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Low birth weight, nephron number, and kidney disease

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Low birth weight, nephron number, and kidney disease. More and more evidence is emerging that highlights the far-reaching consequences of prenatal (intrauterine) programming on organ function and adult disease. In humans, low birth weight (LBW) occurs more frequently in disadvantaged communities among whom there is often a disproportionately high incidence of adult cardiovascular disease, hypertension, diabetes mellitus, and kidney disease. Indeed, many epidemiologic studies have found an inverse association between LBW and higher blood pressures in infancy and childhood, and overt hypertension in adulthood. Multiple animal models have demonstrated the association of LBW with later hypertension, mediated, at least in part, by an associated congenital nephron deficit. Although no direct correlation has been shown between nephron number and birth weight in humans with hypertension, nephron numbers were found to be lower in adults with essential hypertension, and glomeruli tend to be larger in humans of lower birth weight. An increase in glomerular size is consistent with hyperfiltration necessitated by a reduction in total filtration surface area, which suggests a congenital nephron deficit. Hyperfiltration manifests clinically as microalbuminuria and accelerated loss of renal function, the prevalence of which are higher among adults who had been of LBW. A kidney with a reduced nephron number has less renal reserve to adapt to dietary excesses or to compensate for renal injury, as is highlighted in the setting of renal transplantation, where smaller kidney to recipient bodyweight ratios are associated with poorer outcomes, independent of immunologic factors. Both hypertension and diabetes are leading causes of end-stage renal disease worldwide, and their incidences are increasing, especially in underdeveloped communities. Perinatal programming of these 2 diseases, as well as of nephron number, may therefore have a synergistic impact on the development of hypertension and kidney disease in later life. Existing evidence suggests that birth weight should be used as a surrogate marker for future risk of adult disease. Although the ideal solution to minimize morbidity would be to eradicate LBW, until this panacea is realized, it is imperative to raise awareness of its prognostic implications and to focus special attention toward early modification of risk factors for cardiovascular and renal disease in individuals of LBW.

Resumen

Existen cada día más evidencias que documentan las consecuencias a largo plazo de la programación prenatal (intrauterina) de la función orgánica y su relación con la enfermedad en el adulto. En humanos, el bajo peso al nacer (BPN) se presenta con mayo frecuencia en poblaciones marginadas, en las cuales se observa también una incidencia desproporcionadamente mayor de enfermedad cardiovascular, hipertensión, diabetes mellitus y enfermedad renal. Efectivamente, muchos estudios epidemiológicos han reportado una asociación inversa entre el BPN y una presión arterial elevada en la infancia, así como con hipertensión arterial en el adulto. Múltiples modelos en animales de experimentación han demostrado la asociación entre el BPN y el desarrollo posterior de hipertensión, mediado en parte por un déficit de nefronas al nacer. Aunque no se ha demostrado en humanos hipertensos que exista una correlación directa entre el número de nefronas y el peso al nacer, si se ha encontrado que en individuos con hipertensión esencial, el número de nefronas se encuentra disminuido y los glomérulos tienden a ser más grandes en personas con BPN. El aumento en el tamaño del glomérulo es consistente con la hiperfiltración requerida para compensar la disminución en el área total de la superficie de filtración, sugiriendo un déficit congénito de nefronas. La hiperfiltración se manifiesta clínicamente mediante la microalbuminuria y el deterioro acelerado de la función renal; la prevalencia de ambos es mayor en individuos con BPN. Un riñón con un número disminuido de nefronas, tiene una reserva renal menor para adaptarse a excesos en la dieta o el compensar el daño renal, como se demuestra en el trasplante renal, donde injertos pequeños en relación al peso corporal del receptor, se asocian a malos resultados, independientemente de factores de tipo inmunológico. Tanto la hipertensión como la diabetes son las principales causas de insuficiencia renal a nivel mundial y su incidencia ha aumentado, especialmente en países en desarrollo. La programación perinatal de estas dos enfermedades, así como del número de nefronas, pueden por lo tanto tener un efecto sinérgico en el desarrollo posterior de hipertensión y enfermedad renal. Existen evidencias que sugieren que el peso al nacer debe de ser utilizado como un marcador de riesgo a futuro del desarrollo de enfermedad en la vida adulta. Aunque la solución ideal sería el erradicar el BPN, y en tanto no se logre esta panacea, lo recomendable es alertar sobre sus implicaciones pronosticas, poniendo especial atención en la modificación temprana de los factores de riesgo de enfermedad cardiovascular y renal en individuos con BPN.

Genetic factors are important determinants of development and function of major organ systems, and susceptibility to disease. Environmental factors are also important. More and more evidence is emerging highlighting the far-reaching effects of prenatal (intrauterine) programming on subsequent organ function and adult disease. This review will outline the effects of fetal programming on renal development (nephrogenesis) and the risk of hypertension and kidney disease in later life.

Key words: low birth weight, kidney disease, intrauterine programming.

Low birth weight (LBW) is defined by the World Health Organization as a birth weight of <2500 g. LBW and intrauterine growth retardation (IUGR, below the tenth decile for birth weight) occur more frequently in disadvantaged communities and have been associated with a subsequent disproportionately high incidence of cardiovascular disease, hypertension, diabetes mellitus, and kidney disease in these populations [1–4]. In the United States, the incidence of LBW is twice as high in the African American compared with the Caucasian population [1, 5–7]. Risk factors for LBW and IUGR appear to be relatively consistent among different populations, including blacks, those of Asian origin, maternal hypertension, maternal smoking, poor maternal weight gain during pregnancy, shorter maternal height, poor antenatal care, and lower socioeconomic status [1, 8–10]. However, maternal anthropometrics, health, age, and socioeconomic status do not entirely explain the disparity in LBW among African American and Caucasian American infants [6]. Factors intrinsic to black ethnicity may therefore have an independent impact on birth weight.

Fetal malnutrition and IUGR may result broadly from maternal undernutrition and/or placental insufficiency. Henriksen and Clausen have highlighted the importance of distinguishing between these 2 causes of IUGR, because they are likely to have different impacts among different populations [11]. Placental insufficiency results from poor placentation, usually associated with preeclampsia and maternal cardiovascular risk factors. This is likely to have a greater impact on LBW than maternal diet in adequately nourished populations. In poorer communities, however, maternal malnutrition is more prevalent and is likely to have a significant independent effect on fetal outcome in addition to placental insufficiency. Maternal malnutrition is complex, and dietary composition may be more important than total calorie intake in determining pregnancy outcomes, birth weight, and subsequent disease. Moderate maternal undernutrition periconception in sheep has been associated with increased risk of preterm birth [12]. Langley-Evans et al have demonstrated that even short periods of maternal protein restriction during gestation in rats are associated with LBW and subsequent hypertension [13–15]. In humans, increased maternal lean body mass and protein turnover at 18 weeks of gestation are associated with increased length of babies at birth [16]. In an analysis of the long-term effects of different dietary compositions ingested during pregnancy, higher blood pressures were seen at 40 years of age in offspring of mothers who had had a high carbohydrate intake during pregnancy, but whose animal protein intake had been under 50 g daily [17]. Similar dietary composition is highly prevalent among poor communities. In another study, however, ethnic differences in nutritional intake among pregnant women were found not to account for the disparities in LBW among nulliparous women from population groups [5].

Maternal hypertension is a significant risk factor for LBW and is more prevalent among black than white women, making the population-attributable risk of LBW highest among babies of hypertensive black mothers [1]. Furthermore, IUGR of the mother has been identified as a risk factor for IUGR of her offspring [18]. It is tempting to speculate that the increase in maternal hypertension among black women may be part of a vicious cycle resulting from maternal LBW, predisposing to hypertension, which in turn predisposes the offspring to LBW and subsequent hypertension.

LBW AND THE KIDNEY

Multiple animal models have demonstrated the association of LBW (induced by gestational exposure to low protein diet, dexamethasone, gentamicin, vitamin A deprivation, or uterine ischemia) with later hypertension [13, 19–24]. The link between adult hypertension and LBW in these animal models appears to be mediated, at least in part, by an associated congenital nephron deficit occurring with IUGR [19, 21, 23]. Vehaskari et al demonstrated an almost 30% reduction in glomerular number in LBW rats as compared with those of normal birth weight, and the LBW rats had systolic blood pressures that were 20 to 25 mm Hg higher by 8 weeks of age [21]. Similarly, Celsi et al found that prenatal administration of dexamethasone in rats was also associated with LBW and fewer glomeruli compared with controls. In these nephron-deficient rats, glomerular filtration rate (GFR) was reduced, albuminuria was increased, urinary sodium excretion was lower, and tissue sodium content was higher [19]. Studies examining the effect of LBW on the activity of the renin-angiotensin system have found that renin and angiotensin activity and renal messenger RNA levels are reduced in LBW animals, possibly consistent with a degree of volume expansion secondary to sodium retention [21, 22]. These findings in animals lend credence to the hypothesis initially put forward by Brenner et al that a congenital deficit in nephron number, resulting in a decreased filtration surface area and thus a limitation in renal sodium excretion, may be an independent factor determining susceptibility to essential hypertension in humans [25].

LBW AND HYPERTENSION IN HUMANS

Consistent with the animal data, many human studies have also revealed an inverse association between LBW and higher blood pressures in infancy, childhood, and adulthood. In children, most studies have reported higher blood pressures in those who had been of LBW,