Disparities in Renal Endowment: Causes and Consequences

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In humans, nephrogenesis is completed by 36 weeks of gestation. Thus, human kidney development is complete at the time of birth in full-term infants. Those infants born before 36 weeks of gestation are still undergoing nephrogenesis for several weeks after their preterm birth and, accordingly, may be exposed to medications that impact the kidney during its final stages of renal development. The ultimate nephron number (nephron endowment) may influence future response to kidney injury, should it occur. The concept that nephron number may strongly influence blood pressure as well as susceptibility to kidney disease in later life developed in parallel with that of perinatal programming, which holds that the perinatal milieu causes changes that permanently alter organ structure and function, preordaining adult physiology to some extent. Both concepts together may help elucidate, at least in part, the pathogenesis of not only primary but secondary hypertension. This article summarizes human data on nephron number and its evaluation and considers the circumstances, implication, and management of persons born with or acquiring a decreased complement of nephrons early in life. Insufficient data exist to predict outcome or guide management. However, a common-sense approach of avoiding nephrotoxins and minimizing renal stress is indicated.

Index Words: Nephrogenesis; Hyperfiltration; Renal endowment

Renal development in humans is complete by the time a fetus reaches 36 weeks of gestation; subsequently, no new nephrons are formed.[1] However, infants born before 36 weeks of gestation are still undergoing nephrogenesis until they reach the equivalent stage of development; as a result, they often are exposed to medications that impact the kidney during its final stages of renal development. After the completion of nephrogenesis, the kidney grows in length and volume, largely because of increases in the size of the renal tubule, the renal interstitium, and the glomeruli.[1,2] According to the most recent studies, nephron number, when directly assessed in human kidneys, has ranged from 200,000 nephrons/kidney to slightly more than 2 million per kidney, a 10-fold variation.[3,4] Variation in human nephron number has been evident for many years;[5] but, over the past 2 decades, nephron number has been increasingly linked both to risk for kidney disease and hypertension.[6-8] During the same period of time, there has been an increasingly noted association between intrauterine growth, as marked by birth weight, length, and placental size, and subsequent risk in later life for both kidney disease and hypertension, as well as risk for other conditions.[9-11]

The recognition of such risks stems from 2 different disciplines: epidemiology and nephrology. In the late 1980s, Barker et al[9,10] reported an inverse relationship between birth weight and the incidence of coronary disease and hypertension in midlife, introducing a concept of perinatal programming, now often termed developmental origins of health and disease. Their initial observations linking birth weight and future outcome did not include kidney size or nephron number; rather, the concept that nephron number might be related to birth weight was derived from another discipline. It had been hypothesized by Brenner et al,[12,13] at roughly the same time as the first articles about perinatal programming, that hypertension and kidney disease were likely linked to relatively lower glomerular number. It was not long before nephrologists and physiologists who became aware of the perinatal

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programming theory of Barker et al[12,13] asked whether kidney size for body weight and glomerular number might not be lower among people who had been relatively small for dates (small for gestational age) as neonates. Thus, the early reports that birth weight and future cardiovascular disease might be linked stimulated research to establish whether there were perinatal origins of kidney disease.

A number of experimental models soon indicated that perinatal factors indeed could influence future blood pressure, kidney function, and nephron number.[14-23] For example, studies in protein-restricted and protein-calorie–restricted maternal animal models confirmed the clinical observations noted in the initial studies by Barker et al: offspring of restricted mothers had higher blood pressures during adult life,[18,20-22] as well as evidence of decreased lifespan. A number of studies focusing on kidneys in such experimental models showed that the offspring of dams subjected to protein restriction or protein-calorie restriction had offspring with fewer glomeruli, decreased glomerular filtration rate, and evidence of hyperfiltration later in life. Showing that protein restriction or protein-calorie restriction in humans, however, leads to a low number of nephrons has been elusive to date, despite compelling data from animal models. Additional nongenetic manipulations during gestation, such as vitamin A deficiency,[15] glucocorticoid administration,[23] and iron deficiency,[17] also lead to decreases in nephron number (low nephron endowment) in animal models, but parallel data in humans are still limited.

Reviewing the observations in experimental models, a number of investigators speculated that adverse intrauterine conditions might be a potential initiator of intrarenal changes during nephrogenesis and could have far-reaching effects and that might provide at least a partial explanation for the wide variance in nephron number in otherwise apparently normal people. Furthermore, it seemed possible that the intrauterine milieu might also be linked to the propensity of certain ethnic groups to have a high incidence of chronic kidney disease. Stated in another way, if the diet and general health status of whole groups of pregnant women were suboptimal, might not their children be at greater risk for a host of future health problems?

Over time, the concept that antenatal milieu may lead to alterations in nephrogenesis, either through restricted growth or the secondary effects of restricted growth, has become a topic of increasing interest. How these changes occur is unclear. Some have suggested that change occurs by simply altering the normal sequence of nephron development. There might be a change in the normal pattern or timing of key gene activation, or, alternatively, changes in the environment of the fetus such as a maternal low protein diet might induce epigenetic changes.[24-27]

What are the human data concerning birth weight, renal size, and nephron number? Or, to put it another way, how does one assess nephron endowment in human beings? Where are we in being able to manage someone who might have a lower-than-optimal number of nephrons?

Markers of Kidney Function and Kidney Size

A major limiting factor in interpreting kidney data to support the perinatal programming hypothesis in people is that few studies include kidney outcomes with hard data. Kidney tissue is not generally available from normal persons during life, and, even when it is available, counting glomeruli directly is technically demanding.[28-33] Furthermore, when one examines glomerular number in adult life, a legitimate question is whether a decrease in nephron number is because of a lack of nephron development long before the inquiry or nephron loss at a later time. The most accurate measurements of nephron number are direct counts in whole kidneys, obviously not feasible during life.

Thus, a major question is whether it is possible to estimate nephron number reliably when tissue is unavailable. Until there is a relatively noninvasive method for correlating nephron number with kidney mass, there will be difficulties in interpreting the data obtained. However, surrogates for nephron number have been sought. Kidney volume is the most common surrogate used.[34] However, unless kidney volume is linked to an invasive