DOI: 10.1097/JPN.0000000000000024

CE Continuing Education
J Perinat Neonat Nurs • Volume 28 Number 2, 150–154 • Copyright © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins

Transition to Postnatal Renal Function

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ABSTRACT

In-utero the placenta is the primary organ responsible for neonatal homeostasis of fluid and electrolyte balance. With birth, this responsibility now transitions to the neonatal kidney. For successful transition to extrauterine renal physiology to occur maturation of neonatal glomerular filtration must occur, which is dependent on the development of renal blood flow. While these functions are decreased at birth, the term infant's kidneys are still able to manage homeostasis and are sufficient for growth and development. However, stressors can limit the adaptive properties of the neonatal kidney. This is especially important for those infants born before 34 weeks' gestation, when nephrogenesis is not yet complete. Knowledge of the changes in renal physiology is essential in caring for the neonate during transition. This article describes those changes.

Key Words: glomerular filtration, neonatal transition, nephrogenesis, renal blood flow, serum creatinine

Dramatic and rapid physiological changes occur in the neonate that are necessary to ensure successful transition from intrauterine to extrauterine physiology. While changes occurring in the respiratory and cardiovascular systems are immediate, slower adaptations occur with the renal system. The neonatal renal system responds slowly and erratically to the physiologic demands placed on it. And, transition to adult renal function evolves over a period of months to years.

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Disclosure: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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Submitted for publication: November 11, 2013; Accepted for publication: February 9, 2014.

Kidney function involves both nonexcretory and excretory activities. The nonexcretory functions include renin production needed in the regulation of blood pressure, erythropoietin production, metabolism of vitamin D, and synthesis of renal prostaglandins (PGs). Excretory functions are associated with maintenance of plasma osmolality, water and electrolyte balance, and excretion of nitrogenous waste products.

In the transition to extrauterine life, homeostatic regulation reverts from the placenta to the neonatal kidney. Homeostasis is regulated through 2 fundamental functions, the glomerular and the tubular.[1] Under normal conditions, while these functions are reduced at birth, the newborn's kidneys are still able to manage homeostasis and are sufficient for growth and development. The newborn's major physiologic limitation is its limited glomerular filtration rate (GFR), which is influenced by factors associated with transition such as cardiac output, vascular resistance, and mean arterial blood pressure.[1,2] Hypoxia, sepsis, stress, and exposure to nephrotoxic medications can further limit the adaptive properties of the neonatal kidney. This is especially important for those infants born before 35 weeks' gestation, when nephrogenesis is not yet complete.

NEPHROGENESIS

The nephron, the functional unit of the kidney, is composed of 2 major parts, the renal corpuscle and tubules. Nephrogenesis, the formation of the nephron, begins at 7 to 8 weeks' gestation with fetal urine production starting between the 10th and 12th weeks.[3] This process continues rapidly until approximately 35 weeks' gestation. It has been estimated that the fetal kidney contains approximately 35×10^4 nephrons at 20 weeks and approximately 80×10^4 at 40 weeks.[4] In those infants born after 35 weeks, there will be no further increase in the number of nephrons. Changes after birth involve further maturation and hypertrophy of nephrons, which will continue until adult morphology, and size is reached by 3 to 5 years of age.[2,4,5]

The renal corpuscle is a tuft of capillaries (glomerulus) surrounded by a capsule (Bowman's) through which fluid is filtered out of the blood. Bowman's capsule serves as that filtration membrane. Blood enters the glomerulus by way of the afferent arteriole and exits via the efferent arteriole. The fluid that is filtered through the Bowman's capsule becomes known as the filtrate. Approximately 99% of what is initially filtered is then reabsorbed throughout the remainder of the nephron with less than 1% of the filtrate becoming urine.[2] The rate at which fluid filters from the blood into the Bowman's capsule is known as the GFR. In the adult, approximately 20% to 25% of the cardiac output is filtered through the Bowman's capsule. However, in the fetus close to 50% of the combined ventricular output goes to the placenta and only 3% to the kidneys as fetal homeostasis is maintained by the placenta and maternal balance.[2,4]

Fetal urine production and glomerular filtration in the fetus begin at 9 to 10 weeks, and tubular reabsorption around 12 to 14 weeks.[2,4] As fluid homeostasis in the fetus is maintained by maternal and placental exchange, the purpose of fetal renal function is its contribution to the formation of amniotic fluid. Fetal urine is an important component of amniotic fluid and both increase with gestation. Sodium is a major solute in fetal urine. The fetus is not dependent on the kidneys for sodium conservation because sodium is readily transported across the placenta; this changes after birth.

FACTORS INFLUENCING GFR AND RBF

With the cutting of the cord, transition to parallel blood flow begins and changes in cardiac output to the kidneys occur leading to increase of renal blood flow (RBF) and GFR. Cardiac output to the kidneys in the fetus is 3% to 5% increasing to 8% to 10% by the first week of extrauterine life; 15% by 1 month; and adult levels of 20% by 2 years of age.[3] This increasing cardiac output results in the redistribution and increase of RBF. The increase in cardiac output correlates with redistribution of RBF from the medulla to the outer cortex with RBF increasing to approximately 60 mL/min by 40 weeks of gestation.[3] The increased cardiac output contributes to the increased RBF and decreased renal vascular resistance (RVR) resulting in higher renal perfusion pressures and an increase in GFR.[3]

During transition, in term infants GFR increases from approximately 5 mL/min/1.73 m^2 to 40 mL/min/1.73 m^2 in the first week of life. By 2 months of age, the GFR is 65 mL/min/1.73 m^2, reaching adult values of 120 mL/min/1.73 m^2 by 2 years of age.[3,6,7] This transition is markedly decreased in the preterm infant. In those less than 35 weeks' gestation, GFR remains constant at approximately 0.5 to 1 mL/min/1.73 m^2. But after 35 weeks, it can increase 4 to 5 times within a 1-week period, though it still remains less than term infants.[3] This increase in GFR is correlated with the completion of nephrogenesis.[6,7]

During transition, as RBF progressively increases, RVR decreases. This decline in RVR is influenced by as variety of vasoactive factors including angiotensin II (AII), catecholamines, PGs, and nitric oxide (NO).[3,4] A major influence in RVR is that of the Renin-Angiotensin System (RAS). Physiologically, the RAS defends against a fall in blood pressure and/or intravascular fluid volume by both direct and indirect actions on the kidney's and systemic vascular bed. Stimulation of this system leads to (1) systemic vasoconstriction, (2) sodium and water retention in the kidneys, and (3) expansion of the extracellular fluid (ECF) volume. An intact RAS is necessary for normal development.

Renin is an enzyme produced by the juxtaglomerular cells of the nephrons. These cells are located in the walls of the afferent arteriole acting as baroreceptors responding to RBF. The primary stimulus for secretion of renin is renal hypoperfusion and hypoxia. When renal perfusion is decreased, renin release is stimulated. Renin enters the general circulation acting on angiotensinogen (protein produced in the liver) to convert it to angiotensin I. Angiotensin I passes through the pulmonary circulation, where it is converted by angiotensin converting enzyme to AII.

Angiotensin II is a potent vasoconstrictor increasing peripheral vascular resistance. But, it also decreases RBF thereby contributing to decreased GFR by inducing arteriole constriction leading to continued renin production. The RAS is intact in the newborn. Plasma renin and aldosterone concentrations in neonates are 5 to 10 times higher than adults.[3,4,5] High levels are felt to be due to low systemic blood pressure and RBF experienced by the fetus in-utero.

In the fetus, the fetal membranes and amniotic fluid contain large amounts of renin. The placental circulation is major site for conversion of angiotensin I to AII. The increased AII level has an important role in modulating fetal blood pressure in-utero.[2–4] After birth, with the redistribution of cardiac output and increased RBF, renin and AII levels start to decrease over the first month, reaching adult levels by 6 to 9 years of age.

During transition with the need for the neonatal kidney to assume homeostasis, vasodilation factors are important in decreasing RVR. Prostaglandins produced in the renal medulla are potent vasodilators that increase RBF by stimulating vasodilation of the afferent arterioles. Renal blood flow and GFR are also maintained by the vasodilatory effects of NO. It is felt that NO may

offset the high level of RAS activity by modulating the effects of AII and renin release.[3]

EVALUATION OF NEONATAL RENAL FUNCTION

While GFR does increase with gestational age and improves after birth, compared with the adult, GFR in the neonate is low. When interpreting clinical situations, it is important to remember that the low GFR values in neonates are expected rather than indicate that they represent impaired renal function during the first days of life.[4]

Creatinine clearance remains widely used in adults as a clinical parameter for evaluating GFR. It requires an accurate timed urine collection, which is a major drawback in the neonatal period, as it may necessitate bladder catheterization to accurately obtain urine output. In the first year of life, GFR can be calculated on the basis of the Schwartz equation: GFR = KL/SCr, where GFR is expressed as milliliters per 1.73 m^2 and is equal to 0.45 for term infants and 0.33 for premature infants; L is body length in centimeters; and SCr is serum creatinine in mg/dL.[3,8] The Schwartz formula has been shown to correlate very closely with values of creatinine clearance and can be used to estimate GFR without urine collection.[4,8]

However, SCr is the most widely used marker to evaluate GFR in neonatal clinical practice. At birth, SCr is reflective of maternal values regardless of gestational age or renal function, as maternal creatinine is equilibrated with fetal concentrations across the placenta.[1,7,9] The SCr can increase in the first 48 hours after birth. But, by 10 days of age, it will decrease to an average of 0.4 mg/dL in the term infant. This level tends to maintain over the next 1 to 2 years. It will then increase at a rate of 0.02 mg per year as an increase in muscle mass occurs as the child grows.[7,9]

In the preterm infant, the SCr may not change significantly until nephrogenesis is complete, about 34 to 35 weeks' gestation. While it will decline, it may not reach the equivalent to term infant values until 1 to 3 months after birth. However, clinically it is important to realize that in any infant an increase in SCr of more than 0.3 to 0.5 mg/dL/d after the 2 days of life is abnormal and indicates renal dysfunction.[6,7]

Because of limitations of serum creatinine measurements, newer biomarkers to measure GFR in newborns are being evaluated.[3] In the adult population, cystatin C has been found to be a sensitive serum marker for GFR.[10] It is a low-molecular-weight protein not affected by muscle mass, age, or gender. It is freely filtered through the glomerulus, reabsorbed, and catabolized but not secreted by the tubules. Reference ranges for plasma cystatin C levels in preterm infants and neonates have been established.[11]

WATER AND SODIUM BALANCE IN TRANSITION

A physiologic redistribution in body water occurs during transition. At birth, there is a shift of water and electrolytes from the intracellular fluid compartment to the ECF compartment, which causes the ECF compartment to become even more expanded.[12,13] This fluid volume is then subsequently lost as the newborn experiences a diuresis with subsequent weight loss. This redistribution of body water is known as "contraction" and is a normal part of postnatal adaptation. At term, 75% of total body weight is water, and in preterm infants the water content is even higher at 85% of body weight (split in a ratio of 2:1 ECF to intracellular fluid).[13] After this transition, the kidney's concentrating capacity increase and water loss becomes minimized.[4]

In the immediate postnatal period, urine output (UOP) may be less than 1 mL/kg/h due to decreased RBF and GFR. However, during transition with improved cardiac output to the kidneys, RBF and GFR increase and urine output increases during the first 24 hours and by day 3, a diuresis is common. UOP may peak at 5 to 7 mL/kg/h and then decrease as the physiologic ECF volume reduction is completed. Normal UOP is 1 to 3 mL/kg/h during periods of stable fluid balance. The diuresis reduces the ECF content to 30% of total body water over the neonatal period. This fluid loss is an important part of transition needed to facilitate lung function and decreases the risk of patent ductus arterious (PDA), necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia (BPD).[13]

Tubular reabsorption is the movement of substance from the filtrate in the tubule lumen moves back into the capillary system. During this process, there is recovery of salts, nutrients, and water—this allows for balance of continued growth and normal physiologic function. Tubular function is altered in the newborn and matures more slowly than glomerular function.[2,4] While GFR is a measure of glomerular function, FeNa (fractionated excretion of Na) is a measure of tubular function. The FeNa is a specific, indirect way to look at the tubular handling of sodium. It represents the percentage of filtered sodium that is excreted in the urine and calculated as follows:

$$\text{FeNa}(\%) = \text{U/P Na} \div \text{P/U Cr} \times 100$$

Sodium excretion while high in the fetus decreases with increasing gestational age. While FeNa levels in the term infant are elevated immediately after birth at 3% compared with less than 1% in the adult, within days it transitions to adult values as the mechanism for

Table 1. **Implications of postnatal adaptation in renal function**

	Postnatal Maturation	Effect on Neonate
GFR	Dependent on renal blood flow; reduced in term neonates compared with adults; further reduced in premature infants <34 wks' gestation	Increases half-life of drugs; delays clearance of drugs leading to drug accumulation Decreases ability to excrete water load
Altered tubular handling of substances	Reduced tubular secretion & reabsorption	Delayed excretion and prolonged ½ life of drugs
	Reduced sodium reabsorption	Increased sodium loss in urine (especially prematures <34 wks' gestation Limited ability to excrete excess sodium
	Potassium excretion low	Serum potassium levels higher in neonatal period
	Renal buffering mechanisms slower	Neonates in physiological acidotic state compared with adults. Bicarb levels of 18-20 mEq/L normal in term infants
Renal clearance	Reduced	Accumulation of drugs leading to increased risk of toxicity

concentrating and saving sodium mature and develop.[4] This process is delayed in the preterm infant, as the increasing GFR seen after birth, combined with tubular immaturity, results in impaired reabsorption of sodium contributing to sodium urine loss and elevated FeNa.[12] While term infants can reabsorb 99% of sodium that is filtered, infants born prior to completion of nephrogenesis can absorb less than 91% of the sodium that is filtered. FeNa levels of 5% to 6% are normal at 28 weeks. Table 1 describes the implications of postnatal adaptation renal function. Parameters associated with renal function in the first 2 months of life are presented in Table 2.

GFR AND RENAL EXCRETION OF DRUGS

Renal excretion of drugs is dependent on RBF, GFR, and tubular function as well as gestational age and postnatal maturation. The physiologic transitions that occur in renal function and GFR can alter the way newborns handle medications. It has been postulated that the lower RBF and decreased tubular secretory processes in the newborn, and especially the preterm infant, may reduce the amount of drug delivered to the kidney, potentially limiting the effectiveness of a drug.[14]

The decreased GFR leads to delayed clearance of drugs eliminated by kidneys and prolonged drug half-lives. This also makes the neonate more prone to the possible nephrotoxic effects of medications.

Nephrotoxicity can occur through a variety of mechanisms. One common mechanism is damage to the tubules resulting in renal tubular necrosis. Another nephrotoxicity mechanism is vasoconstriction and decreased GFR in a system that already has decreased GFR.[14] Aminoglycosides and nonsteroidal anti-inflammatories, 2 drug classes commonly used in the first weeks of life, can result in nephrotoxicity under these mechanisms.

The use of aminoglycosides can lead to tubular cell death in the proximal segment of the nephron; resulting in renal tubule cell sloughing, intratubular obstruction, and ultimately further GFR reduction.[14] Even if cell death does not occur, aminoglycosides can disrupt tubular function, which can contribute to electrolyte imbalances experienced in the initial weeks of life.[14,15] Aminoglycoside use can also lead to intrarenal vasoconstriction contributing to reduced GFR in the neonatal kidney.[15] Measuring serum trough levels continues to be recommended for those infants being treated for more than 5 days to minimize the risk of toxicity.[16]

Table 2. **Age-related changes in renal function**

Gestation	38-42 wks		25-28 wks	
Postnatal age	Week 1	Week 2-8	Week 1	Week 2-8
SCr (mg/dL)[3,7]	0.5 ± 0.1	0.4 ± 0.1	1.4 ± 0.8	0.9 ± 0.5
GFR (mL/min/1.73 m^2)[3,6]	40 ± 14	65 ± 24.8	11 ± 5.4	15.5 ± 6.2
UOP (mL/kg/24 h)[4,12]	20-75	80-130	15-75	25-120
FeNa (%)[4]	1%-2%	<1%	5%-7%	3%-5%

After birth, the cardiovascular changes that occur during transition allow for spontaneous closure of the ductus arteriosus within the first day of life in term infants. However, in premature infants, the ductal closure may be delayed or does not occur necessitating pharmacological treatment. It is estimated that PDA occurs in 30% to 40% of prematures delivered less than 2 kg, and as high as 70% in those less than 1 kg and 29 weeks' gestation.[17] Indomethacin and ibuprofen are the 2 most studied drugs used in the treatment of PDA. These nonsteroidal anti-inflammatories promote PDA closure by preventing the conversion of arachidonic acid to PGs, inducing constriction and closure of the ductus.[17] However, this also induces vasoconstriction of the renal afferent arteriole resulting in reduced renal perfusion and associated adverse effects such as decreased GFR and UOP, and increased SCr levels. These effects are usually transient but can significantly complicate fluid and electrolyte management in these premature infants.[18] Ibuprofen has been studied as an alternative to indomethacin, while the magnitude of SCr rise and oliguria is less than indomethacin; nephrotoxicity still occurs.[14,18]

The dependence the neonates' RBF and renal function has on effective PG concentration underscores the caution needed in the use of PG-inhibiting drugs. Because of the direct effect these medications have on GFR, caution should be used when treating infants receiving other renally excreted drugs, such as the aminoglycosides and vancomycin.[14,16] The infant should be closely monitored as there is a higher chance that the renal clearance of 1 or more of the drugs will be decreased, resulting in increased risk of adverse effects and nephrotoxicity.[18]

CONCLUSION

During transition, under normal conditions the early neonatal period is characterized by rapid maturation of renal function as homeostatic regulation transfers from the placenta to the neonatal kidney. GFR increases with the redistribution of cardiac output and as RBF increases and RVR decreases adaptation to neonatal renal function progresses reaching adult levels by 2 years of age. While there is rapid maturation occurring during this period, neonatal renal function is still low compared with the adult. Because of immaturity of renal system and changes that occur during adaptation, the nurse needs to be aware that these limitations can lead to alteration in fluid and electrolyte balance in the neonate, especially those born before the completion of nephrogenesis.

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