

# Glomerular Function in Neonates

Hasan Otukesh,<sup>1</sup> Rozita Hoseini,<sup>2</sup> Nahid Rahimzadeh,<sup>3</sup>  
Sara Hosseini<sup>2</sup>

<sup>1</sup>Division of Pediatric Nephrology, Ali Asghar Children Hospital, Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup>Division of Pediatric Nephrology, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>3</sup>Division of Pediatric Nephrology, Rasool Akram Hospital, Tehran University of Medical Sciences, Tehran, Iran

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Glomerular filtration rate is low in fetal and neonatal life. It increases after birth and reaches approximately 20 mL/min/1.73 m<sup>2</sup> at 1 month of age in term and preterm neonates. Various methods have been used to measure glomerular filtration rate in neonates such as inulin clearance, creatinine clearance, and serum cystatin C. Serum creatinine concentrations are influenced by many factors. It is suggested to use other markers which are stable over time and are not affected by muscle mass or tubular reabsorption and secretion. Cystatin C incorporates these characteristics; however, there are some other limitations in the use of cystatin C as a marker of kidney function in neonates. Additionally, the numbers of studies focused on the use of cystatin C in neonates is limited. There is a need for further studies to determine cystatin C's normal range levels and investigate whether cystatin C can replace other tests such as serum creatinine as marker of kidney function in newborn babies. Assessment of newer kidney function tests is also warranted in newborn infants.

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## INTRODUCTION

Glomerular filtration rate (GFR) is as low as one-third to one-fourth of those of adult values in the neonatal period, especially in preterm neonates. Glomerular filtration rate values depend on gestational age, and therefore, are lower in neonates with lower gestational ages. Glomerular filtration rate increases within the first month of life, and the velocity of this increase is lower in preterm neonates. It is necessary for clinicians to track postnatal changes in GFR and the level of GFR at different gestational ages, so that they can recognize the abnormal changes and diagnose kidney failure. In addition, they need to adjust medication doses based on the GFR changes. In this review, we describe the traditional and new methods for GFR estimation in neonates and their advantages and drawbacks.

## GLOMERULAR FILTRATION

In the fetus, the placenta maintains the fluid

and electrolyte balance and clearance of metabolic wastes; thus, GFR is low, but it increases progressively. Within the last months of gestation, GFR increases in parallel with gestational age until the 36th week of gestation, which is due to an increase in the number and size of nephrons. Thereafter, GFR develops more slowly up to the time of birth. At birth, GFR is still relatively low; measured by inulin clearance at birth, it is almost 20 mL/min/1.73 m<sup>2</sup> in term neonates.<sup>1,2</sup> In term infants, there is a large increase in GFR during the first 2 weeks after birth. All determinants of the single-nephron GFR contribute to this increasing by varying degrees. Increases in systemic blood pressure and consequently hydrostatic pressure of glomeruli, pore size of glomerular capillary wall (as well as glomerular capillary surface area) and ultrafiltration coefficient, and plasma flow rate secondary to increase in caliber of afferent and efferent arterioles and the decrease in these arterioles resistance all play some role in maturational increase

in early postnatal GFR.<sup>1</sup>

Some authors believe that this increase in early postnatal GFR is primarily due to an increase in glomerular capillary surface area.<sup>3</sup> In an experimental study, the mechanisms responsible for changes in GFR were investigated in fetal sheep and lambs. This study showed that the striking increase in GFR (occurring in late fetal life and 2 weeks after birth) is due to a small increase in filtration pressure together with a large increase in the ultrafiltration coefficient.<sup>4</sup> However, GFR doubles during the first 2 weeks of life and reaches almost  $50 \pm 10$  mL/min/1.73 m<sup>2</sup> between 2 and 4 weeks after birth (Figure).<sup>1</sup> After the 1st month of life, GFR increases progressively and reaches adult levels between 1 and 2 years of life.

Glomerular filtration rate is low in preterm infants at birth and varies by the gestational age. In these neonates, postnatal GFR develops slowly until 34 to 36 weeks of gestation. Thereafter, GFR increases rapidly, like postnatal GFR in term neonates (Figure). In a study of 41 preterm neonates with gestational ages from 27 to 36 weeks, postnatal increase in GFR was explained in 2 ways: first, an increase in GFR in association

with the increment in gestational age and body weight, and second, another increase in GFR due to renal hemodynamic changes without dependency on gestational age and body weight.<sup>6</sup> Thus, the rapid increase in GFR occurs in preterm infants in a relatively later time.<sup>7</sup> Consequently, doubling GFR occurs later and at the 3rd to 4th week after birth or even later in very preterm infants.<sup>8</sup> At 1 month of life GFR reaches 50 mL/min/1.73 m<sup>2</sup> in most preterm neonates (Figure).

Recently, Vieux and colleagues determined GFR reference values (measured by creatinine clearance) in very premature infants aged 27 to 31 weeks of gestation in a multicenter prospective study.<sup>9</sup> This study included 275 infants and GFR reference values were presented as the 3rd, 10th, 50th, 90th, and 97th percentiles (Table 1). These references help clinicians to adjust medication doses based on GFR and to diagnose kidney dysfunction at early point in very preterm newborns.

#### KIDNEY FUNCTION ASSESSMENT

Various methods have been used to measure GFR in neonates. One of these methods is the clearance measurement. Some endogenous and exogenous



Glomerular filtration rate in preterm and term infants and its trend towards adulthood<sup>2,5</sup>

**Table 1.** Glomerular Filtration Rate Reference Values in Premature Infants<sup>9</sup>

Gestational Age at Birth	Glomerular Filtration Rate, mL/min/1.73 m <sup>2</sup>								
	Day 7			Day 14			Day 21		
	10 <sup>th</sup>	Median	90 <sup>th</sup>	10 <sup>th</sup>	Median	90 <sup>th</sup>	10 <sup>th</sup>	Median	90 <sup>th</sup>
27 weeks	8.7	13.4	18.1	11.5	16.2	20.9	13.3	18	22.7
28 weeks	11.5	16.2	20.9	14.4	19.1	23.8	16.1	20.8	25.5
29 weeks	14.4	19.1	23.8	17.2	21.9	26.6	19	23.7	28.4
30 weeks	17.2	21.9	26.6	20.1	24.8	29.4	21.8	26.5	31.2
31 weeks	20.1	24.8	29.5	22.9	27.6	32.3	24.7	29.4	34.1

substances have been used to measure clearance. These substances include inulin, creatinine, iothexol, ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), and sodium iothalamate. However, frequent blood sampling, urine collection, and constant infusion of exogenous markers limit their use. In most neonatal intensive care units, GFR is measured using Schwartz formula, which is based on serum creatinine level.

### Inulin

Inulin is an exogenous starch-like fructose polymer that is not metabolized, reabsorbed, or secreted by the renal tubular cells. Inulin is filtrated freely from the glomeruli even in preterm neonates as young as 27 weeks.<sup>8</sup> Because of these characteristics of inulin, GFR is very close to inulin clearance. Inulin-based GFR is measured by 3 techniques:

**Urine volume per plasma clearance.** This method is reference for both immature and mature kidneys. Since this method requires constant infusion of intravenous inulin and precise urine collection, it is cumbersome, invasive in neonates, and relatively expensive.

**Constant infusion technique without urine collection.** In this method the rate of infusion of inulin is equal to the rate of its excretion while its serum concentration is constant. Thus, only blood sampling is required together with precise knowledge of infusion rate (mL/min) and inulin concentration in infused serum. In this method, inulin is infused constantly for at least 24 hours rather than for a short-term period, and the results obtained are similar to those obtained by traditional methods of urinary clearance. The benefit of this method is that urine collection is not necessary and the main disadvantage of this method is requirement of careful time-consuming supervision of long-term duration of inulin infusion.

**Single injection technique (plasma disappearance curve).** In this method, there is no requirement to constant infusion of inulin and urine collection, but repeated plasma sampling is required.

Although inulin clearance is the gold standard method of GFR estimation in all age groups including neonates, the methods of GFR measurement by inulin are time consuming, expensive, and cumbersome. Difficulty in obtaining

and preparation of inulin, the need to continuous intravenous inulin infusion, and urine collection are drawbacks to reduce the use of this marker for GFR assessment.

### Other Exogenous Markers

Radiolabeled markers such as iothalamate, technetium-DTPA, and creatinine-EDTA are also used for GFR assessment in children and adults. Limitations of the use of these markers include radiation exposure as well as cost considerations. Additionally, significant renal tubular secretion and consequent GFR overestimation of iothalamate have lowered its use as a GFR marker in clinical practice. Iothexol is a nonionic contrast agent used in GFR measurement. It is filtrated by glomeruli without reabsorption, secretion, and metabolism by the kidneys. The extrarenal clearance of iothexol is very low and it is cleared almost completely by the kidneys. Iothexol clearance measured by a single-injection method is very similar to inulin clearance.<sup>10,11</sup> However, iothexol and all radioactive markers are not recommended for GFR measurement in neonates by most clinicians.

### Creatinine

The source of creatinine is creatine and phosphocreatine of muscles, and therefore, it reflects muscle mass of the body. Plasma creatinine is high and almost 1.1 mg/dL at birth because of circulating maternal creatinine. Then, it falls in the 1st week of life, but is still higher than normal at the end of the 1st week. Thereafter, serum creatinine decreases more slowly to reach 0.4 mg/dL at 2 weeks after birth. In preterm infants, serum creatinine first rises at 2 to 4 days of life and then decreases and reaches to 0.4 mg/dL later and mostly at week 2 to 3 postnatal. The tubular reabsorption of creatinine seems to be the cause of continued high plasma creatinine in these neonates.<sup>12</sup> By maturation of the renal tubules, the total muscle mass of the body, glomerular filtration rate, and tubular secretion determine serum creatinine concentration.

Few studies have assessed and reported reliable reference ranges of serum creatinine in neonates. In the majority of these studies, serum creatinine was measured by the Jaffe assay, and not enzymatic methods. In addition, the number of cases in these studies was low and the selection of patients was not suitable. Boer and coworkers<sup>13</sup> determined the

reference values of serum creatinine in 112 term neonates. All preterm neonates (< 37 weeks) and neonates small for gestational age were excluded because of their immature kidney function. The reference ranges of serum creatinine in neonatal period in this study are shown in Table 2. This and the study of Pottel and colleagues<sup>14</sup> both showed the rapid decline of serum creatinine in the 1st week of life but more slowly after that. Pottel and colleagues<sup>14</sup> demonstrated an elevation in serum creatinine on day 1 after birth. This rising was not reported by Boer and colleagues' study, perhaps due to the lack of cord blood samples or exclusion of all preterm neonates and newborns with proven or suspected kidney dysfunction such as asphyxiated neonates. In addition, the reference values of serum creatinine were lower as compared with Pottel and colleagues' study and this is due to different exclusion criteria in these two studies. In Boer's study, the reduction of serum creatinine after birth continued and then reached to a plateau at 65 to 220 days of life. After this time, although the serum creatinine concentrations increases secondary to increased muscle mass, the measured GFR relative to body surface area remains stable as the kidney maturation is almost complete.<sup>13</sup>

There are several methods to estimate GFR from serum creatinine. Although creatinine-based GFR is not as precise as inulin clearance-based estimates, it is simple, inexpensive, and almost noninvasive. In clinical practice, creatinine clearance (using serum and urine creatinine concentrations) is used to measure GFR; however, its performance requires timely urine collection and is cumbersome especially in neonates. As a result, studies have used equations to estimate GFR by the use of serum creatinine and patient characteristics such as height, weight, gender, and age. Schwartz formula is the most commonly used equation in pediatric age groups, including neonates. Studies with

comparison between GFR estimated by creatinine clearance and the values estimated by the Schwartz formula showed significant correlations in both term and preterm infants. In addition, the GFR obtained by the Schwartz formula is correlated with the inulin single-injection technique.<sup>15</sup> In contrast, there is no significant correlation between GFR measured by this formula with those obtained by the standard inulin clearance. The simplicity of the Schwartz formula leads to the use of this method for estimation of GFR in most centers.<sup>16</sup>

The use of creatinine as a GFR marker in neonates has some problems. First, serum creatinine at birth reflects maternal serum creatinine. It starts to decrease in the first week after birth. In preterm infants, serum creatinine concentrations increase and reach a peak at day 4 after birth because of tubular reabsorption. Second, the clearance of creatinine underestimates the true GFR in neonates, especially in very low birth weight neonates. This phenomenon is due to the passive reabsorption of filtrated creatinine across immature leaky renal tubules in neonates and is more prominent in premature kidney. Third, the Jaffe method measuring serum creatinine has interference with conditions such as hyperbilirubinemia, hypertriglyceridemia, hemolysis, and ketone bodies in blood. This laboratory error leads to GFR underestimation. Enzymatic methods have less interference with these conditions. Fourth, tubular secretion of creatinine (especially in the presence of low GFR) and secretion of creatinine into the intestine result in GFR overestimation. As a result, the ratio of creatinine clearance to inulin clearance is not 1, but 1.2 to 1.3 in neonates with kidney dysfunction.<sup>17</sup> Fifth, growth and changes in muscle mass influence serum creatinine levels. As a result, serum creatinine is age and gender dependent. Finally, serum creatinine is not sensitive to small changes of GFR. As a result, serum creatinine concentrations are influenced by some variables such as maternal kidney function, hydration, catabolic status, and muscle mass. Thus, isolated serum creatinine measurement cannot reveal the glomerular filtration status. It is better to measure serum creatinine periodically for GFR assessment.

Although the serum creatinine levels and the GFR measurement based on this marker help clinicians to assess kidney function in neonates, it is better to use markers that are stable over

**Table 2.** Reference Values for Serum Creatinine Levels in Term Neonates<sup>13</sup>

Age	Serum Creatinine, mg/dL		
	10 <sup>th</sup>	Median	90 <sup>th</sup>
Day 1	0.49	0.62	0.79
Day 3	0.37	0.48	0.61
Week 1	0.31	0.38	0.50
Week 2	0.27	0.35	0.45
Week 4	0.23	0.28	0.36

time and not affected by muscle mass and tubular reabsorption or secretion. This stable marker can show the physiologic changes of kidney function in children younger than 1 year old, including neonates, more precisely.

### Cystatin C

Cystatin C is a proteinase inhibitor involved in intracellular catabolism of proteins, produced by all nucleated cells, freely filtrated across glomeruli, and completely catabolized and reabsorbed in the proximal tubule. Studies have shown that serum cystatin C is a more specific and sensitive marker of GFR in both adults and children.<sup>18-23</sup> Herget-Rosenthal and associates showed that serum cystatin C concentrations detected changes of creatinine clearance with a higher sensitivity (97% versus 83%) compared to serum creatinine levels. In this study, cystatin C provided a negative predictive value of 97%, whereas serum creatinine provided a rate of 87%.<sup>24</sup> Tenstad and colleagues also showed that cystatin C clearance was identical to GFR measured by the EDTA.<sup>25</sup> However, there are limited studies available on reference values of cystatin C in neonates, particularly preterm infants.

The benefits of the use of cystatin C in neonates as a kidney function marker are: (1) There is no interference between cystatin C and bilirubin, hemoglobin, and ketone in laboratory. Bokenkamp and coworkers reported that a mild elevation in serum cystatin C concentration was seen in patients with hyperbilirubinemia.<sup>22</sup> (2) Cystatin C has been shown to be independent of inflammation, muscle mass, age, gender, and nutritional status.<sup>19,20,22,26,27</sup> (3) Cystatin C does not pass through the placenta. In a study by Cataldi and colleagues, there was no correlation between neonatal and maternal serum cystatin C in contrast to serum creatinine at birth.<sup>28</sup> As a result, the values of serum cystatin C reflect only the neonatal GFR. (4) Serum cystatin C level mirrors maturation of the kidney better than other markers such as serum creatinine.

Carolina and associates compared serum creatinine and cystatin C concentrations in the 1st month of life in term neonates. They found that serum creatinine at day 1 after birth was not different from maternal creatinine; in contrast, cystatin C levels were higher than maternal cystatin C. Serum creatinine values progressively reduced in the 1st month. Serum cystatin C concentration

also decreased from day 0 to day 3 after birth and then remained constant up to 1 month of life.<sup>27</sup>

Armangil and coworkers also showed a decrease in serum cystatin C levels by day 3 after birth.<sup>29</sup> In another study, Bokenkamp and colleagues assessed serum cystatin C concentrations in 258 children aged 1 day to 18 years.<sup>30</sup> They found higher serum cystatin C values in the first year of life, with peak values in postpartum period. In the first 4 months of life, a rapid decrease in cystatin C was observed in this study that may be due to GFR maturation. Thereafter, the decrease in cystatin C occurred more slowly by the age of 1 year and then stabled.<sup>30</sup> Harmoinen and coworkers also demonstrated the higher levels of serum cystatin C levels in postpartum period and rapid decrease in serum cystatin C concentrations in the 1st months of life and slower reduction by the age of 3 years.<sup>31</sup> In addition, studies have shown that the serum cystatin C is higher in preterm infants than in term neonates.<sup>27,32,33</sup> The results of these studies demonstrated that the neonatal serum cystatin C was independent of maternal cystatin C and was correlated with maturation of neonatal kidneys.<sup>27</sup> Thus, it appears that the serum cystatin C is a reliable marker in the first weeks of life. Its advantages are that it does not need a 24-hour urine collection, and therefore, it takes a short time to perform; serum cystatin C has been shown to be independent of gestational age<sup>31,34</sup>; and serum cystatin C levels do not change by dehydration in contrast to serum creatinine concentration.<sup>21</sup>

The problems with cystatin C as a marker of kidney function in neonates, however, are the following: (1) unknown handling of cystatin C by immature kidneys; (2) very large scattering of serum cystatin C levels in neonates and then difficulty to establish a formula to measure GFR by cystatin C (to our knowledge, there is no study on the GFR measurement by the cystatin C formulas in neonates); (3) changes in degradation rate of cystatin C and consequently its serum concentration as a result of injury to proximal tubular cells; (4) no enough data regarding comparison between cystatin C and gold standard tests for kidney function assessment in neonates (Giovanni and colleagues compared inulin clearance and serum cystatin C levels in 20 preterm neonates and found a significant correlation between inulin clearance and reciprocal values of cystatin C and creatinine.<sup>35</sup>

All neonates with an inulin clearance greater than 0.5 mL/kg had a serum cystatin C concentration less than 2 mg/L); (5) Influence of C reactive protein, thyroid dysfunction, and corticosteroid therapy on the serum cystatin C concentration<sup>32,36</sup>; (6) higher costs of the measurement of cystatin C than creatinine; (7) lower reliability of cystatin C in comparison with GFR measured by the Schwartz formula<sup>37</sup>; and (8) controversial reports on the association of male gender, older age, greater weight, higher serum C-reactive protein with higher serum cystatin C level.<sup>30</sup>

Some studies determined the range of serum cystatin C in healthy term and preterm neonates. Table 3 summarizes these studies. Further studies with larger number of cases using concurrent gold standard tests are required to determine whether cystatin C can replace other tests such as serum creatinine as a kidney function marker. Studies also are required to allow clarification of whether cystatin C can help diagnose early changes in kidney function among neonates.

Finally, of other kidney function markers is beta trace protein that is produced by glial cells and freely filtrated by glomeruli. However, there is no study in neonates on the use of this marker for kidney function assessment. Thus, there is a need to perform studies on beta trace protein measurement in neonates and compare it with other markers such as cystatin C, creatinine, and gold standard tests.

#### CONFLICT OF INTEREST

None declared.

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**Table 3.** Studies on Reference Range of Cystatin C in Preterm and Term Neonates

Study	Number	Serum Cystatin C, mg/L	Age	Gestational Age, wk
Armangil et al <sup>29</sup>	108	1.80 (1.1 to 2.3)	day 0	32.5 ± 2.6
Armangil et al <sup>29</sup>	108	1.65 (1.0 to 2.1)	Day 3	32.5 ± 2.6
Bokenkamp et al <sup>30</sup>	23	2.16 (1.6 to 2.6)	days 0 to 3	term infants
Bokenkamp et al <sup>30</sup>	14	2.02 (1.5 to 2.4)	days 3 to 30	term infants
Harmoinen et al <sup>31</sup>	58	1.88 (1.01 to 2.9)	days 0 to 7	< 37
Harmoinen et al <sup>31</sup>	50	1.70 (1.2 to 2.3)	days 0 to 7	> 37
Bahar et al <sup>33</sup>	14	1.49 (1.0 to 2.3)	day 3	< 37
Bahar et al <sup>33</sup>	84	1.32 (0.8 to 2.4)	day 3	≥ 37
Finney et al <sup>34</sup>	16	1.48 (0.6 to 3.4)	day 0	24 to 28
Finney et al <sup>34</sup>	14	1.65 (0.6 to 4.4)	day 0	29 to 38
Finney et al <sup>34</sup>	50	1.37 (0.8 to 2.3)	months 0 to 3	term infants
Treiber et al <sup>38</sup>	75	1.97 (1.4 to 3.2)	umbilical cord	34 to 41
Treiber et al <sup>38</sup>	75	1.93 (1.3 to 2.7)	day 3	34 to 41

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Correspondence to:

Division of Pediatric Nephrology, Shahid Labafinejad Medical Center, 9th Boustan, Pasdaran Ave, Tehran, Iran  
E-mail: rozitahoseini@yahoo.com

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