring several urinary indicators of glomerular and tubular impairment and/or injury, such as sodium transport, renin-angiotensin-aldosterone system, and sympathetic activity, which regulate kidney function. As glomeruli constitute 95 % of the renal cortical volume, in the absence of an apparent inducible glomerular hypertrophy at this postnatal phase, renal cortical volume is considered to be indicative of nephron number.³⁴

Albumin levels, N-acetyl-B-D glucosaminidase (NAG) activity, and cathepsin B activity in infants born preterm and with IUGR at a corrected age of 30-40 days were assessed, and values were compared to the data obtained in a population of term, healthy infants. Specifically, urinary protein excretion may be related to both glomerular and tubular functions, whereas albuminuria is a marker of glomerular permeability. NAG is an early, sensitive, persistent, and robust marker of proximal tubule injury and/or dysfunction.³⁵ Total renal volume and cortical volume were reestablished and estimated using 3D ultrasound technology combined with computer-assisted analysis of virtual organs, a highly reproducible and accurate technique for the assessment of organ volumes.^{36,37}

All biochemical parameters tested in newborn infants with IUGR were rather high, whereas a significant increase in cathepsin B activity, proteinuria and, to a lower extent, albuminuria, were observed in preterm newborn infants. Cathepsin B activity showed a significant, strong, and reverse correlation with all substitute markers of nephron number, in addition to a strong and positive correlation with albuminuria.^{36,37}

Total renal volume and cortical volume were significantly lower in newborn infants with IUGR and PB than in control newborn infants. Also, proteinuria and albuminuria and NAG and cathepsin B activity were reversely associated with all indirect markers of nephron number, such as gestational age, birth weight, total renal volume, and cortical volume.³⁷

The lower number of nephrons observed in LBW infants was associated with tubular injury and/or impairment that may coexist with glomerular permeability dysfunction. Recent data indicate that, following utero-placental insufficiency, the kidneys of rats with IUGR showed an alteration in the expression of genes involved in tubular development and function, both at birth and in the early postnatal period.³⁸

These data demonstrate that both IUGR and prematurity alone can modulate nephrogenesis and kidney function, and, if occurring simultaneously, their effects tend to be cumulative.

RECOMMENDATIONS FOR THE PREVENTION OF PRECONCEPTION KIDNEY INJURY

The transgenerational effects of developmental programming suggest that early care aimed at reducing the risk of long-term disease will result in a greater benefit for the subject and subsequent generations.

The preconception stage is a critical period for the development of adequate interventions to ensure both maternal and paternal health and thus prevent the potential onset of NCDs in adult life:

- 1. Implementation of comprehensive, preconception programs for general and specialty health care, and sex education for girls in primary and secondary school because these are the most critical stages in life.
- Preconception guidance in relation to diet modification, weight control, physical exercise, and lifestyle choices to optimize the health of the mother-to-be and the baby's course.
- 3. Identification and management of diseases and their complications, including pre-existing diabetes, renal failure, hypertension, anemia, and infections, which may affect maternal, fetal, and neonatal health.
- 4. Implementation of routine preconception care, immediate postpartum care after each delivery or miscarriage, and interconception care.
- 5. Facilities and governments should implement non-medical health control measures. Regarding poverty-related risk factors, some measures may include a reduction in adolescent pregnancy, access to comprehensive sex education for children and adolescents, warranted access to family

planning, pregnancy spacing, and violence prevention.

These recommendations highlight the need for an early intervention targeted at reducing LBW, SGA babies, prematurity, and a low nephron number at birth in order to prevent CKD and NCDs throughout the course of life thanks to the coordinated intervention of obstetricians, neonatologists, nephrologists, and family physicians.^{11,22,39}

A new proposal is a preventive approach, starting in the perinatal period of preterm and LBW newborn infants based on pluripotent renal stem cell induction to generate new nephrons after birth, and thus improve kidney function and prevent the onset of CKD and end-stage renal disease during the course of life.¹¹

CONCLUSIONS

Fetal kidney development programming has an impact on NCDs through the mediating effect of IUGR, LBW, and prematurity. Most maternal factors with an effect on the infant's LBW and prematurity do not exist in isolation. Their effects on kidney development are very relevant for women in developing countries, where the prevalence of infants with a LBW, born SGA, and PB is high.

The recommendations presented here are consistent with the Sustainable Development Goals proposed by the United Nations, so that reducing poverty, improving food safety, reducing adolescent pregnancy, empowering and educating girls and women, reducing maternal infections, and controlling chronic diseases that may reduce the risk for LBW, SGA, PB, preeclampsia, gestational diabetes, and maternal and child obesity may have a positive impact on the renal health of future generations. ■

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REFERENCES

- World Health Organization. Global Action Plan for the Prevention and Control of NCDs, 2013–2020. [Accessed on: April 6th, 2020]. Available at: https://www.who.int/ publications/i/item/9789241506236
- World Health Organization. Sustainable Development Goals 2015. [Accessed on: March 4th, 2020]. Available at: http://sustainabledevelopment.un.org
- White SL, Perkovic V, Cass A, Chang C, et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. *Am J Kidney Dis.* 2009; 54(2):248-61.

- Abi Khalil C, Travert F, Fetita S, Rouzet F, et al. Fetal exposure to maternal type 1 diabetes is associated with renal dysfunction at adult age. *Diabetes*. 2010;59(10):2631-6.
- Lee YQ, Collins CE, Gordon A, Rae KM, et al. The relationship between maternal nutrition during pregnancy and offspring kidney structure and function in humans: A Systematic Review. *Nutrients*. 2018; 10(2):241.
- Dorey EM, Pantaleon M, Weir KA, Moritz KM. Adverse prenatal environment and kidney development: implications for programing of adult disease. *Reproduction*. 2014; 147(6):R189-98.
- Vieux R, Fresson J, Guillemin F, Hascoet J. Perinatal drug exposure and renal function in very preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2011; 96(4):F290-5.
- Tzur S, Rosset S, Shemer R, Yudkovsky G, et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. *Hum Genet.* 2010; 128(3):345-50.
- Hoy WE, Hughson MD, Bertram JF, Douglas-Denton R, et al. Nephron number, hypertension, renal disease, and renal failure. J Am Soc Nephrol. 2005; 16(9):2557-64.
- Sutherland MR, Gubhaju L, Moore L, Kent A, et al. Accelerated maturation and abnormal morphology in the preterm neonatal kidney. *J Am Soc Nephrol*. 2011;22(7):1365-74.
- 11. Fanos V, Gerosa C, Loddo C, Faa G. State of the art on kidney development: How nephron endowment at birth can shape our susceptibility to renal dysfunction later in life. *Am J Perinatol.* 2019; 36(S 02):S33-6.
- Luyckx V, Brenner B. Birth weight, malnutrition and kidneyassociated outcomes-a global concern. *Nat Rev Nephrol.* 2015; 11(3):135-49.
- Ingelfinger JR, Nuyt A-M. Impact of fetal programming, birth weight, and infant feeding on later hypertension. J Clin Hypertens (Greenwich). 2012; 14(6):365-71.
- 14. Hughson M, Farris A 3rd, Douglas-Denton R, Hoy W, et al. Glomerular number and size in autopsy kidneys: The relationship to birth weight. *Kidney Int.* 2003; 63(6):2113-22.
- Puelles V, Hoy W, Hughson M, Diouf B, et al. Glomerular number and size variability and risk for kidney disease. *Curr Opin Nephrol Hypertens*. 2011; 20(1):7-15.
- Brenner BM, García DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? *Am J Hypertens*. 1988; 1(4 Pt 1):335-47.
- Charlton JR, Springsteen CH, Carmody JB. Nephron number and its determinants in early life: a primer. *Pediatr Nephrol.* 2014; 29(12):2299-308.
- Schreuder MF. Safety in glomerular numbers. *Pediatr* Nephrol. 2012; 27(10):1881-7.
- Paquette K, Fernandes RO, Xie LF, Cloutier A, et al. Kidney size, renal function, angiotensin peptides, and blood pressure in young adults born preterm. *Hypertension*. 2018; 72(4):918-28.
- Ingelfinger JR, Woods LL. Perinatal programming, renal development, and adult renal function. *Am J Hypertens*. 2002; 15(2 Pt 2):46S□9.
- Hoy WE, Bertram JF, Douglas-Denton R, Zimanyi M, et al. Nephron number, glomerular volume, renal disease and hypertension. *Curr Opin Nephrol Hypertens*. 2008; 17(3):258-65.
- Low Birth Weight and Nephron Number Working Group. The Impact of Kidney Development on the Life Course: A Consensus Document for Action. *Nephron.* 2017; 136(1):3-49.

- 23. Myrie SB, McKnight LL, Van Vliet BN, Bertolo RF. Low birth weight is associated with reduced nephron number and increased blood pressure in adulthood in a novel spontaneous intrauterine growth-restricted model in Yucatan miniature swine. *Neonatology*. 2011; 100(4):380-6.
- 24. Boubred F, Laurent D, Buffat C, Tsimaratos M, et al. The magnitude of nephron number reduction mediates intrauterine growth-restriction-induced long term chronic renal disease in the rat. A comparative study in two experimental models. *J Transl Med.* 2016; 14(1):331.
- Kett M, Denton K. Renal programming: cause for concern? *Am J Physiol Regul Integr Comp Physiol.* 2011; 300(4):R791-803.
- Doan T, Briffa J, Phillips A, Leemaqz S, et al. Epigenetic mechanisms involved in intrauterine growth restriction and aberrant kidney development and function. *J Dev Orig Health Dis.* 2020; 1-11.
- Merlet-Bénichou C, Vilar J, Lelièvre-Pégorier M, Gilbert T. Role of retinoids in renal development: pathophysiological implication. *Cur Opin Nephrol Hypertens*. 1999; 8(1):39-43.
- Wlodek M, Mibus A, Tan A, Siebel A, et al. Normal lactational environment restores nephron endowment and prevents hypertension after placental restriction in the rat. *J Am Soc Nephrol.* 2007; 18(6):1688-96.
- 29. Baldelomar EJ, Charlton JR, Beeman SC, Hann BD, et al. Phenotyping by magnetic resonance imaging nondestructively measures glomerular number and volume distribution in mice with and without nephron reduction. *Kidney Int.* 2016; 89(2):498-505.
- Remuzzi G, Benigni A, Remuzzi A. Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. *J Clin Invest.* 2006; 116(2):288-96.
- TaalMW, Brenner BM. Predicting initiation and progression of chronic kidney disease developing renal risk scores. *Kidney Int.* 2006; 70(10):1694-705.
- 32. Tsuboi N, Kanzaki G, Koike K, Kawamura T, et al Clinicopathological assessment of the nephron number. *Clin Kidney J.* 2014; 7(2):107-14.
- 33. Aisa MC, Cappuccini B, Barbati A, Orlacchio A, et al. Biochemical parameters of renal impairment/injury and surrogate markers of nephron number in intrauterine growth-restricted and preterm neonates at 30-40 days of postnatal corrected age. *Pediatr Nephrol*. 2016; 31(12):2277-87.
- Cappuccini B, Torlone E, Ferri C, Arnone S, et al. Renal echo-3D and microalbuminuria in children of diabetic mothers: a preliminary study. *J Dev Orig Health Dis.* 2013; 4(4):285-9.
- Skálová S. The diagnostic role of urinary N-acetyl-B-D glucosaminidase (NAG) activity in the detection of renal tubular impairment. *Acta Medica (Hradec Kralove)*. 2005; 48(2):75-80.
- Rousian M, Verwoerd-Dikkeboom CM, Koning AH, Hop WC, et al. Early pregnancy volume measurements: validation of ultrasound techniques and new perspectives. *BJOG*. 2009; 116(2):278-85.
- 37. Brennan S, Schneider M, Watson D, Kandasamy Y, et al. The renal parenchyma-evaluation of a novel ultrasound measurement to assess fetal renal development: protocol for an observational longitudinal study. *BMJ Open.* 2017; 7(12):e019369.
- Nusken E, Spencer L, Wohlfarth M, Lippach G, et al. Wholetranscript expression analysis identifies new candidate

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genes involved in renal tubular programming after uteroplacental insufficiency in rats. *J Dev Orig Health Dis.* 2015; 6(Suppl 2):S140. 39. Lurbe E, Wühl E. Hypertension in children and adolescent: New perspectives. New York: Springer; 2019.