Plasma Creatinine Rises Dramatically in the First 48 Hours of Life in Preterm Infants

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ABSTRACT. Objective. Published data show that plasma creatinine falls steadily during the first 28 days of life and that creatinine levels in the neonatal period are higher in more premature infants. However, the best reference data commence on day 2 of life. The objective of this study was to document how plasma creatinine changes in the first 48 hours of life and to examine the reason for the apparently high levels of creatinine in preterm infants, compared with maternal levels.

Design. A prospective observational study on a regional neonatal intensive care unit.

Patients. A total of 42 preterm infants, mean gestational age of 29.4 weeks (range: 23–35), mean birth weight of 1.42 kg (.55–2.77), divided into 4 gestation groups: 23 to 26 weeks (n = 9), 27 to 29 weeks (n = 13), 30 to 32 weeks (n = 12), and 33 to 35 weeks (n = 8).

Interventions. Measurement of plasma creatinine and urea concentration in cord blood and in serial samples taken for routine arterial blood gas analysis.

Outcome Measurements. Changes in creatinine concentration with time and relationship to gestational age, birth weight, and illness severity.

Results. Mean creatinine at birth was 73 μmol/L (95% confidence interval [CI]: 68–79 μmol/L). Plasma creatinine rose significantly over the first 48 hours. Mean peak creatinine in the most preterm infants (23–26 weeks) was 221 μmol/L (CI: 195–247 μmol/L). Peak plasma creatinine was inversely related to gestation (Spearman's coefficient: −.73) and birth weight (Spearman's coefficient: −.76). Significant differences in creatinine concentration were seen among different gestational groups at 24 and 48 hours of life. Peak creatinine correlated with a high Clinical Risk Index for Babies score (Spearman's coefficient: .64). The fall in creatinine began later in more premature infants. All 38 surviving infants had normal renal function; their mean plasma creatinine at discharge was 52 μmol/L (CI: 46–58 μmol/L).

Conclusions. Rather than falling steadily from birth, creatinine rises dramatically in the first 48 hours of life, especially in infants of <30 weeks’ gestation. Even large rises in creatinine in the first 48 hours may be expected and should not be used in isolation to diagnose renal failure.

Pediatrics 1999;104(6). URL: http://www.pediatrics.org/cgi/content/full/104/6/e76; creatinine, preterm infant, renal failure.

ABBREVIATIONS. GFR, glomerular filtration rate; CI, confidence interval; RDS, respiratory distress syndrome.

The management of the newborn preterm infant requires meticulous attention to fluid and electrolyte balance and careful assessment of renal function. Creatinine is the most widely used marker of renal function and can be used to estimate glomerular filtration rate (GFR). Current published data show that during the neonatal period creatinine falls steadily from day 2, until it reaches a natural equilibrium between production from muscle and renal clearance. Rises in plasma creatinine concentration of >20 μmol/L a day have been thought to imply impending renal failure.

The best reference data available show that initial creatinine levels in preterm infants are higher than expected and that they take longer to fall to steady state levels. There has been speculation that these high initial levels reflect higher maternal creatinine concentration. However, it is known that fetal creatinine concentration is in equilibrium with that of the mother and that maternal creatinine levels are, in fact, relatively low during the third trimester of pregnancy. Therefore, we would expect creatinine concentration at the time of birth in these infants to be low to normal compared with adult reference data.

However, the infant reference data commence on day 2 of life; therefore, there is a period during the first 48 hours of life that has not yet been documented. The aim of this study was to describe changes in creatinine concentration during this previously undocumented period and to investigate the reason for the apparently high creatinine levels in preterm infants.

METHODS

A total of 42 preterm infants undergoing intensive care at a regional neonatal intensive care unit were selected for study. Infants were recruited into 4 gestation groups: 23 to 26 weeks (n = 9), 27 to 29 weeks (n = 13), 30 to 32 weeks (n = 12), and 33 to 35 weeks (n = 8). Gestation was assessed by maternal menstrual history and ultrasound scan. All infants had radiologic and clinical evidence of respiratory distress syndrome (RDS) and had...
arterial access for routine blood sampling. All were nursed on platforms with overhead servo controlled heaters. Infants with known renal disease or evidence of birth asphyxia were excluded. Ethical committee approval was obtained for the study.

Umbilical cord blood or venous blood taken within the first hour of life was used as the baseline birth sample. Subsequent samples were collected from the small volume of blood normally discarded after blood gas analysis. These blood gas samples were taken as determined by normal clinical practice and no extra blood was taken for the purposes of this study. The samples were spun down and separated immediately. Plasma creatinine was analyzed using the kinetic Jaffe reaction method and urea measured using a urease method, both with Beckman reagents on a Beckman Synchron LX Clinical Chemistry analyzer (Beckman Coulter Ltd, High Wycombe, UK). This method has been validated previously as having minimal interference from noncreatinine chromogens, such as bilirubin.

Clinical data were recorded for each infant including gestational age, birth weight, Apgar score, Clinical Risk Index for Babies score, and ventilatory support required. Intravenous fluids and electrolytes were prescribed according to established protocols: 75 mL/kg/day of fluid on day 1, increasing by 15 mL/kg/day to a maximum of 150 to 165 mL/kg/day. Parenteral nutrition was commenced on day 2 to 4 and increased over 6 days. Individual adjustments were made to maintain neutral fluid balance and electrolyte and glucose homeostasis.

Changes in creatinine and urea over time were recorded for each infant. Data were analyzed with Spearman’s Rank Correlations, paired t tests, and generalized linear modeling, using the statistical package SPSS for Windows Release 7 (SPSS Inc, Chicago, IL). 95% confidence intervals (CI) are given for all results.

RESULTS

A total of 42 infants were studied with a mean gestation of 29.4 weeks (range: 23–35) and a mean birth weight of 1.42 kg (0.55–2.77 kg). The infants were distributed as follows: group 1, 23 to 26 weeks (n = 9; mean: 25.1 weeks), group 2, 27 to 29 weeks (n = 13; mean: 28.1), group 3, 30 to 32 weeks (n = 12; mean: 30.8), group 4, 33 to 35 weeks (n = 8; mean: 34.1). Four infants died after the study period. No infants had significant oliguria, persistent metabolic acidosis, progressive hyperkalaemia, or other clinical evidence of renal failure. No infants required renal replacement therapy, and all surviving infants had normal renal function at discharge.

Creatinine Concentration at Birth

Of the infants, 23 infants had cord blood collected, and an additional 19 had a venous sample within the first hour of life. The mean creatinine concentration at birth was 73 μmol/L (95% CI: 68–79 μmol/L). There were no significant differences in initial creatinine concentration among the different gestation groups.

Rise in Creatinine After Birth

The change in plasma creatinine with age for different gestation groups is shown in Fig 1. In all but 1 infant, the plasma creatinine concentration increased after birth. The mean creatinine concentration for all infants was significantly higher at 24 hours (P < .001) and 48 hours (P < .001) than at birth. Significant differences in creatinine concentration were observed among groups 1, 3, and 4 at both 24 and 48 hours of age (P < .05).

Peak Creatinine Level

The rise in creatinine after birth was greatest in the most premature infants (see Table 1). The peak creatinine concentration was strongly inversely correlated to gestation (Spearman’s coefficient: −.73; P < .01) and birth weight (Spearman’s coefficient: −.76; P < .01). Peak creatinine level in the most premature infants (group 1) was 221 μmol/L (CI: 195–247).

Time to Peak Creatinine Level

The time at which peak creatinine concentration occurred was variable, ranging from 1 to 102 hours.
(median: 31.9 hours). Time to peak creatinine concentration correlated inversely with gestation (Spearman’s coefficient: $-2.62; P, .01$). Plasma creatinine continued to rise for longer in the more preterm infants and did not fall until a mean of 59 hours (CI: 40–78) in group 1 (see Table 1).

### Illness Severity

All but 2 of the infants received mechanical ventilatory support. Peak plasma creatinine was not significantly higher in 4 infants who had evidence of intrauterine growth retardation (weight for age, 10th percentile). There was no correlation between rise in creatinine and Apgar score, but some correlation with illness severity, measured by the Clinical Risk Index for Babies score (Spearman’s coefficient: $.64; P < .01$). There was no evidence of impaired renal function in any of the 38 infants, who survived. The mean plasma creatinine at discharge was 52 $\mu$mol/L (CI: 46–58 $\mu$mol/L).

### Changes in Urea

Mean urea concentration at birth was 3.4 mmol/L (CI: 3.0–3.8 mmol/L). Although overall the urea did rise significantly over time ($P < .001$), it did so in a more variable manner than creatinine, and there were no significant differences among gestation age groups (see Fig 2).

### Discussion

Currently available reference data for plasma creatinine in the first month of life$^4,5$ support the belief that creatinine falls steadily during this period from levels that are initially higher in preterm infants.$^{12}$ Until recently, no published data explained the high levels seen shortly after birth in the preterm infant. Authors have speculated that creatinine is elevated soon after birth because of high maternal levels or poor clearance of a large creatinine load inherited from the mother, although there is no evidence for either hypothesis.$^5$ Our results show that even in the most premature infants, plasma creatinine at the time of birth reflects normal maternal levels. Creatinine rises significantly to a peak around the second day of life before falling steadily in the manner described by Rudd et al.$^4$ and Bueva and Guinard.$^5$ We have demonstrated that the most premature infants have a higher peak in plasma creatinine and that the subsequent fall in creatinine occurs later than in more mature infants.

Plasma creatinine concentration reflects the balance between production from creatine stores in

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**TABLE 1.** Changes in Plasma Creatinine Over Time for Different Gestation Groups

<table>
<thead>
<tr>
<th>Group (Gestation in Weeks)</th>
<th>$n$</th>
<th>Mean Gestation (Weeks)</th>
<th>Mean Birth Creatinine ($\mu$mol/L) (95% CI)</th>
<th>Mean Peak Creatinine ($\mu$mol/L) (95% CI)</th>
<th>Mean Rise in Creatinine From Birth to Peak ($\mu$mol/L) (95% CI)</th>
<th>Mean Time to Peak (Hours) (95% CI)</th>
<th>Mean Final Creatinine ($\mu$mol/L) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (23–26)</td>
<td>9</td>
<td>25.1</td>
<td>80 (67–92)</td>
<td>221 (195–247)</td>
<td>141 (118–163)</td>
<td>59 (40–78)</td>
<td>52 (32–72)</td>
</tr>
<tr>
<td>2 (27–29)</td>
<td>13</td>
<td>28.1</td>
<td>77 (65–89)</td>
<td>179 (158–200)</td>
<td>102 (80–125)</td>
<td>39 (28–51)</td>
<td>64 (49–78)</td>
</tr>
<tr>
<td>3 (30–32)</td>
<td>12</td>
<td>30.8</td>
<td>65 (60–69)</td>
<td>139 (120–158)</td>
<td>74 (53–95)</td>
<td>33 (25–40)</td>
<td>45 (37–54)</td>
</tr>
<tr>
<td>4 (33–35)</td>
<td>8</td>
<td>34.1</td>
<td>73 (67–79)</td>
<td>120 (99–140)</td>
<td>47 (28–66)</td>
<td>15 (8–23)</td>
<td>47 (41–53)</td>
</tr>
<tr>
<td>All</td>
<td>42</td>
<td>29.4</td>
<td>73 (68–78)</td>
<td>165 (150–180)</td>
<td>88 (73–102)</td>
<td>37 (30–44)</td>
<td>52 (46–58)</td>
</tr>
</tbody>
</table>

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**Fig 2.** Mean plasma urea against postnatal age for different gestational age groups. The shaded area represents the 95% CIs for the mean plasma creatinine of all infants.
muscle and clearance by glomerular filtration. Because preterm infants have a small muscle mass, it would be expected that plasma creatinine concentration would be low if renal clearance was normal. In steady states in adults, muscle mass is constant, and creatinine is not reabsorbed by the renal tubule; therefore, creatinine concentration provides a proxy measure of GFR. Formulae have been derived to calculate GFR from plasma creatinine concentration, although they are not valid in the early neonatal period when GFR is changing rapidly.\(^2\)\(^,\)\(^4\)\(^,\)\(^5\) Inulin clearance, the gold standard for measuring glomerular filtration rate, is technically difficult in newborn infants because of the problem of obtaining accurately timed urine collections.

The rise in creatinine that we have demonstrated suggests there is poor creatinine clearance by the preterm kidney in the first few days of postnatal life. Poor creatinine clearance may be attributable to delayed establishment of normal GFR or attributable to reabsorption of creatinine by the immature tubule. Coulthard\(^1\)\(^6\) showed that GFR increases with postconceptional age and that GFR is lower in the immediate newborn period than later. RDS and mechanical ventilation are known to reduce GFR\(^7\)\(^,\)\(^8\) and GFR increases during the recovery phase of RDS.\(^1\)\(^8\)\(^,\)\(^9\) Furthermore, the delay in establishing a normal GFR may be greater in the neonatal period when GFR is changing rapidly.\(^2\)\(^,\)\(^4\)\(^,\)\(^5\) Inulin clearance, the gold standard for measuring glomerular filtration rate, is technically difficult in newborn infants because of the problem of obtaining accurately timed urine collections.

Another possibility is that in the immediate postnatal period creatinine is not fully excreted by the neonatal kidney and that partial reabsorption occurs across the immature tubule. There is experimental evidence for tubular reabsorption of creatinine in newborn rabbits.\(^2\)\(^0\) The same mechanism may explain why creatinine clearance has been shown to underestimate inulin clearance in preterm infants.\(^1\)\(^5\) Guignard and Drukker\(^8\) have suggested recently that reabsorption is the explanation for high creatinine levels seen in newborn preterm infants.

The changes in urea were far more variable than those in creatinine and did not show such a clear relationship with maturity. This probably reflects the fact that urea is heavily influenced by the degree of catabolism and suggests changes in creatinine were not simply secondary to dehydration.

Our results are compatible with those of Guignard and Drukker\(^8\) and clearly demonstrate that plasma creatinine levels in preterm infants do not fall steadily from birth but instead rise in the first 48 hours of life, reach a peak, and then fall to equilibrium levels. The rise continues for longer and is greatest in the most immature infants. Rising plasma creatinine levels in newborn infants are clearly not secondary to high maternal creatinine. They may be attributable to a combination of tubular reabsorption of creatinine and reduced clearance of an endogenous creatinine load that is high relative to the low GFR at this time.

If the infants we studied were all sick and receiving intensive care. They were by definition of their prematurity not in a stable physiologic state and without performing inulin clearance studies we cannot say for certain that their renal function was normal. However, the creatinine levels on day 2 are similar to those widely quoted elsewhere,\(^4\)\(^,\)\(^5\) and none of our infants went on to develop renal failure. Although not physiologically stable, our study is exactly the population in whom clinicians will be trying to interpret the significance of high plasma creatinine levels.

We therefore conclude that in sick preterm infants receiving intensive care, a sharp rise in creatinine, even by as much as twofold to threefold in some cases, may be expected and should not, in isolation, be used to diagnose renal failure. We also would suggest that if high creatinine levels do indeed reflect delay in onset of normal GFR, this has implications for fluid, electrolyte, and drug prescribing in the first 48 hours of life during this phase of rapid physiologic adaptation to extrauterine life.

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