Consequences of Intrauterine Growth Restriction for the Kidney

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Key Words
Intrauterine growth restriction · Low birth weight · Nephrogenesis · Glomerular number · Kidney function · Glomerular hyperfiltration · Glomerulosclerosis · Renin-angiotensin system · Nitric oxide · Insulin-like growth factor I

Abstract
Low birth weight due to intrauterine growth restriction is associated with various diseases in adulthood, such as hypertension, cardiovascular disease, insulin resistance and end-stage renal disease. The purpose of this review is to describe the effects of intrauterine growth restriction on the kidney. Nephrogenesis requires a fine balance of many factors that can be disturbed by intrauterine growth restriction, leading to a low nephron endowment. The compensatory hyperfiltration in the remaining nephrons results in glomerular and systemic hypertension. Hyperfiltration is attributed to several factors, including the renin-angiotensin system (RAS), insulin-like growth factor (IGF-I) and nitric oxide. Data from human and animal studies are presented, and suggest a falling IGF-I and an inhibited RAS in intrauterine growth restriction. Hyperfiltration makes the kidney more vulnerable during additional kidney disease, and is associated with glomerular damage and kidney failure in the long run. Animal studies have provided a possible therapy with blockade of the RAS at an early stage in order to prevent the compensatory glomerular hyperfiltration, but this is far from being applicable to humans. Research is needed to further unravel the effect of intrauterine growth restriction on the kidney.

Introduction

In recent years, evidence has mounted on the relation between low birth weight (LBW) and diseases in adulthood. Since Barker and Osmond [1] linked a higher incidence of cardiovascular disease with the fetal environment, intrauterine growth restriction (IUGR) is used to explain the association between LBW and raised blood pressure, insulin resistance and non-insulin-dependent diabetes mellitus, dyslipidemia and end-stage renal disease (ESRD) [2–10]. In this review we discuss the broad range of the literature on the effects of IUGR on the kidney.

Kidney Development

Three different renal organs are formed during fetal life, the pronephros, mesonephros and metanephros [11, 12]. The first two degrade, but the latter becomes the per-
Renal Consequences of IUGR

Renal development is influenced by any insult disturbing the fine balance in the interactions that form the kidney. In humans, the most important factors influencing fetal development are malnutrition (especially in poor countries) and uteroplacental insufficiency (primary cause of IUGR in western countries) [55, 56]. Another hypothesis that explains the LBW and diseases in later life is based on excessive exposure to glucocorticoids in the fetus due to inhibition of the placental enzyme 11β-hydroxysteroid dehydrogenase [57]. This enzyme converts active steroids into inactive metabolites, thereby protecting the fetus from overexposure of endogenous steroids. If the 11β-hydroxysteroid dehydrogenase is inhibited or if the fetus is exposed to exogenous steroids, fetal growth is inhibited [57].

The resulting IUGR leads to a lower number of nephrons [58–61]. An inverted relationship has been shown between birth weight and nephron number, even in individuals with an appropriate birth weight for gestational age [53, 61–63]. Irrespective of birth size, premature birth can also disturb nephrogenesis and lead to a nephron deficit [64, 65]. Kidney dimensions on ultrasound have been shown to explain the number of nephrons in primates [66], and are reduced in late gestation [67–72], in the first year of life [73–75], and in childhood [75, 76] after IUGR. Kidney weight is also reduced in childhood [77].

The low nephron endowment will lead to a compensation in the residual nephrons [78], resulting in hypertrophy and hyperfiltration [79]. However, this adaptation may have adverse effects in the long run according to the hyperfiltration theory [79–83]: by reabsorbing more sodium and raising glomerular pressure, systemic blood pressure rises and albuminuria may develop. This results in sclerosis of glomeruli, culminating in a vicious circle which may continue to ESRD [80, 83–86]. The prevalence of ESRD indeed is higher in populations with increased rates of LBW [87–90]. The nephron number is inversely related to glomerular volume [63], and glomerular enlargement is found in these ethnic groups with a high incidence of hypertension and progressive renal disease [91, 92], both associated with IUGR [5, 6]. Hayman et al. [93] described in 1939 an association between nephron number and hypertension. An autopsy study in humans from Keller et al. [94] confirms the link between hypertension and fewer, but larger glomeruli, providing evidence for a low number of glomeruli as an explanation for primary hypertension.

A study in rats, using prenatal dexamethasone, shows that there is only a reduction in nephrons when administered on days 15–16 and 17–18 which coincides with an increase in blood pressure [95], again linking the nephron number with hypertension. After maternal protein restriction in the rat, a direct association between blood pressure and glomerular number has also been established [96].

Another renal mechanism that can explain the association between IUGR and hypertension is based on an increased tubular sodium reabsorption. Manning et al. [97] have shown upregulation at both the mRNA and protein level of two critical renal sodium transporters, i.e. bumetadine-sensitive Na-K-2Cl cotransporter (BSC1) and thiazide-sensitive Na-Cl cotransporter (TSC).

Animal Models

In order to study the effects of IUGR on the kidney, various animal models have been used. Some studies utilize naturally occurring IUGR animals [98–104]. Methods to induce fetal growth restriction are based on maternal deprivation of nutrients (total intake [105–118] or a component like protein [34, 119–143], vitamin A [144], sodium [145, 146] or iron [147, 148]), placental embolization [149, 150], surgical reduction of placental blood flow [104, 123, 151–163], or the use of steroids [95, 164–172]. Tables 1–3 provide an overview of the effects of nongenetic IUGR on kidney morphology and function in various animal studies. The results of these animal models of IUGR show that marked structural and functional alterations take place in the kidney. The most important systems that are associated with the low glomerular number will be discussed below, and are depicted in figure 1.
### Table 1. Effect of IUGR on renal macroscopic morphology

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Table 2. Effect of IUGR on renal microscopic morphology

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Renin-Angiotensin System

The RAS plays an important role in the regulation of capillary resistance and composition and volume of the extracellular fluid, especially the distribution of sodium [13]. These factors are closely interrelated with systemic blood pressure and with renal hemodynamics. A normal functioning RAS is also necessary for normal nephrogenesis [13–19]. An inhibition of the RAS in utero can therefore play a role in the etiology of a low nephron number after IUGR. In fact, a low plasma renin activity (PRA) [133, 173] and reduced levels of renal renin protein and mRNA [134] have been described in newborn IUGR rats, even though the results are nonequivocal [174]. However, abnormal maturation of the RAS in the human fetal kidney has been described after IUGR [175], and the RAS does not seem to be inhibited by IUGR, but rather increased: PRA is raised in cord blood of LBW babies, both in utero [176, 177] and at birth [69, 178]. This may be a compensatory mechanism for a faltering nephrogenesis due to a deficiency of another growth factor. Other animal models show changes in the RAS that are more in line with the results in humans. In fetal sheep, gene expression of the RAS is upregulated after maternal steroid treatment [166] leading to a fetal expression that resembles the normal neonatal phase suggesting a premature maturation of the fetal kidney. However, removal of endometrial caruncles, leading to fetal hypoxia and IUGR,
was associated with similar plasma renin concentrations, but reduced levels of renin and angiotensinogen mRNA [154], and treatment with cortisol reduces renin mRNA expression [179]. Fetal treatment with dexamethasone in sheep increases pulmonary angiotensin-converting enzyme (ACE) concentration but not renal ACE [180]. These results indicate activation of the fetal RAS in IUGR and suggest that responsiveness of the fetoplacental vasculature to the peptide is not diminished as would be expected from the elevated plasma angiotensin II (ANG II) levels [178]. Fetal RAS is related to the production and response to prostaglandins, which has been found to be increased in fetal sheep during IUGR [181].

Genetic or pharmacological alterations in the RAS are also known to alter kidney development. When ACE inhibitors are used during pregnancy, especially during the second and third trimester, they have been shown to be fetotoxic, resulting in fetal hypotension, renal tubular dysplasia and anuria-oligohydramnion [182, 183]. These effects of ACE inhibition in the developing kidney are due to a reduction in the renal expression of critical growth factors [184], possibly mediated by angiotensin II receptor type 1 (AT1) [185].

Nephrogenesis in the rat ends around the 8th postnatal day [12, 27, 186–191]. Treatment of neonatal rats (i.e. during active nephrogenesis) with an AT1 antagonist [192–194] or an ACE inhibitor [192, 195, 196] leads to a decreased nephron number and an altered renal water handling, suggesting an important role for ANG II in nephrogenesis. However, not all studies show similar effects. Using proper stereological techniques, McCausland et al. [16] described no difference in glomerular number, size and morphology when neonatal rats were treated with ACE inhibitors or AT1 antagonists, even though gross vascular and tubular damage was evident.

After nephrogenesis, the RAS is likely to be upregulated after IUGR, thereby causing hyperfiltration and hypertension. At a higher age, control rats show an age-dependent decline in PRA whereas IUGR rats develop hyperreninemia [173]. After maternal food restriction, 4-month-old rats show increased ANG II and plasma aldosterone levels [118].

At the age of 19 years, PRA was not related to birth weight z-score in humans [197]. When hypertension has developed, PRA and ANG II levels are found to be the same in rats after prenatal protein restriction [124, 134], but a greater and prolonged response to ANG II has been shown [140] as well as an enhanced expression of AT1 receptor, indicating a faltering downregulation [198]. Nine-month-old sheep born after maternal food restriction show similar AT1 and AT2 receptor expression, but an increase in renal cortex ACE expression [116]. ACE activity in humans shows no correlation with birth weight at birth and 1 month of age, but there is a negative cor-

![Fig. 1. Potential mechanisms leading to low glomerular number and subsequent hypertension.](image-url)
relation at the age of 3 months [199]. In rats, plasma [124] and pulmonary ACE activity is raised [118, 122], but renal ACE activity is unaltered [118, 129]. In 3-month-old pigs, renal and pulmonary ACE concentration is reduced with no difference in plasma ACE concentration [200]. The higher ACE activity is likely to contribute to the hypertension that is linked to IUGR. Control of the glomerular hypertension with ACE inhibitors has been shown to be effective in preventing glomerular damage and hypertension: this has been described after IUGR [127, 201], surgical renal mass reduction [202] and in hypertensive rat strains [203–207]. However, human studies are lacking, which makes it preliminary to suggest such a treatment in men.

Even though studies show conflicting results, most papers suggest that growth failure induces suppression of the fetal RAS, which could be a causal pathway to explain the reduced nephron number. However, in later life the RAS is activated inappropriately, which may contribute to hypertension. Another possible causeway can be the renal sympathetic nerve activity, which has been shown to be increased after induced uteroplacental insufficiency in the rat [160]. This can lead to a reset hyperfiltration, after which RAS is normalized or even reduced while the hyperfiltration and hypertension persist.

Insulin-Like Growth Factor I

In rodent kidney development, insulin-like growth factor I (IGF-I) plays an important role in metanephric morphogenesis [208, 209]: blocking IGF-I expression with antibodies [210] or the IGF-I receptor with antisense oligonucleotides [211] leads to an impaired development. Reduced amounts of circulating IGF lead to a nephron deficit [212] and early glomerulosclerosis [213], whereas treating IGF-deficient mice with IGF-I increases the number of glomeruli [209].

Variations in the IGF-I gene are associated with LBW in some populations [214] but not in all [215], and IGF-I levels are known to be reduced in cord blood from IUGR fetuses [216–218], newborn runt pigs [219] and fetal IUGR rats [220].

In kidney development, there is an interaction between the RAS and IGF-I. ACE inhibition in neonatal rats leads to an increased renal expression of IGFBP-1 [221], thereby inhibiting IGF-I action. By adding IGF-I to the ACE inhibition, the animals show normalized renal function and histology [23]. After long-term IGF-I infusion in fetal sheep, the RAS is intensely activated and kidney mass has increased [222]. IGF-I may therefore be a possible link in the association between IUGR and renal developmental problems.

Nitric Oxide

An important system for the kidney also involves the endothelial function of arteries and the nitric oxide (NO) system. In utero, NO production is upregulated to maintain a low resistance in the fetoplacental circulation [223]. IUGR newborns exhibit a higher endogenous NO production in the first 48 h of life [224].

IUGR rats showed a higher NO excretion at the age of 4 weeks, but a similar excretion at the age of 8 weeks [225]. In adult IUGR rats, endothelial dysfunction in association with a decrease in activity and expression of endothelial NO synthase was described [226, 227]. Others have shown a diminished NO-dependent vasorelaxation [111, 138, 228–231]. Deficiency of NO, induced by exogenous inhibition of NO generation by arginine analogues leads to hypertension [232–234], and increased levels of PRA [234, 235], suggesting a role of RAS activation through endogenous NO inhibition after IUGR.

Uric Acid

The role of uric acid, which decreases the production of NO and produces endothelial dysfunction [236], is subject of renewed interest [237]. An inverted relationship between birth weight and serum uric acid has been shown [238]. Several reports associate a higher serum uric acid level with increased blood pressure [239, 240], cardiovascular events [241, 242] and progression of renal disease [243]. A recent report shows that uric acid leads to glomerular hypertension by inducing arteriolopathy of preglomerular vessels [244]. The serum uric acid level is influenced by renal tubular function, since the uric acid reabsorption is linked to proximal sodium reabsorption. Since IUGR leads to an increased tubular sodium reabsorption [97], uric acid may possibly be a causative agent linking IUGR and adult diseases.

Apoptosis

Nephrogenesis is a process that requires structural formation and reformation, in which apoptosis plays an important role [25, 28–34]. As IUGR influences the for-
formation of nephrons, it has been suggested that apoptosis clears more progenitor cells during development. In fact, apoptosis is found to be altered by IUGR: rats exhibit an increased renal apoptosis as shown by TUNEL assay [34, 133, 155]. Juvenile IUGR rats show an increased caspase-3 activity, which is necessary for DNA fragmentation that characterizes apoptosis [155]. Levels of Bcl-2 (an anti-apoptosis protein) mRNA are reduced, while levels of an apoptosis-related protein (Bax) are increased [155]. This is related to an altered p53 gene expression, which is a known regulator of apoptosis-related proteins [155]. Later in life, no effect of IUGR was described: in kidneys from 9-month-old sheep, similar levels of apoptosis and caspase-3 activity were found after maternal food restriction [116].

**Short-Term Consequences**

In utero, the developing kidney is already functionally affected by growth restriction: fetal urine production, measured by ultrasound, and glomerular filtration rate (GFR) are decreased [68, 245].

Directly postnatal, LBW infants show a higher fractional sodium excretion and decreased glomerular filtration [246, 247]. We have shown that in 1-day-old neonates, the birth weight z-score is associated with the clearance of amikacin, which is a marker for GFR [Schreuder et al., unpubl. data]. Clearance of vancomycin is also lower in LBW neonates [248]. Renal artery blood flow has been shown to be lower in LBW infants [249]. A recent study in extremely LBW infants, born both premature with normal birth weight as well as premature with IUGR, demonstrated that GFR and tubular functions are impaired at the age of 6–12 years when compared with term controls [250]. No difference between the groups born with low versus appropriate birth weight for gestational age was noted. The authors conclude that being born prematurely will impair nephrogenesis, with no additional unfavorable effect of the IUGR [250]. Prematurity has been identified before as a risk factor, and results in a lower glomerular number [64], a high percentage of renal failure in the neonatal period, and an increased risk of renal insufficiency later in life [251]. A recent study in preterm children showed a negative association between GFR and birth weight and between albumin-creatinine ratio and birth weight at the age of 19 years [252]. In contrast, other studies in adolescents described no influence of birth weight on GFR and proteinuria [253, 254].

**‘First Hit-Second Hit’ Hypothesis**

According to the ‘first hit-second hit’ hypothesis [130], the low nephron number influences the presentation and course of accompanying renal disease, thus altering the prognosis. This was first described by Duncan et al. [255] in patients with idiopathic membranous nephropathy, who showed a correlation between birth weight and slopes of reciprocal creatinine regression lines. In children with IgA nephropathy, LBW is associated with a higher incidence of arterial hypertension, and a higher percentage of sclerotic glomeruli in renal biopsy [256]. Minimal change nephrotic syndrome in children with IUGR has an unfavorable course, leading to more relapses, a higher incidence of steroid dependency and more need for cytotoxic agents and cyclosporine [257–259]. Associations between birth weight and diabetic nephropathy [260–262] or renal damage due to urinary tract infection [263] have been reported, but are not undisputed [264–266]. However, a study in rats after prenatal glucocorticoids shows an increased susceptibility to cell death in renal cells [267], which may be the pathway to explain the difference in renal damage after urinary tract infection.

IUGR influences renal function in infancy and childhood, but also aggravates additional renal diseases, possibly as a result of the nephron endowment and subsequent hyperfiltration.

**Long-Term Consequences**

The lower number of nephrons is affected in the long run by both hypertrophy and hyperfiltration, leading to glomerular damage and hypertension.

Studying a group of LBW women aged 23–26 years, Kistner et al. [254] describe no significant difference in proteinuria or mean GFR, even though there are more individuals with an impaired GFR in this group. This is in line with the results of Yudkin et al. [268] who reported no association between albuminuria in adulthood (range 47–75 years of age) and any measure of size at birth, even though there is a higher incidence of microalbuminuria in the group with the thinnest individuals at birth. An increase in albuminuria has also been described in adults after prenatal exposure to the Dutch famine in mid gestation [269]. In a recent study in 19-year-old subjects born very preterm, Keijzer-Veen et al. [252] describe an increase in microalbuminuria and serum creatinine, and a lower GFR after IUGR.
In a group of adult Aborigines, an inverse relationship between birth weight and albumin/creatinine ratio is found [87, 270]. At higher ages, data supports the association between LBW and increased susceptibility to early-onset ESRD [87–90].

Part of the compensation for the nephron endowment consists of glomerular hypertrophy. An increase in the size of glomeruli is also seen in an early phase of kidney damage [91, 92], and glomerular enlargement in donor kidneys is a risk factor for late allograft dysfunction [271, 272]. A combination of a higher incidence of glomerular enlargement and diabetic nephropathy and glomerulosclerosis has been shown in various indigenous populations, like Pima Indians [273, 274] and Australian Aborigines [76, 275, 276]. In a large Aboriginal population a decrease in birth weight correlates with an increase in albuminuria from childhood and overt albuminuria by early adult life [277]. Larger kidneys also seem to be a marker for subsequent nephropathy in patients with diabetes mellitus [278].

Renal cell cancer is associated with hypertension and diabetes mellitus that are both long-term consequences of LBW [279, 280]. In one study though, an association between birth weight and renal cell cancer has been found only in men with a birth weight of over 3,500 g: LBW did not show a clear association [281].

In conclusion, IUGR leads to fewer and larger glomeruli, which is associated with proteinuria and hypertension in the long run.

**Renal Mass Reduction in Men**

A comparison is made with situations where the nephron number is reduced by other causes, e.g. nephrectomy due to nonrenal disease or for donor purposes. However, these results have to be interpreted with caution since the reduction in kidney mass may not have taken place during development but in adulthood. There is a known difference in compensation after renal ablation depending on sex [282–285] and age: compensation is more pronounced when renal reduction is performed before completion of nephrogenesis and development [188, 286–294]. This means that the maladaptive resetting that can be seen after IUGR is different from the changes seen when nephrectomy is performed in adults [295].

After nephrectomy in childhood the remaining kidney enlarges and GFR rises to around 75% of normal values for 2 kidneys [287, 296–299]. Renal reserve capacity decreases during the years after nephrectomy [300]. In the long run, this adaptation is lost, leading to a decrease in GFR, augmented albuminuria and more glomerulosclerosis in most [299, 301–303] but not all reports [297, 298]. Even after uninephrectomy in adults, when GFR rises to 60–70% of normal values for 2 kidneys [304, 305], hypertension and proteinuria are described [306–317] although most studies report no or small risks for hypertension and renal damage or failure [292, 318–325].

Renal agenesis may be a more reliable comparison in terms of the timing of renal mass reduction. It leads to compensatory renal growth [296, 326] and an increased risk of hypertension and kidney failure in adulthood with low GFR, elevated urinary protein excretion and sclerosing glomerular lesions [301, 310, 314, 327–332], even though not all studies show this [322]. In a cohort of 66 patients with congenital solitary kidneys, we have shown that 50% of these children are hypertensive, using antihypertensive drugs, or have microalbuminuria at a mean age of 9 years [Schreuder et al., unpubl. data]. These data warrant regular checkups of patients with congenital renal mass reduction or nephrectomy in childhood.

**Experimental Renal Mass Reduction**

Several animal models are used to study the effect of a nephron endowment on long-term kidney function. Various rat strains show a lower number of nephrons, like the MWF [333], spontaneous hypertensive [334], Milan hypertensive [335] and Prague hypertensive rat [336, 337]. When compared with their respective controls, this results in hyperfiltration, glomerular capillary hypertension, progressive proteinuria and accelerated glomerulosclerosis [81, 338]. When a kidney from a hypertensive rat strain is transplanted into a normotensive rat, hypertension develops and vice versa [339–350], which leads to the conclusion that blood pressure travels with the kidney [351, 352]. However, a recent study showed a lower blood pressure but the same number of glomeruli in the F2 population after crossbreeding a hypertensive with a normotensive rat strain, leading to the conclusion that there is no direct relationship between the nephron number and blood pressure [353].

To induce a low glomerular number, several genetic models are available as well. In mice, a reduced number of glomeruli can be induced by the knockout of one allele of glomerular lesions [301, 310, 314, 327–332], even though most studies report no or small risks for hyperaemia and renal damage or failure [292, 318–325].
Another approach uses a surgical reduction of the nephron number in the fetal or neonatal developmental stage in order to mimic the effect of IUGR on the kidney. In sheep, fetal uninephrectomy leads to diminished renal function later in life [357, 358]. Neonatal uninephrectomy in rats leads to larger glomeruli, hyperfiltration, augmented proteinuria and (salt-sensitive) hypertension [295, 359, 360].

**Concluding Remarks**

Nephrogenesis is a complex process that requires a fine balance of many factors. IUGR leads to LBW, but can also disturb this balance leading to a low nephron endowment. Activation of the RAS, inhibition of NO and IGF-I, raised tubular sodium reabsorption and increased serum uric acid levels are mechanisms that are associated with IUGR and a low glomerular number and may explain the long-term consequences on blood pressure and renal function. The compensatory glomerular hyperfiltration may aggravate kidney diseases and is likely to result in systemic hypertension and renal damage and failure. Further study is required to unravel the mechanisms that result in IUGR and the pathways that explain the association between IUGR and adult diseases. This should eventually lead to interventions to optimize fetal growth, and to prevent adult diseases when IUGR is present. Until then, IUGR and renal mass reduction in childhood are important factors that researchers and clinicians need to acknowledge.

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