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Perinatal nutrient restriction reduces nephron endowment increasing renal morbidity in adulthood: A review

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A B S T R A C T

Perinatal malnutrition has been included among the causes of renal disease in adulthood.
Here, we consider the relationships between early supply of specific nutrients (such as protein, fat, vitamins and electrolytes) and renal endowment. Prenatal and postnatal nutrition mismatch is also discussed.
In addition, this article presents the role of nutrition of both mothers and pre-term infants on nephron endowment, with final practical considerations.

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1. Introduction

The embryonic human kidney develops in three consecutive structures: the pronephros, mesonephros and metanephros. Perinatal programming controls nephrogenesis during the developmental stage up to 34–36 weeks of gestational age. Genes, signalling molecules and transcription factors establish segmental nephron identity and their functional differentiation. Finally, the induction of nephron branching culminates in the final complement of nephrons [1]. In humans, the completion of nephrogenesis occurs before at-term birth. However, in pre-term infants, born before 36 weeks of gestation, renal maturation and nephron endowment is finalised postnatally [2,3].

The causes underlying a reduced number of nephrons are both genetic and environmental. The final renal potential of an individual could be modified by the nature, time, duration and severity of a renal insult before completion of nephrogenesis. Intrauterine stress and postnatal insults in pre-term infants may result in reduction of nephron numbers [4]. Moreover, an ongoing interaction between genes and environment prior to completion of nephrogenesis will contribute in forming the renal potential of an individual. Several factors may interact to increase nephron damage and to reduce nephron endowment [5]. Stressors affecting renal structure and function include urinary tract malformations such as obstructive uropathy, infections, and the administration of nephrotoxic drugs (especially antibiotics, and non-steroidal anti-inflammatory drugs) to mothers and newborns [6,7]. Moreover, perinatal programming for hypertension and diabetes may elicit a synergistic effect with the reduced nephron number leading to the development of chronic kidney disease [3,8].

Barker [6,9,10] and Brenner [11] reported on how a modified embryonic-foetal development resulting in low birth weight (LBW) may lead to a reduced nephron endowment, hypertension and renal diseases in adulthood. In extremely low birth weight (ELBW) infants, nephrogenesis continues after birth only for 40 days, and even less if acute renal failure occurs in the meantime [12]. A congenital nephron deficit, as in ELBW infants with intrauterine chronic retardation, can be exacerbated by perinatal stress (asphyxia, nephrotoxic drugs and acute renal failure) leading to chronic renal failure [13] starting before 14 years of life [14]. The flow of nutrition reaching the foetus provides an integrated signal of nutrition as experienced by recent matrilineal ancestors, which effectively limits the responsiveness to short-term ecological fluctuations during any given pregnancy; this phenomenon is called intergenerational 'phenotypic inertia' [15].

Since perinatal malnutrition has been included among the causes of renal disease in adulthood, this article discusses the role of nutrition of both mothers and pre-term infants on nephron endowment.

2. Early calorie supply and renal endowment

2.1. Low maternal calories

The majority of studies investigating the relationship between nutrition and nephrogenesis have been conducted in animal models. In a range of animal species, experimental maternal undernutrition or placental insufficiency has been associated with reduced nephron numbers [16–26]. When analysing these studies, it must be taken into consideration that nephrogenesis occurs for up to 8–10 postnatal days in rats, whereas it is achieved at 34–36 weeks of gestation in humans.

2.1.1. Studies in animals

2.1.1.1. Foetal undernutrition in rats. Placental restriction is likely to have an impact on early nephrogenesis, reducing nephron

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endowment at birth. At 2 weeks of age, newborn rats with intrauterine growth restriction (IUGR) born from mothers with uterine artery ligation showed a nephron deficit of about 30% and a large compensatory hypertrophy of the nephrons. Moreover, clearance experiments and morphometric studies indicated that overall renal function was impaired and not fully compensated after birth [17]. Furthermore, pregnant rats with nutrient restriction during the critical window in which nephrogenesis occurs delivered newborns with a reduced number of glomeruli per kidney [27], with hypertension in later life [18,28,29] and progression towards glomerulosclerosis [30]. Pregnant rats subjected to a prenatal multideficient diet and treated with sodium overload gave birth to newborns with higher values for glomerular filtration rate and filtration fraction compared with controls [31].

A decrease in glomerular number has been related to increased blood pressure in rats [19,32]. Previous studies have shown the importance of the renin–angiotensin system (RAS) in foetal renal development. Factors in the perinatal environment that suppress the intrarenal RAS in the developing foetus/newborn rats lead to impaired renal development, glomerular enlargement and fewer nephrons at birth, leading to adult hypertension [33,34]. Severe nutritional restriction in pregnant rats leads to altered vascular reactivity and suppression of the newborn's intrarenal RAS [1,18,35]. In intrauterine undernourished rats, a reduced number of nephrons was associated with chymase overactivity, increased intrarenal angiotensin type II (Ang II) production and hypertension [36].

2.1.1.2. Foetal undernutrition in ovines. Maternal nutrient restriction during early midgestation alters the trajectory of renal organogenesis and renal maturation in the ovine foetus. Decreased glomerular number has been related to increased blood pressure in sheep [23]. Maternal nutrient restriction showed growth hormone-insulin-like growth factor and prostaglandin axis deregulation. These changes may be important in the nutritional programming of renal functioning of sheep and in adult blood pressure control [37]. Nutrient restriction during early midgestation increased renin in the late-gestation of ovine foetal kidney, an event that may presage later hypertension in these animals [2]. Therefore, these changes seem to be sex related. Female gender appears to protect against maternal restriction, although with more severe maternal dietary restriction, female offspring are also affected [38].

2.1.1.3. Postnatal undernutrition in rats. Nephrogenesis continues after birth in the rat and may be influenced by postnatal nutrition and growth. Postnatal food restriction in the rat leads to a reduced nephron endowment with compensatory enlargement. In rats, a 25% reduction of glomerular number is observed after postnatal food restriction compared with control rats. Mean glomerular volume was increased by 35% in the growth-restricted rats [39]. Reduced size at birth, with the associated compromised nutrition and growth in the early postnatal period, not only induces a nephron deficit in adult male offspring, but also results in elevated blood pressure. Nevertheless, renal development in the rat can be profoundly affected by postnatal events. [40]

2.1.1.4. Postnatal compensation of foetal undernutrition in rats. Emerging data support the view that, along with fewer nephrons, nutritional programming actively induces a propensity for accelerated postnatal growth via enhanced appetite. More recently, studies of foetal undernutrition have also shown increased appetite and enhanced deposition of more fat than lean tissue [41]. A rat model of severe maternal caloric restriction throughout pregnancy showed increased food intake in offspring well into adulthood; central obesity, hypertension and insulin resistance were also present [41]. A prenatally induced nephron deficit can be restored by correcting growth restriction during lactation. It is important to stress that nutrition is relevant also in the immediate postnatal period [40] when, in the rat, nephrogenesis is almost 80% complete. Although the prevention of a reduced number of nephrons and hypertension seems possible with adequate postnatal feeding, the development of hypertension is shown in subjects with normal birth weight who are fed with inadequate maternal milk and have subsequent high growth rates after lactation. An increase in expression of type 1 angiotensin receptor (AT1R) suggests that inadequate lactation can have an impact on the long-term regulation of the renal RAS [42].

Both prenatal and postnatal periods are important in the programming of hypertension in the rat, acting through distinctly different mechanisms. Still, restriction of both perinatal and early postnatal growth increases blood pressure in male offspring rats. The early postnatal period is another critical time for nephron endowment in the rat [40].

2.1.2. Studies in humans

Human IUGR is often associated with uteroplacental insufficiency and a decline in nutrient and oxygen supply to the foetus. IUGR is associated with reduced nephron number in human infants [43]. Autopsy studies in humans have shown that premature birth before 34–36 weeks of gestation is associated with arrested or impaired nephrogenesis, which may contribute to the development of cardiovascular and renal disease in adulthood [12]. In both human and experimental IUGR, nephron number is commonly reduced by about 25–30%, suggesting the possibility that a finite fraction of total nephrons is subject to nutritional modulation [43]. One possible preventive action is to improve the nutrition of pregnant women: this strategy might decrease the frequency of hypertension in susceptible offspring during their adult lives [1].

Maternal nutrition may have an important influence on renal programming. It is very difficult to find studies in humans that demonstrate maternal hyponutrition as a sole cause of IUGR. Recent studies on the long-term outcomes in children born to pregnant women during the 'Dutch famine' demonstrated microalbuminuria when hyponutrition was present in the second part of gestation [44,46]. Different results emerged from the Leningrad carestia, wherein the population studied was borderline in terms of nutrition [46].

3. Specific nutritional factors and renal endowment

3.1. Protein intake

3.1.1. Studies in animals

Prenatal low-protein exposure reduces nephron number, leading to an age- and gender-related difference in postnatal angiotensin receptor expression. However, the RAS is upregulated in maternal low-protein female offspring during postnatal life, including both upregulation of AT1R, which mediates the classic pressor responses to Ang II, and downregulation of the counter-regulatory type 2 receptor (AT2R) [35,47]. In agreement with this, increased Ang II sensitivity has been observed in maternal low-protein offspring rats at 4 and 7 weeks of age [21,48,49]. Maternal low-protein diet decreased AT2R expression at 4 weeks of age in female offspring rats and increased it at 20 weeks of age [49], thus playing a critical role in determining blood pressure and overall disease risk in a subsequent generation [50].

Rats that were growth restricted *in utero* by maternal protein restriction underwent rapid weight gain when suckled by control-fed dams and died earlier than animals whose mothers were fed the control diet throughout pregnancy and lactation. Mitochondrial abnormalities and DNA damage occurred in the kidney of offspring who died prematurely. Direct measurement *in vitro* supplementation showed that mitochondrial abnormalities occur because of a functional deficit of the mitochondrial cofactor coenzyme Q9 [51].

Protein restriction during lactation confers nephroprotective effects in the male rat and is associated with increased antioxidant expression [52]. Varied protein intakes of 50%, 100% or 130% of the normal protein content in rat milk from the seventh to 15th day of life led to differences in total body weight but not kidney mass [53].

Combined prenatal and postnatal protein restriction in the mouse reduced nephron endowment similarly in both sexes [54].

Protein synthesis rates in kidney and other organs of pigs were greater in the fed than in the food-deprived state. Feeding stimulates protein synthesis, modulating the activation of initiation factors that regulate mRNA binding in the ribosomal complex. Therefore, a high-protein diet does not further enhance protein synthesis or translation initiation factor activation [55].

3.1.2. Studies in humans

Alterations in intrauterine nutrition, especially protein–calorie restriction, may 'programme' the foetus for later susceptibility to hypertension, cardiovascular disease and stroke [10]. Nutritional factors, such as protein intake and calories, can reduce nephron number, cause glomerular hypertrophy and subsequently increase postnatal glomerular fibrosis [16,56]. Support for the hypothesis that variation in foetal and placental development may result from a low ratio of animal protein to carbohydrate came from observational studies of maternal nutrition in pregnancy [57]. Malnutrition caused by a low protein–calorie diet during intrauterine and neonatal life, history of LBW and IUGR may have adverse implications for renal outcome, reduced nephron numbers and perhaps for increased numbers of obsolete glomeruli and provides early objective evidence for future hypertension and renal risk [3,58].

3.2. Fat intake

3.2.1. Studies in animals

Glomeruli from rats fed with fish oil produced lower levels of prostaglandins compared with glomeruli from rats fed with beef tallow [59]. A diet containing various amounts of n-3 and n-6 fatty acids had different affect on the concentration of atrial natruretic peptide (ANP) and alpha-1 receptors. In particular, n-3 increased the ANP receptors and decreased the density of the alpha-1 receptors [60]. However, dietary fat induced alterations in lipid composition of rat glomeruli and changes in affinity but not density of glomerular AT2R compared with normally fed rats [61].

Administration of a diet rich in animal lard in the rat during breastfeeding programmes the development of increased blood pressure, insulin resistance, dyslipidaemia, obesity and mesenteric artery endothelial dysfunction in adult offspring. Renal stereology showed no differences in kidney weight, glomerular number or volume in maternal-diet fat-rich offspring compared with controls, but renal renin and Na^+, K^+-ATPase activity were significantly reduced [62].

3.3. Vitamin A deficiency

3.3.1. Studies in animals

Vitamin A and its analogues (retinoids) are important regulators of cell proliferation, differentiation, immune function and apoptosis. However, vitamin A is the determinant in foetal renal programming of rats in view of its capacity to modulate nephron number and vascular supply of the kidney [63]. Several genes expressed during renal organogenesis that are regulated by retinoic acid have been identified. Transcription factors, such as the Hox family, hepatic nuclear factor 1b, lim-1, RARa2 and b2, are potential targets of retinoic acid. In addition, c-ret, epidermal growth factor receptor and transferrin receptor, which are important for nephron formation, are regulated by vitamin A [64–67]. In 21-day-old rats, the number of nephrons was directly correlated with plasma vitamin A level. The role of c-ret in renal formation is considered essential since null mice for this gene exhibited renal agenesis or rudimental kidneys [68]. In conditions of vitamin A deprivation, proto-oncogene c-ret expression was decreased in the metanephron. However, vitamin A supply restored nephron endowment to normal in offspring of rat mothers exposed to protein restriction [69].

3.3.2. Studies in humans

Indirect evidence has emphasised the role of vitamin A in kidney development in humans. Vitamin A has been found to be lacking in cord and maternal blood in IUGR neonates. However, low circulating levels were common in women who were smokers, abused alcohol or had inadequate dietary practices – all situations associated with IUGR delivery [63]. Finally, maternal vitamin A deficiency accounted for subtle renal hypoplasia in Indian newborns [70].

Experimental designs are lacking because retinoic acid can be teratogenic at high doses. Consequently, vitamin A is not administered during pregnancy to women at risk of giving birth to a LBW infant [69].

3.4. Calcium

Decreased maternal calcium intake during pregnancy promotes pre-term delivery and adult hypertension [71]. A follow-up study of children whose mothers had calcium supplementation in pregnancy showed a lowering of the offspring's blood pressure in childhood. However, calcium supplementation was not associated with any change in birth weight [72].

3.5. Potassium

Potassium-depleted environments showed an *in vitro* inhibition of nephron induction [73].

3.6. Iron

Maternal iron restriction in rats caused hypertension in the adult offspring, perhaps due in part to a deficit in nephron numbers [74].

3.7. Maternal overfeeding

3.7.1. Studies in animals

Different nutritional conditions (IUGR, overfeeding, and IUGR plus overfeeding) were investigated in 4-month-old rats to evaluate the amount of urinary protein excretion as a marker of glomerular damage. Early postnatal overfeeding in rats improved postnatal nephron number. Improved postnatal nutrition was associated with an enhanced number of formed nephrons by an average of 20% compared with control offspring. Therefore, enhanced nephron number was associated with further elevated arterial pressure and glomerulosclerosis [75]. Whether such findings may be extrapolated to the postnatal ongoing formation of nephrons in premature human infants remains a matter of speculation.

3.8. Prenatal and postnatal nutrition mismatch

The foetus is 'normally programmed' in physiological conditions and during hypernutrition. An unfavourable 'lifestyle' is not expected. Thus, the passage from unfavourable environment to a 'too favourable' environment may predispose to pathologies in adulthood [15]. In agreement with this, a mismatch between pre- and postnatal nutrient environments induced altered cardiovascular function in adult male sheep that was not seen in controls where environments were similar between the two periods of life. In particular, an increased blood pressure response to a bolus of Ang II was observed in postnatally undernourished sheep with a normal prenatal diet but not in those

with a restricted prenatal diet. Hence, adult cardiovascular function can be determined by developmental responses to intrauterine nutrition made in expectation of the postnatal nutritional environment. If these predictions are not met, the adult may be maladapted and at greater risk of cardiovascular disease [76].

4. Discussion

4.1. Intrauterine growth restriction

There is a strong association between LBW and reduced nephron endowment. Low nephron endowment in LBW infants has been associated with arterial hypertension and/or altered renal function in adulthood in both rodents and humans [7,9,11,77-80]. LBW infants may have a higher risk of developing hyperfiltration, microalbuminuria and accelerated loss of renal function in adulthood. Thus, a kidney with a reduced nephron number has less renal reserve and adaptation to dietary excesses or compensation to renal injury [8]. Hence, nephron endowment seems to be particularly sensitive to IUGR. If rapid somatic growth occurs subsequent to prenatal growth restriction, the kidney may not be able to respond with an increase in nephron number [81].

Although LBW may be one indication of reduced nephron endowment, a normal birth weight does not necessarily indicate a normal nephron number. Similarly, a low nephron endowment, although a risk factor, is not essential for the development of hypertension and is probably only one of a number of mechanisms contributing to the onset and progression of hypertensive disease [82].

4.2. Maternal undernutrition

The association between LBW and impaired nephrogenesis caused by intrauterine malnutrition was already reported long ago [83]. There is strong evidence of foetal adaptations when the materno-placental nutrient supply fails to match the foetal nutrient demand [84]. Maternal undernutrition generates a permanently low nephron number and increased appetite, the latter ensuring elevated body mass via growth acceleration when postnatal food is available. Therefore, when body mass exceeds the fixed lower excretory capacity, postnatal renal adaptations enhance excretion by mechanisms that create additional disease risk. Maternal and/or foetal undernutrition activates multiple compensatory foetal responses that persist postnatally, promoting later development of hypertension and renal disease in adulthood [85,86]. According to the Barker hypothesis, when resources *in utero* are restricted, their allocation to the development of the kidney and other organs is lacking in favour of the brain and heart. In other terms, according to the 'life history theory', if the total amount of energy to an animal is limited, then increased allocation of energy to one organ system must reduce allocation to one or more other organ systems [87]. Thus, the undernourished foetus protects its brain development by diverting more blood to the brain at the expense of blood supply to other organ systems. Several cellular and molecular mechanisms have been suggested as contributing to the consequent impaired nephrogenesis. The underlying epigenetic mechanisms involve modification of gene expression by altered DNA methylation, histone acetylation and allocation of stem cells [88]. Table 1 summarises the major topics discussed in the literature concerning changes in renal endowment.

Table 1

Topic	Observation	Reference
IUGR and nephron number	Term newborn with IUGR: low nephron number and nephrogenesis completed. Pre-term newborn with IUGR: low nephron number and nephrogenesis uncompleted	[42,90,91]
Flow of nutrition reaching the foetus	Recent matrilineal ancestors effectively limit the responsiveness to short-term ecological fluctuations during any given pregnancy: intergenerational "phenotypic inertia"	[15]
Undernutrition during gestation and early life	Permanent reduced number of nephrons: the "life history theory"	[87]
Protein restriction in pregnant rats	Has a critical role in intergenerational programming of impaired nephrogenesis	[48]
Mismatch between prenatal demand and postnatal nutrition supply	The passage from an unfavourable environment to a "too favourable" environment predisposes to pathologies in adulthood	[45]
Supposed cellular and molecular mechanisms of renal foetal programming	p53 gene family, hepatocyte nuclear factor-1β, Notch, Brn1, IRX, KLF4, Foxi1, PAX2 genes and angiotensin converting enzyme gene insertion/deletion. Epigenetic changes, telomere shortening, fewer stem cells, higher levels of renal apoptosis, mytochondrial dysfunction	[5,87,88]
Gender	Female gender is relatively protective against these prenatal insults	[8]
Postnatal aggravating events of low nephron endowment	Diabetes, vesicoureteral reflux, pyelonephritis, nephrotoxins, nephrotoxic drugs, IGA, partial renal ablation, etc.	[3–8]

4.3. Practical considerations

In a recent survey in a developing country of Africa, about 40% of children with chronic renal failure had an uncertain aetiology and environmental factors were advocated [89]. Close monitoring of renal function of children exposed to *intra utero* undernutrition emphasised the importance of nutritional programmes in populations with high risks of undernutrition [90]. In newborns at term experiencing IUGR, nephrogenesis is completed. They probably have a reduced global number of nephrons compared with healthy newborns [41,91]. The future of these infants may include a peculiar vulnerability to a different spectrum of noxae [92]. Adequate postnatal nutrition is essential [90].

- In VLBW infants, nephrogenesis is not completed and it is not possible to reach the final number of nephrons of at-term healthy newborns with normal birth weight [90]. From a practical perspective, the following procedures in pre-terms are essential:
  - adequate parenteral nutrition, and
  - cautious start of nutrition with fortified maternal milk or formula in the absence of maternal milk.

These interventions will allow the prevention of extrauterine growth restriction, which would otherwise add to the risks of low weight, and gestational age and extreme prematurity at birth. A delay in the start of extra milk feeding will prevent an excess of weight gain after the catch-up growth, lowering the risks associated with the low number of nephrons.

Conflict of Interest

None declared.

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