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 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.

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 intraterine 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 intraterine 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>
<thead>
<tr>
<th>Days After Birth</th>
<th>Mother</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 3 5 7</td>
<td>1 3 5 7</td>
</tr>
<tr>
<td>Plasma creatinine (mg/dL)</td>
<td>0.77 0.80 0.75 0.68</td>
<td>0.85 0.94 0.92 0.78</td>
</tr>
<tr>
<td>Plasma creatinine (µmol/L)</td>
<td>68 71 66 60</td>
<td>75 83 81 69</td>
</tr>
<tr>
<td>Plasma sodium (mEq/L = mmol/L)</td>
<td>135 133 138 138</td>
<td>136 139 137 135</td>
</tr>
<tr>
<td>Plasma potassium (mEq/L = mmol/L)</td>
<td>4.1 4.0 4.4 4.4</td>
<td>5.5 5.7 5.1 5.0</td>
</tr>
<tr>
<td>Plasma HCO₃⁻ (mmol/L)</td>
<td>22 — 24 —</td>
<td>18 19 17 20</td>
</tr>
<tr>
<td>Plasma Pco₂ (mm Hg)</td>
<td>35 — 39 —</td>
<td>36 38 40 41</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).
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.

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”. 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 Smith and recently reiterated by Guyton and Hall: 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 neonates and piglets. In a recent abstract, Henderson et al 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, maturational 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.

ACKNOWLEDGMENTS

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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).
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