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].
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 metaanalysis 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 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 Rodriguez [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-guanosine 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 processes 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],

Koleganova N. et al. Prenatal Causes of Kidney Diseases
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:


