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Acute kidney injury in the fetus and neonate

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A B S T R A C T

Acute kidney injury (AKI) is an under-recognized morbidity of neonates; the incidence remains unclear due to the absence of a unified definition of AKI in this population and because previous studies have varied greatly in screening for AKI with serum creatinine and urine output assessments. Premature infants may be born with less than half of the nephrons compared with term neonates, predisposing them to chronic kidney disease (CKD) early on in life and as they age. AKI can also lead to CKD, and premature infants with AKI may be at very high risk for long-term kidney problems. AKI in neonates is often multifactorial and may result from prenatal, perinatal, or postnatal insults as well as any combination thereof. This review focuses on the causes of AKI, the importance of early detection, the management of AKI in neonates, and long-term sequela of AKI in neonates.

Contents

1. Postnatal kidney adaptation to extrauterine environment

Understanding the unique kidney adaptation that takes place

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early after birth is a crucial element in the prevention and management of neonatal AKI. There is great variability in nephron numbers at birth, ranging from 300,000 to 1.8 million nephrons per kidney. This variability is attributed to genetic and fetal environmental factors [1].

Fetal urine production starts at 9–10 weeks. Fetal urine contributes to the amniotic fluid and increases with gestation [2]. During intrauterine life, fetal hemostasis is regulated by the placenta; however, the kidney is involved in critical functions including urine production, lung maturation, and hormonal production. Glomerular filtration rate (GFR), renal blood flow (RBF), and tubular functions progress with renal growth and nephrogenesis. In the near-term period, the fetal kidneys achieve sufficient glomerular and tubular development to allow the adaptation to extrauterine life [3].

Whereas adult RBF is about 20% of the cardiac output (COP), the fetal kidneys receive only 3–5% of COP and this reaches about 10% by first week of life and the adult level by age 2 years [4]. Similarly, GFR increases from about 5 to 40 mL/min/1.73 m^2 during the first week of life. It continues to increase to 65 mL/min/1.73 m^2 by two months of age and reaches the adult level of 120 mL/min/1.73 m^2 by two years of age [5]. The increase in GFR is attributed to increased RBF and decreased renal vascular resistance (RVR).

Renal vascular resistance is under the control of many vasoactive factors including angiotensin II, prostaglandins, nitric oxide (NO), and catecholamines [4]. Angiotensin II levels are higher in the newborn than in adults; levels decrease during the neonatal period and early childhood until reaching adult levels by 6–9 years of age [4,6]. Angiotensin II is a potent vasoconstrictor that increases RVR and subsequently contributes to decreased GFR [6]. This vasoconstrictor effect is opposed by the vasodilator effect of prostaglandins, especially on the afferent arterioles [7]. NO functions primarily as an afferent arteriole vasodilator. Endothelial NO synthase and angiotensin receptors are highly expressed in immature nephrons and downregulated at the end of nephrogenesis [3]. The renal sympathetic nervous system increases renal vascular tone in afferent and efferent arterioles. The upregulation of $\alpha 2$ receptors is associated with a downregulation of $\beta 2$ receptors. Fetal renal vasculature is more sensitive to $\alpha 2$ receptor stimulation than in neonatal period [3].

The urinary flow rate increases 10-fold during fetal life 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) [3]. The maximum urine concentration capacity of the full-term fetus (700 mOsm) does not reach adult levels (1400 mOsm) until 6–12 months of age [8]. This blunted concentration capacity is attributed to reduced tonicity of the medullary interstitium, low expression of aquaporins, and a relative tubular insensitivity to antidiuretic hormone (ADH). Higher production of prostaglandin E_2 in neonates may inhibit the tubular effect of ADH [9].

Electrolyte regulation also evolves during transition to extrauterine life. Excretion of sodium is higher during fetal life than in the newborn and adults. This high rate of sodium excretion may be related to high circulating concentrations, high sensitivity to natriuretic factors, a large extracellular fluid volume, relative insensitivity to aldosterone, and immaturity of tubular sodium reabsorption. In contrast to adult physiology, sodium is mainly reabsorbed in the distal portion of the immature tubules in the fetus [10]. Sodium excretion decreases with increasing gestational age [6].

The fetus requires a positive potassium balance for normal growth. In preterm infants, hyperkalemia is usually evident due the immaturity of the distal tubules. The peritubular and luminal permeability of potassium may be contributing to the physiologic positive balance. In premature infants immediately following birth, there is a shift of potassium from the intracellular to the extracellular compartment [11]. Once the kidney adapts to the extrauterine environment, there is the onset of diuresis which facilitates potassium excretion and the regulation of serum potassium levels. Finally, the newborn infant has a diminished threshold for renal bicarbonate excretion.

Neonatal kidneys are unique; studies in human [12] and non-human primates [13] showed that although no new nephrons are formed after birth in term infants, nephrogenesis continues in preterm babies after birth (until about 36 weeks of gestational age. Using human autopsy samples Faa et al. [14] showed that kidney maturation continues after birth in preterm babies. Thus, nephrogenesis is a process not restricted to the intrauterine life, but may be an ongoing process. Some studies suggest that the extrauterine environment and AKI are detrimental to optimal nephrogenesis [15,16].

2. Definition and incidence of AKI

2.1. Challenging diagnosis in a challenging population

In spite of all the limitations of using serum creatinine levels to define AKI in the neonate, it is still the most widely used marker. Creatinine levels change in even healthy newborns in the first days to weeks of life [17]. Neonatal serum creatinine levels initially reflect maternal creatinine and take several days to reach equilibrium. As such, neonates' serum creatinine decreases over the first weeks of life, with the rate of decline dependent on gestational age at birth [18]. In infants born at term, there is a rapid rise in both glomerular and tubular function during the immediate postnatal period; however, this abrupt increase is dampened in preterm infants with a gestational age less than 34 weeks [19,20]. In very low birth weight infants with a GA <30 weeks, renal function has been shown to rise very slowly during the first two months of life [21]. This difference between preterm and term infants has been attributed to the immaturity of the kidney at birth and to delayed adaptation to extrauterine life in preterm infants [17,19,21]. In addition, it is important to consider that creatinine is a marker of kidney function and its rise lags after the onset of kidney damage. Serum creatinine may not increase until 25–50% of renal function is lost [22]. As such, serum creatinine is not an ideal biomarker for the early detection of AKI in neonates; nonetheless, we know that small changes in SCr are independently associated with poor outcomes.

2.2. Towards a working definition of neonatal AKI

Defining AKI in neonates remains a challenging dilemma for both neonatologist and nephrologist. Historically, neonatal AKI was defined in terms of absolute serum creatinine levels. More recently, proposed definitions are based upon the degree of increase in serum creatinine levels rather than a single absolute cut-off value. These definitions may have more biological plausibility but do require serial creatinine measurements; this may be of concern in preterm babies who are especially susceptible to anemia from iatrogenic blood losses.

In 2000 Gouyon and Guignard defined renal insufficiency of very preterm babies as a daily increase in serum creatinine of >0.50 mg/dL from day 0–1 and 0.30 mg/dL/24 h during the remainder of the first week of life [23]. Oliguria was defined as urine volume of <1 mL/kg/h over a period of 24 h; severe oliguria was defined as urine volume of <0.5 mL/kg/h. Subsequent AKI definitions have also used varying combinations of rising serum creatinine, oliguria, and elevated blood urea nitrogen (BUN) levels [24,25], with the most widely used definition between 1995 and 2005 as an absolute SCr of $\geq$1.5 mg/dL.

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