2. The development of renal function

Maria Bitsori
Specialist Paediatrician & Consultant Paediatric Nephrologist, Department of Paediatrics
University Hospital of Heraklion, Greece

Summary. Renal function starts to develop in foetal period and continues to evolve throughout the first years of life until it reaches its complete, adult level. Under this process the kidneys are obliged to changes that give the renal function during childhood its particular characteristics. The human kidney begins to develop in the 5th gestational week and starts to produce urine between the 10th and 12th week of gestation. Nephrogenesis is complete around the 35th-36th week so that a term neonate is born with all its nephrons, something which is not the case for a premature one, born before nephrogenesis is complete. The entire process of foetal kidney development has been recently shown to be regulated by many genes and gene products, such as cytokines and growth factors, as well as the intrauterine environment itself, in a particular way known as epigenetics.

The kidney regulates homeostasis by two fundamental functions, the glomerular and the tubular. In neonates both functions are deficient and although the neonatal kidneys are well equipped to sustain physiological processes, they are severely limited in their response to stress. Neonates have glomerular filtration rate (GFR) as low as 20 ml/min/1.73 m2 at birth, which rises gradually to reach the adult rates at 18 months. Additionally, due to immature tubular

Correspondence/Reprint request: Dr. Maria Bitsori, Specialist Paediatrician & Consultant Paediatric Nephrologist
Department of Paediatrics, University Hospital of Heraklion, Greece.
function, neonates have reduced concentrating capacity, negative sodium equilibrium and reduced bicarbonate levels and they are, thus, prone to dehydration and hyponatremia.

No new nephrons are made during childhood but the existing ones grow in size and mature in function. Although glomerular and tubular function evolve to mature levels between 12-18 months, the child kidney keeps lower adaptation capacities and remains vulnerable to injuries throughout childhood.

**Introduction**

Renal function starts to develop in early foetal period and continues to evolve throughout the first years of life until it reaches its complete, adult level. Under this process the kidneys are obliged to changes that give the renal function during infancy and childhood its particular characteristics. Although the most challenging event for the developing kidneys is the transition from intrauterine to extrauterine life, managing homeostasis for a continuously growing organism during infancy and childhood is also demanding. Moreover, under the recent advances of medical care of the newborn, we are now well aware of the importance of the 9-month process of gestation on kidney development and future renal function.

New data obtained from advances in genetics and molecular biology, new technological potentials for early diagnosis of abnormalities and prompt intervention, and improved methods of studying renal physiology and support renal function have dramatically changed renal care in early life. In this chapter an overview of the evolution of renal function in childhood is given, with a clinical perspective and with emphasis on new diagnostic and evaluative aspects.

**Embryology**

The foetal histopathologist Edith Potter, in her landmark book *Normal and Abnormal Development of the Kidney* published in 1972 set the basis of our contemporary understanding of normal kidney development and the origin of congenital malformations, which constitute the most important cause of impaired renal function in early life. In humans, kidney development starts at 5 weeks of gestation with two transient, mesenchyme-derived kidney-like paired structures, the *pronephros* and the *mesonephros*. The definite kidney (*metanephros*) forms by day 28 after fertilisation when ureteric bud branches from the mesonephric duct and the metanephric blastema, consisting of clusters of mesenchymal cells, condenses around it. The ureteric bud after several divisions will ultimately form the collecting system, ureter, renal pelvis, calyces and collecting ducts and the metanephric mesenchymal cells
will either surround evolving ureteric branch tips to form nephrons or form interstitial fibroblasts.²

The primitive glomeruli appear at approximately 9 weeks of gestation and urine production starts between the 10th and 12th week.³ Nephrogenesis is completed by 32-34 weeks. Potter estimated that a human kidney contained $35 \times 10^4$ nephrons at 20 weeks of gestation and about $80 \times 10^4$ at 40 weeks. More recent studies suggest, however, that the majority of nephrons form in the final third trimester of gestation and the final nephron number can be highly variable, with mean numbers ranging between $64 \times 10^4$ and $130 \times 10^4$. After birth there will be no further increase in nephron number. Further development involves hypertrophy and adaptational changes so that glomeruli reach adult morphology and size by 3.5 years of age.³

**Genetic programmes and epigenetics in kidney development**

Early experiments in mice and identification of mutant genes in human renal agenesis or hypodysplasia have yielded much insight into the role of several genes and molecular pathways that control the whole procedure of nephrogenesis.

Potter’s original studies described in detail different types of dysplasia and defined for the first time the key anatomical differences between cystic dysplasia and congenital polycystic kidneys: in the former, cysts formed in the context of abnormal renal development whereas in the latter, cysts formed from normally developed nephrons.¹ Whereas the genetic basis of congenital polycystic kidneys has been well known, Potter wrote that dysplastic kidneys appear never to be genetic or chromosomal in origin, a view that has not proven to be correct in light of current knowledge.¹ In the early 1990s investigators proved that aberrant human kidney differentiation could be caused by mutations of genes normally active in the maturing kidney, discovering the cause of the WAGR (Wilms’ tumor, aniridia, genitourinary anomalies and mental retardation) syndrome where both the *Wilms tumor 1 (WT1)* and its neighbouring *Paired box 6 (PAX6)* genes are deleted.⁴ Since then there has been an explosion of knowledge about genes that are expressed during kidney development, some of which were found to be mutated in individuals with syndromic kidney and urinary tract malformations. This way, *paired box 2 (PAX2)* gene associated with vesicoureteral reflux (VUR) and renal hypodysplasia and *hepatocyte nuclear factor 1B (HNF1B)* gene associated with cystic dysplasia and hydronephrosis were discovered.³,⁴ These and several other genes that have been found to be implicated in renal tract development in animal studies are currently under investigation about their role in the much more common non-syndromic
renal conditions, such as solitary kidney, VUR, duplications or posterior urethral valves.

Recently the role of foetal environment and epigenetics in renal development is under investigation. During development, specific intrauterine circumstances, directly related to environmental factors can modulate the transcriptional potential of DNA sequence, without affecting the sequence itself. This way epigenetic marks are established, which are maintained through cell division and might persist across generations. There is now growing evidence that epigenetic changes play a role in kidney development and future renal diseases. Intrauterine growth retardation and low birth weight have been epidemiologically associated with hypertension cardiovascular disease and chronic kidney disease. Moreover, animal models of foetal growth restriction produced by inappropriate maternal diet or exposure to medications have shown a marked reduction of foetal nephron number and kidney function. Molecular mechanisms that have been implicated include inhibition of the renin-angiotensin system (RAS) in utero, reduced circulating insulin-like growth factor-1 (IGF-1) and increased apoptosis and are believed to be susceptible in epigenetic changes in humans.

This progress in our understanding of foetal kidney and urinary tract development together with technological advances that made antenatal screening for malformations of kidneys and urinary tract part of the routine care of every pregnancy have dramatically improved neonatal renal care.

**Renal function in utero**

During pregnancy, foetal fluid homeostasis is maintained by the bi-directional exchange between mother and foetus through the placenta and the only, but very important, purpose of foetal renal excretory function is its contribution to the formation of the amniotic fluid. Foetal urine is produced from approximately the 10th week of gestation in increasing amounts, reaching 25-40 ml/h at term and is a major constituent of amniotic fluid. Disturbances on the foetal cycle of swallowing amniotic fluid, gastrointestinal reabsorption and renal excretion may lead to oligohydramnios (less than expected amount of amniotic fluid at any specific stage of gestation) or polyhydramnios (> 2 litres of amniotic fluid). The former condition is seen in renal agenesis and urinary tract obstruction and is responsible for the “foetal compression” or Potter’s syndrome of pulmonary hypoplasia and characteristic facies. The latter, is caused either by primary overproduction of amniotic fluid, upper gastrointestinal obstruction or foetal polyuria encountered in diabetes insipidus and several inherited renal diseases such as Bartter’s syndrome or congenital nephrotic syndrome. Because of the free passage of small chemical particles
across the placenta, the concentration of basic biochemical markers of the baby at the time of birth equilibrate those of the mother. Thus, creatinine levels of newborn at time of birth are close to maternal levels. 

**Neonatal renal function**

Overall renal function at birth, both glomerular and tubular is reduced in comparison with later childhood and adult values, even corrected for the adult body surface area of 1.73 m². Nevertheless, the neonatal kidneys are very well equipped to manage homeostasis and sustain normal development and maturation from the very first moment of birth. The kidneys have, however, severely limited adaptive properties in their response to stress, due to anoxia, sepsis, exposure to nephrotoxic medications or –not rarely- the occurrence of these factors in combination. This is especially true for premature neonates, born before 35 weeks of gestation, when nephrogenesis is not complete.

**Glomerular function**

At birth, systemic blood pressure (BP) is low and the intravascular resistance high, resulting in a very reduced kidney perfusion. The kidneys of the newborn receive only 15-20% of the cardiac output, in contrast to the 25% observed in the adult. This hypoperfusion in combination with a severely limited filtration surface are the basic reasons of the very low glomerular filtration rate (GFR) of the neonate. Thus, in a healthy term neonate the GFR at birth is just 20 ml/min/1.73m² and about 10-15 ml/min/1.73m² in a premature one. This low GFR limits all renal functions, especially with regard to water and electrolyte homeostasis and the excretion of waste products. During the first month of life GFR increases rapidly due to a rise of systemic BP and a concomitant fall in renal vascular resistance, but it hardly exceeds 40 ml/min/1.73m² in the term neonate. Autoregulation of GFR, that is maintenance of glomerular filtration when BP falls, remains deficient during early infancy, thus the kidneys of neonates and young infants are more susceptible to hypovolaemic injury.

Knowledge of these low GFR values during the neonatal period has important implications in interpreting clinical situations. Low GFR values are rather expected than representing impaired renal function during the first days of life. On the other hand, when neonates with conditions affecting renal function are evaluated, for example renal dysplasia, the clinician should have in mind that considerable increase of GFR during the first weeks represents a natural phenomenon rather than improvement and lack of this increase is not stabilisation but worsening.
Tubular function

Contrary to glomerular function which increases rapidly but remains defective during neonatal period, tubular function, responsible for water, electrolytes and acid-base balance, matures more progressively and is more efficient in some mechanisms than it is in adult life.11

Water management

During foetal life water is abundant and is exchanged freely between mother and foetus without any concentrative mechanisms. At birth the total body water (TBW) accounts for 75% of the weight of the newborn, most of which is extracellular fluid (ECF). Within days the total amount of water starts to decrease due to very little fluid intake and the increasing GFR and at the same time a shift of fluids between compartments commences.10 The ECF space contracts and water enters the cells, which increase in number and size. These changes result in the so called “physiological weight loss” of 5-10% of birth weight for the term neonate and somewhat higher in premature neonates, which occurs within the first week of life.7 After this period the kidneys’ concentrating capacity increases and water loss is minimised. However, because the renal concentration mechanism matures in the 2nd month of life, the neonatal concentrating capacity remains low and conditions of water depletion, such as vomiting, diarrhoea or phototherapy may lead to dehydration.10 On the other hand, the dilutional mechanism, a much older one in evolutionary terms, is much more effective during the neonatal period.12 This does not, however, mean that the infant can excrete water load efficiently, because this function is again limited due to the low GFR of the newborn. The practical implications of these particularities of water handling during neonatal period are that fluid therapy for this age group should be carefully monitored. The greatest risk, particularly for the smallest babies is dehydration but they are equally unable to handle important fluid overload.

Sodium management

Sodium is essential for growth and a positive sodium balance is a prerequisite for adequate growth and development. The increased water loss right after birth is accompanied by sodium loss, which is more prominent in premature neonates.7 Fractional excretion of sodium (FENa) immediately after birth can be as high as 5% compared with 1% in the adult, but it falls within days as the mechanisms for concentrating and saving sodium develop quickly to compensate for the very low concentration in salt of the human milk, at least
in the term neonate. This process is delayed in premature infants who may require oral sodium supplementation to remain in positive balance. After the first few days and throughout early infancy the babies’ kidneys are in a sodium-conserving state. Late hyponatraemia might be seen in rapidly growing very low birth weight infants during the first 2 months, due to avid incorporation of sodium in the tissues and not due to increased losses.

**Acid-base balance and other substances**

The tight regulation of acid-base homeostasis is achieved through buffer systems and appropriate respiratory and renal adaptations. At birth, respiratory adaptive responses are adequate and work immediately in a spontaneously breathing and neurologically intact neonate. The renal compensatory mechanisms are slower and limited due to low neonatal GFR and the not yet developed tubular transport systems of bicarbonate and hydrogen ions. Thus neonates are in a physiological acidotic state, with healthy term newborns to have bicarbonate levels of 18-20 mEq/L compared with 24-26 mEq/L in the adult, a level which is reached at about 1 year of age. Premature infants may have bicarbonate levels as low as 14 mEq/L. Disease states or drug therapy may aggravate this situation, making this age group prone to severe acidosis.

Potassium excretion is low during gestation and remains so during the first months of life. Thus tissue and serum potassium levels are higher in neonatal period and early infancy than later. Thus, potassium values of 6 mEq/L or even 6.2 mEq/L in premature babies are considered normal in early infancy.

Phosphorus is an essential element not only for growth but also for metabolism and its mechanisms of reabsorption are well developed at birth and work more efficiently than they do in adult life. Phosphate values are high during neonatal period and infancy, especially in breast-fed infants.

During the first year of life generalised aminoaciduria might be noted as well as transient glucosuria in premature neonates. Thus in infants investigated for possible tubulopathies such findings should be carefully interpreted.

**Maturation and evaluation of renal function**

As the child grows, urine excretion and GFR increase and concentration capacity improves until renal function reaches the adult levels by the completion of 2 years. Maturation changes occur more rapidly during the first six months of life and are slower thereafter. Early studies showed that the earliest age that all kidney functions were within the adult range was seven months, but this would be only considered as exceptional.
Renal function in clinical practice is usually evaluated through measurement of substances in serum and urine and calculations which might include urine and serum measurements or different more complex ones with the use of isotopes like CrEDTA. Normal values of usual parameters of renal function in the first years of life are presented in Table 1.

**Table 1.** Age-related changes in renal function parameters.

<table>
<thead>
<tr>
<th></th>
<th><strong>Premature infant</strong></th>
<th><strong>Term infant</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st week</td>
<td>2nd week</td>
</tr>
<tr>
<td>Daily excretion of urine (ml/kg/24h)</td>
<td>15-75</td>
<td>20-75</td>
</tr>
<tr>
<td>GFR (mL/min/1.73m²)</td>
<td>10-15</td>
<td>15-20</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Max. Urine Osmolality (mOsm/kg H₂O)</td>
<td>400-500</td>
<td>500-600</td>
</tr>
</tbody>
</table>

**Urea and creatinine**

Urea is not particularly useful for the estimation of renal function during the first months of life, as it rather reflects the infant’s metabolic state than the renal function. It is usually low during the very anabolic situation of fast growing of infancy and when increases, it usually occurs in the catabolic face of diseases and not due to renal dysfunction. In later childhood, conditions that might affect urea independent of GFR are presented in Table 2.

**Table 2.** Conditions that affect urea independent of GFR.

<table>
<thead>
<tr>
<th>Increase</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>High protein diet</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Tissue traumatic injury</td>
<td>Steroids</td>
</tr>
</tbody>
</table>
Serum creatinine is a better index of renal function in infancy and childhood. Its concentration is highest at birth, reflecting maternal creatinine levels. During the first 2 weeks of life serum creatinine decreases rapidly to reach the stable neonatal levels of 0.5 mg/dL and continues to drop, but at a lower rate, in the following month to be stabilised at 0.3-0.4 mg/dL during infancy. In premature neonates creatinine levels increase transiently with a peak at day 4, and a more progressive decline towards normal neonatal levels at about 4 weeks of age. Although creatinine concentration reflects muscle mass and would be expected to rise with age, during the first 2 years of age little change occurs. This is because of the dramatic rise of GFR and therefore creatinine clearance during the first 2-3 years of age. Beyond that time increase in muscle mass is reflected in creatinine concentration (Figure 1).

![Figure 1. Serum creatinine in association with age.](image)

**Cystatin C**

Cystatin C is a protease inhibitor that is present in all nucleated cells in the body. In adults its concentration is more stable than that of creatinine and independent of muscle mass or inflammatory state, so it is a much more sensitive and specific renal function marker than creatinine. In children over 2 years of age cystatin levels approach those of adults and are between 0.53 and 0.95 mg/L. Its concentration is higher in neonates and infants but there are only very limited data for this age group (Table 3). Cystatin C is very useful for evaluating renal function in cases of malnutrition.
Table 3. Cystatin C reference values.

<table>
<thead>
<tr>
<th>Age</th>
<th>Cystatin-C (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean/median (range)</td>
</tr>
<tr>
<td>24–28 weeks</td>
<td>1.48 (0.65–3.37)</td>
</tr>
<tr>
<td>29–36 weeks</td>
<td>1.65 (0.62–4.42)</td>
</tr>
<tr>
<td>0–3 months</td>
<td>1.37 (0.81–2.32)</td>
</tr>
<tr>
<td>4–11 months</td>
<td>0.98 (0.65–1.49)</td>
</tr>
<tr>
<td>1–3 years</td>
<td>0.79 (0.50–1.25)</td>
</tr>
<tr>
<td>4–8 years</td>
<td>0.80 (0.49–1.29)</td>
</tr>
<tr>
<td>9–17 years</td>
<td>0.82 (0.53–1.29)</td>
</tr>
</tbody>
</table>

Creatinine clearance

Creatinine clearance remains a widely used clinical parameter for evaluating GFR. It is calculated by the following formula in timed urine collection:

\[
ClCr = V \times UCr/SCr \times 1.73 \text{m}^2/\text{BSA} \ (\text{ml/min}/1.73 \text{m}^2)
\]

ClCr: creatinine clearance, V: volume of urine per minute, UCr: urine creatinine (mg/dL), SCr: serum creatinine (mg/dL), BSA: body surface area (m²).

The major drawback of this calculation is that it requires accurate timed collection, which is only assured through bladder catheterisation in the younger ages.

Schwartz formula, the results of which correlate very closely to those of creatinine clearance, can be used to estimate GFR without urine collection:¹⁷

\[
eGFR = K \times \text{Body length (cm)}/\text{SCr} \ (\text{SCr: serum creatinine, mg/dL})
\]

K is a constant which depends on urinary creatinine per unit of body size and its values for different ages are as follows:

Low birth-weight infants < 12 months, 0.33; Term infants < 12 months, 0.45; Children 2-12 years and females 13-21 years, 0.55; Males 13-21 years, 0.70.

Conclusions

Kidneys and urinary tract develop during intrauterine life under genetic and epigenetic control, the molecular events of which have only now started to
be unravelled. Children’s kidneys have distinct characteristics which allow them to respond to the passage from the intrauterine to extrauterine environment and to manage homeostasis in a continuously growing organism thereafter. Although glomerular and tubular function evolve to mature levels between 12-18 months, children’s kidneys keep lower adaptation capacities and remain vulnerable to injuries throughout childhood.

References