Why Do Newborn Infants Have a High Plasma Creatinine?

Jean-Pierre Guignard, MD, and Alfred Drukker, MD, PhD*

ABSTRACT. Background. Plasma creatinine (Pcr) levels at birth are greatly elevated in relation to the size (and the muscle mass) of the newborn infant and remain so for 1 to 2 weeks. Particularly intriguing is the fact that Pcr levels are higher in preterm than in term infants and for a longer postnatal period. The smaller the birth weight, the higher the Pcr. This cannot be explained by maternal transfer of Pcr or by the absolute and relative (to adult body surface area) reduced glomerular filtration rate of the newborn. Perhaps the renal handling of creatinine is involved.

Design. In 522 pairs of mothers and fetuses, maternal and fetal Pcr were compared from 16 weeks of gestation until term. Pcr was measured in 66 newborns of various birth weights and followed for 1 month. Creatinine clearance (Ccr) and inulin clearance (Cin) were measured simultaneously in adult (n = 8) and newborn (n = 20) New Zealand White rabbits. In the latter, nephrogenesis continues after birth and they are therefore a good animal model for the study of the renal function in premature infants.

Patient. A case of a premature male infant is presented (gestation: 29 weeks; birth weight: 1410 g) suspected of having sepsis because of premature rupture of membranes and postpartum maternal fever. This suspicion was not confirmed. Blood chemistry evaluation showed a high Pcr at birth (0.85 mg/dL, 75 μmol/L), even higher than that of the mother (0.77 mg/dL, 68 μmol/L). The Pcr started to decrease after ~1 week but remained elevated throughout 1 month of follow-up.

Results. From the maternal-fetal Pcr measurements it was quite evident that during the second half of gestation the small molecular weight creatinine (113 dalton, 0.3 nm radius) of the mother and fetus equilibrates at all maternal Pcr levels. The newborn Pcr levels were not only high at the time of birth but remained so for more than 3 weeks. It was also shown that the smaller the infant the higher the Pcr levels. The results of the animal experimental data showed that adult rabbits had the normal physiologic pattern in which Ccr overestimates Cin (Ccr/Cin ratio >1.0). In contrast, the results in the newborn rabbits showed an unexpected underestimation of the Ccr vis-à-vis Cin (Ccr/Cin ratio <1.0). This means, as is explained at length in the “Discussion” of this article, that the preterm newborn infant reabsors creatinine along the renal tubule.

Conclusion. The riddle of the high Pcr levels in term and particularly in preterm newborns seems to be solved. Once the umbilical cord is severed, the perfect intrauterine maternal-fetal biochemical balance is disturbed. Thereafter, the already transferred exogenous, adult-level creatinine will rapidly disappear in the first urine specimens passed by the now autonomous newborn infant. A new steady state is achieved in due time, based on independent neonatal factors. One of these factors is the unusual occurrence of tubular creatinine reabsorption. We hypothesize that this latter temporary phenomenon is attributable to back-flow of creatinine across leaky immature tubular and vascular structures. With time, maturational renal changes will impose a barrier to creatinine. From that point onwards, total body muscle mass, glomerular filtration rate, and tubular secretion will in health determine the Pcr level of the individual.

M any publications including textbooks in pediatrics and pediatric nephrology mention the fact that plasma creatinine concentration (Pcr) in the newborn period is as high as in the adult. This is unusual because the production of creatinine is dependent on the infant’s muscle mass—which is much less than that of the adult—and the healthy newborn is not in renal failure although the absolute and relative (to adult body size) glomerular filtration rate (GFR) is low.

In this article we will review the data pertaining to the clinical findings of a high Pcr in the term and premature infant and present a summary of animal experiments in newborn rabbits that together shed new light on the pathogenesis of the high Pcr levels in the newborn infant.

PATIENT AND METHODS

Case Report

M.C., a 26-year-old healthy multipara went into labor at 29 weeks of gestation, ~30 hours after premature rupture of membranes. She delivered a normal male infant weighing 1410 g, appropriate for gestational age. The physical examination of the newborn shortly after birth did not show any abnormalities or evidence of persistent ductus arteriosus. The mother developed postpartum fever that was attributed to the premature rupture of the membranes. No antibiotics were given and breastfeeding was continued. The infant was observed in an incubator in the neonatal intensive care unit. He did not develop signs of respiratory distress, although the rate of breathing increased to 70 breaths per minute. For safety reasons the infant was on continuous positive airway pressure ventilation for 3 days. Urine output was normal. Urinalysis showed initially mild proteinuria (urinary protein/creatinine ratio: 31 g/mol) as normally seen immediately after
birth, which resolved in a matter of days. The child underwent a complete sepsis work-up ~10 hours after birth. At that time, the acid-base status and the blood biochemistry of the infant were also determined (see Table 1). All cultures in the mother and the child eventually proved either to be negative or not significant in number. The laboratory tests of the mother were normal. She went home 8 days after giving birth. The infant had an uneventful further course and was discharged from the nursery after 4 weeks with a weight of 1920 g. Table 1 summarizes the main laboratory data of the mother and the child during their hospital stays.

### Maternal-Fetal Transfer of Creatinine

Pcr levels were measured with routine laboratory methods simultaneously in a large cohort of pairs of mothers and fetuses (n = 522) from 16 weeks of gestation until term.

### Plasma Creatinine in Newborn Infants

We determined Pcr levels in healthy term and preterm infants with routine laboratory methods.\(^1\,\,\,^2\)

### Animal Experiments

Creatinine clearance (Ccr) and inulin clearance (Cin) were measured in newborn and adult New Zealand White rabbits. Because nephrogenesis in the newborn rabbit is not yet completed at birth, the newborn rabbit is a good model for the study of renal function in premature infants. The results of these studies have been reported elsewhere.\(^3\,\,\,^4\)

### RESULTS

Figure 1 shows the results of the maternal-fetal Pcr measurements. It is quite evident that during the second half of gestation the small molecular weight creatinine (113 dalton, 0.3 nm radius) of the mother and fetus equilibrates at all maternal Pcr levels. In Fig 2, the Pcr levels in term and premature infants are depicted. The Pcr levels are not only high at the time of birth but remain so for >3 weeks. Figure 2 also shows that the smaller the infant the higher the Pcr levels. The results of the animal experimental data will only shortly be summarized here. Adult rabbits showed the normal physiologic pattern in which Ccr overestimates Cin (Ccr/Cin ratio = 1.21). In contrast, the results in the newborn rabbits showed an unexpected underestimation of the Ccr vis-à-vis Cin (Ccr/Cin ratio = 0.84).

### DISCUSSION

From ~10 weeks of gestation and throughout intrauterine life, the kidneys produce increasing amounts of urine, a major constituent of amniotic fluid. However, in utero, the kidneys do not play a significant role in maintaining fetal homeostasis. That function is almost exclusively taken over by the placental fetal-maternal exchange. The composition of the blood at birth therefore reflects almost completely that of the mother. This holds true for Pcr as shown in Fig 1. The direct Pcr data in both full term and premature infants can be found in Fig 2. This figure shows that Pcr levels in the neonate are indeed high for the size (and the muscle mass) of the newly born.\(^1\,\,\,^2\) The Pcr after birth is often temporarily higher than that in the mother at the time of birth (see “Case Report” and Table 1). We were also intrigued to find that the smaller the infant the higher the Pcr levels and that the high Pcr remained elevated for a considerable amount of time (Fig 2). These data are certainly incompatible with the notion that the abnormally high levels of Pcr are attributable only to maternal transfer of creatinine, as still often cited in textbooks on pediatric nephrology. The exceptionally high Pcr levels in premature infants can also not be explained by maternal transfer of creatinine from mothers with higher Pcr levels than those of term infants. Figure 1 shows that during the entire intrauterine period studied, the ratio of maternal/fetal Pcr shows minimal fluctuations and basically remains constant in a large cohort of women with different end-points of gestation. At this point, we can therefore only conclude that Pcr at birth is high for the body size and the muscle mass of the infant, factors that determine Pcr levels when renal excretory function is normal for age.

That this is indeed the case is illustrated by the above described premature infant. Shortly after birth he had only one exceptional laboratory finding: a very high Pcr level for body size and muscle mass, in the absence of any clinical or (other) laboratory sign of acute or chronic renal failure (see Table 1). The clinical course of the infant was rather benign, taking into account his degree of prematurity and the fact

### TABLE 1. Laboratory Data in Mother and Infant

<table>
<thead>
<tr>
<th>Hours After Birth</th>
<th>Mother</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Days After Birth</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Plasma creatinine (mg/dL)</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>Plasma creatinine (µmol/L)</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Plasma sodium (mEq/L = mmol/L)</td>
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<td></td>
<td>Plasma potassium (mEq/L = mmol/L)</td>
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<td></td>
<td>Plasma HCO3 (mmol/L)</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Plasma Pco2 (mm Hg)</td>
<td>35</td>
</tr>
</tbody>
</table>

**Fig 1.** The ratio of maternal and fetal serum creatinine levels from 15 weeks of gestation until birth (522 pairs of mothers and fetuses).
Inulin is neither reabsorbed nor secreted by the kidney, so inulin acts as a measure of glomerular filtration rate (GFR). However, creatinine is a byproduct of muscle metabolism and is excreted by the body. Creatinine is filtered at the glomerulus and reabsorbed back into the bloodstream, which means that the ratio of creatinine clearance (Ccr) to inulin clearance (Cin) is not equal to 1.0. This is because the body can change its production of creatinine in response to changes in muscle mass.

The ratio of Ccr/Cin is used to estimate GFR in clinical practice, but it is not a perfect measure. For example, in newborns, who have lower muscle mass than adults, the ratio of Ccr/Cin is lower than 1.0. This is because creatinine production is not directly proportional to muscle mass.

The ratio of Ccr/Cin is also affected by the presence of renal disease. For example, in patients with renal disease, the ratio of Ccr/Cin is higher than 1.0 because creatinine production is increased to compensate for the decreased GFR.

In conclusion, the ratio of Ccr/Cin is a useful measure of GFR, but it is not a perfect measure. It is affected by changes in muscle mass and renal disease. Therefore, it is important to use other measures of GFR, such as clearance of exogenous substances, to get a more accurate estimate of GFR.

ACKNOWLEDGMENTS

This work was supported in part by Grant 32–036574/92 from the Swiss National Science Foundation. We thank our colleague Professor Patrick Hohlfeld of the Department of Obstetrics and Gynecology for collecting the maternal and newborn cord-blood samples, as well as Dr Vera Matos and Anelia Bueva for valuable help.

REFERENCES

5. Pitts RF. Physiology of the Kidney and Body Fluids. 3rd ed. Chicago, IL: Year Book Publishers; 1974:49–157
8. Coulthard MG, Hey EN, Ruddock V. Creatinine and urea clearances compared to inulin clearance in preterm and mature babies. Early Hum Dev. 1985;11:11–19
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Pediatrics 1999;103;e49

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