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The Effect of Preterm Birth on Kidney Development and Kidney Function over Time

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1. Introduction

In the last decades the survival of (extremely) preterm born and small for gestational age individuals has improved significantly. (Faranoff 2003; EXPRESS 2009) Many articles have been published showing a relation between unfavourable perinatal factors (eg growth restriction, maternal factors, maternal and postnatal medication use such as antenatal steroids and nephrotoxic agents) and increased risk for diseases in later life, like cardiovascular disease, diabetes mellitus, unfavourable lipid profile (together: the metabolic syndrome) and renal impairment. Recently, an increasing amount of studies have been published concerning the effects of preterm birth and these adult diseases as well. This chapter discusses the normal kidney development and the effect of premature and small for gestational age birth on kidney development and kidney function over time.

2. Developmental origins of health and diseases

Since several decades epidemiological research is performed to elucidate the pathophysiological mechanisms in the 'developmental origins of health and diseases' hypothesis, also known as the Barker hypothesis, or the fetal origins of adult disease hypothesis. In 1986 Barker first suggested a correlation between birth weight and ischaemic heart disease in adults in England and Wales. (Barker & Osmond, 1986) In this study the neonatal mortality in the period of 1921 – 1925 was positively related to the ischaemic heart disease in the same regions in the period of 1968-1978. Also other diseases were related to infant mortality, suggesting that poor living conditions, including poor nutrition, in early life is an important factor in development of disease on the short and long run. Furthermore, weight at the age of 1 year was negatively related to cardiovascular mortality at adult age. Therefore, it was suggested that processes linked to growth and acting in prenatal or early postnatal life strongly influence the risk of ischaemic heart disease. Many studies concerning the developmental origins of health and diseases are published in the years thereafter. (Barker & Osmond, 1988; Barker et al. 1993; Irving et al., 2000; Langley et al., 1994) Hypertension, hyperlipidemia, diabetes mellitus type II, stroke, coronary heart disease and renal impairment all seem to be related to low birth weight. (Barker & Bagby, 2005)

Still, the pathophysiological mechanisms are not precisely elucidated yet. Both genetic and environmental factors seem important. Genetic variation and gene expression will influence organogenesis. If unfavourable environmental factors are present at the crucial time of organ development (the critical window of development) it is likely that organ structure is

altered and function may be influenced in a negative way as well. In addition it has been postulated that accelerated postnatal growth in these subjects will aggravate the negative effect on organ function and risk of diseases over time (figure 1).

In a large cohort of middle aged adults (50-58 yr), who were exposed to undernutrition during the dutch famine it was shown that undernutrition in early gestation (first trimester) increases the risk for coronary heart disease and a more atherogenic plasma lipid profile. (Roseboom et al., 2006) Microalbuminuria and obstructive lung disease were more prevalent in those subjects who were exposed to undernutrition in mid gestation. Late gestation undernutrition increased the risk for glucose intolerance. Accelerated postnatal growth is thought to further increase risk of disease in adult life, but it has not been demonstrated whether this growth is the cause or consequence of earlier growth restriction-related adult diseases. (Hales & Ozanne, 2002) In addition, catch up growth probably amplifies this effect by accelerated cellular aging (telomere shortening). This was suggested in a rat model: low protein diet offspring pups had significantly fewer large telomeres compared to control (normal diet offspring pups). (Jennings et al., 1999; Tarry-Adkins et al., 2009)

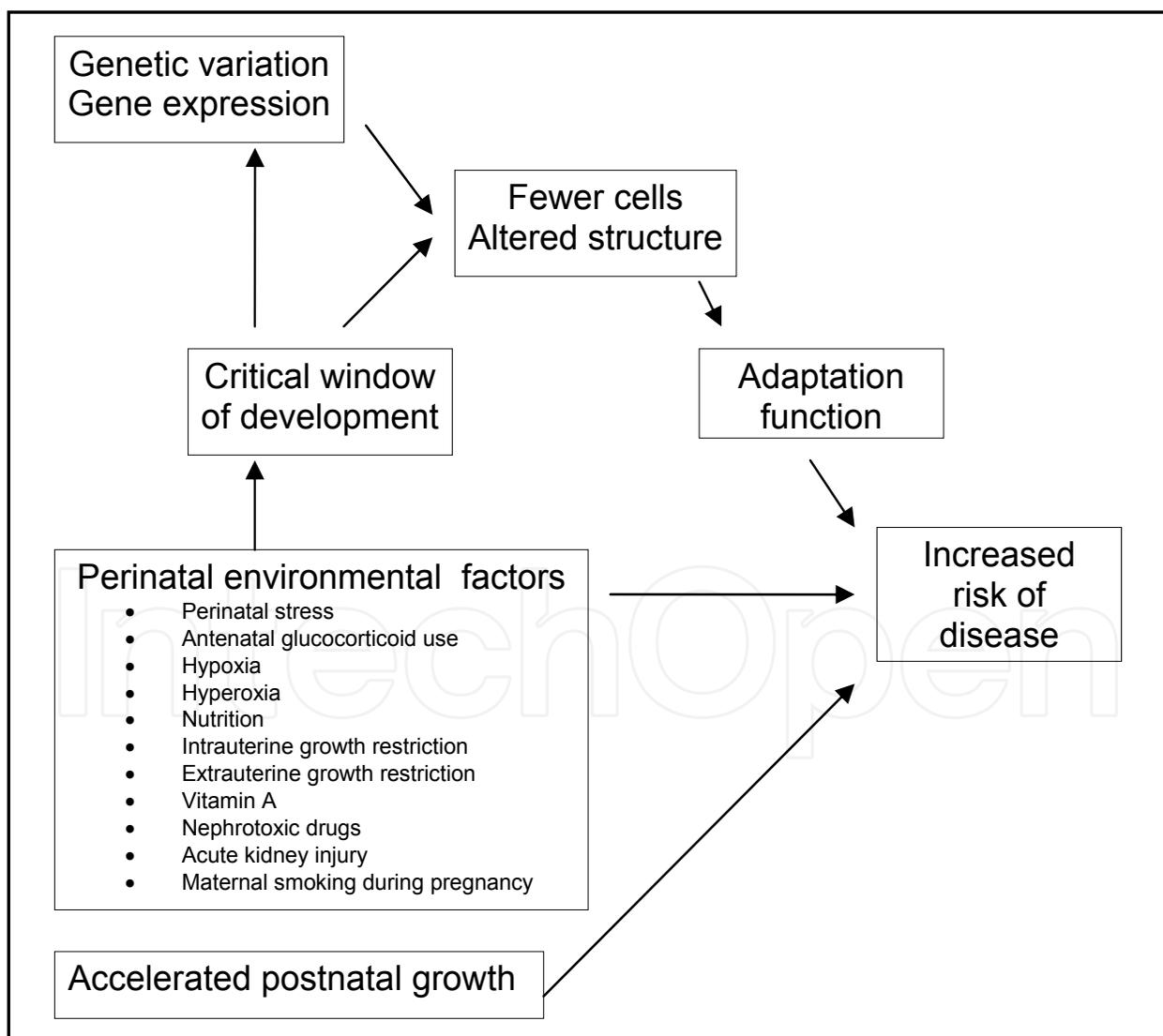


Fig. 1. Factors in Developmental Origins of adult Health and Disease (DOHaD).

The role of decreased renal development has been studied increasingly. Nephron endowment may result in glomerular and systemic hypertension, and in a decreased renal functional reserve capacity leading to a higher risk for decrease in renal function in later life (see below: hyperfiltration theory). Also, endothelial dysfunction and underdevelopment of the kidneys may be related to changes in the renin-angiotensin-system (RAS) and therefore increase blood pressure.

Low birth weight is mainly caused by malnutrition of the fetus, due to placenta insufficiency or maternal malnutrition, leading to redistribution of nutrients in favour of the development of the brain. Changes in cardiac output, hormone production, and sensitivity to hormones are thought to be altered and affect organs like lungs, pancreas and kidneys. This adaptation to the 'low nutrient' situation (programming), may lead to an increased susceptibility for malfunction of these specific organs after birth when the 'low nutrient' situation is discontinued. Other environmental factors, as hypoxia, hyperoxia, nephrotoxic medications, vitamin A deficiency, and variation in genes and genetic expression are also important in the context of the 'developmental origins of health and diseases' hypothesis. The effect of these factors on renal development are described in more detail below.

Lungs, pancreas and kidney are known to develop until the last few weeks of gestation. It is not completely elucidated whether premature birth decreases final development of these organs. Premature birth itself may therefore play an additional role in the increased risk for diseases in later life. In a Swedish study lower gestational age (GA) was associated with an increased blood pressure at the age of 49 years in 44 men. This correlation was stronger in the lower range of gestation (GA 30-38 weeks) (Siewert-Delle et al., 1998). In a study of 24 year old subjects born prematurely an increased blood pressure and insulin concentration was shown compared to subjects born at term. There was no difference in blood pressure between small for gestational age (SGA) preterm subjects and appropriate for gestational age (AGA) preterm subjects. In 2005 and 2008 we described an increased systolic blood pressure at 19 and 20 years of age in both SGA and AGA preterms (GA < 32 weeks) compared to the general population and to term born controls of the same age. (Keijzer-Veen et al, 2005; Keijzer-Veen et al, 2008) Ex-utero growth and development during the third trimester of the preterm infant was suggested to be more important in development of cardiovascular risk factors than growth retardation alone. (Irving et al, 2000) This was also demonstrated in women born preterm (GA < 32 weeks), at term SGA subjects and at term controls between 23 and 30 years of age in Sweden. Systolic blood pressure was only increased in the preterm subjects. Also the number of hypertensive blood pressure readings were higher in the preterm group (Kistner et al., 2000).

3. Hyperfiltration theory

It is suggested that the kidneys also are 'programmed' in intrauterine growth restricted fetuses. A deficit of nephrons is measured in several studies, possibly affecting long term renal function. (Langley-Evans et al., 1999; Lucas et al., 1997; Merlet-Benichou et al., 1994; Zeman, 1968) Also alterations in the renin-angiotensin-system (RAS) are thought to be important to increase blood pressure at adult life in these individuals.

In 1992 Brenner postulated the 'hyperfiltration theory', which enables to understand the possible mechanical pathway in the hypothesis that renal diseases at adult age is associated with intrauterine growth restriction (figure 2). Malnutrition of the fetus can lead to intrauterine growth restriction and impairment of renal development including deficit in

nephron numbers (Hinchliffe et al, 1992), which causes a decreased filtration surface area. Renal hemodynamic alterations, like hyperfiltration, are needed to improve the glomerular filtration in order to maintain normal renal function. This phenomenon is accompanied with glomerular and systemic hypertension. Glomerular hypertension may cause damage of nephrons leading to acquired glomerular sclerosis which decreases nephron numbers and filtration surface (vicious circle). (Brenner & Anderson, 1992; Brenner & Chertow, 1994; Martyn et al., 1996) Major criticism exists that no study confirmed the presence of an increased renal and systemic blood pressure as a consequence of hyperfiltration in growth restricted individuals. Brenner implicates that all kinds of nephron deficit are associated with the development of hypertension. He refers to studies in persons with unilateral agenesis and ablative surgery as in kidney donors. (Hakim et al., 1984; Thorner et al., 1984) Other studies show normal blood pressures ranges after 20 years of follow up in healthy kidney donors. (Goldfarb et al., 2001; Iglesias-Marquez et al., 2001) These individuals however, seem more healthy than the general population in first place. It seems more likely that hypertension is an additional factor in the pathway of impaired renal function in low birth weights.

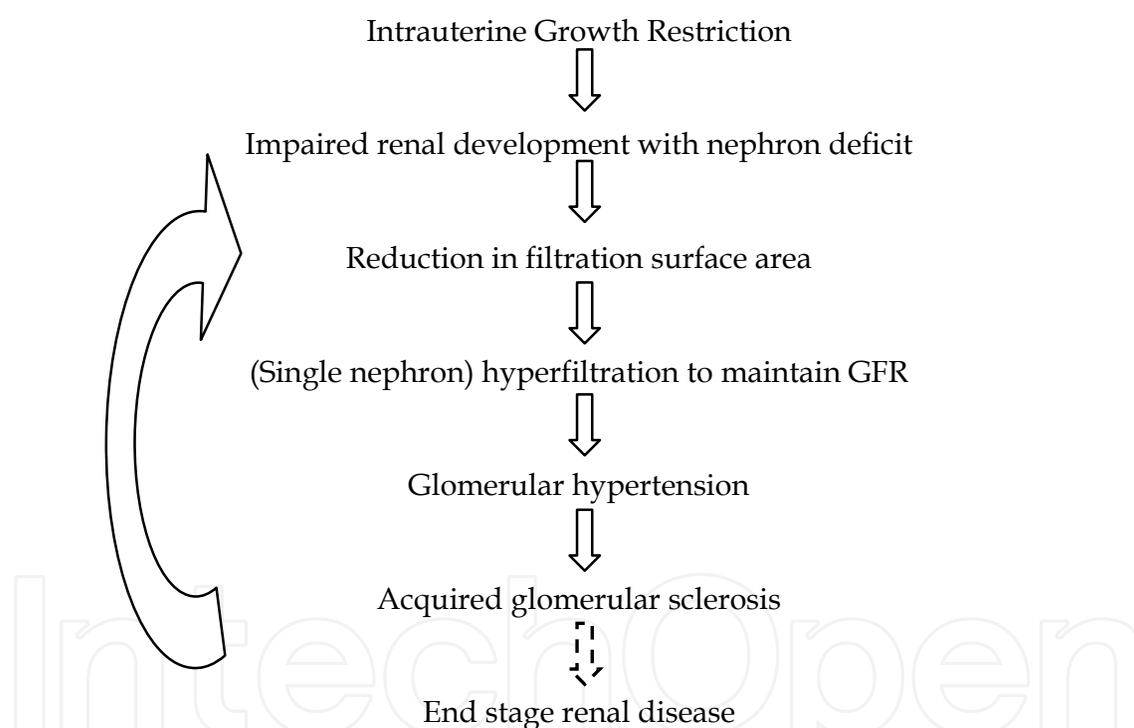


Fig. 2. Hyperfiltration theory. GFR: glomerular filtration rate. (adapted from Brenner & Chertow, 1994)

A strong relation between birth weight and renal size, nephron number, albuminuria and systolic blood pressure is shown in Aboriginal communities. (Singh & Hoy, 2004) In these communities diseases like type II diabetes, cardiovascular diseases and renal diseases take epidemic proportions. In another study in deceased 56 African Americans and Caucasians the kidneys were microscopically investigated. (Hoy et al., 2003) Nephron number was measured by stereologic estimation. Here, also nephron number was related to birth weight. Also, nephron number was inversely related to glomerular volume, suggesting that glomerulomegaly is a marker of an increased risk of groups of patients or populations with

progressive renal disease. These findings support the 'hyperfiltration theory' saying that birth weight is a risk factor for the development of progressive renal disease. (Singh & Hoy, 2004; Hughson, 2003)

4. Kidney development

4.1 Normal kidney development

In mammals, three different pair of renal organ system exist through embryologic development. The pronephros and mesonephros develop within the first 5 weeks of pregnancy and regress during development. They have no or limited renal function. The permanent kidney development start at approximately the 7th week of gestation with the outgrowth of the ureteric bud from caudal end of the mesonephric duct, meeting the metanephric blastema which together will differentiate into nephrons. (Moritz & Wintour, 1999) In addition, integration of small vessel growth is required in nephron formation. The first urine producing nephrons are developed within the first ten weeks of gestation and the amount is increasing with age. Driving forces to the outgrowth of the ureteric epithelium are direct cell-to-cell interactions, which are dependent of mesenchymal growth factors. These factors induce intracellular signalling and the expression of several gene products. (Jahnukainen et al., 2001) Many regulatory factors are involved, like fibroblast growth factor (FGF)-2, endothelial growth factor (EGF), bone morphogenetic protein-7, retinoic acid receptor expression, and PAX2, WT1, Wnt-11 genes. (Burrow et al., 2000; Burrow et al., 2007) PAX2 and WT1 are important in the proliferation and cell survival of the metanephric development. (Jahnukainen et al., 2001) Most nephrons are formed after the 20th week and at the age of 34-36 weeks the nephrogenesis is finished. At term birth, no new nephrons are formed. On average 750,000 nephrons per kidney are formed with a wide inter-individual range (250,000 to 2,000,000). (Hughson 2003, 2006, Nyengaard et al., 1992; Keller et al., 2003) The intrauterine renal blood flow and glomerular filtration rate is low, due to high vascular resistance. The urine production increases with fall in renal vascular resistance after birth maintained by a delicate balance in vasodilatory and vasoconstricting factors which is easily disturbed by illness of the neonatal infant (sepsis, cardiovascular distress, medications). Plasma creatinin levels fall from maternal levels to neonatal levels within three weeks. (Drukker & Guignard, 2002)

Also renal tubular function is recognised at early gestation (12-14 weeks) and rapidly developing. Tubular function in the neonate is characterized by reduced renal concentration and acidification ability, which improves in the first year of life. This phenomenon is more pronounced in preterm born subjects and in newborns suffering obstructive uropathy. (Chevalier, 1996) Urine calcium excretion is high, which can be aggravated by calciuric drugs, such as furosemide and glucocorticoids. In neonates, urine production and sodium excretion is relatively high compared to older children and adults, but fractional sodium excretions normalises within a few weeks. The concentrating capacity of the distal convolute tubule and collecting ducts increase within the first year of life.

4.2 Kidney development in preterm born individuals

As nephrogenesis is ongoing until the gestational age of 34-36 weeks, preterm born individuals suffer a diminished number of nephrons at birth. Many studies have shown lower renal volume in growth restricted subjects, both in animals and humans. Question is:

Is the premature infant capable of ongoing nephrogenesis after birth? and which factors may disturb this phenomenon?

From a study in 56 deceased extremely premature human infants and 10 deceased full term born controls it appeared that nephron number was highly correlated to gestational age and that glomerulogenesis had stopped after 40 days postnatal. (Rodriguez et al., 2004) A limited postnatal glomerulogenesis in preterm born individuals was shown and postnatal renal failure further inhibited the glomerulogenesis. In a small Italian study an active glomerulogenesis at preterm birth was seen but also ceased after a short period. (Faa et al., 2010) Therefore, nephron deficit (oligonephronia) in preterm born individuals probably exists throughout life placing the patient at risk for renal function deterioration. (Hughson et al., 2003; Singh et al., 2004)

In addition, histological changes are seen as well in the preterm born kidney. Animal studies in premature born baboons have shown abnormal glomeruli in the outer renal cortex, which contain the most newly formed glomeruli. Enlargement of the Bowman's space and shrinkage of the glomerular tuft are described. (Sutherland 2009) Glomerulomegaly and sausage shape kidneys may be a compensatory mechanism through hyperfiltration in oligonephronia. (Konje et al., 1996 Konje et al., 1997) Several studies have shown a reduced renal length and volume after SGA and preterm birth. (Konje et al., 1997; Spencer et al., 2001; Singh et al., 2004; Keijzer-Veen et al., 2010a) Konje showed lower renal volume in SGA born individuals compared to AGA. Differences were already shown at 26-28 weeks of gestation. (Konje et al., 1997) An Australian study showed lower renal volume in LBW aboriginal children (5-18 yr). (Spencer et al., 2001) Singh et al. also described that lower renal volume in aboriginals represents kidneys with reduced nephron number (Singh et al., 2004). We described decreased renal size in very preterm born individuals compared with full term born controls. (Keijzer-Veen et al., 2010a) Also, an increased number of renal anomalies was suggested in this study population.

4.3 Factors affecting kidney development

Both antenatal, perinatal and postnatal factors have been associated with impaired renal development in the neonate. Maternal factors like use of antenatal steroids, antihypertensive medication are studied. In addition, the infant may also suffer other conditions affecting postnatal renal development, like hypoxia, hyperoxia, use of nephrotoxic medications, acute kidney injury, vitamin A deficiency, and variation in genes and genetic expression. Effects of these factors are describes in more detail below.

Variation in genes and genetic expression: Epigenetic mechanisms are capable to induce important changes in the tissue-specific gene expression. Unfavorable environmental factors may influence promoter methylation, genetic imprinting and metastable epialleles and may alter tissue function. The critical window for epigenetic changes is not known. (Gluckman et al., 2008 and Wadhwa et al., 2009) Additional population based studies are conducted and results awaiting.

Antenatal steroid use: Glucocorticoids are important regulators of fetal growth and development. They affect gene transcription and cell differentiation and maturation in at least 15 different tissues. (Ballard et al., 1995) With the use of antenatal glucocorticoids preterm survival has improved significantly by accelerated maturation of lungs and surfactant production, increase in blood pressure and renal blood flow and GFR, with a decrease in urinary sodium excretion. (Kari et al., 1994) Increased nephrogenesis is

suggested when glucocorticoids are used at late pregnancy, while early administration was affecting nephrogenesis in a negative way in several animal studies. (Jahnukainen et al., 2001) (Gughaju et al., 2011).

Hypoxia: Perinatal hypoxia is a common feature in preterm born individuals. Underdevelopment of the lungs, and unfavourable perinatal conditions (sepsis, cardiovascular instability, metabolic changes) all increase the risk for hypoxic periods. Also spontaneous hypoxic events occur often in premature born infants. Hypoxia-induced tissue injury increase the risk for neurological but also renal morbidity. (Petrova & Metha, 2011) Renal ultrasound shows an increased hyperreflectivity of the renal parenchyma after hypoxic episodes. (Streitman et al., 2001) Hypoxia may lead to acute tubulus necrosis and *acute kidney injury* and deterioration of renal function. Mostly, the damage seems reversible, but loss of nephrons is not repaired and therefore is likely to increase the risk for renal disease in later life. (Askenazi et al., 2006)

Hyperoxia: Impaired angiogenesis is a wellknown result from hyperoxic state in preterm neonates leading to an increased risk for retinopathy of prematurity and bronchopulmonary dysplasia. It is suggested that an impaired renal angiogenesis may contribute a decreased renal development. (Gughaju et al. 2011) Further studies are needed to elucidate the effect of hyperoxia on renal development.

Nephrotoxic medications: Use of nephrotoxic medication in preterm neonates quite common. Aminoglycosides (gentamycin) are associated with nephron endowment and acute tubulus necrosis. (Gilbert 1996) Drug therapeutic monitoring strategies should be performed. Indomethacin (prostaglandin synthetase inhibitor) is also known to decrease renal blood flow due to decrease in prostaglandin production and vasoconstriction. Diuresis and natriuresis decreases and serum creatinine levels may rise. Ibuprofen exerts less effect on kidney function. (Giniger et al., 2007) The effect seems temporary, but it is not known if renal function over time is influenced if these medications are prescribed in early life.

Intrauterine growth restriction (IUGR): As describes above, many studies have shown an effect of (very) low birth weight and adult diseases. However, low birth weight subjects are not per definition exposed to growth restriction. Subjects born prematurely have lower birth weights than subjects born at term, but they both may have grown normally until that period of gestation. The extent of intra uterine growth restriction can therefore be expressed best by adjusting birth weight for gestational age. (Arnold et al., 1991) The most common way to describe (birth) weight is to express weight as a standard deviation score (SDS), which in fact is a z-score for birth weight, instead of using the SI units like (kilo)grams. A birth weight SDS of zero means that the subject's birth weight is the equal to the mean birth weight of all subjects born at the same gestational age. Lower birth weight than would be expected given that certain gestational age leads to a birth weight (SDS) below zero (also known as small for gestational age or SGA). Subjects with higher birth weights than would be expected given their gestational age will have a birth weight (SDS) above zero (also known as appropriate for gestational age or AGA). Normally the SDS ranges mainly between -3 and +3. The definition of IUGR is an arbitrary value between 0 and minus infinity, depending on the reference population, which is used to calculate the SDS. IUGR is most commonly defined as a birth weight (SDS) < 0 or < -2.

Extrauterine growth restriction (EUGR): Poor postnatal growth is known as a serious problem in very prematurely born individuals. In a large study including the data of 24,371 premature neonates it was shown that the incidence of EUGR was common (28%, 34% and

16% for weight, length and head circumference) and the incidence increased with gestational age and birth weight. (Clark et al., 2003) More recently it was shown that also postnatal growth restriction affected renal function over time in children born prematurely. At the age of 7 years blood pressure was slightly increased and renal size decreased in both 23 IUGR and 16 EUGR children in a study from France. (Bachetta et al., 2009)

Vitamin A deficiency: Vitamin A (retinoid acid) plays a critical role in fetal organogenesis, and it suggested that deficiency may induce malformations. Vitamin A is involved in normal branching of the ureteric. In a rat model a 50% reduction of vitamin A levels reduced nephron number by 20%. (Lelievre-Pegorier et al., 1998) However, postnatal supplementation of Vitamin A did not improve nephrogenesis in preterm born rats suggesting that vitamin A supplementation is of more importance during pregnancy. (Sutherland et al., 2009) Human studies seem scarce. In 2007 it was suggested that maternal vitamin A deficiency may induce kidney hypoplasia in their children. (Goodyer et al., 2007) Adequate Vitamin A intake should be undertaken.

Salt overload: Cardoso et al has suggested an increased risk for hypertension and reduced GFR after postnatal sodium overload in a study of 27 Wistar rats. (Cardoso et al., 2009) Offspring of the sodium overloaded pregnant rats had higher blood pressure, proteinuria and decreased renal function 90 days postnatally. Lipid profile was also disturbed and changes in the renin-angiotensin system was observed.

Renin-Angiotensin-System: A low renal blood flow leads to an increase in renin production by juxta-glomerular apparatus, which increases blood pressure by renin-angiotensin-system (RAS) in two ways. First renin converts angiotensinogen into angiotensin I (AT I), which is converted to angiotensin II (AT II) by angiotensin-converted enzyme (ACE). AT II stimulates α -receptors causing vasoconstriction in small vessels leading to an increase in blood pressure. Second, AT II stimulates aldosterone hormone production in the adrenal glands that stimulates sodium resorption and water retention in the distal convolute tubulus leading to an increase of circulating volume and blood pressure. In addition to the role to regulate blood pressure, the RAS is also thought to be an important factor in the renal development. Renal abnormalities are shown in animals in which RAS was blocked during renal development. (Guron & Friberg, 2000) Use of ACE inhibiting or AT II receptor blockage are therefore contraindicated during pregnancy.

Konje studied the active renin levels and AT I levels in the umbilical vein in preterms and IUGR fetuses. (Konje et al., 1996) AT I levels were increased in intra uterine growth restricted infants born preterm. Explanation could be hypoxia, increased sympatic nerve activity and catecholamin production (all present in growth restricted fetuses), but also a proliferation of juxta-glomerular cells (and thus renin producing cells). Protein restriction in pregnant rats leads to suppression of RAS in the fetus, associated with a inhibition of nephrogenesis and development of the ascending limb of Henle. (Lasaitiene et al., 2004) Also an increased ATII₁ receptor expression is shown in undernourished fetal rats. This may be a direct effect of protein restriction or a response to a decreased ATII concentration. (Sahajpal & Ashton, 2003) Martyn showed a decrease in inactive renine levels in adults exposed to malnutrition and intrauterine growth restriction. (Martyn et al., 1996) Fetal alterations in RAS activity may affect blood pressure in adult life. However, data are limited and not convincing. Further investigation is needed to elucidate the role of RAS in nephrogenesis and hypertension in adult life and the consequences for preterms and intrauterine growth restricted subjects.

5. Preterm birth and renal function over time

The plasma creatinin levels inversely correlate with the birth weight and gestational age during the first days of life. Creatinine falls within the first three weeks of life. (Bueva & Guignard, 1994) The normal fall in fractional sodium excretion is delayed in preterm born individuals. (Drukker & Guignard, 2002) Normal maturation of urine concentrating capacity takes about 1 year. Newer laboratory methods for renal function, like Cystatin C and Urinary Neutrophil gelatinase-associated lipocalin (*N-GAL*) are under investigation for the prediction of renal damage in this patient group as well. Further studies are upcoming.

With the knowledge that renal development is likely to be unfinished in preterm born individuals, and further development may be impaired, and that the preterm subject may suffer severe co-morbidity, and other risk factors for renal function impairment, the question rises what the implications are for renal health over time?

To elucidate the effect of preterm birth over time the information from long term follow up cohort studies are crucial. However, neonatal intensive care and general pediatric care are improving significantly. Therefore, extrapolation of the data from the older cohort studies to current time is not justified. On the other hand, more recent cohort studies only describe short period of follow up, and large cohorts are needed to demonstrate small differences between these 'younger' groups. In addition, most studies are limited because of small sample size and very low birth weight criteria are used instead of birth weight adjusted for gestational age. (Arnold et al., 1991)

Recently, Zanardo described an increased urinary microalbumin to creatinin ratio in 23 Italian toddlers (age 18 months) born after intra uterine growth restriction compared to 21 AGA born subjects. (Zanardo et al., 2011) Also, arterial intima media thickness and systolic blood pressure were increased in the SGA group. In this study the SGA group was born much more premature (mean gestational age 32 weeks compared to 38 weeks in the AGA group). Gestational age could have influenced the results. No blood samples were taken in this study. (Zanardo et al., 2011) A Polish study in 78 subjects born with a birth weight < 1,000 gr showed higher Cystatin C levels in the ELBW group compared to 38 controls at the mean age of 6.7 years. Renal volume was also significantly lower in the ELBW group. (Kwinta et al., 2011) Iacobelli found that neonatal hypotension was an independent risk factor for the development of microalbuminuria at the age of 7 years in 48 very preterm born individuals. (Iacobelli et al., 2007) No significant difference in renal function, size and blood pressure was seen between preterms and controls. In contrast, in a Swedish study renal function was not different between preterm born AGA ($N= 29$) and at term SGA ($N= 39$) children at the age of 9-12 yrs. Absolute renal volume was lower in the preterms, but after adjustment for body surface area the difference disappeared. (Rakow et al., 2008). Kistner et al. described blood pressure and renal function in 50 women born preterm and AGA, at term born SGA and at term born controls at the age of 29 years. Casual and ambulatory systolic blood pressure was increased in the preterm born group. No significant differences between groups were found in renal function. (Kistner et al. 2000; Kistner et al., 2002)

In the Netherlands two large prospective cohorts are available and ongoing. Additional studies are planned. The first large cohort study in the Netherlands is the **POPS study** (Project Of Preterms and Small for gestational age infants), which includes 94% of all individuals born with a gestational age < 32 weeks and/or a birth weight < 1500 grams in

the Netherlands in 1983 ($N=1338$). At the ages of 3, 6, 12 and 24 months and 5, 10, 14, and 19 years of age these subjects were tested for general health, cognitive development and motor skills and disabilities and quality of life. At the age of 19 years blood pressure, blood samples and urine samples were taken to evaluate the risk factors for cardiovascular disease, diabetes type 2, lipid profile deterioration and renal impairment. Pulse wave velocity and intima media thickness were measured. Of 1338 study subjects, 962 survived until the age of 14 years and 28 were lost to follow up. At the age of 19 years 934 were eligible for inclusion in the POPS19 study. Five hundred and ninety six subjects participated in this study (64%). Of these 596 subjects, 422 were born very preterm (GA < 32 weeks) and 174 had a very low birth weight < 1500 gram and a GA > 32 weeks. Blood pressure was significantly higher in all preterm born, independent of the birth weight. (Keijzer-Veen et al., 2005a) Renal function was normal, but not in favour of the small for gestational age born subgroups with higher levels of serum creatinine and increased microalbuminuria. (Keijzer-Veen et al., 2005b) No difference in intima-media thickness nor pulse wave velocity was found. (Finken et al, 2006a) Also the lipid profile was equal in all groups. (Euser et al., 2005) Insulin resistance was predicted by rapid postnatal weight gain until 3 months post term and by adult body composition. (Finken et al, 2006b)

An additional study in a subset of premature infants, comparing small for gestational age (SGA), appropriate for gestational age (AGA) and at term born controls. In this study renal function was measured in more detail. Inulin and para-aminohippuric acid clearances were measured with a continuous infusion, as well as renal reserve capacity. Renal ultrasound and 24 hour blood pressure monitoring were also performed. This study showed that blood pressure is increased in preterm born individuals compared to at term born controls. (Keijzer-Veen et al. 2010b) No differences between SGA and AGA infants was found. Renal function was normal in all individuals but lower in SGA preterm subjects. (Keijzer-Veen et al. 2007) Also the renal reserve capacity and effective renal plasma flow was reduced in SGA preterm subjects. The number of renal anomalies (mainly ectasia of the urinary system) was higher in preterm born individuals, and the renal size was decreased compared to controls. There was a difference in left and right kidney, and renal size differed between gender. (Keijzer-Veen et al. 2010a)

More recently, the **Generation R study**, a population based prospective cohort study from fetal life until young adulthood in Rotterdam, the Netherlands is conducted. (Jaddoe et al. 2010) In total, 9,778 mothers with a delivery date from April 2002 until January 2006 were enrolled in the study. Of all eligible children at birth, 61% participate in the study. General follow up rates exceed 75% at age 4 years. In addition, more detailed assessments are conducted in a subgroup of 1,232 pregnant women and their children. Data collection in the prenatal phase and postnatal phase until the age of 4 years includes questionnaires, detailed physical and ultrasound examinations, behavioral observations and biological samples. (Jaddoe et al. 2007) Renal ultrasound was performed antenatal and postnatal.

Results in regard to renal development and function: Maternal smoking was associated with reduced kidney size in the offspring. A curved shaped association between the number of cigarettes smoked in the third trimester of pregnancy and fetal kidney size was found. Small kidney size in fetal life tends to persist in early childhood. (Geelhoed et al. 2009 and Taal 2011) Preferential fetal blood flow to the brain was also associated with smaller kidneys in late pregnancy. (Verburg et al. 2007)

6. Clinical implications and future perspectives

The survival of extremely preterm birth, even at gestational age of 22-23 weeks has improved tremendously. One-year survival rates of 9.8% in 22 weeks of gestation and 53% in 23 weeks of gestation have been described in Sweden in the period 2004-2007. (EXPRESS group 2009) In this study the overall mortality was 30% in all 22-26 weeks of gestation at the age of 1 year and only 45% of survivors had no major morbidity at the age of 1 year. To improve normal ex-utero growth (like in-utero) and development the ESPGHAN guidelines recommend a high protein intake of at least 3 g/kg/day, a phosphate intake of 60-90 mg/kg/day and a calcium intake of 120-140 mg/kg/day. (Agostoni et al. 2009) However, it is to be investigated if renal development also benefits this protein, calcium- and phosphate load. Follow-up of these children should include the evaluation of nephrocalcinosis incidence and glomerular and tubular function over time. Moreover, the extremely preterm born subjects (gestational age 22-24 weeks) are likely to have an increased exposure to factors depriving kidney development in the neonatal intensive care unit. It is hypothesized that renal function loss will become evident at even younger age compared with individuals born less premature or in the early eighties or nineties.

In addition, with increasing prevalence of obesity and increased salt intake in adults and children, the risk for the metabolic syndrome and renal function loss is increasing in the general population. It has been shown that the risk for renal function loss was twofold in children obese born prematurely compared to obese children born at term. (Abitbol et al 2009) Therefore, childhood obesity and salt intake overload should be avoided in all children, especially when born premature.

It is important to acknowledge the problem of disturbed nephrogenesis in the preterm born infant, and to prevent further disturbed development by good clinical practice. Primary prevention of preterm birth and IUGR and secondary prevention of other factors affecting renal development like hyperoxia, hypoxia, infection with decreased renal blood flow (blood pressure regulation and toxins), nephrotoxic medications and extra-uterine growth restriction should be addressed daily at the neonatal intensive care units. Clinicians should evaluate the effects of their actions. Long term follow-up is advised by simple urinary test (proteinuria/microalbuminuria) and blood pressure screening. Patients with abnormalities should be referred to a paediatrician for more detailed renal function measurement.

7. Conclusion

This chapter has shown the normal kidney development and the effect of premature birth. Nephron endowment is a risk factor for glomerular hyperfiltration and renal function deterioration over time. Prevention of premature birth and intrauterine growth restriction, prevention of childhood obesity and salt and protein overload should be highly advocated in all populations and health care organizations. The importance of prevention of further renal damage in premature born individuals is not to be underestimated.

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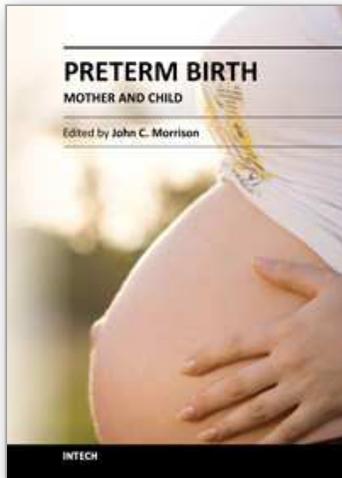
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While there are many studies and books regarding preterm birth, both the obstetric and in the neonatal/pediatric literature, what is missing is the integration of data from obstetrics through neonatal course and into pediatrics as the neonate transverses childhood. A continued dialogue between specialties is essential in the battle against preterm birth in an attempt to relieve the effects or after-effects of preterm birth. For all of our medical advances to date, preterm birth is still all too common, and its ramifications are significant for hospitals, families and society in general.

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