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REVIEW

The implications of fetal programming of glomerular number and renal function

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Abstract Large epidemiological studies suggest a clear relation between low birth weight and adverse renal outcomes evident as early as during childhood. Such adverse outcomes may include glomerular disease, hypertension, and renal failure. Data from autopsy material and from experimental models suggest that reduction in nephron number via diminished nephrogenesis may be a major mechanism, and factors that lead to this reduction are incompletely elucidated. Other mechanisms appear to be renal (e.g., via the intrarenal renin–angiotensin–aldosterone system) and nonrenal (e.g. changes in endothelial function). It also appears likely that the outcomes of fetal programming may be influenced postnatally, for example, by the amount of nutrients given at critical times.

Keywords Fetal · Epigenetics · Pediatrics

Introduction

Recent studies have demonstrated an increased prevalence of end-stage renal failure in adults who were small for gestational age (SGA) at birth [2, 3]. However, whether low birth weight is a primary risk factor for renal dysfunction in later life requires further examination. Such questions as whether epidemiological evidence that low birth weight infants have a higher risk of renal dysfunction in later life is robust and whether a reduction in nephron number is involved must be more definitively answered. Whether specific mechanisms are involved and whether programming of renal disease ends with birth or continues with postnatal modification are questions requiring further study. The present review aims to address these issues.

Epidemiological and experimental evidence for altered renal function after low birth weight at term

A relatively lower birth weight has been associated with many subsequent health problems. Approximately 10 years ago, Lackland and coworkers reported that low birth weight was associated with early onset end-stage renal failure in US residents from a variety of ethnic backgrounds [1]. Of 1,230 cases with ESRD, 70% of patients (858) were black, 72% (892) were male, 19% (233) had diabetes, 29% (359) had hypertension, and 46% (571) were "other." The odds ratio (OR) for renal failure was 1.4 (95% confidence interval [95%CI], 1.1–1.8) for the entire group including patients with diabetes mellitus and hypertension. More recently, Li et al. reported that more men who self-reported having had a relatively low or a relatively high birth weight also had evidence of chronic kidney disease (CKD) when screened using estimated glomerular filtration rate (eGFR) [4]. A U-shaped association between birth weight and CKD in men was observed, compared with men whose birth weight was between 3,000 and 3,999 g, those whose birth weight was less than 2,500 g had 1.65-fold odds (95%CI, 1.24–2.20) of

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CKD, and those whose birth weight was 4,500 g or over had 1.41-fold odds (95%CI, 1.06–1.88) of CKD [4].

One difficulty with such associational studies is that the primary effects of low birth weight on renal function cannot be separated from conditions that were also associated with SGA birth, such as maternal diabetes mellitus type 2 and arterial hypertension during gestation.

A recently published report from a population-based cohort of 7,457 young Norwegian adults participating in the Nord Trøndelag Health [HUNT 2] Study was of great interest because the subjects were young and generally free of chronic conditions such as diabetes mellitus and hypertension [5]. The authors observed a birth weight-dependent increase in the incidence of renal failure that was evident as early as 20–30 years of age in a cohort without obvious confounders. Compared with men with birth weight appropriate for gestational age (n=2,755), ORs for low–normal creatinine clearance (<100 mL/min) were 1.66 (95%CI, 1.16–2.37) if SGA (n=261) and 2.40 (95%CI, 1.46–3.94) if very SGA (n=101); similar results were seen in women [5]. Lopez et al. reported similar results in children [6].

Focusing on end-stage renal disease, a hard clinical endpoint, a recent large population-based cohort study reported that of 2,183,317 children born in Norway between 1967 and 2004, 526 developed end-stage renal disease. Those with a birth weight below the tenth percentile (SGA) had a higher risk of end-stage renal failure than those who were not SGA (relative risk 1.5; 95% CI, 1.2–1.9). Furthermore, the development of end-stage renal disease in former SGA patients compared to controls appeared to be more probable below 14 years of age than after age 15 [2]. Patients under the age of 14 years are unlikely to have factors predisposing for chronic renal failure such as diabetes mellitus and hypertension. Thus, the reason for higher incident end-stage renal disease under age 15 is unclear, particularly whether a separate analysis excluding congenital malformations would come up with the same results. While the study of Vikse et al. was able to show an association between birth weight and end-stage renal disease, not all studies have been able to demonstrate altered renal function in SGA children [7].

In a current meta-analysis by White and coworkers that included 32 studies, 16 reported a significant association between low birth weight and risk of CKD and 16 observed a null result. The combination of weighted estimates from the 18 studies for which risk estimates were available (n= 46,249 plus 2,183,317 from the record linkage study) gave an overall OR of 1.73 (95%CI, 1.44–2.08). Combined ORs were consistent in magnitude and direction for risks of albuminuria (OR, 1.81; 95%CI, 1.19–2.77), end-stage renal disease (OR, 1.58; 95%CI, 1.33–1.88), or low eGFR (OR, 1.79; 95%CI, 1.31–2.45) [8].

Glomerular disease in childhood and relation to birth weight

Idiopathic or minimal lesion nephrotic syndrome in childhood is usually associated with a good prognosis and an initial complete response to glucocorticoids with resolution of proteinuria in about 90% of patients [9]. A poor course is either characterized by steroid dependence (relapses when glucocorticoids are tapered) or steroid resistance (lack of response to glucocorticoids). Retrospective clinical studies have reported that children with a history of low birth weight who have idiopathic nephrotic syndrome have a higher incidence of relapses and steroid dependence [10, 11, 15]. Children with such a course have a higher need for additional therapy to control their nephritic syndrome, for example, alkylating agents and cyclosporine A. Other, more recent studies have confirmed a more severe course and a higher rate of steroid resistance in children with nephrotic syndrome with a history of having been SGA babies [12, 13]. However, the underlying mechanisms are not yet delineated.

Data reported in the 1990s indicate that up to 30% of patients with IgA nephropathy presenting in childhood eventually develop end-stage renal failure [14]. A retrospective study of 62 children with IgA nephropathy reported a threefold greater number of sclerotic glomeruli among those children with IgA nephropathy who were born SGA compared to those who were not [11, 15]. However, no recent data linking birth weight with progression of IgA nephropathy appear to be available.

Most children who develop acute post streptococcal glomerulonephritis recover well. However, a recent paper speculated that low birth weight [16] may be associated with adverse outcomes. In a case report of a child with bilateral renal hypoplasia and, at age 8, an episode of acute glomerulonephritis, a poor outcome was hypothesized due to the low nephron endowment [17]. The authors review the literature on acute post infectious nephritis and suggest that fewer nephrons may be associated with poorer outcome. Whether children with a history of low birth weight are more prone to develop focal renal scarring has been addressed in both a study by Hellström et al. [19] and in a commentary by Winberg [18], both raise the possibility that renal endowment may play a role in the response to acquired renal disease in the context of an influence of low birth weight on renal scarring due to urinary tract infection.

Intrauterine growth restriction and later morbidity: animal models

Most data originating from human studies are based on epidemiological associations. Although epidemiological

methods minimize confounding factors as much as possible, such studies are associative and cannot prove causal relationships between an initial programming event such as intrauterine growth restriction (IUGR) and later morbidity. Therefore, animal studies have been utilized to demonstrate causal relationships. The most widely used models are a physical model of uterine artery ligation in the rat and protein restriction in the rat and other mammalian species. In this section, space limitations permit us to cover only principles of the animal models.

The ligation of both uterine arteries reduces blood flow to the placentas of individual rat fetuses. This model is, therefore, considered reminiscent of placental insufficiency in humans. Uterine artery ligation is commonly used to examine metabolic disorders such as diabetes mellitus [20, 21] and also to explore the effects on renal disease [25].

Protein restriction has been the most widely used method for demonstrating how IUGR affects the cardiovascular system and the kidney [22–24]. Although a number of mammalian models of protein restriction have been employed, most studies have been carried out in rats. In such work, pregnant rats are fed an isocaloric but protein-restricted diet, varying from 10% to 40% of normal protein intake. This model mimics protein restriction, which is thought to be a frequent cause for IUGR in developing countries.

Recently, the protein-restricted model was employed to examine susceptibility to acquired renal diseases. For example, using a protein restriction animal model, we studied male IUGR offspring of protein-restricted mothers and observed that these offspring subsequently had increased susceptibility to a more severe and potentially chronic course when an acute mesangioproliferative glomerulonephritis [injection of an anti-Thy-1.1 antibody] was induced [24]. Such studies suggest that animal models may have additional utility for addressing putative causal relationships between IUGR and kidney disease and may help to delineate the mechanisms of fetal programming of renal disease.

More details on animal models and their use in unraveling mechanisms of fetal programming may be obtained from recent overviews [26, 27].

Low nephron number and fetal programming of renal function

Nephron number has been acknowledged as a determinant of susceptibility to renal disease [28, 29] and, possibly, to the development of hypertension both in animal models [30] and in human beings [31–33]. During nephrogenesis, both intrinsic and extrinsic factors with myriad interactions "program" nephron number, ultimately resulting in what has been called "nephron endowment" [34]. Following the completion of nephrogenesis, no further nephrons are formed, but subsequent nephron loss due to aging or renal injury decreases nephron number.

The sequence and timing of nephrogenesis (in rodents, usually complete by 14 days of life) and a number of the mechanisms by which the different steps occur appear tightly regulated [34, 35]. Table 1 shows some of the genes involved in nephrogenesis and lists abnormalities that may occur when there are mutations. Mice with deletion of genes that are important for crucial steps of nephrogenesis, such as paired homeobox-2 (Pax-2) or glial cell line-derived neurotrophic growth factor (GDNF) [36], have a decrease in nephron number. Likewise, patients with specific mutations

Table 1 Gene defects leading to congenital renal disorders with pathological nephron formation (modified according to [70])

Disease	Impairment of nephron development	Genes	Syndromes
Nephrotic syndrome	Glomerular defect	WT1	Frasier, Denys–Drash, WAGR
		NPHS1	Finnish type NS
		LMX1B	Nail-patella syndrome
		LAMB2	Pierson syndrome
		NPHS2	Steroid-resistant NS
Oligomeganephronia	Few large nephrons	PAX2	
Renal aplasia (agenesis)	Absence of kidney, usually unilateral, rarely bilateral	EYA1	Branchio-oto-renal syndrome
Renal hypoplasia	Reduced number of nephrons	PAX2	Renal coloboma
		SALL1	Townes–Brocks
		GLI3	Pallister–Hall
Renal dysplasia	Abnormal nephrons and reduction in number	FRAS1, FREM2	Fraser
		SOX9	Campomelic dysplasia
		NPHP1, 4, 5	Senior–Loken

NS nephrotic syndrome

in genes involved in nephrogenesis may have a decrease in nephron number [35].

It was recently reported that common variants of two genes, PAX2 [37] and RET [38], are associated with renal size in humans. However, a variant in GDNF did not appear linked with renal size in humans [39]. However, such association studies require replication in additional populations before conclusions can be reached.

Although the final complement of nephrons is likely genetically predetermined to some extent, it may be compromised by adverse environmental conditions. IUGR is probably the best investigated condition that results in impaired nephrogenesis and nephron underdosing. Among the factors that have been shown to interfere with nephrogenesis during the critical period are selective vitamin deficiencies, certain antibiotics, maternal infections, hyperglycemia, and steroid administration [40, 41]. Unfortunately, the data from studies of such factors are difficult to interpret, since timing and dosage appears to be important—e.g., steroid administration can program the renin–angiotensin–aldosterone system (RAAS), but the effect depends on when during gestation the drug is administered.

Given the complexity of nephrogenesis, it is doubtful that low nephron number is the sole consequence of materno-fetal disturbances during the critical period of nephrogenesis. However, it seems likely that an adverse intrauterine environment may result in additional structural and/or functional defects, for example, altered tubular handling of sodium, potassium, or chloride or aberrant or inappropriate activation of other vasoactive systems (i.e., the RAAS) that may have detrimental consequences on long-term kidney function [41].

In most human studies, a strong correlation has been noted between glomerular number and low birth weight on one hand [42] and kidney mass on the other, suggesting that either birth weight or kidney volume might roughly correlate with nephron number, permitting these measures to be used as surrogate markers. Another surrogate marker for nephron number might be glomerular size or volume. It is well known that nephron reduction in animal models and human beings is accompanied by glomerular enlargement, presumably as a compensatory mechanism. Glomerular enlargement is most likely caused by hyperfiltration of remaining glomeruli in order to sustain whole kidney function [43]. The concept that hyperfiltering glomeruli progress to glomerular sclerosis in the setting of low nephron number was first addressed by Brenner in his hyperperfusion injury hypothesis [31, 44], which posited that hyperfiltration had the potential to accelerate the progression of renal insufficiency.

Increased blood pressure is often present in the setting of renal insufficiency, but a relationship between low nephron number and higher blood pressure likely develops much earlier in the pathophysiological cascade. Support for this concept was provided most clearly by Keller et al. [32] who reported a small case control autopsy study that observed that persons dying with hypertension had about 50% fewer glomeruli with a mean volume about 50% larger compared to people without hypertension. Limitations included the fact that there were only ten people in each group and all were Caucasian. These relationships have been confirmed in a larger autopsy study in white Americans, but could not be confirmed in African Americans [33]. The general paucity of glomerulosclerosis in both studies would argue against accelerated nephron loss as the primary cause of lower nephron number. These findings are at least compatible with the concept that higher blood pressure might derive, in part, from reduced nephron endowment [31]. The underlying pathogenic mechanisms, however, are not as yet clear from human studies. These issues have been studied in greater depth in rats and sheep. Such animal studies indicate that an experimentally induced loss of a critical nephron mass during fetal development or shortly after birth favors the development of hypertension and subsequent kidney damage [45]. In human beings with unilateral kidney aplasia [46] as well as in kidney transplant recipients of small donor kidneys with lower nephron number, there is an increased risk of hypertension and, in the case of transplants, graft failure [47, 48]. In children with congenital unilateral renal agenesis, elevated 24 h blood pressure was noted compared with children who had unilateral renal nephrectomy after birth [49]. On the other hand, donation of a kidney or unilateral nephrectomy of the adult [either man or rat] leads to increased risk of proteinuria, but not necessarily to marked hypertension [50].

Other mechanisms contributing to fetal programming of renal function

A number of vasoactive systems that contribute to nephrogenesis appear to be altered in response to change in the intrauterine milieu. An important indicator of changes in the intrauterine milieu that might lead to fetal programming of renal disease is thought to be alteration in the RAAS. Experimental models of fetal programming have reported an increased renal renin expression in adult rats that had been born IUGR after maternal protein restriction [51–53]. Furthermore, in neonatal rats born to protein-restricted dams, there was a suppression of the RAAS [22]. More recently, it was reported that the adrenal expression of the angiotensin II 1b receptor [AT_{1b}-R] in rats with IUGR is increased. This is likely due to an epigenetic mechanism, as the authors observed that the proximal promoter of the $AT_{1b\text{-}R}$ gene was hypomethylated, which would facilitate

heightened transcriptional activity [53]. In humans, there is only one AT_1 receptor, rendering it unclear whether these findings would apply to humans. However, in a recent clinical study, increased salt sensitivity was reported to be present in children with low birth weight, which might indicate a higher aldosterone activity or a change in AT_1 receptor expression or affinity [54].

These results may indicate that the RAAS is primarily suppressed after IUGR before it becomes hyperactive later in life, which might contribute to hypertension and renal disease.

Another renal alteration that has been reported in models of maternal protein restriction is an alteration in the activity of 11β-hydroxysteroid dehydrogenase [11βHSD]. This enzyme, present in the cells of the distal renal tubule, converts active cortisol into inactive cortisone [55]. Under physiological circumstances, this reaction protects the mineralocorticoid receptor from stimulation by cortisol. In the IUGR rat model, renal 11βHSD expression is reduced, allowing for increased mineralocorticoid activity [56]. Interestingly, a reduction of 11βHSD has been reported in the placenta of human pregnancies complicated by IUGR [57, 58]. These observations might imply that maternal cortisol, which is usually inactivated by the placental 11βHSD2 can pass to the fetus. As a consequence, cortisol may lead to growth restriction and potentially to a programming of renal 11βHSD in the unborn child [55, 56].

In addition to renal mechanisms, programming of extrarenal tissues has been investigated with regard to potential roles in increasing the risk of future renal and vascular disease. For example, the endothelium and its interaction with vascular smooth muscle cells may contribute to the likelihood of future renal and vascular disease. Low-birth-weight human newborns at 3 days of life have been demonstrated to have an attenuated forearm skin vasodilation response to local application of acetylcholine [59]. Similar findings have been reported on older children and young adults [60]. In addition, a study in which sodium nitroprusside, which causes endothelium-independent vasodilation, was administered did not reveal differences between children with low and normal birth weight [61]. Thus, the endothelium, with its multiple signaling systems, particularly the NO system, may be important in programming of adult disease. Impaired NO-mediated vasodilation, increased generation of superoxide, and decreased expression of soluble guanylate cyclase have been proposed as potential mechanisms [27]. Whether such mechanisms might contribute to renal dysfunction is unknown at present.

Another extrarenal mechanism that has been considered in the context of fetal programming of kidney disease is increased sympathetic nerve activity, since there is a relation between birth weight and basal heart rate in adulthood [62]. The hypothesis that increased sympathetic nerve activity is a consequence of a challenging intrauterine environment is supported by animal data reporting that denervation of renal sympathetic nerve supply leads to a normalization of blood pressure in IUGR rats [63]. Such a mechanism is of almost certain importance for renal function, since sympathetic nerve activity regulates intrarenal renin synthesis and salt retention.

Postnatal modification of fetal programming of kidney disease

One of the first potential strategies considered to prevent morbidity after IUGR is the avoidance of hyperalimenta-

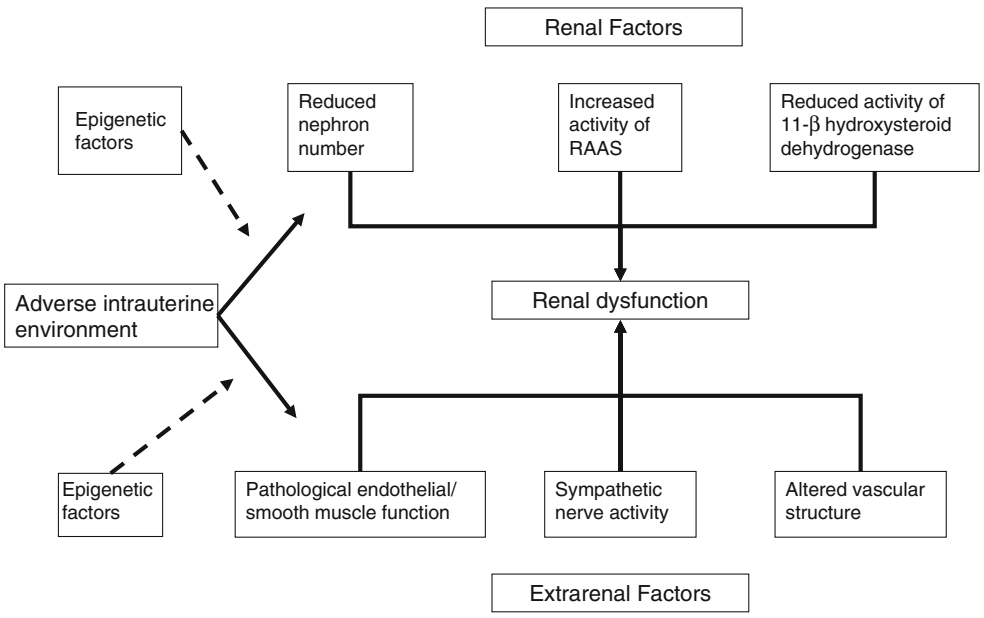

Fig. 1 Potential renal and extrarenal mechanisms involved in the perinatal programming of renal function. These factors are influenced via an adverse intrauterine environment, potentially by epigenetic mechanisms

tion. Data concerning the offspring of two famines that occurred during World War II, the Dutch famine, and the Siege of Leningrad show different results. Offspring of women who endured the Dutch famine at the end of World War II had a higher incidence of metabolic diseases such as diabetes mellitus type 2 later in life if their mothers had been in the third trimester during the nutrient deprivation [64]. In contrast, there was no increase in either the incidence of glucose intolerance or type 2 diabetes among offspring whose mothers were pregnant during the Siege of Leningrad [65]. The traditional explanation, although challenged, is that intrauterine nutrient deprivation led to a programming of endocrine systems towards energy saving in fetal life. If there was continued nutrient deprivation after birth, this would be well tolerated by a baby whose intrauterine environment was also deprived [as in the Leningrad offspring]. In contrast, rapid reconstitution of energy supplies and, therefore, relative surplus of energy, as in the offspring of the Dutch famine, would lead to deposition of adipose tissue, predisposing to pathological glucose tolerance. Details concerning this so-called match–mismatch phenomenon is summarized in a recent review by Gluckman et al. [66]. There is considerable evidence that rapid increase in caloric and protein intake postnatally plays an important pathophysiological role in developmental origins of health and disease [67]. Low birth weight and premature infants grow at different rates, and rapid "catch-up" growth may not be good. For example, babies who had higher calorie and protein intake from infant formula boosted from 284 to 301 kcal/100 ml and from 1.4 to 1.8 g/100 ml of protein had an increase of diastolic blood pressure by 3.5 mmHg at the age of 6–8 years [68]. In another study, accelerated catch-up growth was associated with higher blood pressure [69]. Given such reports, the International Societies of Paediatric Endocrinology and the Growth Hormone Research Society presently discourage nutrient-enriched diets for low-birth-weight infants [67].

Whether these observations are of importance for renal function as well is not yet known and might be subject for future studies. In the previously mentioned retrospective study in 62 children with idiopathic nephrotic syndrome in which the authors looked at the course of the disease and related it to birth weight and weight gain in the first 24 months of life, there was no association between the extent of postnatal catch-up growth and the severity of disease [12].

Conclusions

Adverse outcomes after low birth weight include glomerular disease, hypertension, and renal failure. Reduction in nephron number may be a major mechanism, and factors that lead to this reduction must be elucidated. It also appears likely that the outcomes of fetal programming may be influenced postnatally, for example, by the amount of nutrients given at critical times (Fig. 1). Thus, it is important to consider how much hyperalimentation should be provided during a newborn intensive care unit stay, or whether, in some circumstances, it should be avoided.

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