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Neonatal renal physiology

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ABSTRACT

The renal system plays a tremendous role in growth and development of infants and children. The kidney itself also undergoes a maturation process as it transitions from the fetal to the extrauterine environment. Renal function continues to undergo further adaptive changes in the neonatal period. It is important for the clinician caring for neonates to be aware of the expected fluid shifts, electrolyte handling, and renal functional capacity as these "normal" changes will become quite relevant when medical or surgical pathology is present. The preterm neonates are especially vulnerable due to their functionally immature kidneys. Renal function in the preterm neonate is not only immature at birth but there is a significant delay in the renal function to achieve its full capacity. This review highlights the physiologic adaptations of the kidney and its effects on the body during the neonatal period.

Introduction

The function of the kidney is not only different between the fetus and the neonate but it continues to "mature" and adapt as the neonate develops. During the early developmental period, the placenta is primarily responsible for maintaining the fetal fluid–electrolyte homeostasis, the acid–base balance, and the excretory requirements of the fetus. The fetal kidney during this period is largely involved in maintaining the amniotic fluid level and regulating fetal blood pressure.[1] Urine production is present when the fetus reaches 16th week of gestational age. Nephrogenesis is complete by 34th–36th week of gestation; however, the maturation of the kidney continues through the postnatal period.[2] Renal function in the newborn is both qualitatively and quantitatively different from adults and has a substantial range which is dependent on gestational age. Following birth, there is a rapid increase in glomerular filtration and a decrease in renal vascular resistance in response to an increase in mean arterial blood pressure.[2] Nephrogenesis is considered complete in the term infant. However, there are significant functional changes that continue to take place as the infant matures. For example, the capacity to concentrate urine to the level observed in adult kidneys is only reached much later after birth.[3] Understanding these changes is important in distinguishing normal development from a pathophysiologic state.[4]

The renal system in very low birth weight (VLBW) or premature infants is profoundly different from that of a term infant. There is a delay in renal function in VLBW infants related to immaturity with prolonged adaptation of the renal system to extrauterine life.[5]

In discussing renal physiology, it is worthwhile to remember the quote by Earnest Startling (1909) describing the physiology of the organ:

> The kidney presents in the highest degree the phenomenon of sensibility, the power of reacting to various stimuli in a direction which is appropriate for the survival of the organism; a power of adaptation which almost gives one the idea that its component parts must be endowed with intelligence.

These "component parts" play an important role in fluid–electrolyte balance, blood pressure control, acid–base balance, and excretion of metabolic by-products. Here we review some of the adaptive responses that are regulated by the kidney soon after birth. Having an understanding of the normal physiologic changes can better prepare the surgeon in planning an operation as well as optimizing pre-operative and post-operative care.

Embryology

The development of the urogenital system begins its embryologic transformation as early as the 3rd week of gestation.[6] It is derived from the intermediate mesoderm of the urogenital ridge that is present along the posterior wall of the abdominal cavity in the developing fetus. The intermediate mesoderm develops into the nephrotome that ultimately distinguishes into the pronephros (the rudimentary kidney), mesonephros (the nonfunctional kidney), and the metanephros (the permanent kidney). While the pronephros totally disintegrates, the mesonephros may be functional momentarily during the early fetal period, producing urine by the 5th week of gestation, but it degenerates almost entirely by the 11th–12th week of gestation leaving only its caudal tubules to develop into

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some aspects of the genital system in males.[7] The metanephros, on the other hand, develops into the ureteric bud (outgrowth of the mesonephric duct) and a metanephric blastema. The ureteric bud progresses to develop into the ureters, renal pelvis, and the collecting tubules, while the metanephric blastema forms the nephrons that constitute the excretory system of the kidney.

The differentiation and development of the kidney is regulated by a number of molecular factors. The mesenchymal expression of transcription factors such as Wilms' tumor-suppressor gene 1 (WT1) triggers the ureteric bud to induce differentiation. WT1 also regulates the production of glial-derived neurotrophic factor (GDNF) and hepatocyte growth factor (HGF) which would further stimulate the ureteric bud to branch and grow into the calyx of the kidney. The bud also stimulates the mesenchyme via fibroblast growth factor 2 (FGF2) and bone morphogenetic protein 7 (Bmp7) to block apoptosis and stimulate the proliferation of the metanephric mesenchyme.[8] Further differentiation of the mesenchyme into epithelium for the nephron is mediated through the upregulation of paired-box gene 2 (pax2) and wingless-related (WNT4) molecules.[9] The nephron is thought to achieve functionality with nearly 1 million nephrons per kidney by the 32nd gestational week.

With differential longitudinal growth of the embryo, the kidneys “ascend” from their initial location in the pelvis to their final location in the upper retroperitoneum. Concurrently, they rotate around their vertical and horizontal axes so that their final orientation is such that the upper poles are slightly more medial and anterior. The vasculature and nervous innervation also correspondingly ascend along with the kidneys. Alterations in the normal molecular and anatomic development of the kidneys may result in congenital malformations such as ectopic kidneys, hypoplastic or agenetic kidneys, and ureteral anomalies.

Renal blood flow

Renal blood flow (RBF) is only about 3–7% of the cardiac output in the fetus.[10] In the neonate, renal blood flow relative to body weight, kidney weight, and surface area continues to be lower than the adult levels and utilizes only 10% of cardiac output by 1st week of life. The eventual increase in RBF to 25% of cardiac output is due to a combination of increased renal perfusion pressure and decreased renal vascular resistance. The clearance of p-aminohippurate has traditionally been used to reflect the measure of effective renal plasma flow (ERPF). The ERPF has been reported as low as 20 ml/min/1.73 m^2 in the premature infant compared to 45 ml/min/1.73 m^2 by 35 weeks of gestation and 83 ml/min/1.73 m^2 in term infants. ERPF progressively increases to reach 300 ml/min/1.73 m^2 by toddler age, and finally reaches adult rate of 650 ml/min/1.73 m^2 by 2 years of age. This increase in blood flow over time is also associated with a proportionally higher flow to the outer cortical region. This change in ERPF over time demonstrates that even though the kidneys are able to autoregulate relatively early in life, they do so with relatively lower efficiency and at a lower baseline.[5]

Glomerular filtration rate

The glomerular filtration rate (GFR) is determined by the balance of Starling forces across the capillary wall, rate of plasma flow, permeability of the glomerular wall, and total surface area of the capillaries. GFR is established during intrauterine life, but it is insignificant because the kidneys do not primarily function as a water- and fluid-regulating organ. GFR begins immediately after birth when the kidney assumes its role in fluid, water, and electrolyte regulation.[11] GFR in the newborn is about 40 ml/min/1.73 m^2 and reaches 66 ml/min/1.73 m^2 by 2 weeks of age. Adult levels of 100–125 ml/min/1.73 m^2 are reached at around 2 years of age.[12] In addition, maximal urine concentration capacity of the term infants (700 mOsm) does not reach adult levels (1400 mOsm) until 6–12 months of age.[10] An increase in the GFR is generally much lower in VLBW infants and reaches normal levels much later in childhood when compared to the term infants with a rate of increase dependent on various perinatal factors. As mentioned above, due to the limited RBF and GFR, neonates and especially those who are premature have a limited ability to handle fluid loads. Gheissari et al.[13] reported that normal levels of GFR in VLBW infants were still not reached at 2 years of age when compared to term infants. Lacobelli et al.[14] reported that GFR reached normal levels in the VLBW infants at 8 years of age. Variations in GFR are clinically relevant because they affect fluid and electrolyte homeostasis as well as excretion of drugs.

Creatinine clearance

Creatinine is a metabolic product that is irreversibly converted from creatine which is a skeletal muscle by-product and therefore the serum creatinine level correlates well with body muscle mass. It is freely filtered in the Bowman's space, and its clearance provides a good estimate of GFR. However, this relationship gets complicated in the newborn infants. Several studies have recently shown that plasma creatinine in most infants actually increases after birth.[15,16] Reabsorption of creatinine is only present in the first postnatal days and is probably explained by the passive reabsorption of the filtered creatinine across immature leaky tubules leading to an underestimation of the true GFR in this population.[17] The more preterm the infant, the higher the plasma creatinine will rise before it begins to decline to a steady state level.[18,19] Creatinine clearance is known to show significant variability in the premature infants.[20] Lack of precise measurement of creatinine levels due to the instability of plasma creatinine and the uncertainty of its renal tubular handling (prolonged in the case of premature infants) during the first days of life renders the use of serum creatinine levels unreliable as a surrogate for determining true renal function. This is important to keep in mind, as many clinicians associate the rising creatinine in neonatal patients with renal impairment.

Another marker that is used to represent GFR is cystatin C. It is freely filtered across the capillaries in the glomerulus and is completely reabsorbed by the proximal tubules. Its ability to detect changes in the estimated GFR has been reported to be better than creatinine, thus its clinical use has been recommended in the neonatal population.[21,22] Despite efforts to develop better biomarkers for the estimation of GFR, the true creatinine clearance continues to remain as the best index of GFR measure in this population.

Fluid and electrolyte balance

The balance of nutrients, solutes, and water in the amniotic fluid throughout gestation ensures fetal homeostasis and a stable electrolyte concentration in the fetus. At birth, water constitutes about 80% of total body weight. Soon after birth, redistribution of body fluids occurs, with early postnatal weight loss corresponding to the isotonic contraction of extracellular water through disposal of excess sodium and water via the kidneys. This postnatal diuresis results in a decrease in 5–10% of body weight. The ability to maintain a negative water and sodium balance through a high

sodium excretion is inversely proportional to the infant's maturity. As a result, this process results in a greater loss and lasts longer in premature infants.

At birth, extracellular fluid (ECF) is about 44% of total body weight which subsequently decreases to 30% in the first 6 months of life and then to 20% by adolescence. ECF is composed of interstitial fluid and intravascular fluid. However, the majority of excess proportion of ECF in the neonates is due to higher interstitial fluids. This becomes relevant as neonates have difficulty mobilizing excess fluids and electrolytes which may clinically result in pulmonary or peripheral edema.

The site where most of the sodium exchange is done is the distal tubule. Growing term infants maintain a positive sodium balance whereas preterm infant under 35 weeks of gestation tend to have a negative sodium balance in the first 3 weeks after birth which may result in hyponatremia (< 130 mEq/l). This is due to a higher sodium delivery and lower reabsorption in the distal tubules as well as the intestine of premature infants compared to term infants.[23] Therefore, premature infants under 33 weeks of gestation require 3–5 mEq of sodium/kg/day for the first several weeks of life. However, excessive sodium administration to term newborn infants may result in fluid retention, edema, and hypernatremia. Fractional excretion of sodium (FENa) is highest during the first 10 days of life and decreases to below 0.4% by 1 month of age which is comparable to adults. FENa may increase secondary to hypoxia, diuretics, respiratory distress, hyperbilirubinemia, and increased fluid or salt intake.[1]

The major regulators of FENa are the renin–angiotensin–aldosterone system, atrial natriuretic peptides, prostaglandins, and catecholamines.[24] It is the balance between these factors that compensates for the immaturity of the nephron in order to maintain systemic homeostasis.

The kidney also plays an important role in maintaining potassium balance in the body. Potassium is freely filtered by the glomerulus and reabsorption occurs in the proximal tubules. There is some reabsorption in the ascending loop, but the final urinary concentration is determined by its secretion in the distal tubule. The fetus requires a positive potassium balance for normal growth. In preterm infants, hyperkalemia is usually evident due the immaturity of the distal tubules. It is also believed that the peritubular and luminal permeability of potassium may be contributing to the physiologic positive balance. A major determinant of potassium balance is cellular metabolism. In the premature infants, immediately following birth, there is a shift of potassium from the intracellular to the extracellular compartment.[25] Once the kidney adapts to the extrauterine environment, there is the onset of diuresis that facilitates potassium excretion and the regulation of serum potassium levels.

Calcium balance in the body is maintained by a well-coordinated mechanism between the gastrointestinal tract, bone, and kidney. The kidney maintains calcium homeostasis by regulating its reabsorption throughout the nephron via various active and passive processes. The fraction of calcium that is physiologically active in blood is the ionized calcium that is tightly regulated by the parathyroid hormone. Although there is a strong correlation between serum total calcium levels and serum ionized calcium, total calcium can be a poor predictor of calcium status especially in neonates. Low levels of calcium are common in premature infants, but seldom result in tetany or decreased cardiac contractility.[26] Calcium levels tend to stabilize and reach childhood levels by the first week of life.

Phosphorus is similarly and concordantly regulated with calcium. It has an important role in bone structure and various metabolic processes. The normal plasma phosphorus level is 3–4 mg/dl, and this level is maintained through a balance between intestinal absorption versus renal excretion. Renal excretion is the primary mechanism by which phosphorus is regulated in the body. Parathyroid hormone (PTH) is the most potent hormone that controls urinary excretion of phosphorus. Elevation in phosphorus levels induce the secretion of PTH, which in turn leads to the secretion of phosphorus via the kidneys. Excess phosphorus develops a complex with calcium resulting in a decrease in the production of calcitriol thereby reducing calcium absorption in the gut.

Acid–base balance

The acid–base balance is regulated by a combination of the respiratory, buffer, and renal systems. The buffer system constitutes the bicarbonate–carbonic acid buffer, hemoglobin–oxyhemoglobin buffer, protein buffer, and the phosphorus buffer mechanisms. The buffer systems are adapted to serve as the primary mechanism for maintaining acid–base balance in the newborn.[27] With low serum bicarbonate levels and ongoing physiologic demands, the premature infants have a tendency to be acidotic. It is known that administering bicarbonate to the premature does little to benefit the overall state of the infant due to the associated risks, including intraventricular hemorrhage, deteriorating cardiac function, and the worsening of intracellular acidosis.[28] However, if there is a critical need to administer bicarbonate, it should be done at a very slow rate in order to minimize fluctuations in cerebral hemodynamics.[29,30] The term infant is more accommodated to counter the acid–base balance due to a more mature regulatory mechanism, but the principles of management are comparable to the premature infants. Term neonates, with the exception of those having congenital complications, usually have a stable physiologic transition from fetal life to extrauterine surrounding. Cardiovascular, respiratory, and cerebral hemodynamic mechanisms are in equilibrium with each other and generally result in a balanced acid–base hemostasis. The acid–base balance is maintained closely by complex interactions between the respiratory system and the kidneys. The acceptable values in term infants compared to preterm infants (< 28 weeks) are as follows: pH > 7.30 (> 7.28), $PaCO_2$ 40–50 (40–50), bicarbonate (HCO_3^-) 20–24 (18–24), and PaO_2 50–70 (50–65).[31] The respiratory effort in the term infants is almost always stable with marginal predisposition to respiratory acidosis. At the same time, the buffer systems and tubular handling of the term infant kidney are also mature to handle any non-respiratory-induced acidosis within 72 h following birth.[32]

Renin–angiotensin–aldosterone axis

The renin–angiotensin system (RAS) is responsible for regulating blood pressure, renal hemodynamics, and fluid and electrolyte balance. Renin is the key component of the system. It is produced in the kidney by the juxta-glomerular cells and triggers the formation of angiotensin I which subsequently gets converted to angiotensin II (ATII) by angiotensin-converting enzyme. ATII increases systemic blood pressure by increasing peripheral resistance through its vasoconstrictory activity on small vessels. Furthermore, ATII can increase cardiac output through increasing myocardial contractility. In addition to the endocrine effects of RAS, an intra-renal autocrine effect also exists that regulates renal function as ATII is the primary vasoconstrictor of the renal vasculature[33] which can modulate reabsorption of sodium and water by the kidney.

Components of RAS are present during early gestation, but its activity and function is somewhat different from that seen in adults. At birth, plasma renin activity is increased and continues to

stay elevated through infancy and begins to decline to adult levels by 6–9 years of age.[34] RAS is also likely responsible for regulating growth and development of the nephron by the virtue of its presence in the kidney prior to fetal urine production. The mechanism controlling release of renin is well established by late gestation. Hypotension, hemorrhage, furosemide, ACE inhibitors, prostaglandins, vasopressin, and atrial natriuretic peptide are all known factors that influence renin secretion. Aldosterone is one component through which angiotensin regulates sodium reabsorption in the kidneys to regulate fluid and electrolyte balance. The fetal response to secrete aldosterone is less than that seen in adults due to the relative insensitivity of the adrenal gland.[35] This effect in addition to immaturity of the kidney may also contribute to the negative sodium and water balance seen in premature infants.

Summary

Renal function in the neonate undergoes significant changes over the course of days to weeks. It is therefore important for the surgeon to evaluate the neonate patient based on a dynamic scale. The diuretic phase takes place within 2–3 days after birth, during which urine production is relatively high. This phase also coincides with the reduction in total body water and weight. The fluid intake needs to be managed accordingly, since this period also coincides with the occurrence of pathologic states such as PDA. By the 5th–7th postnatal day, renal function starts to stabilize and slowly progresses to ultimately reach the adult state. The normal physiologic trends will be disrupted in newborns with congenital disorders such as congenital diaphragmatic hernia, congenital adrenal hyperplasia, and congenital cardiac defects. In these circumstances, serial monitoring and measurement of urine flow and urine and serum electrolyte concentrations will be important in guiding fluid and electrolyte management. It is recommended that urine output be maintained at around 2 ml/kg/day with a urine osmolality of 250–290 mOsm/kg or specific gravity of 1.010–1.013.[36]

In premature infants, the lack of maturity of the kidneys together with the likely occurrence of complications such as patent ductus arteriosus (PDA), necrotizing enterocolitis, congestive heart failure, respiratory compromise, or intraventricular hemorrhage (IVH) makes fluid and electrolyte management more challenging. Therefore, it is imperative to understand the capacity and limitations of the kidney when considering therapeutic interventions. An understanding of the fluid and electrolyte handling, hemodynamic changes, and acid–base balance during the neonatal period time is important in the successful management of patients with various pathophysiologic disturbances.

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