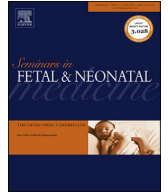




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Renal function in the fetus and neonate – The creatinine enigma

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A B S T R A C T

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The use of serum creatinine levels to estimate glomerular function in infants is admittedly fraught with inherent inaccuracies which are both physiological and methodological in nature. This characteristic can understandably reduce the neonatal clinician's confidence in the ability of serum creatinine levels to provide useful information relevant to their patients' medical care. The aim of this review is to provide further insight into the peculiarities of serum creatinine trends in both premature and term infants with special focus on the maturational and developmental changes occurring in the kidney during this crucial time-period. Though newer markers of glomerular function are gaining increasing traction in the clinical realm, the most prominent of which is currently cystatin C, creatinine nonetheless remains an important player in the scientific evolution of glomerular filtration rate (GFR) estimation. Not only do its limitations provide a level of distinction for newer markers of GFR, but its advantages persist in refining the precision of newer GFR formulae which incorporate multiple patient characteristics.

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1. Introduction

Creatinine has long been used as the bedside standard to estimate glomerular filtration rate (GFR) in the clinical arena, not only due to

its biochemical properties, but also the ease and widespread availability of serum sampling methods. In this regard, the limitations of creatinine have been well described in the medical literature, and, for our purposes, are perhaps at their most significant in the respectively “smaller” arena of approximating GFR in neonates. We begin with a general review of creatinine as a biomarker of glomerular filtration,

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followed by a discussion on the use of creatinine in neonates relative to the developmental and maturational changes occurring in the kidney during the perinatal period. We conclude with a review of alternative methods that may be useful in the evaluation of glomerular filtration in term and premature infants.

2. Use of creatinine clearance to estimate glomerular filtration rate

Creatinine is an endogenous, low molecular weight substance (113 Da) produced through muscle catabolism at a rate proportional to total muscle mass. It is freely filtered in the glomerulus, is not plasma protein bound, nor is it metabolized by the kidney. These properties make it a useful molecule in the estimation of GFR, primarily through the use of formulae that directly measure or approximate the volume of plasma from which creatinine must be removed to account for its appearance in glomerular filtrate per minute – otherwise known as creatinine clearance. There are, however, other properties that relegate creatinine clearance to a position of mediocrity when attempting to estimate GFR in some clinical situations, several of which arise in the neonatal time-period. Secretion of creatinine by the proximal tubule (thereby bypassing glomerular filtration altogether) is well documented in most age groups, though the rate of secretion is not consistent or predictable within an individual over time, nor across groups of individuals. This extra-glomerular elimination may represent a significant proportion of overall clearance, especially in patients who have a relatively diminished GFR, which, as we discuss later, includes many infants [1].

Thus, estimated GFR (eGFR) values determined via serum creatinine (S_{cr}) may lead to significant overestimation of a patient's true GFR over time, as the secreted fraction is inappropriately ascribed to glomerular filtration. This in turn may mask modest changes in glomerular creatinine clearance that occur early in acute kidney injury (AKI), an effect which can be significant even up until 25–50% of baseline renal function has been lost. Indeed, elevation of serum creatinine is often not detectable in infants and children as late as 24–72 h following an initial renal insult. Other factors, such as hepatic injury, variations in muscle mass, abnormalities in protein catabolism, and/or patient fluid status, may further complicate the accuracy of GFR values determined using creatinine clearance [1–4].

3. Use of serum creatinine in the infant population

The interpretation of serum creatinine levels poses an additional quandary in premature and term infants. Not only are infants at significant risk for wide variations in fluid status, protein catabolism, and hepatic function over time (especially in the neonatal intensive care unit), but, for the first several days of a neonates' life, S_{cr} levels are more reflective of the mother's renal function than that of the child, primarily related to placental transfer of creatinine. Furthermore, in premature infants, serum creatinine may rise for the first several days following birth, the degree and duration of rise being proportional to the degree of prematurity. This rise in creatinine is thought to be secondary to tubular resorption of creatinine by the immature kidney, compounded by the total body fluid loss and intravascular volume contraction typically encountered in newborn premature infants. Significant tubular resorption of creatinine may persist for up to three weeks in some premature infants, which in turn promotes underestimation of the infant's true GFR using contemporary eGFR formulae. This is in stark contrast to the aforementioned tendency of eGFR formulas to overestimate GFR in most other patient populations, where tubular secretion of creatinine predominates. Following this initial rise in S_{cr} , premature infants will then typically demonstrate a more gradual decrease in creatinine levels than term infants, presumably secondary to slower

maturation of glomerular function and diminished baseline functional nephron mass (Fig. 1). To put this in perspective, healthy term infants readily reach baseline S_{cr} levels within 2 weeks of age; however, even relatively healthy premature infants may take as long as 3–8 weeks before stabilization occurs [3,5,6].

Both creatinine clearance and GFR are known to be positively correlated with postnatal age, increasing steadily over the first several months of life. Additionally, when mean creatinine clearance and GFR values are compared between groups of infants with differing gestational ages, values for the higher gestational age group will surpass that of the lower gestational age group, regardless of the postnatal day on which they are compared. As such, there exists a wide range of “normal” creatinine values in infancy, related to the variation in rates of kidney maturation which are proportional to gestational and postnatal age (Table 1) [3,5,7,8].

4. Variations in serum creatinine values based on assay method

Another important limitation associated with the use of creatinine as a marker of GFR concerns the variation in sampling methods that are used to calculate serum levels. Earlier sampling methods utilize the Jaffe reaction, a colorimetric assay which can quantify the content of chromogens within serum. This method provides relatively imprecise results, as chromogens other than creatinine (bilirubin, for example) contribute to the reaction, in effect falsely elevating creatinine concentrations by as much as 20%. Though steps can be taken to remove interfering chromogens, this method has largely gone out of favor, having been replaced by enzymatic detection strategies which are much more accurate, particularly at concentrations <1 mg/dL (the range in which most pediatric and neonatal patients tend to reside). Newer methods using either gas or liquid chromatography coupled with isotope dilution mass spectrometry are available, and provide even more accurate and standardized results [9].

5. Developmental physiology of glomerular filtration

Glomerular filtration rate is currently the best measurement we possess to determine the magnitude of a patient's functional renal mass. As GFR is a moving target in the neonatal population, it is important to further outline the developmental physiology of glomerular filtration in order to understand how GFR changes over time in the fetus and neonate.

In biological systems, filtration is governed by the Starling principle of microvascular fluid exchange, as demonstrated by the

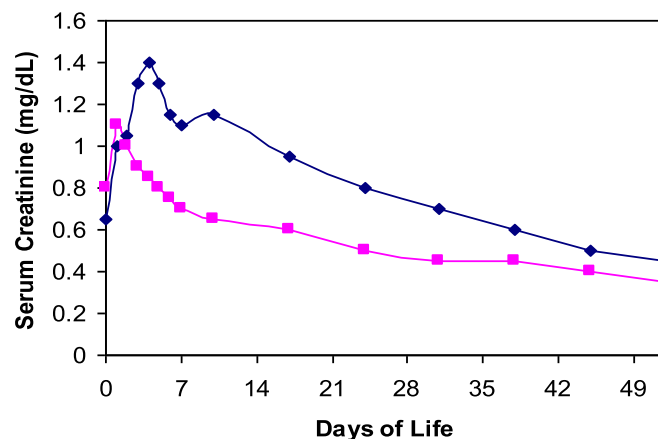


Fig. 1. Mean serum creatinine trends in premature infants <27 weeks' gestation (blue diamonds) and 31–32 weeks' gestation (pink squares) (Adapted from Gallini et al. [5]).

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