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Review Article

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PRENATAL CAUSES OF KIDNEY DISEASES

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Abstract

Deleterious environmental factors during pregnancy influence fetal development and increase the risk of cardiovascular and kidney disease in adult offspring. Undernutrition, protein restriction, excess salt, corticosteroids, or placental insufficiency disturb kidney development, causing a lower number of nephrons (referred to as nephron underdosing). This in turn leads to hypertension and accelerated loss of kidney function in the adult life of the offspring. The 'nephron underdosing' can be observed with or without intrauterine growth restriction. A lower number of nephrons have been confirmed in humans with hypertension.

Introduction

Prevalence and causes of low birth-weight

Defined by the traditional birth-weight cut-off (<2500g) approximately 15 percent of children have a low birth-weight [1] but in underdeveloped countries the proportion may be even higher, although this is not well documented because of under-reporting. Birth-weight can be low either in newborns at term (defined as small for gestation age – SGA; below the 10th percentile) or in newborns born prematurely. Being 'small for gestational age' is the result of restricted intra-uterine growth, potentially caused by a number of factors, including poor nutrition and cigarette smoking, which are the most common predisposing factors in developing countries [2]. Several epidemiological studies documented a clear association between lower birth-weight and pathology in adult life, including increased rates of coronary heart disease, strokes, type 2 diabetes mellitus, adiposity, metabolic syndrome and osteoporosis. [3-7]. Even in the absence of risk factors during the gestational period, events in the perinatal period may also cause adverse effects in adult life [8, 9]. When, in addition, risk factors are operational in adult life, the sequelae acquired in the perinatal period may definitely be amplified further [10].

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Underlying mechanisms linking maternal constraint to fetal outcome

In the development of mammals, environmental information (such as nutrient status) is relayed from the mother to the offspring through the placenta and through lactation. So called 'maternal constraint' is responsible for the fact that for instance, growth of the fetus corresponds to the size of the mother's body [11]. Maternal constraint may further comprise limitations, for example placental size and/or perfusion, impacting on nutrition of the fetus. Modification of gene expression, especially the expression of growth factors, may also play a role. [12]

The hypothesis proposed by Barker [13] provided a framework linking developmental deficits to pathology in adult life. The concept implies that adaptive responses of the fetus to stimuli of maternal origin increase the long-term risk of disease in the offspring. Such fetal responses include changes in metabolism, hormone production or tissue sensitivity to hormones – all of which may affect the development of various organs, resulting in persistent alterations of physiological and metabolic homeostatic set points. In this perspective reduced overall fetal body growth is seen not as a causal factor for the long-term consequences, but rather as a marker of a coordinated fetal response to an adverse intrauterine environment. The long term consequences of such adverse intrauterine environments may not be evident at birth, but as a consequence of altered tissue and organ development may alter adaptive responses later in life [14].

Disruption of fetal development depends on the nature, intensity, and timing of the environmental challenges:

- Toxins or extreme conditions may cause severe defects – teratogenesis.
- A substantial, but not disruptive challenge, such as malnutrition during pregnancy, may induce an immediate defence response of the developing organism, causing a phenotype called 'thrifty' [6], usually involving growth reduction.
- Environmental influences which do not elicit immediate defence mechanisms may still result in phenotypic adaptation.

It has been hypothesised that such adaptations, termed 'predictive adaptive responses' [15], are an effort to adjust the physiology to the anticipated later environment. According to this interpretation, poor intrauterine nutrition leads to accumulation of fat tissue, 'because' it will be beneficial if the postnatal environment continues to offer scarce food supply. If on the other hand the postnatal environment is nutrient rich, this 'protective' mechanism would lead to adiposity and increased cardiovascular risk.

The effects of developmental plasticity have been documented by numerous animal studies. Dietary, endocrinal, or physical challenges at various time points during pregnancy and weaning induce long-lasting changes in the physiology of the offspring. The most commonly used animal models involve prenatal nutrient imbalance induced by a global undernutrition of the mother [16] or by protein restriction using an isocaloric diet [17].

The nutrition of the fetus depends on several factors:

- on the delivery of oxygen via the uterine circulation,
- on the quality of placentation including the placental transfer function,
- and finally on the ability of the fetus to deliver the nutrients from the placenta to peripheral tissues.

For example dietary deprivation of the mother rat in the pre-implantation period causes low birth-weight of the offspring and hypertension in adult life [18].

Another example is exposure of the mother rat to glucocorticoid excess. The adult offspring of such mother rats present with hypertension [19], insulin resistance [20], altered gene expression in the brain and increased sensitivity to stress [21].

Fetal programming of kidney structure

Nephron underdosing and hypertension

Maternal dietary restriction causes lower nephron numbers in the kidneys of the offspring (nephron underdosing).

Low birth-weight [22] as well as low placenta weight [23] predispose to hypertension, as originally proposed by Brenner [24]. In humans a correlation exists between blood pressure and birth-weight: the lower the birth-weight the higher the blood pressure in the adult [25] and it has been documented that subjects with hypertension have significantly fewer nephrons compared to age- and gender-matched controls [26].

Low birth-weight is also linked to increased cardiovascular risk which may in turn be mediated in part by reduced renal function – a known major cardiovascular risk factor [27]. A history of low birth-weight is also associated with higher salt sensitivity of blood pressure [28] and is paralleled by reduced vascular calibers, for example of retinal arterioles [29].

The age at which low nephron number arises seems to be an important factor in the development of hypertension. Fehrman-Ekholm *et al.* [30] found that the prevalence of hypertension in 402 living kidney donors was not different from the general population. A metanalysis by Boudville *et al.* [31] including 5,145 living kidney donors showed no more than an approximately 5 mmHg increase in blood pressure after kidney donation. This corresponds to observations in American soldiers uninephrectomised during the Second World War and studied 45 years later [32]. In contrast if one kidney is missing at birth the risk of hypertension approaches 50 percent by the age of 40 years and this is accompanied by a high risk of kidney dysfunction [33]. These findings in humans are similar to what is seen in animal models: neonatal uninephrectomy causes salt-sensitive high blood pressure and glomerulosclerosis [34] while scarcely any blood pressure change is seen after uninephrectomy at a later age.

Development of hypertension in subjects with lower nephron number depends on a number of as yet unspecified factors. In rat models the severity of hypertension in the offspring depends on gender, with males having more severe blood pressure increase [35]. Genetic background modifies the increase of blood pressure in humans. Low nephron number correlates well with hypertension in Whites but not in Blacks [36, 37].

In the rat the renin-angiotensin system expressed in the kidney during development seems to play a crucial role in regulating the nephron number and being altered by maternal undernutrition [38, 39].

Nephron underdosing and kidney malfunction

Low birth-weight with presumed nephron deficit does not only increase the risk of hypertension later in life [17, 40], but is also associated with lower glomerular filtration rate (GFR) at a young age [41], specifically with a more rapid progression of primary kidney disease [42, 43] and a higher risk of preterminal or terminal renal failure [44-46]. Progression of any chronic kidney disease may be further facilitated by comorbidities which are more prevalent in individuals with low birth-weight: hypertension, insulin resistance, dysglycaemia, and diabetes. Extremely low birth-weight may even cause a unique form of nephrotic syndrome, in other words, focal segmental glomerulosclerosis [47]. Individuals born with one kidney have at a young

age a higher risk of proteinuria, hypertension and reduced renal function [33].
Manalich documented that neonates with low birth-weight have fewer but bigger glomeruli [48] as found in animal experiments where this is associated with renal malfunction [41] including renal failure [49]. Recent studies demonstrated that birth-weight correlates directly with kidney size in infants and children as well as with nephron numbers at all ages [36, 50-52].

It is thought that low numbers of glomeruli at birth lead to compensatory hypertrophy in order to maintain the filtration rate with consecutive single nephron hyperfiltration, intraglomerular hypertension, premature sclerosis of the glomeruli and finally accelerated loss of kidney function [53, 54]. In humans nephrogenesis is completed by the 36th week of pregnancy [55]. Nonetheless Rodriquez [55] demonstrated that in premature (<35 wk) newborns nephrogenesis may continue even postnatally for up to 40 days after birth, but the final nephron number still remains subnormal. Some of the interventions used in premature newborns (for example, non-steroidal anti-inflammatory drugs, gentamycin) are known nephrotoxins and have been shown to diminish nephron number in rodents [56]. Children born small for their age (SGA) [57] are not only born with small kidneys, but their kidney growth is subsequently reduced until 18 months of age.

In a study of 422 young people (46.7 percent men) Keijzer-Veen *et al.* found that participants with intrauterine growth-restriction at birth or premature birth had subtle kidney damage more often as reflected by the presence of albuminuria and lower GFR at the age of 19 ± 0.2 years [58]. Hoy *et al.* [59] calculated that in Australian Aborigines low birth-weight is responsible for 27 percent (95 percent CI, three to 45) of the population-based prevalence of albuminuria in young adults. Furthermore, in this population, low birth-weight correlated with small kidney size and subjects with smaller kidneys have had elevated blood pressure and albuminuria more often [52].
In experimental studies a relatively constant observation is the development of kidneys with lower nephron numbers in offspring of mothers exposed in pregnancy to low protein intake [38], uterine underperfusion [60], maternal hyperglycaemia [61], maternal hyperinsulinaemia [62], inhibition of the renin-angiotensin system [38], high and low maternal salt intake [63] or corticosteroids [64].

In offspring of dams fed a protein deficient diet, the standard procedure to study renal maldevelopment, elevated blood pressure and reduced nephron number were observed; this was accompanied by increased response to salt loading [38] and impaired vasodilatation of the systemic arteries [65]. Epigenetic mechanisms are thought to be highly relevant for tissue-specific gene expression and fetal programming. The epigenetic modifications include changes in methylation of cytidine-guannosine nucleotides in promoter regions, changes in histone acetylation modifying chromatin structure, and post-translational interference by micro RNAs [66]. The epigenetic modifications of DNA acquired during development remain unchanged in mitotic cell divisions throughout a lifetime. It has been shown, in the rat, that maternal dietary protein restriction causes changes in methylation of the promoter for the hepatic glucocorticoid receptor and the peroxisome proliferator-activated receptor α (PPAR-α) with consecutive alteration of target gene expression in the offspring influencing carbohydrate and lipid metabolism [67, 68] and presumably also renal development. There is increasing focus on the role played by epigenetic process in developmental plasticity. Epigenetic change may involve both imprinted and non-imprinted genes, and maternal nutrition has been demonstrated to influence the methylation of both types. Epigenetic modifications have also been demonstrated in p53 in the kidney influencing renal apoptosis [69], in the angiotensin II type 1b receptor in the adrenal gland modifying blood pressure [70],

and in the hypothalamic glucocorticoid receptor influencing response to stress [71]. The epigenetic modification in response to stimuli in the mother is gene-specific. For example a low protein diet in the mother modifies the methylation of the PPAR-α but not of the closely related PPAR-γ in the offspring [67]. The phenotypic manifestations of these epigenetic modifications may be obscure until later in life if they affect genes responding to specific environmental challenges (for example, overnutrition, high-fat diet and so on). Moreover such epigenetic modifications can be transferred on to further generations (in other words, F2) without further insults to the F1 generation [72].

Another key player in kidney development is the renin-angiotensin system. A properly functioning renin-angiotensin system is crucial for kidney development. The expression of angiotensinogen in the rat kidney increases during late gestation and reaches a maximum around birth where the expression is considerably higher than in the adult. Renin mRNA is detected in the kidney from embryonic day 17 and levels are approximately 20-fold and 10-fold higher than in adults at embryonic day 20 and at birth, respectively [73]. The renal content of angiotensin II is several-fold higher in newborns than in adults. Angiotensin II has been shown to modulate growth in several cell and tissue types [74, 75]. The expression of angiotensin II receptors in neonatal kidneys is also higher than in adult life [76]. The type 1 angiotensin II receptor (AT1) is found in the renal glomeruli of newborn rats during cellular proliferation and differentiation. The expression of type 2 angiotensin II receptor (AT2) is high during fetal development and decreases after birth, suggesting its role in cell differentiation [78]. These data explain that RAS blockade interferes with kidney development.

Other studies found reduced expression of the antiapoptotic homeobox gene product paired box 2 (Pax-2) in kidneys with a reduced number of nephrons [79, 80].

The role of the environment in later life

Both clinical and experimental data document interaction between the environment in early development and the environment in later life [16, 81]. A telling example is children born small who later develop obesity and a greater risk of lifestyle disease [82]. In an experiment by Vickers *et al.* [16] rats born to mothers that were undernourished during pregnancy were characterised by hyperphagia, accelerated weight gain, hyperinsulinaemia, hyperleptinaemia and hypertension compared with those born to normal mothers. With respect to kidney disease this implies that apart from the amplification of renal risk by hypertension, the increased risk of kidney dysfunction imposed by low birth-weight is further potentiated by obesity in adult life in this age of a worldwide obesity epidemic [83].

References:

1. Gluckman, P.D. and M.A. Hanson, The consequences of being born small - an adaptive perspective. Horm Res, 2006. 65 Suppl 3: p. 5-14.
2. Bergmann, R.L., K.E. Bergmann, and J.W. Dudenhausen, Undernutrition and growth restriction in pregnancy. Nestle Nutr Workshop Ser Pediatr Program, 2008. 61: p. 103-21.
3. Barker, D.J. and C. Osmond, Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet, 1986. 1(8489): p. 1077-81.
4. Kensara, O.A., et al., Fetal programming of body composition: relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. Am J Clin Nutr, 2005. 82(5): p. 980-7.
5. Osmond, C., et al., Early growth and death from cardiovascular disease in women. BMJ, 1993. 307(6918): p. 1519-24.

6. Hales, C.N. and D.J. Barker, Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia, 1992. 35(7): p. 595-601.

7. Cooper, C., et al., Growth in infancy and bone mass in later life. Ann Rheum Dis, 1997. 56(1): p. 17-21.

8. Rich-Edwards, J.W., et al., Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. BMJ, 1997. 315(7105): p. 396-400.

9. Frankel, S., et al., Birthweight, body-mass index in middle age, and incident coronary heart disease. Lancet, 1996. 348(9040): p. 1478-80.

10. Barker, D.J., et al., Size at birth and resilience to effects of poor living conditions in adult life: longitudinal study. BMJ, 2001. 323(7324): p. 1273-6.

11. Gluckman, P.D. and M.A. Hanson, Maternal constraint of fetal growth and its consequences. Semin Fetal Neonatal Med, 2004. 9(5): p. 419-25.

12. Charalambous, M., S.T. da Rocha, and A.C. Ferguson-Smith, Genomic imprinting, growth control and the allocation of nutritional resources: consequences for postnatal life. Curr Opin Endocrinol Diabetes Obes, 2007. 14(1): p. 3-12.

13. Barker, D.J.P., Fetal origins of coronary heart disease. BMJ, 1995. 311(6998): p. 171-174.

14. Gluckman, P.D. and M.A. Hanson, Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. Pediatr Res, 2004. 56(3): p. 311-7.

15. Gluckman, P.D., M.A. Hanson, and H.G. Spencer, Predictive adaptive responses and human evolution. Trends Ecol Evol, 2005. 20(10): p. 527-33.

16. Vickers, M.H., et al., Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. Am J Physiol Endocrinol Metab, 2000. 279(1): p. E83-7.

17. Langley-Evans, S.C., S.J. Welham, and A.A. Jackson, Fetal exposure to a maternal low protein diet impairs nephrogenesis and promotes hypertension in the rat. Life Sci, 1999. 64(11): p. 965-74.

18. Kwong, W.Y., et al., Maternal undernutrition during the preimplantation period of rat development causes blastocyst abnormalities and programming of postnatal hypertension. Development, 2000. 127(19): p. 4195-202.

19. Levitt, N.S., et al., Dexamethasone in the last week of pregnancy attenuates hippocampal glucocorticoid receptor gene expression and elevates blood pressure in the adult offspring in the rat. Neuroendocrinology, 1996. 64(6): p. 412-8.

20. Nyirenda, M.J., et al., Glucocorticoid exposure in late gestation permanently programs rat hepatic phosphoenolpyruvate carboxykinase and glucocorticoid receptor expression and causes glucose intolerance in adult offspring. J Clin Invest, 1998. 101(10): p. 2174-81.

21. Welberg, L.A., J.R. Seckl, and M.C. Holmes, Prenatal glucocorticoid programming of brain corticosteroid receptors and corticotrophin-releasing hormone: possible implications for behaviour. Neuroscience, 2001. 104(1): p. 71-9.

22. Barker, D.J., S.P. Bagby, and M.A. Hanson, Mechanisms of disease: in utero programming in the pathogenesis of hypertension. Nat Clin Pract Nephrol, 2006. 2(12): p. 700-7.

23. Barker, D.J., et al., Maternal and social origins of hypertension. Hypertension, 2007. 50(3): p. 565-71.

24. Brenner, B.M., D.L. Garcia, and S. Anderson, Glomeruli and blood pressure.

Less of one, more the other? Am J Hypertens, 1988. 1: p. 335-347.

25. Jarvelin, M.R., et al., Early life factors and blood pressure at age 31 years in the 1966 northern Finland birth cohort. Hypertension, 2004. 44(6): p. 838-46.

26. Keller, G., et al., Nephron Number in Patients with Primary Hypertension. N Engl J Med, 2003. 348(2): p. 101-108.

27. Shrestha, K. and W.H. Tang, Cardiorenal syndrome: diagnosis, treatment, and clinical outcomes. Curr Heart Fail Rep. 7(4): p. 167-74.

28. de Boer, M.P., et al., Birth weight relates to salt sensitivity of blood pressure in healthy adults. Hypertension, 2008. 51(4): p. 928-32.

29. Mitchell, P., et al., Evidence of arteriolar narrowing in low-birth-weight children. Circulation, 2008. 118(5): p. 518-24.

30. Fehrman-Ekholm, I., et al., No evidence of accelerated loss of kidney function in living kidney donors: results from a cross-sectional follow-up. Transplantation, 2001. 72(3): p. 444-9.

31. Boudville, N., et al., Meta-analysis: risk for hypertension in living kidney donors. Ann Intern Med, 2006. 145(3): p. 185-96.

32. Narkun-Burgess, D.M., et al., Forty-five year follow-up after uninephrectomy. Kidney Int, 1993. 43(5): p. 1110-5.

33. Argueso, L.R., et al., Prognosis of patients with unilateral renal agenesis. Pediatr Nephrol, 1992. 6(5): p. 412-6.

34. Woods, L.L., D.A. Weeks, and R. Rasch, Hypertension after neonatal uninephrectomy in rats precedes glomerular damage. Hypertension, 2001. 38(3): p. 337-42.

35. Woods, L.L., J.R. Ingelfinger, and R. Rasch, Modest maternal protein restriction fails to program adult hypertension in female rats. Am J Physiol Regul Integr Comp Physiol, 2005. 289(4): p. R1131-6.

36. Hughson, M.D., et al., Hypertension, glomerular number, and birth weight in African Americans and white subjects in the southeastern United States. Kidney Int, 2006. 69(4): p. 671-678.

37. Rostand, S.G., S.P. Cliver, and R.L. Goldenberg, Racial disparities in the association of foetal growth retardation to childhood blood pressure. Nephrol Dial Transplant, 2005. 20(8): p. 1592-7.

38. Woods, L.L., et al., Maternal Protein Restriction Suppresses the Newborn Renin-Angiotensin System and Programs Adult Hypertension in Rats. Pediatr Res, 2001. 49(4): p. 460-467.

39. Vehaskari, V.M., D.H. Aviles, and J. Manning, Prenatal programming of adult hypertension in the rat. Kidney Int, 2001. 59(1): p. 238-45.

40. Zandi-Nejad, K., V.A. Luyckx, and B.M. Brenner, Adult hypertension and kidney disease: the role of fetal programming. Hypertension, 2006. 47(3): p. 502-8.

41. Hallan, S., et al., Effect of intrauterine growth restriction on kidney function at young adult age: the Nord Trondelag Health (HUNT 2) Study. Am J Kidney Dis, 2008. 51(1): p. 10-20.

42. Na, Y.W., et al., Effect of intrauterine growth retardation on the progression of nephrotic syndrome. Am J Nephrol, 2002. 22(5-6): p. 463-7.

43. Zidar, N., et al., Effect of intrauterine growth retardation on the clinical course and prognosis of IgA glomerulonephritis in children. Nephron, 1998. 79(1): p. 28-32.

44. Lackland, D.T., et al., Low birth weights contribute to high rates of early-onset chronic renal failure in the Southeastern United States. Arch Intern Med, 2000. 160(10): p. 1472-6.

45. Li, S., et al., Low birth weight is associated with chronic kidney disease only in men. Kidney Int, 2008. 73(5): p. 637-42.

46. Vikse, B.E., et al., Low birth weight increases risk for end-stage renal disease. J Am Soc Nephrol, 2008. 19(1): p. 151-7.

47. Hodgin, J.B., et al., Very low birth weight is a risk factor for secondary focal segmental glomerulosclerosis. Clin J Am Soc Nephrol, 2009. 4(1): p. 71-6.

48. Manalich, R., et al., Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. Kidney Int, 2000. 58(2): p. 770-3.

49. Aihie Sayer, A., et al., Prenatal exposure to a maternal low protein diet shortens life span in rats. Gerontology, 2001. 47(1): p. 9-14.

50. Spencer, J., Z. Wang, and W. Hoy, Low birth weight and reduced renal volume in Aboriginal children. Am J Kidney Dis, 2001. 37(5): p. 915-20.

51. Hoy, W.E., et al., Nephron number, hypertension, renal disease, and renal failure. J Am Soc Nephrol, 2005. 16(9): p. 2557-64.

52. Singh, G.R. and W.E. Hoy, Kidney volume, blood pressure, and albuminuria: findings in an Australian aboriginal community. Am J Kidney Dis, 2004. 43(2): p. 254-9.

53. Lackland, D.T., Mechanisms and fetal origins of kidney disease. J Am Soc Nephrol, 2005. 16(9): p. 2531-2.

54. Brenner, B.M. and H.S. Mackenzie, Nephron mass as a risk factor for progression of renal disease. Kidney Int Suppl, 1997. 63: p. S124-7.

55. Rodriguez, M.M., et al., Histomorphometric analysis of postnatal glomerulogenesis in extremely preterm infants. Pediatr Dev Pathol, 2004. 7(1): p. 17-25.

56. Kent, A.L., et al., Renal glomeruli and tubular injury following indomethacin, ibuprofen, and gentamicin exposure in a neonatal rat model. Pediatr Res, 2007. 62(3): p. 307-12.

57. Schmidt, I.M., et al., Impaired kidney growth in low-birth-weight children: distinct effects of maturity and weight for gestational age. Kidney Int, 2005. 68(2): p. 731-40.

58. Keijzer-Veen, M.G., et al., Microalbuminuria and lower glomerular filtration rate at young adult age in subjects born very premature and after intrauterine growth retardation. J Am Soc Nephrol, 2005. 16(9): p. 2762-8.

59. Hoy, W.E., et al., A new dimension to the Barker hypothesis: low birthweight and susceptibility to renal disease. Kidney Int, 1999. 56(3): p. 1072-7.

60. Wlodek, M.E., et al., Growth restriction before or after birth reduces nephron number and increases blood pressure in male rats. Kidney Int, 2008. 74(2): p. 187-95.

61. Amri, K., et al., Altered nephrogenesis due to maternal diabetes is associated with increased expression of IGF-II/mannose-6-phosphate receptor in the fetal kidney. Diabetes, 2001. 50(5): p. 1069-75.

62. Bursztyn, M., et al., Adult hypertension in intrauterine growth-restricted offspring of hyperinsulinemic rats: evidence of subtle renal damage. Hypertension, 2006. 48(4): p. 717-23.

63. Balbi, A.P., R.S. Costa, and T.M. Coimbra, Postnatal renal development of rats from mothers that received increased sodium intake. Pediatr Nephrol, 2004. 19(11): p. 1212-8.

64. Woods, L.L. and D.A. Weeks, Prenatal programming of adult blood pressure: role of maternal corticosteroids. Am J Physiol Regul Integr Comp Physiol, 2005. 289(4): p. R955-62.

65. Brawley, L., et al., Dietary protein restriction in pregnancy induces hypertension and vascular defects in rat male offspring. Pediatr Res, 2003. 54(1): p. 83-90.

66. Goldberg, A.D., C.D. Allis, and E. Bernstein, Epigenetics: a landscape takes shape. Cell, 2007. 128(4): p. 635-8.

67. Lillycrop, K.A., et al., Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. J Nutr, 2005. 135(6): p. 1382-6.

68. Lillycrop, K.A., et al., Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. Br J Nutr, 2007. 97(6): p. 1064-73.

69. Pham, T.D., et al., Uteroplacental insufficiency increases apoptosis and alters p53 gene methylation in the full-term IUGR rat kidney. Am J Physiol Regul Integr Comp Physiol, 2003. 285(5): p. R962-70.

70. Bogdarina, I., et al., Epigenetic modification of the renin-angiotensin system in the fetal programming of hypertension. Circ Res, 2007. 100(4): p. 520-6.

71. Weaver, I.C., et al., Epigenetic programming by maternal behavior. Nat Neurosci, 2004. 7(8): p. 847-54.

72. Burdge, G.C., et al., Dietary protein restriction of pregnant rats in the F0 generation induces altered methylation of hepatic gene promoters in the adult male offspring in the F1 and F2 generations. Br J Nutr, 2007. 97(3): p. 435-9.

73. Gomez, R.A., et al., Distribution of renin mRNA and its protein in the developing kidney. Am J Physiol, 1989. 257(5 Pt 2): p. F850-8.

74. Bagby, S.P., et al., Proliferative synergy of ANG II and EGF in porcine aortic vascular smooth muscle cells. Am J Physiol, 1993. 265(2 Pt 2): p. F239-49.

75. Gomez, R.A., Molecular biology of components of the renin-angiotensin system during development. Pediatr Nephrol, 1990. 4(4): p. 421-3.

76. Millan, M.A., et al., Novel sites of expression of functional angiotensin II receptors in the late gestation fetus. Science, 1989. 244(4910): p. 1340-2.

77. Tufro-McReddie, A., et al., Ontogeny of type 1 angiotensin II receptor gene expression in the rat. J Clin Invest, 1993. 91(2): p. 530-7.

78. Grady, E.F., et al., Expression of AT2 receptors in the developing rat fetus. J Clin Invest, 1991. 88(3): p. 921-33.

79. Zhang, S.L., et al., Pax-2 and N-myc regulate epithelial cell proliferation and apoptosis in a positive autocrine feedback loop. Pediatr Nephrol, 2007. 22(6): p. 813-24.

80. Quinlan, J., et al., A common variant of the PAX2 gene is associated with reduced newborn kidney size. J Am Soc Nephrol, 2007. 18(6): p. 1915-21.

81. Eriksson, J.G., et al., Early growth and coronary heart disease in later life: longitudinal study. BMJ, 2001. 322(7292): p. 949-53.

82. Eriksson, J.G., et al., Early adiposity rebound in childhood and risk of Type 2 diabetes in adult life. Diabetologia, 2003. 46(2): p. 190-4.

83. Nguyen, S. and C.Y. Hsu, Excess weight as a risk factor for kidney failure. Curr Opin Nephrol Hypertens, 2007. 16(2): p. 71-6.