

# Reference ranges for plasma creatinine during the first month of life

P T RUDD, E A HUGHES, M M PLACZEK, AND D T HODES

Department of Paediatrics and Neonatal Medicine, Institute of Child Health, Hammersmith Hospital, London; Department of Paediatrics, Hillingdon Hospital, Uxbridge, Middlesex

**SUMMARY** A reference range of plasma creatinine levels for the first month of life derived from 238 babies of 25-42 weeks' gestation is presented. Measurements were performed on a Beckman Creatinine Analyser 2, which uses the Jaffé rate reaction method. There was a decline in plasma creatinine level with increasing postnatal and gestational age. Infants undergoing mechanical ventilation at age 2 days had a significantly increased creatinine level.

With increasing resources being devoted to the care of the preterm infant there is a need for a reference range for plasma creatinine levels in the neonatal period so that renal failure can be identified and treated promptly. True creatinine is inversely proportional to the glomerular filtration rate corrected for body length.<sup>1</sup> Previous studies have shown that there is a 2-fold rise in glomerular filtration rate in the first 14 days of life<sup>2</sup> and that glomerular filtration rate is proportional to gestational age.<sup>3</sup> Thus it is to be expected that there will be a wide variation in plasma creatinine levels in newborn infants. Stonestreet and Oh<sup>4</sup> measured plasma creatinine concentrations in 57 low birthweight infants but obtained only 81 values. Feldman and Guignard<sup>5</sup> measured plasma creatinine in 56 babies, the most immature of whom were of 30 weeks' gestation. Many babies receiving intensive care are less mature than this.

## Materials and methods

**Subjects.** Samples were taken from 238 babies during an 8-month period. Informed consent was obtained from the parents of these babies, the study having been approved by the hospital ethical committee.

Blood samples (100 µl) were obtained by heel-prick, venepuncture, or through an umbilical artery catheter at 2, 7, 14, 21, and 28 days after birth when blood was obtained for routine tests.

Babies from the regional neonatal intensive care unit at Hammersmith Hospital were studied together with those from the subregional intensive care unit at Hillingdon Hospital, babies from the lying-in ward, and infants seen at baby clinics during the first month of life. The weights of the babies according to gestational age are shown in Table 1.

Table 1 Birthweights of the infants studied

Gestation (weeks)	Number of babies	Birthweight (g)	
		Mean	Range
25-28	33	930	660-1300
29-32	78	1435	750-2270
33-36	54	2015	1040-2960
37-42	73	2900	1600-4360

Gestational age was calculated from the first day of the mother's last menstrual period and a Dubowitz *et al.*<sup>6</sup> gestational assessment was performed on all infants in the neonatal intensive care units. If this differed by more than 2 weeks, the most reasonable value was taken using other information—such as antenatal ultrasound findings.

The following were excluded from the study: babies with congenital heart disease, babies in cardiac failure from a patent ductus arteriosus, or those who had received indomethacin during the previous 48 hours, babies who had become oliguric as a result of birth asphyxia, and those with various renal anomalies or muscle disease.

Because the aim was to establish a reference range, certain factors which might influence the plasma creatinine values were considered at 2 and 7 days in each gestational age group as follows: pre-eclamptic toxæmia in the mother; birth asphyxia defined as an Apgar score of 4 or less at one minute or 6 or less at five minutes; severe acidosis with a recorded arterial pH of 7.1 or less in the first week of life; gentamicin administered at a dose of 2.5-3.0 mg/kg per day for babies under 1000 g and 5-6 mg/kg per day for babies over 1000 g; the volume of fluid given on the 2nd and 7th days of life; mechanical ventilation at 2 and 7 days. There were 74 infants of 32 weeks or less for whom creatinine values were available at 2 days. Of these, 32 received ventilation

and 28 of these had idiopathic respiratory distress syndrome.

### Biochemical method

The Beckman Creatinine Analyser 27<sup>8</sup> measures the rate of production of the red complex formed when creatinine reacts with alkaline picrate. Plasma (30  $\mu$ l) is needed for a single analysis, of which 25  $\mu$ l is introduced into the machine, the reading being made at 25.6 seconds, reducing interference from early and late-reacting chromogens.

Bilirubin was not found to interfere with the creatinine analyses. The study was carried out on pooled baby sera and bilirubin was added to a level of 400  $\mu$ mol/l. Because high levels of plasma pyruvate are present during the lactic acidosis which may occur in babies with severe respiratory distress syndrome,<sup>9</sup> a pyruvate interference study was performed in which increasing amounts of pyruvate were added to plasma and the effects on creatinine measured. The addition of 0.1 mmol/l of pyruvate to a plasma sample produced a rise of 5  $\mu$ mol/l in the creatinine value.

Using a control serum with plasma creatinine at 53  $\mu$ mol/l the standard deviation (SD) of 11 measurements was  $\pm 3.9$   $\mu$ mol/l, with a coefficient of variation (CV) of 6.4%; similarly at a concentration of 128  $\mu$ mol/l the SD was  $\pm 5.3$   $\mu$ mol/l with a CV of 4.4% on 22 measurements. The between-batch variation at a plasma creatinine level of 141  $\mu$ mol/l on 42 analyses gave an SD of  $\pm 3.9$   $\mu$ mol/l and a CV of 2.8%.

### Results

There was a fall in plasma creatinine concentrations both with increasing postnatal and gestational age (Table 2 and Figure). The 2-day values of plasma creatinine are given in three columns in the table,

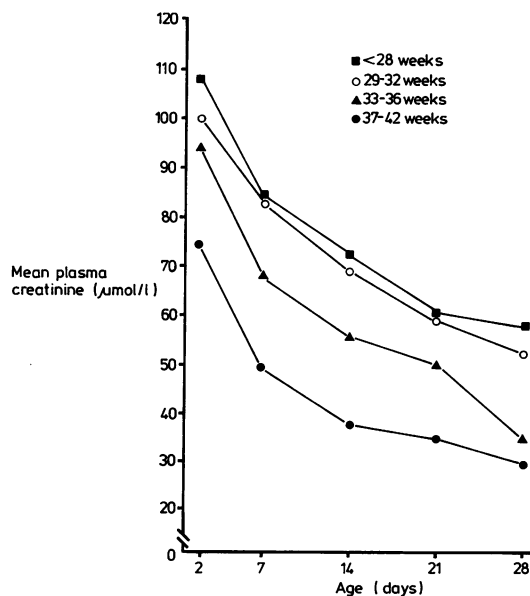


Figure Relationship between mean plasma creatinine levels and postnatal age in the different gestational age groups. Infants undergoing mechanical ventilation at 2 days are excluded.

because of the appreciable difference between plasma creatinine level in babies receiving mechanical ventilation and those breathing spontaneously. When the data were analysed using an unpaired *t* test only the infants of 29–32 weeks' gestation receiving mechanical ventilation were found to have a significantly increased plasma creatinine level ( $P < 0.01$ ). Similarly, the severely acidotic infants in this gestational age group were found to have a raised creatinine level ( $P < 0.01$ ), but all these babies were also receiving mechanical ventilation.

Table 2 Plasma creatinine values in the first month of life

Gestation (weeks)	Postnatal age (days)						
	2	2	2	7	14	21	28
	All babies	Breathing spontaneously	Ventilated	All babies			
28	116 $\pm$ 40 (n = 24)	108 $\pm$ 20 (n = 8)	121 $\pm$ 45 (n = 16)	84 $\pm$ 32 (n = 22)	72 $\pm$ 32 (n = 25)	60 $\pm$ 33 (n = 25)	58 $\pm$ 24 (n = 24)
29–32	104 $\pm$ 38 (n = 50)	100 $\pm$ 32 (n = 36)	115 $\pm$ 43 (n = 16)	83 $\pm$ 41 (n = 56)	69 $\pm$ 32 (n = 42)	59 $\pm$ 32 (n = 29)	52 $\pm$ 33 (n = 30)
33–36	93 $\pm$ 39 (n = 36)	94 $\pm$ 39 (n = 32)	87 $\pm$ 46 (n = 4)	68 $\pm$ 44 (n = 31)	55 $\pm$ 36 (n = 27)	50 $\pm$ 37 (n = 20)	35 $\pm$ 24 (n = 12)
37–42	75 $\pm$ 38 (n = 27)	75 $\pm$ 38 (n = 27)	—	50 $\pm$ 36 (n = 39)	38 $\pm$ 20 (n = 19)	35 $\pm$ 20 (n = 19)	30 $\pm$ 18 (n = 15)

Mean plasma creatinine  $\mu$ mol/l  $\pm$  2 SD.

Conversion SI to traditional units: 1  $\mu$ mol/l  $\approx$  0.0113 mg/100 ml.

Factors which were thought might influence the plasma creatinine values were also analysed using multiple regression. This enabled us to look at the effect of mechanical ventilation and other factors in all babies at a particular postnatal age. The analysis is able to take into account the fall in creatinine level with increasing gestational age, which is necessary with a larger sample than that included in the unpaired *t* test. Using this method of analysis mechanical ventilation was associated with an increased plasma creatinine level at 2 days ( $P < 0.05$ ) but severe acidosis did not have a significant effect on the creatinine. Gentamicin administration had no significant effect on creatinine, nor did pre-eclamptic toxæmia, birth asphyxia, or fluid administration.

The following equation relating creatinine to gestational age and postnatal age was derived from the data, in which all babies except those ventilated at 2 days were included:

$$\log_e \text{ creatinine} = 6.400 - 0.3026 \times \log_e \text{ age in days} \\ - 0.4927 \times \text{ gestation in weeks}$$

From this equation a normal range has been derived (Appendix). While the values derived from the equation correspond closely to the value we obtained in babies 7–28 days of age, the 95% confidence limits for babies of 2 days are well outside the 2 SD values given in Table 2.

## Discussion

We have shown a fall in plasma creatinine level with increasing gestational and postnatal age. These values are in accordance with the measurements made of glomerular filtration rate by Guignard *et al.*<sup>2</sup> and Siegel and Oh<sup>3</sup> on neonates. There was a significant increase in plasma creatinine level in babies undergoing mechanical ventilation for respiratory distress which corresponds to the finding of Guignard *et al.* of a reduced glomerular filtration rate in infants with this condition.<sup>10</sup>

Unlike Feldman and Guignard,<sup>5</sup> who studied the effect of gentamicin on the creatinine level during the first month of life, we were unable to demonstrate a significant effect of this drug. However, our observations were made only in the first week, and it is possible that later observations might have produced different results. There was no correlation between concentration of plasma creatinine and fluid input. While the relationship between fluid input and urea was not examined in this study, it is known that urea values are affected both by the fluid and protein intake, each of which shows considerable variation in the newborn preterm infant.

Although the most accurate measurements of glomerular filtration rate are made by using either

radioisotopes or inulin clearance, these methods are not suitable for routine use in the low birthweight baby. Counahan *et al.*<sup>11</sup> have shown that measurement of plasma creatinine is a more reliable indicator of glomerular filtration rate than creatinine clearance in children, even if a 24-hour urine collection, difficult to obtain in babies, has been completed. The most accurate measurements of true creatinine are made using high performance liquid chromatography but this method is not widely available.

Several factors make the Beckman method particularly useful for the measurement of creatinine in newborn babies. The amount of plasma required is small (25  $\mu$ l) and results can be obtained quickly. Bilirubin had no effect on the creatinine values in our study and that of Cottrell and Frings.<sup>7</sup> Furthermore, lipids do not appear to interfere with the methods unless present at a very high plasma concentration. While pyruvate has an effect on the measurement, it decays quickly unless a preservative is added. Ketones interfere with this method but they were not seen in any baby during this study.

Because the values derived from the equation (Appendix) lie well outside the values we obtained for babies at 2 days, it is suggested that the data presented in Table 1 are used as a reference range of plasma creatinine. It is hoped that this information will be used in the identification and treatment of renal failure in the preterm infant.

## Appendix

A range of creatinine derived from the equation given in the results.

### Median values of plasma creatinine ( $\mu$ mol/l) ( $\pm 95\%$ confidence limits)

Gestation (weeks)	Age (days)				
	2	7	14	21	28
28	130 $\pm 90$	84 $\pm 61$	68 $\pm 50$	60 $\pm 44$	55 $\pm 40$
30	111 $\pm 81$	76 $\pm 56$	62 $\pm 45$	55 $\pm 40$	50 $\pm 37$
32	101 $\pm 74$	69 $\pm 50$	56 $\pm 41$	50 $\pm 36$	45 $\pm 33$
34	91 $\pm 67$	63 $\pm 46$	51 $\pm 37$	45 $\pm 33$	41 $\pm 30$
36	83 $\pm 60$	57 $\pm 41$	46 $\pm 34$	41 $\pm 30$	37 $\pm 27$
38	75 $\pm 55$	51 $\pm 38$	42 $\pm 30$	37 $\pm 27$	34 $\pm 25$
40	68 $\pm 50$	47 $\pm 34$	38 $\pm 28$	33 $\pm 24$	31 $\pm 22$

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Correspondence to Dr P T Rudd, Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, Du Cane Road, London W12 0HS.

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