

# URINARY URIC ACID/CREATININE RATIO AS AN ADDITIONAL MARKER OF PERINATAL ASPHYXIA

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**Purpose:** To study the validity of urinary uric acid (UA) as a marker of perinatal asphyxia in term and premature infants.

**Methods:** The urinary ratio of UA to creatinine (Cr) was obtained within 24 hours after birth in four groups of infants: 17 term infants and 18 premature infants with perinatal asphyxia, and 22 healthy term infants and 20 premature infants without perinatal asphyxia. Perinatal asphyxia was defined as an Apgar score of 3 or less at 1 minute or 5 or less at 5 minutes, and/or a first blood gas pH of less than 7.25 and a base deficit of at least 12 mmol/L.

**Results:** The urinary ratio of UA to Cr was significantly higher in term infants with perinatal asphyxia than in term infants without asphyxia ( $1.53 \pm 0.71$  vs  $0.73 \pm 0.45$ ;  $p < 0.005$ ). The same result was found between premature infants with and without perinatal asphyxia ( $3.89 \pm 1.84$  vs  $2.45 \pm 0.88$ ;  $p < 0.01$ ). The urinary ratio of UA to Cr in premature infants was significantly higher than in term infants. When the urinary ratio of UA to Cr was greater than 0.95, perinatal asphyxia was identified with a sensitivity of 80% and a specificity of 71% in term infants. In premature infants, a cut-off value of UA/Cr for perinatal asphyxia of 2.9 had a sensitivity of 71% and a specificity of 70%.

**Conclusions:** The results of this study indicate that the urinary ratio of UA to Cr may be used as an additional marker of perinatal asphyxia in term and premature infants. In comparison with other markers such as xanthine, hypoxanthine, and ascorbic acid, it is a simple, quick, and inexpensive way to detect hypoxic episodes in a neonatal intensive care unit within 24 hours after birth.

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Asphyxia is a common occurrence during the perinatal period. Although it is a major contributor to perinatal morbidity and mortality, the diagnosis and evaluation of asphyxia can be problematic [1, 2], especially in premature infants. No clear definition of clinical and biochemical asphyxia is available.

In the past few decades, elevated concentrations of many biochemical substances such as lactate, uric acid (UA), xanthine, and hypoxanthine have been detected in cerebrospinal fluid, cord blood serum, plasma, and urine after hypoxic insult [3-10]. However, exact and objective means of assessing the severity of asphyxia are controversial or often lacking.

When the cell lacks oxygen, anaerobic metabolism ensues with the production of large quantities of meta-

bolic degradation products such as lactic acid. In parallel, the production of ATP is dramatically reduced and ATP is metabolized to ADP and AMP, and as far as hypoxanthine [3, 11]. Hypoxanthine is further degraded by the action of xanthine oxidase to xanthine and UA. Increasing plasma concentrations of purine degradation products induced by hypoxia will lead to an increase in the urinary excretion of UA.

We hypothesized that perinatal asphyxia of both term and premature infants may be associated with an increased excretion of UA in the urine [3]. There have been very few studies of the relation between neonatal asphyxia and the urinary ratio of UA to creatinine (Cr) [12]. Reports of this ratio in studies of asphyxiated premature infants are even more rare. The purpose of

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this study was to assess whether the urinary ratio of UA to Cr is a clinically useful test for perinatal asphyxia in term and premature infants.

## Materials and Methods

During the 12-month period from July 1996 to June 1997 at National Taiwan University Hospital and Provincial Tao-Yuan Hospital, urine samples were collected within 24 hours after birth in a total of 77 term and preterm infants. These infants were grouped into term infants with asphyxia, term infants without asphyxia (control group for term infants), preterm infants with asphyxia, and preterm infants without asphyxia (control group for preterm infants). The gestational age of all term infants was greater than 37 weeks and the gestational age of all premature infants was less than 35 weeks.

There were 17 term infants with perinatal asphyxia, 22 healthy term infants, 18 preterm infants with asphyxia, and 20 preterm infants without asphyxia. All term and preterm infants in the control groups were born with an Apgar score of at least 8 at 5 minutes without fetal distress, history of emergent delivery, or any maternal risk factors such as pregnancy-induced hypertension, maternal diabetes, preeclampsia, toxemia, infection, chronic hypertension, placental bleeding, intrauterine growth retardation, positive meconium staining of amniotic fluid, or other systemic disease during pregnancy.

The term and preterm asphyxia groups were defined by the presence of at least two of the following attributes: the need for cardiorespiratory resuscitation in the immediate postnatal period, low Apgar score (3 or less at 1 minute, or 5 or less at 5 minutes), initial arterial blood pH of less than 7.25, and a base deficit of at least 12 mmol/L [2, 12, 13].

All urine specimens were spot urine and collected immediately after birth. After collection, urine samples were frozen at -20°C until further analysis. UA concen-

tration was measured by the enzymatic spectrometric method as described by Fossata et al [14]. Cr concentration was measured by the Jaffe reaction [15].

Statistical comparisons of measured values among the four groups were performed using the two-tailed Student's *t*-test of means. A *p* value of less than 0.05 was defined as statistically significant.

## Results

Urine samples were collected from all 77 infants. The basic data for the four groups of infants are summarized in Tables 1 and 2. The distribution of girls and boys was not significantly different between the term and premature infants (25 term boys, 14 term girls, *p* = 0.95; 20 preterm boys, 18 preterm girls, *p* = 0.11). The birth body weight and gestational age of asphyxiated infants and healthy control infants are shown in Tables 1 and 2 and were not significantly different between term and premature infants. The cesarean section rate was higher in asphyxiated premature infants than controls (*p* = 0.01). In term infants, the UA/Cr ratio was significantly higher in the asphyxia group than in the control group ( $1.53 \pm 0.7$  vs  $0.73 \pm 0.4$ , *p* = 0.0004). In premature infants, the UA/Cr ratio was also significantly higher in the asphyxiated group than in the control group ( $3.9 \pm 1.8$  vs  $2.45 \pm 0.88$ , *p* = 0.003). The urinary ratio of UA to Cr in healthy premature control infants was significantly higher than in healthy term control infants ( $2.45 \pm 0.88$  vs  $0.73 \pm 0.4$ , *p* = 0.001). Interestingly, a significant urinary UA/Cr ratio was found in asphyxiated term and premature infants ( $3.9 \pm 1.8$  vs  $1.53 \pm 0.7$ , *p* = 0.001). The gestational age ranged from 37 to 42 weeks in term infants and from 29 to 34 weeks in premature infants.

When the urinary ratio of UA to Cr was greater than 0.95, perinatal asphyxia was identified with a sensitivity of 80% and a specificity of 71% in term infants. In

**Table 1.** Demographic and perinatal characteristics of asphyxiated and healthy term infants

Characteristic	Asphyxiated infants (n = 17)	Healthy infants (n = 22)	<i>p</i> value
Birth weight, g	3,127 ± 437	3,325 ± 483	0.19
Gestational age, wk	39.1 ± 1.6	38.9 ± 1.1	0.73
Vaginal delivery, No.	7	15	0.95
Cesarean section, No.	10	7	0.09
Apgar score (1 min)	1.5 ± 1.2	8.5 ± 0.5	< 0.001
Apgar score (5 min)	4.1 ± 1.7	9.0 ± 0.0	< 0.001
UA/Cr	1.53 ± 0.7	0.73 ± 0.4	< 0.001

UA/Cr = urinary uric acid to creatinine ratio.

**Table 2.** Demographic and perinatal characteristics of asphyxiated and healthy premature infants

Characteristic	Asphyxiated infants (n = 18)	Healthy infants (n = 20)	p value
Birth weight, g	1,599 ± 431	1,748 ± 398	0.28
Gestational age, wk	31.2 ± 2	31.6 ± 1.4	0.40
Vaginal delivery, No.	2	10	0.11
Cesarean section, No.	16	10	0.01
Apgar score (1 min)	2.8 ± 2.1	6.9 ± 1.3	< 0.001
Apgar score (5 min)	5.6 ± 1.9	8.7 ± 0.6	< 0.001
UA/Cr	3.9 ± 1.8	2.45 ± 0.88	0.003

UA/Cr = urinary uric acid to creatinine ratio.

premature infants, a cutoff value for UA/Cr of 2.9 had a sensitivity of 71% and a specificity of 70%.

## Discussion

Although low Apgar score is the most established predictor of asphyxia in infants, it should be remembered that the Apgar score is not specific for asphyxia and may be depressed for reasons other than asphyxia. Other data are, therefore, required to establish the diagnosis of perinatal asphyxia. pH values are quickly normalized after the onset of respiration, owing to the elimination of carbon dioxide. On the other hand, lactate and base deficit are closely interrelated. In this study, the UA level in a single urine sample collected in the first 24 hours of life was elevated in both term and preterm infants with perinatal asphyxia.

ATP degradation products such as xanthine, hypoxanthine, and UA are valuable chemical indicators of tissue hypoxia [5, 7, 11, 16]. The use of urinary concentrations of these substances instead of serum concentrations has been suggested as a valid alternative to the measurement of adenosine nucleotide breakdown during hypoxic states [12, 17–20]. After considering the rapid changes and broad overlap observed in hypoxanthine concentrations both in asphyxiated and control infants reported in previous studies, we hypothesized that concentrations of urinary UA, which is the end product of purine metabolism, might be correlated with hypoxic episodes. The detection of hypoxanthine requires more sophisticated techniques such as fluorimetry, PO<sub>2</sub> measurement, or high-performance liquid chromatography, and these methods are impracticable in most neonatal units. In contrast, the biochemical method that we applied to determine the urinary UA/Cr ratio is readily available.

Renal handling of UA along the nephron includes glomerular filtration, tubular reabsorption, tubular

secretion, and further reabsorption distal to the secretory site [21, 22]. Disorders or medications that decrease renal excretion of UA include maternal toxemia, extracellular fluid contraction, renal failure, hypertension, and diuretics; these factors must be taken into consideration because they will decrease the urinary ratio of UA to Cr. The results of urinary uric acid measurement must be interpreted from urine samples collected before giving diuretics to avoid a pseudonegative result. However, urine collection may be difficult in anuric or oligouric infants.

In this study, the urinary ratio of UA to Cr in hypoxic term infants on the first day was very close to that reported by Mehes et al [20] and Bader et al [12]. The mean value of the urinary UA/Cr ratio in healthy term neonates was less than 1. In a study in mongrel puppies, Stapleton and Arant found that fractional excretion of UA during the first 24 hours decreased from about 70% at a gestational age of 29 to 31 weeks to 39 ± 14% at a gestational age of 38 to 40 weeks [23]. This finding suggests that premature infants might show a higher concentration of urinary UA. In normal premature neonates, the urinary UA/Cr value is variable and depends on gestational age and renal maturation [23]. Further prospective studies are needed to determine the normal value of UA/Cr in premature infants of different gestational age. The majority of extremely low birth weight (ELBW; < 1,000 g) infants are sick at birth and have respiratory distress, and collection of normal data from a sufficient number of ELBW infants to establish normal concentrations is more difficult. Our premature normal and asphyxia infants were all of more than 28 weeks gestational age.

In this study, the UA/Cr ratio was remarkably higher in hypoxic premature infants than in hypoxic term infants ( $p = 0.001$ ), and in healthy preterm infants than in healthy term infants ( $p = 0.001$ ). These findings can be explained by the later onset of Cr excretion by the relatively immature kidneys and renal tubules in premature infants. The rapidly increasing Cr clearance may account for the previous finding of a significant

difference between the UA/Cr ratio in normal infants and infants with asphyxia, which disappeared after the first 24 to 48 hours [20]. Therefore, we collected the first urine within 24 hours after birth.

This study found that, in a neonatal intensive care unit, the examination of the first urine sample obtained within 24 hours after birth provided a sensitivity of 80% and a specificity of 71% in term infants with perinatal asphyxia. The sensitivity and specificity were somewhat lower (70%) in premature infants with perinatal asphyxia. Further prospective, large population studies are necessary to establish the reliability of the urinary UA/Cr ratio as a predictor of perinatal asphyxia.

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