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Maternal determinants of renal mass and function in the fetus and neonate

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A B S T R A C T

The impact of adverse maternal and early gestational issues, ranging from maternal–fetal interactions all the way through to premature birth, are recognized as having influence on the subsequent development of chronic diseases later in life. The development of chronic kidney disease (CKD) as a direct result of early life renal injury or a sequela of diseases such as hypertension or diabetes is a good model example of the potential impact that early life events may have on renal development and lifelong function. The global monetary and human resource cost of CKD is exorbitant. Socio-economic factors, along with other factors (genetic and environmental) may significantly influence the timing and display of phenotypic expression in fetuses and neonates at risk for developing CKD, yet very few of these factors are studied or well understood. In general our focus has been directed at treatment once CKD is established. This strategy has been and remains short-sighted and costly. Earlier understanding of the intrauterine determinants of renal mass development (i.e. environmental "biomes", poor maternal–fetal health, socio-economic factors impacting early life events, diet, access to value based health care and educational opportunities on disease evolution) may allow us an opportunity for earlier intervention. This article aims to provide some foundation for improved understanding of the maternal determinants of renal mass and function in the fetus and neonate.

1. Introduction

The health-related costs of chronic kidney disease (CKD) exceed US$28 billion per year and impact close to three-quarters of a million Americans [1–4]. It is very likely that some of these individuals developed the initial stages of CKD early in life [1–4]. Indeed, adverse/stressful exposures in the fetal environment and/or the neonatal period likely modify the target organ structure and/or epigenetic profile whereby long-term functionality may be compromised [5]. Infants and children who develop early CKD are at significant risk for associated health problems beyond those directly attributable to kidney disease, as they have not completed their physiologic or intellectual maturity [4]. A variety of different states that impact intrauterine stress such as maternal psychosocial stress, undernutrition, and energy excess (i.e. hyperglycemia) may impact on interactions with the outside environment in the postnatal period and ultimately lead to a chronic disease susceptible state such as CKD [5,6].

Kidney development (nephrogenesis) in humans begins around nine weeks of gestation [7,8], with the majority of nephrons (60%) forming during the third trimester [9]. On average the nephron endowment of a human kidney is determined by 36 weeks of gestation [10]. Nephrons cannot regenerate and the number of functional nephrons gradually declines over time associated with an age-dependent decline in glomerular filtration rate (GFR) that is observed in elderly adults [11]. For premature infants, nephrons continue to form postnatally, but data observed in premature infants (birth weight <1000 g) suggests that postnatal nephron development ceases after 40 days. In the ex-utero environment, the most recently formed nephrons are particularly vulnerable to maldevelopment and dysfunction [12,13]. The reader is referred to an excellent review by Little et al. [14] for a more in-depth review of the developmental interactions and possibilities for renal regeneration.

Long-term childhood CKD studies are key to our understanding of the impact of the maternal/fetal environmental on chronic disease development (i.e. CKD). This is especially true since it is possible that adaptive renal developmental and functional

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plasticity in the fetus, neonates, children, and adults may provide opportunity for manipulation/intervention of both environmental and prior-exposure factors to impact programming of renal biologic systems. For example, straightforward dietary manipulation and tight blood pressure control in adult CKD patients may have profound effects on CKD progression and outcomes. Whereas these approaches are important, addressing such risk factors in the fetal stage may alleviate the need for long-term (and expensive) treatment as we age. Currently, North American and European investigators are monitoring childhood cohorts of patients with CKD in order to better understand the natural progression and treatment of CKD and to identify significant risk factors for patients at risk for developing progressive CKD [6,15–19].

2. Fetal determinants of CKD

Surviving in a stressful or resource-poor (or excess) environment forces a fetus to make "developmental programming choices" in utero about how to utilize scarce resources or handle excess resources in a way that maximizes the likelihood of survival in early life [5]. This adaptation occurs even at the expense of increased susceptibility to chronic diseases later in life. This theory, proposed by David Barker (the Barker hypothesis) has revolutionized how we medically conceptualize chronic disease development over a lifetime [20]. This kind of developmental programming among low birth weight infants has been suggested to be causative for adulthood hypertension, insulin resistance, and coronary artery disease [21–23]. When applied to CKD, the Barker hypothesis presents a unifying hypothesis that implicates a net reduction in nephron mass/structure from either congenital abnormalities and/or environmental stressors that ultimately leads to CKD. The observation that human nephron numbers vary widely (ranging from ~0.25 million to 2 million per kidney [24]) allowed Dr Barry Brenner (nephrologist) to propose that either a congenital or programmed reduction in nephron number might explain why some individuals are more susceptible to hypertension and CKD as they age [25]. Brenner elaborated that, with a reduction in nephron number, a normal GFR can only be maintained if individual nephrons enlarge to increase their total surface area available for renal work [26]. Although this would initially be adaptive, over time the excessive single nephron workload or hyperfiltration leads to nephron dropout, scarring, and progressive renal injury [27]. Low nephron number may result from genetic defects in, or environmental impacts on, the signaling pathways involved in congenital abnormalities of the kidney and urinary tract (CAKUT) [28] (see Chapter 1 in this issue of *Seminars*). The mechanisms by which intrauterine growth retardation (IUGR) and low birth weight results in low nephron number have been studied in rat models of poor intrauterine environments. Adverse intrauterine environments can be induced experimentally by caloric restriction (or excess) or protein restriction or uterine artery ligation and placental insufficiency [29]. Offspring develop with low nephron numbers and later in life develop hypertension, proteinuria, and glomerular scarring, especially in the setting of additional postnatal stressors such as high protein diet or additional glomerular injury [30–36]. Studies of the mechanism by which IUGR may induce hypertension have suggested roles for hormonal and neural pathways [32,37–41]. Other studies have indicated that altered gene expression may be the result of epigenetic regulation [32,42,43] which impacts phenotypic expression.

3. The impact of prematurity

Even without specific renal birth defects, theoretical, experimental and observational data suggest that there is an increased risk of CKD for infants born prematurely. An analysis of 426 participants enrolled in the Chronic Kidney Disease in Children Study cohort determined whether abnormal birth history [defined by low birth weight (LBW) <2500 g], prematurity (gestational age <36 weeks), small for gestational age (SGA; birth weight <10th percentile for gestational age), or requirement for intensive care unit (ICU) care at birth were associated risk factors for poor growth outcomes in children identified with subsequent CKD (median baseline GFR was 42.9 mL/min per 1.73 m^2). A high SGA prevalence (14%), LBW (17%), prematurity (12%), and intensive care unit care post delivery (40%) was associated with CKD development. This led the investigators to conclude that SGA and LBW are novel risk factors associated with short stature and lower weight percentiles in children with mild to moderate CKD independent of kidney function [19]. Similarly, a recent retrospective systematic review of 31 cohort/case–control studies found a 70% increase in the risk of developing progressive CKD by adulthood for infants with a birth weight of <2.5 kg [44]. Clinical signs of reduced nephron mass among patients born prematurely may include hypertension, proteinuria (microalbuminuria), and CKD. Two premature (<30–32 weeks gestation) patient case series ($N = 50$ in each study) found that children born prematurely had smaller kidneys and higher blood pressure compared to full term controls, even though their GFR remained normal [45,46]. Microalbuminuria, which may be an early and sensitive indicator of kidney disease and a marker for future cardiovascular morbidity [47], was also found to be more prevalent among children aged 8–11 years who were born prematurely or with low birth weight [48,49].

Animal studies have also demonstrated a similar clinical presentation and progression of CKD in the face of reduced nephron endowment. In rodents, nephron development normally continues for 5–7 days postnatally and prenatal exposure to low protein and low vitamin A supply, perinatal exposure to gentamicin, and antenatal exposure to steroids all reduce nephron number in offspring [50,51]. In fact, mice born one or two days prematurely develop a CKD phenotype by five weeks of age, exhibiting hypertension, albuminuria, and a reduced nephron number [52]. Additional evidence comes from a baboon model of prematurity in which animals are delivered prematurely and maintained under conditions that very closely approximate the neonatal intensive care unit (NICU), including mechanical ventilation and treatment with nephrotoxins [53,54]. In similar fashion to human infants, the nephrons of the premature baboons demonstrate a high percentage of histological abnormalities postnatally [53].

4. Maternal determinants of CKD

The nutritional state of a woman from the time of her own mother's conception may influence how well she can nourish a future fetus. The concepts of preconceptional health status (and education) in providing an optimum environment for the future fetus, and the potential for negative renal health impact, need to be considered from a personal and public health perspective [5]. Animal studies consistently demonstrate that poor nutrition in the preconception period or during medication-related in-vitro exposures may lead to reduced nephron number in offspring [5]. In fact there is increasing evidence (human and animal studies) that vitamin A deficiency might negatively effect the intrauterine environment and significantly reduce nephron number [55]. Focused investigation on micronutrients and how they are delivered is an important, cost-effective, and commonsense method of understanding CKD evolution resulting from an altered maternal fetal environment [56].

Hsu and colleagues hypothesized that CKD development may be programmed prenatally. To address their hypothesis they