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SYMPOSIUM

The role of maternal nutrition, metabolic function and the placenta in developmental programming of renal dysfunction

VFI Richter,* JF Briffa,* KM Moritz,† ME Wlodek* and DH Hryciw*

**Department of Physiology, The University of Melbourne, Parkville, Vic., and †School of Biomedical Sciences, University of Queensland, St. Lucia, Qld, Australia*

SUMMARY

The intrauterine environment is critical for the development of the foetus. Barker and colleagues were the first to identify that adverse perturbations during foetal development are associated with an increased risk of developing diseases in adulthood, including cardiorenal disease. Specifically for the kidney, perturbations *in utero* can lead to nephron deficits and renal dysfunction by a number of mechanisms. Altered programming of nephron number is associated with an increased risk of developing kidney disease via glomerular hypertrophy and reduced vasodilative capacity of the renal blood vessels; both of which would contribute to hypertension in adulthood, with males being more susceptible to disease outcomes. Additionally, alterations in the renin-angiotensin system (RAS) such as an upregulation or downregulation of specific receptors, depending on the nature of the insult, have also been implicated in the development of renal dysfunction. Sex-specific differences in the expression of the RAS during late gestation and in the early postnatal environment have also been identified. Extensive research has demonstrated that both uteroplacental insufficiency and maternal malnutrition alter renal development *in utero*. Equally, exposure to maternal diabetes and maternal obesity during development are also associated with an increased risk of developing renal disease, however, the mechanism behind this association is poorly understood. Therefore, identifying the link between an adverse intrauterine environment and the programmed kidney disease risk in adulthood may facilitate the development of strategies to alleviate the epidemics of cardiorenal disease worldwide, in addition to understanding why males are more susceptible to adult-onset cardiovascular diseases.

Key words: gestational diabetes, intrauterine growth restriction, maternal malnutrition, maternal obesity, renal dysfunction, uteroplacental insufficiency.

INTRODUCTION

The term 'developmental programming' encompasses the Barker hypothesis, which states that in response to an unfavourable intrauterine environment the foetus will adapt in order to compensate.[1] Consequently, the growth trajectory and organ development of the foetus are altered in response to a poor intrauterine environment. The most common consequence of perinatal insults, in relation to the kidney, is a reduction in nephron endowment, the critical filtering component of the kidney required for adequate renal function. In a normal healthy adult, the number of nephrons per kidney is highly variable; however the average nephron number is between 900 000 and 1 million per kidney.[2] Nephrogenesis, the process of nephron formation, is a complex process involving significant remodelling and controlled apoptosis of nephrons.[3] In humans, nephrogenesis completes prior to birth, during the third trimester, thus emphasizing the importance of the intrauterine environment.[4] However, many studies investigating the timing of insults relating to renal development have been conducted in the rat, where nephrogenesis begins at 12 days of gestation and is completed by postnatal day 8.[4] Notably, rodent models have been used to identify critical genes responsible for nephrogenesis, including potential mechanisms for their activation and inhibition.[5] Mature nephrons cannot regenerate once nephrogenesis ceases, thus resulting in the permanent reduction in nephron endowment when altered nephrogenesis occurs.

The renin-angiotensin system (RAS) plays a critical role in regulating sodium reabsorption, aldosterone production and vascular constriction, and is also important for nephron development.[6,7] The RAS forms during development in both humans and rodents, and controls blood pressure and fluid balance in the body via the production of angiotensin II (ANGII).[8,9] ANGII binds to two receptors, angiotensin type 1 receptor (AT1) and angiotensin type 2 receptor (AT2), and is critical in the regulation of growth in the developing kidney.[10] Specifically, ANGII binding to AT1 is critical for adequate proliferation of the renal tubules and branching morphogenesis during development, whilst ANGII binding to AT2 controls both the cessation of proliferation and induction of apoptosis in the kidney.[11,12] However, the role for these receptors has primarily been characterized during adult life, while less is understood *in utero* during development and in relation to sex-specific differences.

Renal development can be affected by a number of conditions *in utero*. In particular, perturbations such as uteroplacental

Correspondence: Dr Deanne H Hryciw, Department of Physiology, The University of Melbourne, Parkville, Vic. 3010, Australia. Email: deanne.skelly@unimelb.edu.au

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insufficiency, maternal malnutrition, gestational obesity and gestational diabetes will be the focus of this review. In addition, the involvement of the RAS and vascular system will be discussed as potential mechanisms for the development of renal dysfunction. The major changes to the offspring, which are associated with the insults described in this review, are summarized in Table 1.

Uteroplacental insufficiency

Uteroplacental insufficiency affects 10% of pregnancies worldwide and occurs when the function of the placenta is altered, resulting in inadequate nutrient and oxygen delivery to the developing foetus.[13] This form of growth restriction, common in Western culture, differs from maternal malnutrition where food supply is often restricted, which is prevalent in developing countries.[14] Epidemiological studies have identified that a low birth weight increases the risk of developing chronic kidney disease, as defined by a reduction in glomerular filtration rate (GFR) and albuminuria.[15] While reduced GFR is often associated with the development of renal dysfunction, it is important to note that an enhanced GFR ($\geq$ 90 mL/min per 1.73 m^2) can also contribute to the development of reduced renal function.[16] At this time the exact mechanism behind this observation is unknown, however, a current hypothesis has linked the reduction in nephron number to an increased risk of developing renal dysfunction.[17] This hypothesis is supported by several studies which have shown a direct link between the total number of nephrons and birth weight in humans.[18,19] Additionally, Barker and colleagues postulated that reduced renal development may have long-term consequences for the health of the cardiovascular system.[20]

Although human studies identified the importance of the intrauterine environment in the development of organ dysfunction in later life, much of our understanding of the underlying mechanisms linking low birth weight and altered development has come from animal models. Rat models of uteroplacental insufficiency commonly utilize a uterine vessel ligation surgery technique during late gestation (gestation day 18; term = 22 days) that restricts the blood flow to the foetus, impairing nutrient and oxygen transport across the placenta.[21–23] The timing of this surgery results in a growth restriction of around 10%,[23] mimicking the degree of growth restriction which occurs in the Western world due to uteroplacental insufficiency where food availability is not restricted. This model of growth restriction, which includes our laboratory's model, identified that uteroplacental insufficiency reduces nephron number and increases glomerular volume, which is likely to be a compensatory mechanism in order to retain the surface area of the glomeruli to maintain a physiological GFR.[21–23] However, glomerular hypertrophy results in an increased pressure within the glomeruli themselves, which may ultimately lead to renal dysfunction and systemic hypertension.[17,24] While both male and female offspring are equally affected by nephron deficits,[25] males develop renal dysfunction associations whilst females are relatively protected, at least during early adult life.[22,23,26] Similarly in sheep models of uteroplacental insufficiency, induced by umbilico-placental embolization on day 110 of gestation (term = 147 days), there is a reduction in nephron number regardless of gender.[27] However, this model of growth restriction leads to approximately 50% reduction in birth weight,[27] which is more severe than the approximately 10% reduction in body weight that occurs in human uteroplacental insufficiency.

Elevations in apoptotic factors within the kidneys of models of uteroplacental insufficiency have identified genes critical for renal development.[28] In particular, elevated expressions of pro-apoptotic genes, including Bcl-2-associated X protein and tumour protein p53 mRNA, are associated with altered renal development in uteroplacental insufficiency.[28] Mechanistically this may be the result of the oxidative stress that develops in the offspring as a response to the reduced oxygen supply which occurs due to decreased placental function, leading to reduced DNA methylation of pro-apoptotic genes.[28]

Uteroplacental insufficiency has also been associated with alterations in the RAS, which may result in the pathogenesis of renal dysfunction. We have previously reported that expression of the AT1 gene in male offspring is affected by uteroplacental insufficiency,[26] with an increased expression of this receptor at 6 months of age, which is not seen in their female counterparts at a similar age.[22,26] In another rat model of uteroplacental insufficiency, where uterine perfusion is reduced at gestation day 14, renin and angiotensinogen expression are reduced, which downregulates the RAS.[29]

Finally, alterations in vascular function may also have implications on the ability of the pre- and post-glomerular arterioles to

Table 1 Renal alterations in offspring born to uteroplacental insufficiency, maternal malnutrition, gestational diabetes and gestational obesity

Type of Insult	Birth weight	Nephron endowment	Glomerular hypertrophy	Altered RAS	Renal apoptosis	Reduced renal vasodilation	References
Uteroplacental insufficiency	↓	↓	↑	↓ renin mRNA ↑ AT1 (males only)	↑	↙	15,22,23,25–28,30,34
Maternal malnutrition	↓	↓	?	↓ renin mRNA ↓intrarenal ANGII (males only)	↑	↙	34,35,39,42,45,46,81
Gestational diabetes	↑ ↔ ↓	↓	↑	↑intrarenal ANGII ↑ renal angiotensinogen ↑renin mRNA	↑	↙	49,54,57–59,63,65,82
Maternal obesity	↑ ↔ ↓	?	↑	↑renin mRNA ↓renin activity (males only)	?	↙	69,71,74,75

adequately control glomerular pressure, leading to altered renal development. Importantly, growth restricted males develop hypertension, which is due to reduced relaxation in both mesenteric and femoral arteries, whilst the females are protected against these vascular changes and hypertension.[23,30,31] This finding might suggest that growth restriction will also cause vascular stiffness in the renal arteries and veins, however no-one has yet investigated changes in renal vascular function in this model of growth restriction. If this hypothesis is correct, alterations in both renal vascular function, along with nephron deficits and glomerular hypertrophy, will likely contribute to the hypertension in these male offspring.

Maternal malnutrition

Maternal malnutrition, similarly to uteroplacental insufficiency, reduces the nutrient supply to the growing foetus, limiting the growth potential of the offspring and leading to a low birth weight.[32] The effects maternal malnutrition has on the development of intrauterine growth restriction was first observed during the Dutch famine, where food supplies were restricted.[33] The children who were born to these mothers malnourished during pregnancy had an increased albumin/creatinine ratio in adulthood which is indicative of microalbuminuria.[33]

While a number of animal models have demonstrated that offspring exposed to maternal malnutrition during gestation have reduced body weight, kidney size and nephron number at birth,[34,35] there are considerable variations in the degree of these reductions. A study conducted by Woods *et al.* in Sprague–Dawley rats fed a low protein diet (8.5% protein; chow = 19% protein) throughout pregnancy, reduced the number of nephrons in male offspring.[34] However a study by Langley-Evans *et al.* in male and female Wistar–Kyoto offspring identified a reduction in nephron number when mothers were exposed to a low protein diet (9% casein) throughout gestation, during mid-gestation only and during late-gestation only, but did not reduce nephron number when mothers were exposed to the low protein diet during early gestation only.[36] However, it is important to consider that variations in results may exist due to the differences between the strains of rat. In particular, Sprague–Dawley rats are prone to spontaneous weight gain.[37] Therefore, it is likely that under conditions of dietary restrictions that spontaneous obesity may still develop, which could enhance circulating concentrations of obesity-related adipokines such as leptin, which has been postulated to alter the development of nephrons.[38] More recently, Woods and colleagues identified that female Sprague–Dawley offspring were relatively protected from nephron deficits when exposed to a low protein diet (8.5% protein; chow = 19% protein) *in utero*, suggesting both the timing and degree of protein restriction may alter the outcome of these findings, particularly when investigating sex specific differences.[39]

Maternal protein restriction during pregnancy is also associated with alterations in the ability of the offspring's kidneys to regulate the RAS.[34] Specifically, maternal malnutrition reduces renal renin mRNA expression and intrarenal concentrations of renin in both male and female offspring, in addition to reducing intrarenal ANGII concentrations in male offspring.[34] Moreover in rodents, following maternal malnutrition, postnatal intrarenal ANGII concentrations remain low in postnatal life, indicating a permanent alteration to the RAS, which would perpetuate past the postnatal development of nephrons.[40] Expanding upon this, a number of factors have been implicated in the process of nephrogenesis and are summarized in the review by Moritz *et al.*[5]

However, the role for the RAS in altered nephrogenesis in models of maternal malnutrition is controversial. While exposure to maternal malnutrition has demonstrated reductions in AT2 receptor expression in offspring at birth, only females retained this downregulation into postnatal life.[41] Further, Welham *et al.* reported that maternal malnutrition is associated with increased apoptosis in mesenchymal cells at embryonic day 13, prior to the appearance of AT2 receptors.[42] While apoptosis occurring during nephrogenesis has been suggested as a possible mechanism relating to reduced nephron endowment, it remains unclear which of the renal cell types may be affected by this process.[42] More recently, Cooke and associates identified that in response to maternal malnutrition, both male and female Wistar–Kyoto offspring had enhanced G protein coupled receptor, GPR91, mRNA and protein expression in the kidney on embryonic day 19.[43] Interestingly on postnatal day 21 both renal expression of the AT1 and the G protein alpha subunit (Gqα/11α; which is implicated in vasodilatory tone in vascular smooth muscle cells) protein was enhanced only in male offspring, indicating that ANGII undergoes signalling via AT1 receptor/Gqα/11α pathways,[43] possibly resulting in renal dysfunction as shown in rodent models of hypertension. On the other hand, renal expression of AT2 protein expression was increased, regardless of sex, in these offspring at postnatal day 21, while renin mRNA was only decreased in female offspring.[43] Therefore, enhancement of the GPR91 pathway may assist in the explanation between a poor intrauterine environment and the development of renal dysfunction.

Another possibility of programmed renal dysfunction may occur due to alterations in mitochondrial gene expression. Baboon foetuses (165 days; term = 183 days) whose mothers were fed 70% of the average dietary intake (chow = 15% protein) develop alterations in the mRNA expression of mitochondrial dynamic proteins and metabolite transport, including cytochrome C oxidase subunit VIa polypeptide 1, cytochrome C oxidase subunit VIc, adenosine triphosphate synthase proteolipid P3 and ATP synthase proteolipid P1.[44] Particularly, these alterations have been observed in a sex-specific manner with females being affected to a greater extent compared to their male counterparts.

Endothelial dysfunction in offspring may also contribute to the renal dysfunction in models of maternal malnutrition. In order to mimic maternal malnutrition, Franco and colleagues fed rats 50% of the average dietary intake (chow = 22% protein) throughout pregnancy.[45] Consequently, rats demonstrated an increased response to noradrenaline induced vasoconstriction in the aorta of both genders, which may be explained by alterations to the nitric oxide-cyclic guanosine monophosphate pathway.[45,46] As a result, these alterations to the vasculature may contribute to increased glomerular hypertension in the kidneys, thereby further exacerbating renal dysfunction.

Gestational diabetes

Gestational diabetes mellitus (GDM) has also been linked to adverse postnatal outcomes for offspring, including obesity and

altered glucose tolerance.[47,48] However, studies investigating renal dysfunction in children born to mothers who had GDM are contradictory. For example, studies in Pima Indians identified that children born to GDM mothers develop albuminuria in adulthood,[49] a hallmark indicator of renal disease. Conversely, Becerra *et al.* failed to identify any risk of renal dysfunction in infants born to mothers suffering from GDM.[50] However the inclusion of only 12 mothers with GDM may have affected the efficacy of results.[50] Similar studies have also failed to identify the presence of renal dysfunction in offspring.[51,52] The differences in these studies might be due to the age that the children were investigated, as renal dysfunction may only develop in adulthood. In addition, factors such as degree of glycemic control and the presence of pre-existing but undetected diabetes[51] in each study may lead to variable outcomes from the studies. Therefore, there is a substantial gap in our knowledge pertaining to the epidemiological effects in children born to mothers suffering from GDM.

Animal models have identified renal deficits and dysfunction resulting from maternal hyperglycemia during pregnancy in their offspring. In mice injected with glucose (1 mL of 25% glucose as needed to maintain glucose above 200 mg/dL) on gestation day 7.5 (8.1 ± 1.2 mmol/L glucose prior to injection and 20.2 ± 4.9 mmol/L glucose after injections) resulted in foetal hyperglycemia *in utero* due to an increased transfer of glucose across the placenta, which may cause developmental alterations in kidney development.[53] Current research indicates that foetal hyperglycemia associated with GDM increases the number of apoptotic podocytes in developing glomeruli and also upregulates caspase-3 activity, which is responsible for the regulation of renal apoptosis.[54] Additionally, offspring from GDM mothers have an increased renal angiotensinogen and renin mRNA expression, which may increase ANGII expression, which would also result in increased apoptosis.[54,55] Foetal hyperglycemia increases RAS activation, which signals via the nuclear factor-κB (NF-κB) signalling pathway to increase the rate of nephron apoptosis, thus reducing nephron endowment.[54] Although the NF-κB pathway is associated with apoptosis in a number of cells around the body,[56] the functional impact of this pathway on renal apoptosis is controversial in diabetic nephropathy, with the NF-κB pathway shown to be dysregulated in some human patients.[57] The mechanism for this is poorly understood, however the NF-κB pathway is associated with renal apoptosis during development in a mouse model.[54] Therefore, future studies are required to determine the effect of the NF-κB pathway in renal development in human children born to GDM mothers.

In Wistar–Kyoto rats, a single intraperitoneal injection of streptozotocin (25 mg/kg), causing moderate hyperglycemia (11.2–15.0 mmol/L), on the first day of pregnancy resulted in enlarged kidneys and the development of focal glomerulosclerosis in male offspring at 26 weeks.[58] In addition, renal parameters such as GFR were enhanced, indicating the presence of renal dysfunction. In another study, C57Bl/6J mice were injected with streptozotocin (80 mg/kg) from days 6.5 until 8.5 of gestation, inducing GDM, and kidneys of offspring were excised on embryonic day 14.5.[59] These male and female offspring had reductions in the development of ureteric tips and branching points, reduced branching numbers and reductions to the development of the ureteric tree, including volume and length.[59] In addition, nephron endowment was reduced in these offspring on embryonic day 18.5, suggesting that nephron deficits may result from reduced branching morphogenesis. Similarly to the pathways associated with renal dysfunction in maternal malnutrition, rabbit kidneys exposed to hyperglycemia results in GPR91-associated renal dysfunction occurring via activation of cyclooxygenase 2, enhancing the release of renin.[60,61]

Furthermore, offspring born to GDM might have altered vascular function. Under normal conditions, insulin has the ability to modulate the activity of blood vessels, which induces vasodilation. As a consequence of GDM, elevated plasma insulin has been demonstrated in the offspring.[62] Thus, excessive concentrations of plasma insulin in GDM may enhance pre-glomerular vasodilation, as shown in cultured adult rat glomerular mesangial cells.[63] As a result, glomerular hypertension and hypertrophy may occur, either directly or indirectly via the insulin-like growth factor receptor,[63] ultimately enhancing glomerular capillary permeability.[64] Alterations to vascular resistance in male offspring born to mothers with GDM include reductions in the endothelial vasodilatory response in mesenteric microvessels via alterations to the endothelium.[65]

Maternal obesity

Obesity during gestation is a substantial concern for Western culture, with 50% of women of childbearing age classified as overweight or obese in the United States of America and United Kingdom.[66] The health and development of the children may be affected, with complications such as neural tube defects, macrosomia, growth restriction and insulin resistance developing in children born to overweight mothers.[67] Although the effects of obesity and the presence of a high-fat diet (HFD) are well understood to contribute to renal dysfunction,[68] the effects that obesity and a HFD during pregnancy have on their children's renal function is less well understood. In particular, there is a gap in knowledge pertaining to the development of nephron deficits in infants born to obese mothers, which warrants further investigation.

Much of the understanding of the effect maternal obesity has on offspring renal outcomes has come from animal models. In Sprague–Dawley rats, exposure to a HFD 10 days prior to mating and throughout gestation (20% animal lard) reduced the number of aortic smooth muscle cells and endothelial cell volume.[69] This, in conjunction with reduced renin and Na^+-K^+-ATPase activity, may exacerbate the development of hypertension; however no nephron deficit was identified.[69] Nevertheless, there were a number of limitations in this study, which may have affected the efficacy of the results. Pup number was reduced at birth, which may have resulted in enhanced nutrition to each individual offspring. This particularly may be important when considering the role of leptin in postnatal development of nephrons,[70] where offspring exposed to a leptin antagonist developed nephron deficits in early postnatal life.[38]

Notwithstanding the limited data investigating the link between nephron endowment and maternal obesity, animal models have implicated alterations in endothelial and the RAS function in the development of renal dysfunction in the offspring.[71] Similarly, in Sprague–Dawley rats a HFD prior to and during pregnancy and lactation increased renal renin mRNA expression in male and female offspring at 30 and 90 days of postnatal life.[72] While

there is good evidence that obesity results in reductions to sodium excretion and enhanced sodium reabsorption,[73] there is a gap in knowledge pertaining to plasma and urine concentrations of sodium in offspring of maternal obesity. In a Sprague–Dawley model of maternal HFD, male offspring developed glomerulosclerosis and impaired renal function (shown by an enhancement of urine albumin excretion).[74] The majority of studies investigating the effects of maternal obesity have been centred on male offspring, with the effects more apparent in male offspring, such as hyperinsulinemia, hyperleptinemia, hypertension, and left ventricular hypertrophy.[75] Importantly, female offspring exposed to a HFD purely during gestation showed similar renal alterations, but to a lesser degree.[76] The presence of albuminuria, podocyte injury, possibly via reduced nestin expression, and glomerulosclerosis without the presence of alterations in GFR suggests that these occur independently of altered renal hemodynamics.[75,76]

There is some suggestion that the sympathetic nervous system plays a role in the programming of renal dysfunction in offspring, as it is well understood that leptin affects the activity of the hypothalamus.[77] However, limited studies have been performed to investigate this. Despite this gap in knowledge, it is well established that the renal sympathetic nerve activity and blood pressure both increase when exposed to a HFD in rabbits and these changes can be reversed with the administration of leptin antagonists,[78,79] implicating leptin in the development of renal dysfunction. Further, in offspring exposed to a HFD (13.3% fat) *in utero* and during lactation, leptin resistance develops in postnatal life along with hypertension and increased renal sympathetic nerve activity.[80] However, it remains unclear whether these changes are associated with increased visceral fat or whether they are attributable to changes in the programming of the sympathetic nervous system.

CONCLUSION

Perturbations to the intrauterine environment result in a number of deleterious outcomes for the offspring including hypertension and renal dysfunction. In addition to uteroplacental insufficiency and maternal malnutrition, GDM and maternal obesity may also contribute to the pathogenesis of kidney disease in offspring. Importantly, alterations in the RAS, induction of apoptosis, reduction in nephron endowment (and subsequent glomerular hypertrophy) and reduced vasodilation have all been implicated in the development of renal dysfunction in both human and animal studies. Understanding the role of developmental programming and adverse intrauterine environments will assist in the development of strategies to ameliorate the effects and progression of renal dysfunction.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Barker DJ, Martyn CN. The maternal and fetal origins of cardiovascular disease. *J. Epidemiol. Community Health* 1992; **46**: 8–11.
2. Bertram JF, Douglas-Denton RN, Diouf B, Hughson MD, Hoy WE. Human nephron number: Implications for health and disease. *Pediatr. Nephrol.* 2011; **26**: 1529–33.
3. Coles HS, Burne JF, Raff MC. Large-scale normal cell death in the developing rat kidney and its reduction by epidermal growth factor. *Development* 1993; **118**: 777–84.
4. Bagby SP. Maternal nutrition, low nephron number, and hypertension in later life: Pathways of nutritional programming. *J. Nutr.* 2007; **137**: 1066–72.
5. Moritz KM, Wintour EM, Black MJ, Bertram JF, Caruana G. Factors influencing mammalian kidney development: Implications for health in adult life. *Adv. Anat. Embryol. Cell Biol.* 2008; **196**: 1–78.
6. Moritz K, Cuffe J, Wilson L *et al.* Sex specific programming: A critical role for the renal renin-angiotensin system. *Placenta* 2010; **31**, S40; doi:10.1016/j.placenta.2010.01.006.
7. Guron G, Friberg P. An intact renin-angiotensin system is a prerequisite for normal renal development. *J. Hypertens.* 2000; **18**: 123–37.
8. Shutz S, Le Moullec JM, Corvol P, Gasc JM. Early expression of all the components of the renin-angiotensin system in human developent. *Am. J. Pathol.* 1996; **149**: 2067–79.
9. Wintour EM, Alcorn D, Butkus A *et al.* Ontogeny of hormonal and excretory function of the meso- and metanephros in the ovine fetus. *Kidney Int.* 1996; **50**: 1624–33.
10. Aguilera G, Kapur S, Feuillan P, Sunar-Akbasak B, Bathia AJ. Developmental changes in angiotensin II receptor subtypes and AT1 receptor mRNA in rat kidney. *Kidney Int.* 1994; **46**: 973–9.
11. Iosipiv IV, Schroeder M. A role for angiotensin II AT1 receptors in ureteric bud cell branching. *Am. J. Physiol.* 2003; **285**: 199–207.
12. Wolf G. Angiotensin II and tubular development. *Nephrol. Dial. Transplant.* 2002; **17**: 48–91.
13. Baschat AA, Hecher K. Fetal growth restriction due to placental disease. *Semin. Perinatol.* 2004; **28**: 67–80.
14. Henriksen T, Clausen T. The fetal origins hypothesis: Placental insufficiency and inheritance versus maternal malnutrition in well-nourished populations. *Acta Obstet. Gynecol. Scand.* 2002; **81**: 112–14.
15. White SL, Perkovic V, Cass A *et al.* Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. *Am. J. Kidney Dis.* 2009; **54**: 248–61.
16. Thomas C, Thomas L. Renal failure–measuring the glomerular filtration rate. *Dtsch. Arztebl. Int.* 2009; **106**: 849–54.
17. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other?. *Am. J. Hypertens.* 1988; **1**: 335–47.
18. Brenner BM, Mackenzie HS. Nephron mass as a risk factor for progression of renal disease. *Kidney Int. Suppl.* 1997; **63**: 124–7.
19. Merlet-Benichou C, Leroy B, Gilbert T, Lelievre-Pegorier M. Placental insufficiency and its effect on the fetus and adult disease. *Lancet* 1993; **341**: 827–8.
20. Barker DJ, Osmond C. Low birth weight and hypertension. *BMJ* 1988; **297**: 134–5.
21. Schreuder MF, Van Wijk JA, Fodor M, Delemarre-van de Waal HA. Influence of intrauterine growth restriction on renal function in the adult rat. *J. Physiol. Biochem.* 2007; **63**: 213–19.
22. Wlodek ME, Mibus A, Tan A, Siebel AL, Owens JA, Moritz KM. Normal lactational environment restores nephron endowment and prevents hypertension after placental restriction in the rat. *J. Am. Soc. Nephrol.* 2007; **18**: 1688–96.
23. Wlodek ME, Westcott K, Siebel AL, Owens JA, Moritz KM. Growth restriction before or after birth reduces nephron number and increases blood pressure in male rats. *Kidney Int.* 2008; **74**: 187–95.
24. Merlet-Benichou C, Gilbert T, Muffat-Joly M, Lelievre-Pegorier M, Leroy B. Intrauterine growth retardation leads to a permanent nephron deficit in the rat. *Pediatr. Nephrol.* 1994; **8**: 175–80.
25. Schreuder MF, Nyengaard JR, Fodor M, Van Wijk JA, Delemarre-van de Waal HA. Glomerular number and function are influenced by spontaneous and induced low birth weight in rats. *J. Am. Soc. Nephrol.* 2005; **16**: 2913–19.
26. Moritz KM, Mazzuca MQ, Siebel AL *et al.* Uteroplacental insufficiency causes a nephron deficit, modest renal insufficiency but no

hypertension with ageing in female rats. *J. Physiol.* 2009; **587**: 2635–46.
27. Zohdi V, Moritz KM, Bubb KJ *et al.* Nephrogenesis and the renal renin-angiotensin system in fetal sheep: Effects of intrauterine growth restriction during late gestation. *Am. J. Physiol.* 2007; **293**: 1267–73.
28. Pham TD, Maclennan NK, Chiu CT, Laksana GS, Hsu JL, Lane RH. Uteroplacental insufficiency increases apoptosis and alters p53 gene methylation in the full-term IUGR rat kidney. *Am. J. Physiol.* 2003; **285**: 962–70.
29. Grigore D, Ojeda NB, Robertson EB *et al.* Placental insufficiency results in temporal alterations in the renin angiotensin system in male hypertensive growth restricted offspring. *Am. J. Physiol.* 2007; **293**: 804–11.
30. Mazzuca MQ, Wlodek ME, Dragomir NM, Parkington HC, Tare M. Uteroplacental insufficiency programs regional vascular dysfunction and alters arterial stiffness in female offspring. *J. Physiol.* 2010; **588**: 1997–2010.
31. Tare M, Parkington HC, Bubb KJ, Wlodek ME. Uteroplacental insufficiency and lactational environment separately influence arterial stiffness and vascular function in adult male rats. *Hypertension* 2012; **60**: 378–86.
32. Belkacemi L, Nelson DM, Desai M, Ross MG. Maternal undernutrition influences placental-fetal development. *Biol. Reprod.* 2010; **83**: 325–31.
33. Painter RC, Roseboom TJ, Van Montfrans GA *et al.* Microalbuminuria in adults after prenatal exposure to the Dutch famine. *J. Am. Soc. Nephrol.* 2005; **16**: 189–94.
34. Woods LL, Ingelfinger JR, Nyengaard JR, Rasch R. Maternal protein restriction suppresses the newborn renin-angiotensin system and programs adult hypertension in rats. *Pediatr. Res.* 2001; **49**: 460–7.
35. Sahajpal V, Ashton N. Renal function and angiotensin AT1 receptor expression in young rats following intrauterine exposure to a maternal low-protein diet. *Clin. Sci.* 2003; **104**: 607–14.
36. Langley-Evans SC, Welham SJ, Jackson AA. Fetal exposure to a maternal low protein diet impairs nephrogenesis and promotes hypertension in the rat. *Life Sci.* 1999; **64**: 965–74.
37. Levin BE, Dunn-Meynell AA, Balkan B, Keesey RE. Selective breeding for diet-induced obesity and resistance in Sprague–Dawley rats. *Am. J. Physiol.* 1997; **273**: 725–30.
38. Attig L, Larcher T, Gertler A, Abdennebi-Najar L, Djiane J. Postnatal leptin is necessary for maturation of numerous organs in newborn rats. *Organogenesis* 2011; **7**: 88–94.
39. Woods LL, Ingelfinger JR, Rasch R. Modest maternal protein restriction fails to program adult hypertension in female rats. *Am. J. Physiol.* 2005; **289**: 1131–6.
40. Langley-Evans SC, Welham SJM, Sherman RC, Jackson AA. Weanling rats exposed to maternal low-protein diets during discrete periods of gestation exhibit differing severity of hypertension. *Clin. Sci.* 1996; **91**: 607–15.
41. McMullen S, Langley-Evans SC. Maternal low-protein diet in rat pregnancy programs blood pressure through sex-specific mechanisms. *Am. J. Physiol.* 2005; **288**: 85–90.
42. Welham SJ, Wade A, Woolf AS. Protein restriction in pregnancy is associated with increased apoptosis of mesenchymal cells at the start of rat metanephrogenesis. *Kidney Int.* 2002; **61**: 1231–42.
43. Cooke CL, Zhao L, Gysler S, Arany E, Regnault TR. Sex-specific effects of low protein diet on in utero programming of renal G-protein coupled receptors. *J. Dev. Orig. Health Dis.* 2014; **5**: 36–44.
44. Pereira SP, Oliveira PJ, Tavares LC *et al.* Effects of moderate global maternal nutrient reduction on fetal baboon renal mitochondrial gene expression at 0.9 gestation. *Am. J. Physiol. Renal. Physiol.* 2015; **308**: F1217–28.
45. Franco MC, Arruda RM, Dantas AP *et al.* Intrauterine undernutrition: Expression and activity of the endothelial nitric oxide synthase in male and female adult offspring. *Cardiovasc. Res.* 2002; **56**: 145–53.
46. Brawley L, Itoh S, Torrens C *et al.* Dietary protein restriction in pregnancy induces hypertension and vascular defects in rat male offspring. *Pediatr. Res.* 2003; **54**: 83–90.
47. Fetita LS, Sobngwi E, Serradas P, Calvo F, Gautier JF. Consequences of fetal exposure to maternal diabetes in offspring. *J. Clin. Endocrinol. Metab.* 2006; **91**: 3718–24.
48. Meigs JB, Mittleman MA, Nathan DM *et al.* Hyperinsulinemia, hyperglycemia, and impaired hemostasis: The Framingham Offspring Study. *JAMA* 2000; **283**: 221–8.
49. Nelson RG, Morgenstern H, Bennett PH. Intrauterine diabetes exposure and the risk of renal disease in diabetic Pima Indians. *Diabetes* 1998; **47**: 1489–93.
50. Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: A population-based case–control study. *Pediatrics* 1990; **85**: 1–9.
51. Aberg A, Westbom L, Kallen B. Congenital malformations among infants whose mothers had gestational diabetes or preexisting diabetes. *Early Hum. Dev.* 2001; **61**: 85–95.
52. Persson M, Fadl H. Perinatal outcome in relation to fetal sex in offspring to mothers with pre-gestational and gestational diabetes – A population-based study. *Diabet. Med.* 2014; **31**: 1047–54.
53. Horal M, Zhang Z, Stanton R, Virkamaki A, Loeken MR. Activation of the hexosamine pathway causes oxidative stress and abnormal embryo gene expression: Involvement in diabetic teratogenesis. *Birth Defects Res. A Clin. Mol. Teratol.* 2004; **70**: 519–27.
54. Tran S, Chen YW, Chenier I *et al.* Maternal diabetes modulates renal morphogenesis in offspring. *J. Am. Soc. Nephrol.* 2008; **19**: 943–52.
55. Sequeira Lopez ML, Pentz ES, Robert B, Abrahamson DR, Gomez RA. Embryonic origin and lineage of juxtaglomerular cells. *Am. J. Physiol.* 2001; **281**: 345–56.
56. Mercurio F, Manning AM. NF-kappaB as a primary regulator of the stress response. *Oncogene* 1999; **18**: 6163–71.
57. Morcos M, Sayed AA, Bierhaus A *et al.* Activation of tubular epithelial cells in diabetic nephropathy. *Diabetes* 2002; **51**: 3532–44.
58. Yan J, Li X, Su R, Zhang K, Yang H. Long-term effects of maternal diabetes on blood pressure and renal function in rat male offspring. *PLoS ONE* 2014; **9**: e88269.
59. Hokke SN, Armitage JA, Puelles VG *et al.* Altered ureteric branching morphogenesis and nephron endowment in offspring of diabetic and insulin-treated pregnancy. *PLoS ONE* 2013; **8**: e58243.
60. Peti-Peterdi J. High glucose and renin release: The role of succinate and GPR91. *Kidney Int.* 2010; **78**: 1214–17.
61. Toma I, Kang JJ, Sipos A *et al.* Succinate receptor GPR91 provides a direct link between high glucose levels and renin release in murine and rabbit kidney. *J. Clin. Invest.* 2008; **118**: 2526–34.
62. Schwartz R, Gruppuso PA, Petzold K, Brambilla D, Hiilesmaa V, Teramo KA. Hyperinsulinemia and macrosomia in the fetus of the diabetic mother. *Diabetes Care* 1994; **17**: 640–8.
63. Abrass CK, Raugi GJ, Gabourel LS, Lovett DH. Insulin and insulin-like growth factor I binding to cultured rat glomerular mesangial cells. *Endocrinology* 1988; **123**: 2432–9.
64. Pete G, Hu Y, Walsh M, Sowers J, Dunbar JC. Insulin-like growth factor-I decreases mean blood pressure and selectively increases regional blood flow in normal rats. *Proc. Soc. Exp. Biol. Med.* 1996; **213**: 187–92.
65. Rocha SO, Gomes GN, Forti AL *et al.* Long-term effects of maternal diabetes on vascular reactivity and renal function in rat male offspring. *Pediatr. Res.* 2005; **58**: 1274–9.
66. Thangaratinam S, Rogozinska E, Jolly K *et al.* Effects of interventions in pregnancy on maternal weight and obstetric outcomes: Meta-analysis of randomised evidence. *BMJ* 2012; **344**: e2088.
67. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: A systematic review and meta-analysis. *JAMA* 2009; **301**: 636–50.
68. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. *Ann. Intern. Med.* 2006; **144**: 21–8.

69. Armitage JA, Lakasing L, Taylor PD *et al.* Developmental programming of aortic and renal structure in offspring of rats fed fat-rich diets in pregnancy. *J. Physiol.* 2005; **565**: 171–84.
70. Briffa JF, McAinch AJ, Romano T, Wlodek ME, Hryciw DH. Leptin in pregnancy and development: A contributor to adulthood disease? *Am. J. Physiol.* 2015; **308**: E335–50.
71. Fan L, Lindsley SR, Comstock SM *et al.* Maternal high-fat diet impacts endothelial function in nonhuman primate offspring. *Int. J. Obes. (Lond.)* 2013; **37**: 254–62.
72. Samuelsson AM, Morris A, Igosheva N *et al.* Evidence for sympathetic origins of hypertension in juvenile offspring of obese rats. *Hypertension* 2010; **55**: 76–82.
73. Briffa JF, Grinfeld E, Jenkin KA *et al.* Diet induced obesity in rats reduces NHE3 and Na/K-ATPase expression in the kidney. *Clin. Exp. Pharmacol. Physiol.* 2015; **42**: 1118–26.
74. Jackson CM, Alexander BT, Roach L *et al.* Exposure to maternal overnutrition and a high-fat diet during early postnatal development increases susceptibility to renal and metabolic injury later in life. *Am. J. Physiol. Renal. Physiol.* 2012; **302**: 774–83.
75. Parente LB, Aguila MB, Mandarim-de-Lacerda CA. Deleterious effects of high-fat diet on perinatal and postweaning periods in adult rat offspring. *Clin. Nutr.* 2008; **27**: 623–34.
76. Flynn ER, Alexander BT, Lee J, Hutchens ZM Jr, Maric-Bilkan C. High-fat/fructose feeding during prenatal and postnatal development in female rats increases susceptibility to renal and metabolic injury later in life. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2013; **304**: R278–85.
77. Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science* 2004; **304**: 108–10.
78. Armitage JA, Burke SL, Prior LJ *et al.* Rapid onset of renal sympathetic nerve activation in rabbits fed a high-fat diet. *Hypertension* 2012; **60**: 163–71.
79. Lim K, Burke SL, Head GA. Obesity-related hypertension and the role of insulin and leptin in high-fat-fed rabbits. *Hypertension* 2013; **61**: 628–34.
80. Prior LJ, Davern PJ, Burke SL, Lim K, Armitage JA, Head GA. Exposure to a high-fat diet during development alters leptin and ghrelin sensitivity and elevates renal sympathetic nerve activity and arterial pressure in rabbits. *Hypertension* 2014; **63**: 338–45.
81. Leeson CP, Kattenhorn M, Morley R, Lucas A, Deanfield JE. Impact of low birth weight and cardiovascular risk factors on endothelial function in early adult life. *Circulation* 2001; **103**: 1264–8.
82. Amri K, Freund N, Vilar J, Merlet-Benichou C, Lelievre-Pegorier M. Adverse effects of hyperglycemia on kidney development in rats: In vivo and in vitro studies. *Diabetes* 1999; **48**: 2240–5.