Renal Development and Neonatal Adaptation

M. Saint-Faust, MD[1] F. Boubred, MD[2] U. Simeoni, MD, PhD[2]

[1] Department of Neonatology, Universitary Hospital, Nice, France
[2] Department of Neonatology, Universitary Hospital, La Conception and Aix-Marseille University, Marseille, France

Address for correspondence Marie Saint-Faust, MD, Department of Neonatology, Universitary Hospital, Archet2, Nice, France (e-mail: mariestfaust@hotmail.fr).

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Abstract

The structural and functional development of the kidney is responsible for a significant impact on postnatal adaptation to extrauterine life. Prenatal or neonatal impairment of nephrogenesis may carry long term, lifelong consequences in terms of reduced nephron endowment, chronic kidney disease, and cardiovascular risks at adulthood. Intrauterine growth restriction, preterm birth, congenital renal, and urinary tract anomalies are for long widely incriminated. Neonatal administration of nephrotoxic drugs has been associated with short-term acute kidney injury and longer chronic kidney disease. This review attempts at offering a comprehensive understanding of the renal development, the neonatal renal transition to extrauterine life and subsequent maturation phase during early infancy. It also focuses on developmental and maturational changes that impact lifelong renal function and adult health.

Keywords
- renal development
- neonatal adaptation
- intrauterine growth restriction
- drugs toxicity

Kidney development is a long and complex process. Morphologic stages which lead to the definitive kidney have been well understood for decades. Postnatal maturation of renal function has been for long one of the fundamental concerns for neonatologists and nephrologists. The amplitude of postnatal changes has major consequences for intensive care approaches, including the management of oxygenation, hemodynamics, fluid, electrolytes, acid–base balances, drug therapy, and renal failure. Immaturity of glomerular and tubular functions requires drastic adaptations in preterm infants. More recently, it has been published that kidney immaturity or developmental impairment may have not only a short-term impact, but also lifelong consequences with an increased risk of chronic kidney disease and hypertension at adulthood, because of perturbations in the individual early-acquired nephron endowment.

Kidney Development

Mammalian renal development progresses through three stages involving tissue derived from the mesoderm. The pronephros gives rise to the intermediary kidney, the mesonephros (which has some filtering functionality) which subsequently gives rise to the metanephros. The processes leading to its final structure include reciprocal induction between the metanephric mesenchyme (MM) and the ureteric bud (UB). Through these inductive steps, the nephrogenesis occurs and results in the development of the glomerulus, tubules, and the renal collecting system. Metanephric development begins during the fifth week of gestational age, and develops from a specific interaction between the epithelial UB and the undifferentiated MM, called metanephric induction. This interaction is crucial for the mesenchymal differentiation and the induction of branching division (►**Fig. 1**). The UB arises in response to different signals (many molecules, transcriptional factors, growth factors, and regulation genes) elaborated by the mesenchyme, and then undergoes branching morphogenesis.[1] It requires a fine balance of these factors that might be disturbed by various prenatal events. This process is a fundamental step toward establishing the architecture of the kidney and determining the number of nephrons, which form the filtration units of adult kidney. At 20 to 22 weeks of gestational age, branching morphogenesis is complete and leads to the collecting system. Mesenchymal cells, in close contact with the invading UB, undergo the epithelial–mesenchymal transition,

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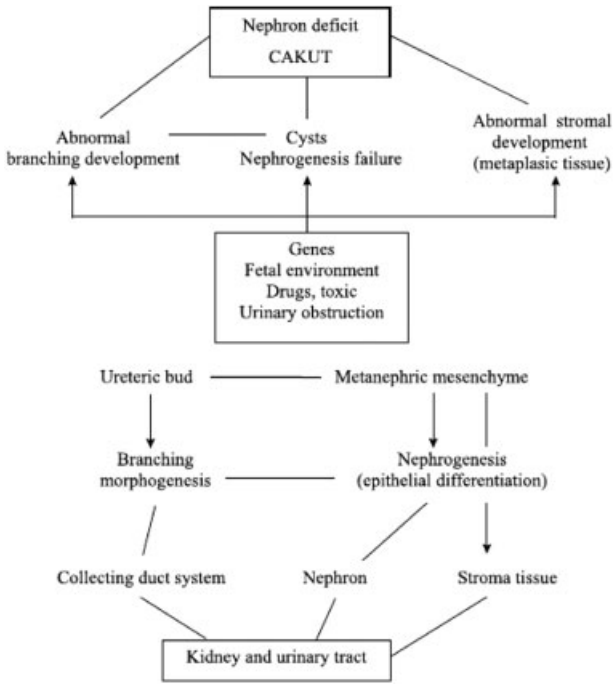

Fig. 1 Simplified schematic process of normal and pathologic kidney development.

resulting in the transformation of all epithelial cells types of nephrons and leading to the coordinated growth and differentiation of multiple highly specialized stromal, vascular and epithelial cell types.[1]

An emerging paradigm provides support for the requirement for a third cell type, the angioblast, which appears to be involved in maintaining the condensed mesenchyme in a differentiated state. In fact, recent studies have identified an interaction between angioblasts and the condensed mesenchyme as a new crucial interaction, in addition to the classically recognized metanephric induction.[2] Other's data provide evidence supporting a key role for vascular endothelial growth factor (VEGF) and its receptor in renal development by promoting endothelial cell differentiation, capillary formation, and proliferation of tubular epithelia.[3]

The induced MM leads to the nephrons, through consecutive stages of condensation, renal vesicle, vascular cleft and S-shaped body. The glomerular capillary tuft is formed via recruitment and proliferation of endothelial and mesangial cells precursors. Nephrons develop in successive stages from the inner to the outer area of the fetal kidney in parallel with the vascular system. In the human, the primitive glomerulus appears at approximately 9 to 10 weeks of gestational age. Nephrogenesis is achieved by 34 to 36 weeks of gestation.[1,4] About 60% of the nephrons develop during the third trimester of gestation, while nephrogenesis may continue ex utero in preterm infants.[5]

At birth, the final nephron number ranges from 300,000 and 1.8 million per kidney. Such variation in nephron number is because of genetic factors and fetal environment.[1,6] Several genes and molecular pathways are involved in regulating the complex process of formation of the renal collecting system and nephrogenesis, such as, transcriptional regulators (i.e., *PAX 2*, *WT1*, and *EYA1*), growth factors (i.e., insulin growth factor [IGF], epidermal growth factor [EGF], transforming growth factor [TGF]), oncogenes, the extracellular matrix, and vascular factors (VEGF, FLK1, FLT1, *PAX 2*, glial cell-derived neurotrophic factor GDNF).[2,3,7] The site of metanephric induction is critical for normal kidney development; ectopic ureteric budding is associated with congenital anomalies of the kidney and urinary tract. Blockade of VEGF receptor, inhibition of the renin angiotensin system (RAS), knockout for cyclooxigenase 2 (COX-2) gene expression and ablation of *SIX2* expression are associated with impaired nephrogenesis including glomerular cysts, dysplastic tubules, tubular dysgenesis, and a normal cap mesenchyme (►**Table 1**).[1,8–10]

Renal Physiology

The Fetus

In utero, fetal homeostasis is assigned to the placenta. The kidney is involved in urine production, essential in fetal well being, and in hormonal production (1,25(OH)2D3 and erythropoietin). Glomerular filtration rate (GFR), renal blood flow (RBF), and tubular functions progress with renal growth and nephrogenesis. In the near term period, fetal kidney shows sufficient glomerular and tubular development to allow the adaptation to extrauterine life.[11]

Glomerular Function and Renal Blood Flow

During intrauterine life, nephrogenesis plays an important role in maturation of the GFR. GFR in the fetus is low, even at the end of gestation, and depends on RBF and various factors. Systemic arterial blood pressure, around 40 to 60 mm Hg, and RBF are low compared with the newborn or adults. In sheep, the fetal kidney receives only 3% of cardiac output (15% in the neonatal period). Such low RBF is correlated to elevated renal vascular resistances. This state is mainly because of a subtle equilibrium between vasoconstrictive factors, including RAS and renal nervous system, and vasorelaxing factors such as prostaglandins, nitric oxide (NO), and other factors. In the fetal kidney, RAS is upregulated and contributes to the maintenance of RBF and renal perfusion pressure. RAS is of crucial importance in the antenatal period as angiotensin II acts as a potent growth factor controlling at least partly nephrogenesis. The renal sympathetic nervous system increases renal vascular tone in afferent and efferent arterioles; an upregulation of α_2 receptors is associated with a downregulation of β_2 receptors, but fetal renal vasculature is more sensitive to α_2 receptor stimulation than in neonatal period.[11]

Vasoconstrictive forces are counterbalanced by vasodilating factors that act on the glomerular afferent arteriole to maintain sufficient RBF. These factors are mainly prostaglandins, NO, and the kallikrein–kinin system. Prostaglandins, E2, and I2, in particular, are of major importance. They are produced by the placenta, membranes and the fetus, from action of two enzyme isoforms, type 1 and type 2 cyclooxygenases (COX-1 and COX-2). COX-2 is constitutive in fetal kidney and appears essential for renal growth, development,

Table 1 Syndromes and genes defects associated with abnormal kidney development (CAKUT)

Syndrome	Gene defects	Kidney malformations
Renal coloboma syndrome	*PAX 2*	Hypoplasia, VUR
Renal cysts and diabetes syndrome	*HNF1b*	Dysplasia, hypoplasia
Branchio-oto-renal syndrome	*EYA1, SIX1*	Unilateral or bilateral agenesia/dysplasia
Renal tubular dysgenesis	*RAS components*	Tubular dysplasia/dysgenesis
Campomelic dysplasia	*SOX9*	Dysplasia, hydronephrosis
Townes-Brock syndrome	*SALL1*	Dysplasia, hypoplasia, VUR
Simpson-Golabi-Behmel syndrome	*GPC3*	Medullary dysplasia
Kallmann syndrome	*KAL1, FGFR1, PROK*	Renal agenesis
Fraser syndrome	*FRAS1*	Dysplasia, renal agenesis
Alpert syndrome	*FGRG2*	Hydronephrosis
Alagille syndrome	*JAGGED1*	Cystic dysplasia
Meckel–Gruber syndrome	*MKS1, MKS3*	Cystic renal dysplasia
Hypoparathyroidism, deafness and renal anomalies syndrome (HDR)	*GATA3*	Dysplasia, VUR
Di George syndrome	*22q11*	Agenesia, dysplasia, VUR
Beckwith–Wiedemann syndrome	*P57*	Dysplasia
Pallister–Hall syndrome	*GLI3*	Dysplasia
Nail–patella syndrome	*LMX1B*	Agenesia, glomerular anomalies
Smith-Lemli-Opitz syndrome	*7 hydroxy-cholesterol reductase*	Agenesia, dysplasia
Zellweger syndrome	*PEX1*	Cystic dysplasia, VUR
Glutaric aciduria type II	*Glutaryl CoA dehydrogenase*	Cystic dysplasia

Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; VUR, vesicoureteral reflux

and function.[12] Administration of COX inhibitors during pregnancy decreases RBF, impairs renal function, and induces oligohydramnios. NO is synthesized by endothelial cells, and vasodilates the afferent arteriole. In sheep, inhibition of NO leads to increased renal vascular resistance, impaired renal function, and reduced sodium excretion. Other factors including endothelin and atrial natriuretic factors can modulate renal hemodynamics. In rat, as nephrogenesis continues after birth, COX-2, endothelial NO synthase and angiotensin receptors are highly expressed in immature nephrons and downregulated at the end of nephrogenesis. Vasoactive factors participate in nephrogenesis and in regulation of the intrarenal vascular repartition.[11]

Tubular Function

In adults, kidney plays an important role in homeostasis. During intrauterine life, homeostasis is assigned to the placenta and fetal kidney is principally devoted to the excretion of hypotonic urine as a component of amniotic fluid. Maturation of tubular functions follows the development of nephrons. Formation of urine, the main component of amniotic fluid in the third trimester, begins by 12 weeks of gestation.[11] The urinary flow rate increases 10-fold from 6 mL/h at 20 weeks to 60 mL/h at 40 weeks of gestational age. Fetal urine is hypotonic (range, 100–250 mOsm/kg H_2O). Compared with maternal plasma, potassium and phosphorus plasmatic levels are higher in fetus, suggesting a specific maturation of tubular channels and transporters.[11] Excretion of sodium is higher during fetal life than in the newborn and adults. Such a high rate of sodium excretion may be related to various factors, including high-circulating concentrations and high sensitivity to natriuretic factors, large extracellular fluid volume, relative insensitivity to aldosterone, and immaturity of tubular sodium reabsorption. In contrast to adult physiology, sodium is mainly reabsorbed in distal portion of the immature tubules. The Na^+-H^+ exchanger (NHE) 3 channel is thought to be responsible for the bulk of tubular reabsorption of sodium. Its expression and activity is dependent on the tubular Na^+/K^+ adenosine triphosphatase (ATPase), which is downregulated in the immature kidney.[13]

Potassium is important for cell growth and cell function. The balance of potassium is positive in the fetus, due in part to active transplacental transport. Renal excretion of potassium is low and tends to increase toward term. Potassium excretion increases with increasing glomerular and tubular surface area, with maturation of tubular Na^+/K^+ ATPase activity and with the progressive development of tubular sensitivity to aldosterone. As for potassium, the fetus is characterized by a positive phosphorus balance resulting from a transplacental transport, a high rate of tubular reabsorption of phosphorus and a relative parathyroid insufficiency. Calcium is important for adequate mineralization and growth of the fetal skeleton.

Vitamin D–dependent calcium binding proteins are present in the fetal kidney. Calcium homeostasis is assigned by fetal kidney through the production of 1,25(OH)2D3, rather than regulation of calcium excretion. During fetal development, the placenta regulates fetal acid–base balance. Reabsorption of bicarbonates and chloride in the proximal tubule increases with gestational age, which allows the kidney to participate in acid–base homeostasis, near term. This function is mainly related to the maturation of carbonic anhydrase activity.

The fetus produces an elevated rate of hypotonic urine (1.5 L per day).[11] Urine concentration capacity is blunted in the immature kidney. This defect is related to various factors including a low sensitivity of the collecting duct to arginine vasopressin (AVP), a structural immaturity of the loop of Henle with preferential distribution of blood flow to inner cortex, a low-gradient concentration in the medulla due to limited protein intake to generate significant amounts of urea, and a low expression of aquaporin 2 (*AQP2*). *AQP2*, a water channel, is located in the apical membrane of collecting duct cells and is involved in water reabsorption.[14] Tubular function is dependent on structural maturation of the nephron and on various mediators including the RAS, aldosterone, prostaglandins, atrial natriuretic peptide, and cortisol. Cortisol in particular has a potent maturational effect. The sensitivity of renal tubules to such hormonal factors increases during gestation and continues after birth. Such relative tubular immaturity allows the production of amniotic fluid at a sufficient rate and prepares fetus to the postnatal adaptation.[11]

The Newborn

Glomerular Function and Renal Blood Flow

In term neonates, nephrogenesis is complete at birth and postnatal maturation of glomerular structure consists of an increase of glomerular membrane permeability, filtration surface area, corpuscular glomerular diameter, and intrarenal redistribution of blood flow. Glomerular size reaches adult values at 3 years of age. Birth is considered to act as a stimulus for the accelerated postnatal maturation of renal function. Transition of fetal circulation to extrauterine life is characterized by a rapid increase in systemic blood pressure. GFR is influenced by various factors including blood pressure, RBF, and structural determinants. In sheep, RBF is low and increases markedly in the first 24 hours after birth. Renal vascular resistances are elevated immediately after birth and decrease during the first postnatal days. RBF and GFR are delicately regulated, principally by angiotensin II, which exerts a vasoconstrictive effect on the efferent arteriole, and by the vasodilating effect of prostaglandins on the afferent arteriole, both allowing glomerular filtration pressure to be sufficient. Again, GFR is maintained by a delicate balance of vasoconstrictor and vasodilator forces.[15,16] At birth, GFR is low compared with adult values, and is correlated with gestational age: 20 mL/min/1.73 m^2 in term and less than 15 mL/min/1.73 m^2 in very low birth weight infants. RBF dramatically increases from 6% of the cardiac output to 10% after the first postnatal week. GFR rapidly increases during the first month of life (range, 2.5–3-fold increase).[17]

Plasma creatinine is currently used as the main indicator of renal function in neonates.[18] However, it remains a very poor marker given that it is filtered and secreted in part by renal tubular cells. In many neonatal intensive care units, GFR is often estimated using the modified or standard Schwartz formulae that are based on serum creatinine level a constant and length. However, these formulae are often highly inaccurate[19] and its utilization/interpretation in the neonatal population should be carefully considered given the potential error due to rapidly changing anatomy and physiology. Other markers of GFR including inulin clearance and radiolabeled markers (iothalamate, technetium-diethylenetriamene pentaacetate, creatinine-EDTA) are not used routinely in neonates, because of technical difficulties.[20] Serum cystatin C (CysC) concentrations may reflect GFR more closely in preterm infants, as they are unaffected by physiological variables, as birth weight, gender, muscle mass, inflammatory state or nutritional conditions. CysC does not pass through the placenta and its values may reflect only the neonate's GFR. Studies have shown that CysC is a more specific and sensitive marker of GFR in both adults and children, moreover in neonates there is a lack of available data on reference values of CysC.[21]

Postnatal maturation depends on gestational age, with a delayed maturation in low birth weight infants (►**Fig. 2**). In term neonates, plasma creatinine concentration is elevated at birth (range, 60–70 µmol/L or 0.68–0.79 mg/dL), reflecting maternal level, and stabilizes at the end of the first week (range, 30–40 µmol/L or 0.34–0.45 mg/dL). Tubular reabsorption of creatinine might participate in high plasma creatinine levels in neonates. In preterm infants, plasma creatinine concentration at birth is also elevated (range, 90–110 µmol/L or 1.02–1.25 mg/dL), increased during the first 2 days, peaked

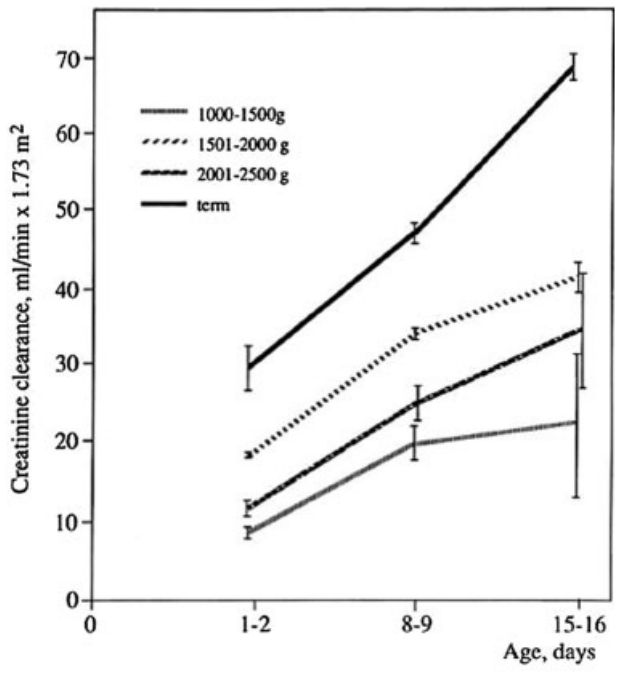

Fig. 2 Postnatal maturation of glomerular filtration rate in term and preterm infants.

between 48 and 96 hours of age, reaching 130 to 140 µmol/L (range, 1.47–1.59 mg/dL) and decreased thereafter to the normal reference range (►**Fig. 3**).[18,22] They are by definition of their prematurity, not in a stable physiologic state and at higher risk for developing renal function impairment as a consequence of hypotension, hypovolemia, perinatal asphyxia, and nephrotoxic drugs.

Tubular Function

Postnatal maturation of renal tubules follows the maturation of GFR and is characterized by a 10-fold increase in proximal tubular length and diameter within the weaning period. After birth, regulation of homeostasis is transferred from placenta to the kidney. Postnatal fluid and electrolytic adaptation is characterized by a transient increase in urine output during the first week of life, due to the contraction of extracellular volume. Commonly, neonates lose around 5 to 10% of their birth weight. Very low birth weight infants may undergo even a higher weight loss, up to 15%. After birth, maturation of proximal tubules is rapid. In rat, Na^+/K^+ ATPase activity increases markedly in the first 2 weeks with enhanced expression of proximal NHE exchangers. Fetal and maternal production of endogen glucocorticoids (GC) during the neonatal period favors such maturation.[11] The neonate is able to achieve a maximal urinary dilution with urine osmolarity as low as 40 to 60 mOsm/L. Diluting capacity tends to mature rapidly in the newborn and preterm infants who, at 36 weeks of postconceptional age, have a urine dilution capacity similar to adults. Fractional excretion of sodium in neonates is around 1%. Within the limits allowed by GFR, neonates, even preterm infants, tolerate a large range of fluid intake (150 mL/kg/day) without major alterations in water and electrolytes parameters. Diluting capacity is greater than concentrating capacity, which is limited to 400 to 600 mOsm/L. This specificity might be explained by reduced tonicity of the medullary interstitium, low expression of aquaporins (water channels), and a relative tubular insensitivity to antidiuretic hormone (ADH). Higher production of prostaglandins E2 in neonates may inhibit the tubular effect of ADH. In infants, functional maturity and full urinary concentrating ability (range, 1,300–1,400 mOsm/kg) are reached at approximately 18 months of age.[23]

The newborn infant has a diminished threshold for renal bicarbonates excretion. Expansion of extracellular volume may result in depressed proximal tubular bicarbonate reabsorption. When extracellular fluid is contracted, renal reabsorption increases and urinary pH becomes more acidic. In preterm infants, immaturity of Na^+/K^+ ATPase, decreased activity of carbonic anhydrase, and immaturity of epithelial cells structure and function may favor prolonged depressed tubular bicarbonates reabsorption. The normal range for plasma bicarbonates concentration is lower in preterm infants (range, 16–20 mmol/L) than in term infants (range, 21–24 mmol/L).

Pathophysiology

Pharmacological Interactions

The number of pregnant women or women of childbearing age receiving drugs increases regularly. These drugs can cross the placenta and may impair function and structure of the fetal kidney. The newborn may in turn develop acute kidney injury which can lead to progressive severe renal insufficiency and neonatal death. Selective COX-2 inhibitors and nonselective nonsteroid anti-inflammatory drugs (NSAID), angiotensin converting enzyme (ACE) inhibitors and angiotensin type 1 receptor (AT1-R) antagonists are the main drugs affecting the development and function of perinatal kidney. The renal adverse effects of in utero exposure to NSAID vary from transient fetal oligohydramnios to severe and lethal renal failure in babies. Rapidly after initiation of indomethacin therapy, a reduction of fetal urine production and oligohydramnios occur. Experimental and human studies show that NSAID decrease fetal GFR as a consequence of RBF reduction and increased urinary osmolality (because of enhanced activity of AVP). A risk of neonatal acute kidney injury increases with prolonged and cumulative dosing, a short time-period between treatment and delivery, a preexisting fetal distress and a low birth weight. Such adverse effect may be reversible after discontinuation of the offending drug.[24] Ibuprofen, another COX-inhibitor, is less likely to reduce GFR. In addition to the

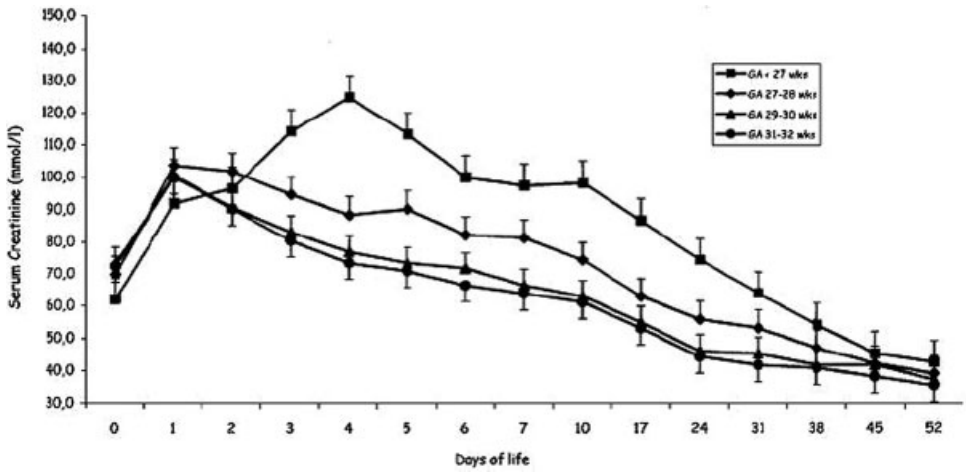

Fig. 3 Postnatal maturation of glomerular filtration rate in extremely low gestational age neonates.

changes of renal function, a singular renal nephrotoxic dysplasia attributable to chronic antenatal exposure to NSAID has been described. Such lesions are associated with increased expression of renin in the juxtaglomerular apparatus. The severity of the renal hypoperfusion induced by NSAID may lead to irreversible renal injury involving glomerular and tubular segments, and may distract the development of fetal kidney. Such effects have been noted recently after prenatal exposure to the selective COX-2 inhibitors proposed as an alternative to nonspecific NSAID aiming at preventing adverse effects.[24]

When administered during pregnancy, inhibitors of RAS, including angiotensin-converting enzyme (ACE) inhibitors and AT1-R antagonists, might induce a variety of serious fetal complications, with high mortality rate. These complications, named ACE inhibitor fetopathy, include intrauterine growth restriction (IUGR), profound fetal and neonatal hypotension refractory to any treatment, renal failure, oligohydramnios associated with limb deformities, pulmonary hypoplasia, hypocalvaria, and increased rate of fetal loss. Renal histology shows typically proximal tubular dysgenesia. A wide range of adverse fetal and neonatal renal effects have been reported, from transient oligohydramnios to severe acute kidney injury (requiring peritoneal dialysis) and lethal renal failure. The risk of teratogenicity increases with chronic administration and stage of fetal exposure, especially during the second and third trimester. When therapy is discontinued rapidly before the second trimester, limited or no adverse renal effects are noted. Experimental studies have shown that maternal antenatal administration of various drugs can also affect nephrogenesis in absence of clinical renal function impairment in the fetus and newborn infants.[24]

In rodents and sheep, antenatal maternal administration of GC at a specific time of pregnancy reduces nephron number and induces hypertension in adult offspring. The mechanisms by which GC alter the fetal kidney structure remain unclear. Several pathways are suspected. In utero exposure to GC may (1) disturb cell differentiation/proliferation ratio at the expense of reduced proliferation, (2) reduce UB branching, (3) alter gene expression of specific genes involved in kidney development, or (4) reduce renal AT1-R and renin gene expression.[25]

Antenatal maternal administration of cyclosporine A (CsA) alters fetal growth and nephrogenesis leading to a permanent nephron deficit in young rabbits offspring (average of 25–30%).[26] CsA may act through blockage of the conversion of MM to epithelium. In humans, the outcome of infants exposed in utero to CsA have not demonstrated evidence of changes in renal function and morphology in children.[27] However, data are scarce, and long-term follow-up (maximum 7 years) is insufficient to definitively conclude that there are limited exposure adverse effects in adults.

Antenatal maternal administration of ampicillin and aminoglycosides reduces nephron number (range, 20–30%) and induces hypertension in adult rat offspring. Reduced nephron number results of a defect in UB branching morphogenesis affecting the first branching division.[24] This toxic effect corresponds, in fact, to the first stage of renal development: gentamicin exposure during late stages of nephrogenesis does not appear to induce a nephron deficit, but may lead to tubular injury if levels become toxic. Other aminoglycosides, such amikacin and netilmicin, have less adverse renal effects. Antenatal maternal administration of ampicillin is associated with a 20% reduction of nephron number in rat offspring. An increased rate of apoptosis reaction in mesenchyme area is the suspected leading event of oligonephronia. Such experimental observations have not been found in human. Other drugs, such as chlorambucil and antineoplastic drugs can impair renal development with urinary tract malformation and renal agenesia. In most cases, newborn infants do not develop acute kidney injury postnatally.[24] However, experimental studies suggest that prenatal exposure to certain drugs may lead to reduced nephron number, followed by hypertension and renal function at adulthood. One must be careful in extrapolating data from animals to humans, because major interspecies differences in renal sensitivity to drugs exist, so long-term follow-up of infants exposed in utero to drugs are needed.

The Immature Kidney

Nephrogenesis is incomplete in preterm infants. Impairment of mesenchymal cell differentiation has been suggested. Compared with term neonates, GFR is lower in preterm infants and increases progressively after birth. Blood pressure and RBF are low in preterm infants. The immature kidney is particularly dependent on vasodilator forces to maintain a sufficient GFR, allowed by elevated renal vascular resistances from RAS upregulation.[28] The delay in establishing a normal GFR is more profound in preterm infants, where there is an underlying immaturity of glomerular filtration until nephrogenesis is complete at 34 to 36 weeks of postgestational age. The age at which preterm infants overtake normal term infants' renal function is still unknown. Recent data have suggested that preterm birth affects postnatal nephrogenesis with altered glomerular structure and possibly reduced nephron endowment.[29] Various perinatal problems, such as perinatal asphyxia, respiratory distress syndrome (RDS), jaundice can cause renal stress and may impair renal glomerular and tubular functions. Maternal administration of NSAID, low apgar score, intubation at birth, RDS and ibuprofen given to the newborns have been demonstrated to be independent predictors of renal impairment, in reducing GFR, particularly in preterm infants. In most cases, GFR increases during the recovery phase.[30–32]

Low neonatal concentrating capacity is of limited importance in healthy neonates. However, preterm infants are more vulnerable to free water intake and excessive extrarenal water loss (skin loss, diarrhea, etc.), with a risk of osmotic diuresis and hypernatremic dehydration, which may be enhanced because of a lower threshold for renal glucose excretion. Their fractional excretion of sodium is elevated (nearly 5 vs. $< 1\%$ in term infants) and only reaches term values after 2 or 3 weeks.[30] Renal transport activity directly relates to postnatal age and glomerular function.

As they are prone to renal water and salt wasting, fluid and electrolytes intakes have to be adapted. A postnatal contraction of the extracellular fluid volume occurs during the first postnatal days of life and translates into a 2 to 3% daily; 10

Table 2 Glomerular and tubular consequences of immature kidney

Fluid-electrolytes therapy in preterm infants	Glomerular immaturity: consequences	Tubular immaturity: consequences
Day 1–Day 2: Volume: 80–100 mL/kg/d Na: 0 K: 0 (except if $<$ 3.5 mmol/L)	– Reduced ability to salt/water overload excretion – Hyperkalemia – High sensitivity to vasoactives drugs – Increased risk of renal failure – Reduced clearance of drugs	– Sodium wasting – Metabolic acidosis – Reduced urine concentration capacity with preserved urine dilution capacity – Glucosuria – Elevated urinary calcium excretion – High sensitivity to diuretics
Day 3–Day 5: Volume: 120–140 mL/kg/d Na: 2–4 mmol/kg/d K: 1–2 mmol/kg/d		
$>$ Day 5: Volume: 140–170 mL/kg/d Na: 4–6 mmol/kg/d K: 1–3 mmol/kg/d		

to 15% total weight loss should be expected. Moreover, the kidney of preterm infants cannot efficiently excrete excessive water and sodium loads, which increases the risk of bronchopulmonary dysplasia, intracerebral hemorrhage, and necrotizing enterocolitis. It is thus recommended to introduce sodium, potassium, and phosphorus only by postnatal day 2 or 3 and then, when postnatal weight loss is complete, to adapt individually electrolytes intake (especially sodium intake), to maintain a positive balance. Sodium is essential for postnatal growth.[33] Glomerular and tubular consequences of renal immaturity are shown in ►**Table 2**. Such glomerular and tubular consequences have been blunted by maternal administration of synthetic GC (betamethasone and dexamethasone). Prenatal administration of GC improves systemic blood pressure, RBF, and GFR, and accelerates the maturation of tubular function with enhanced proximal reabsorption of sodium and excretion of potassium. Such effects are due to increased expression and activity of sodium exchangers, of Na^+/K^+ ATPase, and to increased renal sympathetic activity.[25]

Preterm infants are more likely to receive drugs in neonatal intensive care. Many of these drugs require renal elimination and undergo glomerular filtration or tubular metabolism. As these mechanisms are immature in the preterm infant, they remain at significant risk for adverse effects from these medications. Many drugs used in the neonatal period such as penicillin, aminoglycosides, vancomycin, furosemide, phenobarbital need pharmacological adaptations such as reduced dosage or longer dosing intervals to limit drug accumulation.[30] For example, circulating levels of drugs such as vancomycin or aminoglycosides need to be monitor to optimize dosing and reduce toxicity.[32] Administration of NSAID (indomethacin or ibuprofen) for the closure of patent ductus arteriosus impairs renal function, induces oliguria, reduced RBF and GFR.[28]

Long-Term Consequences of Nephron Number Reduction

It has been suspected for long that a reduced nephron number is associated with an enhanced risk of hypertension and chronic kidney disease in adulthood.[34,35] Reduced nephron endowment is associated with renal changes including increase in single nephron glomerular filtration rate and glomerular and tubular hypertrophy. Such hemodynamic changes are responsible for glomerular injury through increase in glomerular capillary hypertension. Then a vicious circle takes place leading to glomerulosclerosis, chronic renal insufficiency, and hypertension. Experimental studies from human subjects are highly suggestive that these hypotheses are correct. Recent data have supported an inverse relationship between reduced nephron endowment and essential hypertension.[36] An adult born with congenital agenesia is at higher risk of developing systemic hypertension and early chronic kidney disease.[34,35] At birth, a wide variation in nephron number (range, 300,000–1.8 million) is because of genetic factors and mostly to fetal environment. Furthermore, an ongoing interaction between genes and environment from prenatal to adult life would contribute toward forming the renal potential of an individual. Various perinatal factors have been shown to induce reduced nephron number including low birth weight, IUGR, maternal nutrient deficiency (vitamin A, iron depletion), maternal protein or global nutrition deficit, drugs, maternal and fetal stress, and maternal gestational diabetes.[5] Any adverse event occurring before completion of nephrogenesis likely compromises renal growth and produces a longer lasting effect on final renal function. On contrary, preterm birth with postnatal environmental stressors (malnutrition, stress, and nephrotoxic drugs), or renal/urinary tract malformations are associated with impaired nephrogenesis which may lead to a reduction in nephron endowment and increasing vulnerability for impaired renal function in both the early postnatal period and later in life. Perinatal events are less likely to affect renal function during the neonatal period but are associated with high risk of hypertension and renal disease at adulthood. Consequently, long-term follow-up is needed, with close assessment of blood pressure and markers of renal outcome (creatinine, microalbuminuria) even during early childhood, to prevent adverse evolutive cardiovascular and renal diseases. Improvement of maternal nutrition during and before pregnancy, as a

preconceptional monitoring, should also influence renal programming. Early identification of children at high risk of reduced renal reserve allows subsequent monitoring, and also prolonged treatment with renal protective agents, as ACE inhibitors or angiotensin receptor blockades. But, more structured studies should be implemented to investigate the role of these two drugs in managing proteinurias and glomerulosclerosis in children with renal conditions.[37]

Early detection of potential indicators of hyperfiltration, such as impaired renal reserve (low renal volume detected by ultrasound or scintigraphic measurement) and blunted solute clearance, may provide subtle clues to the presence of reduced nephron number, thus providing early objective evidence of hypertension, microalbuminurias, and renal risks. Unfortunately, to date no investigation method for early detection is available and validated. Future studies in radiological techniques and biochemical indicators are needed and may provide important advances in long-term follow-up of children and young adults at risk.

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