Renal, cardiovascular and metabolic effects of fetal programming

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Abstract

Disturbed fetal development has long-lasting effects on the offspring, specifically a higher risk of renal, cardiovascular and metabolic disease in adult life as postulated by Barker’s hypothesis. Relevant to renal outcomes of the offspring are maternal factors such as pre-eclampsia, malnutrition, smoking, drugs etc. The main renal abnormalities in the offspring include reduced nephron number and higher risk of low glomerular filtration rate, albuminuria, hypertension and worse outcome of primary kidney disease. Relevant to renal outcomes is also the predisposition to obesity and type 2 diabetes.

Keywords: heart; intrauterine programming; kidney; metabolism; vasculature

Introduction

Disturbed fetal development has long-lasting effects in the offspring, increasing the risk of diseases in adult life. Adverse conditions during pregnancy like pre-eclampsia, malnutrition, smoking, alcoholism, certain drugs or the presence of maternal disease, e.g. diabetes, may affect birth weight and subsequently the health of the offspring [1]. These consequences on the health of the offspring are the result of fetal programming, i.e. an example of environmental modulation of the transcription of the genetic code by epigenetic modification of DNA. Of interest with respect to the kidney is the observation that faulty renal development in utero causes a lower final number of nephrons, thus predisposing to hypertension and accelerated loss of renal function during later life and aggravating the evolution of primary kidney disease. Recently, numerous clinical and experimental observations documented that fetal undernutrition and/or low birth weight increases the risk of hypertension, kidney disease, cardiovascular disease and diabetes, to name only a few [2]. Against the current background of a worldwide pandemic of obesity and overweight, it is therefore important that children of obese mothers are more frequently at risk to develop metabolic disorders, e.g. insulin resistance, dyslipidaemia as well as hypertension and kidney disease [3, 4]. In the past, it was thought that only maternal conditions impact on fetal development, but recently, paternal factors have been shown to impact on the phenotype of the offspring as well: male rats on a high-fat diet cause impaired glucose tolerance in female offspring, thought to be the result of epigenetic modification of sperm DNA [5]. Thus, fetal programming may be influenced by environmental conditions to which either parent has been exposed.

Programming of renal diseases: the impact of nephron number

Kidney development is a fine orchestrated process. The final number of nephrons (‘nephron endowment’) depends on both genetic and environmental factors [6, 7]. An inborn nephron deficit, even a moderate one, is a risk factor for the development of hypertension and chronic disease including kidney disease in adulthood [8, 9]. The number of nephrons is undoubtedly determined genetically (Table 1), but a growing body of evidence indicates that in addition, glomerular number is influenced as well by non-genetic factors that affect the intrauterine environment, i.e. intrauterine malnutrition due to low protein intake or poor health of the mother, placental malfunction, glucocorticoid treatment, vitamin A deficiency and salt intake, to name only a few (Fig. 1) [10–17]. Protein restriction of the mother, particularly during the last third of gestation (the period of most intensive nephrogenesis), results in a 20–30% reduction in nephron number and the subsequent development of hypertension in later life [18, 19]. The environmental events influencing nephron formation occur at the same time that major changes in DNA occur, particularly methylation and histone acetylation which modify gene expression in life. These changes may interact with mutations of several genes known to be involved in nephrogenesis [6] (Table 1).

Since the nephron number cannot be directly measured, patients at risk can only be determined by the assessment and knowledge of the various risk factors and surrogate parameters of nephron development (Table 2).
humans, low nephron numbers correlate with low birth weight which can therefore be regarded as an indirect marker of fewer nephrons. Low birth weight in term newborns was shown to be associated with increased susceptibility to many subsequent diseases in adulthood [20]. A recent observation in monogenetic twins showed that in the twin with lower birth weight, the rate of loss of GFR was accelerated illustrating the potential impact of fetal malnutrition on the evolution of primary kidney disease in adult life [21]. Higher glomerular diameters, as often seen in individuals with low birth weight, correlated closely with a higher incidence of proteinuria and lower survival rate in IgA glomerulonephritis [22]. The adverse impact of low birth weight on the evolution of primary kidney disease has been clearly documented in a variety of experimental studies [23–25].

In summary, clinical findings argue for a role of nephron endowment for the evolution and progression of acquired renal disease as postulated by Winberg [26].

Programming of cardiovascular disease: development of hypertension in adult life

On the basis of animal experiments and clinical observations, Brenner et al. [8] had postulated more than 20 years ago that a low number of nephrons (‘nephron

| Table 1. Genetic control of nephrogenesis—which genes govern renal development (modified according to Dotsch [7]) |
|---|---|---|---|
| Genes | Impairment of nephron development | Renal disease | Syndromes with renal involvement |
| WT1 | Glomerular defects | Nephrotic syndrome | Frasier syndrome, Denys-Drash syndrome, WAGR syndrome |
| NPHS1 | Few, but large nephrons | Oligomeganephronia | Brachno-oto-renal syndrome |
| LMX1B | Absence of one or rarely both kidneys | Renal aplasia (agenesis) | |
| LAMB2 | Lower nephron number | Renal hypoplasia | Townes–Brock syndrome |
| NPHS2 | | | Pallister–Hall syndrome |
| PAX2 | | | |
| EYA1 | | | |
| PAX2 | | | |
| SALL1 | | | |
| GLI3 | | | |
| GDNF | | | |
| FRAS1, FREM1 | Lower number of abnormal nephrons | Renal dysplasia | Fraser syndrome |
| SOX9 | | | Campomelic dysplasia |

NS, nephrotic syndrome; WAGR, Wilms tumour, Aniridia, Genitourinary anomalies, mental Retardation.

Table 2. How can we identify patients with potentially impaired intraterine development who are at risk for prenatally programmed diseases in later life?

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<tr>
<td>Babies with intraterine growth retardation/small for gestational age (due to under-/malnutrition or under-/malperfusion)</td>
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<tr>
<td>Babies with low birth weight (as a surrogate parameter of impaired intraterine development)</td>
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<tr>
<td>Babies who are large for gestational age (due to maternal diabetes)</td>
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<tr>
<td>Babies who had a history of intraterine exposure to drugs (i.e. corticosteroids, gentamicin, ACE-inhibitors, cyclosporine A etc.)</td>
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Fig. 1. Factors that directly or indirectly affect fetal development and may thus favour programming of diseases that occur in later life.
underdosing’) predisposes to the development of hypertension later in life. Increased blood pressure is often present in the setting of renal disease and is a major factor in the rate of progression of renal disease, but a relationship between low nephron numbers and higher blood pressure values presumably develops much earlier in the pathophysiological cascade. Support for the Brenner concept was provided most clearly by Keller et al. [9]; in a small case–control autopsy study, they reported that patients with hypertension had ~50% fewer glomeruli with a mean volume ~50% larger compared with people without hypertension. These relationships have been confirmed in a larger autopsy study in Caucasian Americans but could not be documented in African Americans [27]. Experimental data also support this paradigm, i.e. in rats and sheep, unilateral nephrectomy in the perinatal period resulted in later hypertension which preceded any decline in renal function [28]. Of note, children with a solitary kidney (due to unilateral agenesis) also experienced increased blood pressure [29], whereas the same loss of nephrons (unilateral nephrectomy, living kidney donation) at adult age does not lead to higher blood pressure [30]. This observation indicates that it is not the number of nephrons per se which leads to hypertension, but most likely the time and environment during which the nephron deficit occurs, i.e. a vulnerable period during development.

Apart from ‘nephron underdosing’, non-renal mechanisms have been postulated to play as well a role in cardiovascular programming [31], i.e. the concept that an altered environment (i.e. high salt diet) in pregnancy causes a lasting imprint, e.g. hyper-responsiveness of the kidney to stress even in the absence of any nephron deficit and late-life hypertension [32], mainly but not exclusively due to increased activation of the sympathetic adrenal system [33].

Programming of vascular dysfunction: role of endothelial dysfunction

Experimentally, developmental programming of the aortic structure has been documented in offspring of rats on a high-fat diet [34], calorie-restricted mice [35] and also rats on high salt [17]. Of note, a progressive long-lasting effect on modelling of both central and muscular arteries— independent of postnatal salt intake and systemic blood pressure—is associated with increased oxidative stress and lower availability of nitric oxide (NO), indicating endothelial dysfunction. NO synthesis and/or bioavailability is known to be altered in pathological pregnancies, i.e. due to intrauterine growth restriction or pre-eclampsia, thus leading to changes in placental blood flow which could result in limiting fetal growth and development [36]. The exact mechanisms involved in the development of endothelial dysfunction and hypertension caused by intrauterine under- or malnutrition remain to be elucidated, however.

Programming of obesity and dysglycaemia: the current health epidemic

In the past 30 years, the prevalence of obesity and overweight has doubled in Western societies. Data from the Framingham Heart Study show that obesity contributes to 60–70% of cases with essential hypertension, thus posing a significant risk of morbidity and mortality [37]. Moreover, it is known that offspring of obese women are 36% more likely to develop type 2 diabetes than controls [38]. Evidence from experimental studies also supports the hypothesis that maternal obesity, overweight or high-fat diet is associated with obesity and hypertension in the offspring. Offspring of rats fed a high-fat diet for 10 days prior to mating, during pregnancy and in the suckling period become obese in adulthood. Interestingly, only the female progeny develop hypertension [39]. Both male and female offspring of diet-induced obese C57Bl/6J mice demonstrate obesity-related hypertension by 3 months of age [40]. Male offspring of C57 mice on a high-fat diet develop increased systolic blood pressure and hypertriglyceridaemia, despite no elevation of body fat, but the female littermates show programmed obesity and hypertension [41]. Maternal obesity and diabetes are known to alter the development of appetite circuits in the neonatal rodent brain, which may in the long run predispose to an imbalance in appetite and sympathetic control [42].

Even mild maternal overnutrition has been shown to induce increased adiposity, glucose intolerance and altered brain appetite regulators in the offspring [43]. Maternal obesity causes accelerated fetal pancreatic β-cell maturation which may contribute to premature β-cell function loss and type 2 diabetes [44]. Hyperglycaemia in the mother was associated with hyperglycaemia in the fetus stimulating fetal pancreatic β-cells to produce increasing amounts of insulin [45]. One of mechanisms underlying the growth-promoting action of insulin during fetal development resulting in newborn macrosomia is presumably the ability of fetal hyperinsulinaemia to increase the availability of farnesylated p21-Ras [46].

Postnatal modification of fetal programming: the effect of ‘catch-up’ growth

A potential strategy to modify the effects of fetal programming is the avoidance of hyperalimentation after birth in small-for-gestational age or low-birth-weight babies, in order to prevent the so-called ‘catch-up’ growth. Here, in addition to experimental evidence, the late outcome of the offspring of two famines during World War 2, the Dutch famine [47] and the siege of Leningrad [48] provides important information. In the Dutch Hunger Winter of 1944–45, if pregnant women were exposed to the famine during early gestation, hypertension was seen in the offspring at adult age, while reduced maternal caloric intake in late gestation was associated with increased adult adiposity and glucose intolerance [47] in their offspring. In contrast, offspring
whose mothers were pregnant during the siege of Leningrad did not experience a higher incidence of glucose intolerance or type 2 diabetes, respectively [48]. The traditional explanation, although challenged, is that intrauterine nutrient deprivation led to programming of endocrine systems towards energy saving in fetal life. If the nutrient deprivation continued after birth, this would be well tolerated by a baby whose intrauterine environment was deprived (as in the Leningrad offspring). In contrast, rapid reconstitution of energy supply and, therefore, a relative surplus of energy, as in the offspring of the Dutch famine, would lead to a rapid increase in weight (i.e. rapid ‘catch-up’ growth) associated with deposition of adipose tissue, predisposing to pathological glucose tolerance. There is considerable evidence that a rapid increase in caloric and protein intake postnatally plays an important role in the developmental origins of health and disease. Low-birth-weight and premature infants grow at different rates, and rapid ‘catch up’ growth may not be good. In fact, accelerated ‘catch-up’ growth is associated with higher blood pressure [49, 50]. Given such reports, the International Societies of Paediatric Endocrinology and the Growth Hormone Research Society presently discourage nutrient-enriched diets for low-birth-weight infants [7].

Summary and conclusion

In recent years, ample experimental and clinical evidence has been provided for an important role of the intrauterine and perinatal milieu for the development of adult renal, cardiovascular and metabolic diseases. We know that for the development of the fine structure of many organs, a delicate balance is needed between too little and too much energy provided, for example, by a high-protein intake during pregnancy. We have also learned that birth weight is a good surrogate parameter for intrauterine development. We have further increased our knowledge about toxins and drugs that interfere with kidney development and particularly nephron formation during the fetal period. This newly gained knowledge has led to the birth of a new subspeciality in medicine, and particularly paediatrics, i.e. the fetal origin of diseases or diseases associated with disturbances of the intrauterine period. Here, newborns at risk could be identified early on by their history or by birth weight so that treatment could be changed accordingly and offspring could be more closely followed until adulthood. In addition, this new look at the developmental origin of diseases also sheds light on diseases that we currently encounter as increasing health problems, i.e. hypertension, obesity and associated problems. By gaining more insight into the conditions under which the diseases develop and the pathomechanisms involved, we may be able to identify new treatment strategies in the near future.

Conflict of interest statement. None declared.

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Received for publication: 07.3.2012; Accepted in revised form: 1.4.2012