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 mol/L), even higher than that of the mother (0.77 mg/dL, 68 mol/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 reabsorbs 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.

ABBREVIATIONS. Pcr, plasma creatinine concentration; GFR, glomerular filtration rate; Ccr, creatinine clearance; Cin, inulin clearance.

Many 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...
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also shows that the smaller the infant the higher the
15 weeks of gestation until birth (522 pairs of mothers and fetuses).

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Fig 1. The ratio of maternal and fetal serum creatinine levels from
15 weeks of gestation until birth (522 pairs of mothers and fetuses).

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 re-
ported 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 \(\sim 10\) weeks of gestation and throughout in-
trauterine 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 com-
pletely 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 con-
siderable amount of time (Fig 2). These data are
certainly incompatible with the notion that the ab-
normally 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 intra-
uterine period studied, the ratio of maternal/fetal
Pcr shows minimal fluctuations and basically re-
mains 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 excre-
tory 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>
<thead>
<tr>
<th>TABLE 1. Laboratory Data in Mother and Infant</th>
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<tr>
<td><strong>Mother</strong></td>
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<tr>
<td>Days After Birth</td>
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<tr>
<td>Plasma creatinine (mg/dL)</td>
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<tr>
<td>Plasma creatinine ((\mu)mol/L)</td>
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<td>Plasma sodium ((mEq/L = mmol/L))</td>
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<td>Plasma potassium ((mEq/L = mmol/L))</td>
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<td>Plasma HCO(_3) ((mmol/L))</td>
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<td>Plasma Pco(_2) (mm Hg)</td>
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Fig 2. Plasma creatinine levels in healthy full-term infants and three groups of premature infants with an uneventful postnatal course, from birth until 3 weeks of life (from Reference 1).

that the mother had premature rupture of membranes with postpartum fever. Pcr levels in the infant started to fall toward the end of the first week of life but remained elevated for at least a month (see Table 1), because the normal Pcr of an ~2000 g infant is usually close to 0.4 mg/dL (35 μmol/L).

The level of Pcr in an otherwise healthy preterm newborn is indeed exceptional because the production, and thus the plasma level and the urinary excretion of creatinine, is a measure of total body muscle mass, which by any standard, is low in a newborn infant and certainly in a premature infant such as described above. The only source for endogenous creatinine is from the degradation of creatine and phosphocreatine in muscle. Since muscle mass in health is rather constant during long periods of time and proportional to the cube of body length, the production of creatinine and its plasma level is also very constant. The excretion of creatinine, which is freely filtered at the glomerulus, is almost exclusively via the urine. The constant blood levels of creatinine, entirely excreted by the kidneys, was the basis for choosing creatinine as an endogenous marker of GFR. However, in humans, the clearance of creatinine is not equivalent to that of exogenous inulin, a substance also freely filtered by the glomerulus and neither reabsorbed nor secreted by the tubule. The difference between Ccr and Cin is attributable to the fact that in contrast to inulin, creatinine does undergo tubular secretion. It follows that in humans the ratio of Ccr/Cin is not 1.0 but ~1.2 to 1.4, because of the addition of creatinine to the final urine after glomerular filtration.5

Because inulin is neither reabsorbed nor secreted along the tubule, Cin is the gold standard for measuring GFR. Its measurement however, is invasive, cumbersome (particularly in young children), and relatively expensive. As a result, Ccr is used in clinical medicine and even in clinical research as a second best, realizing that Ccr overestimates true GFR (Ccr/Cin >1.0). In parentheses it should be added that dogs differ in this respect from humans because they have a Ccr/Cin ratio that is ~1.0. This means that in dogs no tubular secretion of creatinine occurs. This also shows that the tubules of the dog are rather impermeable to both inulin and creatinine, “a conclusion that can justifiably be extended to those animals—including man—in which creatinine is excreted in part by tubular secretion”.6 Tubular reabsorption of creatinine, which should give a ratio of Ccr/Cin <1.0, has thus far never been described.

We now come to the animal experiments in which Ccr and Cin were measured. These experiments showed that adult rabbits indeed had an overestimation of Ccr (Ccr/Cin = 1.21). In contrast, all clearance data in the neonatal animals showed that Ccr was lower than Cin (Ccr/Cin = 0.84). As pointed out above, there is only one renal physiologic explanation for this unusual finding as originally proposed by Smith4 and recently reiterated by Guyton and Hall2: tubular reabsorption of creatinine. This is a very unusual renal physiologic phenomenon, apparently only found in the newborn infant. Our experimental data are supported by suggestions in three studies of human neonates8 and piglets.9 In a recent abstract, Henderson et al10 describe a follow-up of Pcr in eight premature infants during the first 4 days of life. The Pcr cord blood levels were high (0.61–0.92 mg/dL; 54–81 μmol/L) and even rose significantly during the first 50 hours of extrauterine life (see also Table 1). Plasma urea levels did not show a similar change.

The riddle of the high Pcr levels in term and particularly in preterm newborns thus 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.

CONCLUSION

Based on the above basic studies we suggest the following course of events. The high Pcr levels of the newborn immediately after birth represent the maternal Pcr levels. Shortly thereafter the tubular reabsorption of creatinine seems to be responsible for the continued high Pcr levels of the newborn and in particular the preterm infant. We hypothesize that this latter temporary phenomenon is attributable to back-flow of creatinine across leaky immature tubular and vascular structures. With time, maturation renal changes will impose a barrier to creatinine. From that point onwards, total body muscle mass, GFR, and tubular secretion will determine the Pcr level of the individual.

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