

## Blood pH and urinary uric acid-creatinine ratio in newborns with asphyxia

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### Abstract

**Background** Asphyxia is one of the leading causes of death in the world. Prematurity (28%), sepsis (26%), and asphyxia (23%) are the most common causes of death in newborns. In Indonesia, the newborn mortality incidence is 82 per 1,000 live births. Blood pH is a routine laboratory examination to diagnose newborn asphyxia, but it is preferable to avoid such invasive procedures in newborns. An examination of urinary uric acid-creatinine (UA/Cr) ratio may be useful as an alternative method for diagnosis of asphyxia. Hypoxia causes anaerobic metabolism which will increase the blood acidity, while creatinine will decline as a result of incomplete renal function in newborns.

**Objective** To assess for a possible correlation between blood pH and urinary UA/Cr ratio in newborn asphyxia.

**Methods** We conducted an observational, cross-sectional study in Prof. Dr. R. D. Kandou Hospital, Manado, North Sulawesi, from November 2013 to April 2014. Subjects were full term newborns with asphyxia. Blood pH and urinary UA/Cr ratio were compared with Pearson's correlation test. Data was analyzed with SPSS version 22 software and P values <0.05 were considered to be statistically significant.

**Results** Forty subjects met the inclusion criteria. Their predominant risk factor for asphyxia was fetal distress. Subjects' mean blood pH was 7.1 (SD 0.1) and mean urinary UA/Cr ratio was 3.7 (SD 1.9). There was a moderate negative correlation between blood pH and urinary UA/Cr ratio ( $r = -0.55$ ;  $P < 0.001$ ).

**Conclusion** In newborns with asphyxia, lower blood pH is correlated with higher urinary UA/Cr ratio. [Paediatr Indones. 2015;55:352-6].

**Keywords:** newborn asphyxia, blood pH, urinary UA/Cr ratio

Newborn asphyxia is the failure to start breathing and maintain respiratory function in newborn infants. Asphyxia is a major cause of death worldwide. Neonatal mortality due to asphyxia was estimated to be 30%, with greater risk of death in developing countries.<sup>1</sup> Lawn *et al.* reported that the three most common causes of neonatal death are prematurity (28%), sepsis (26%) and asphyxia (23%).<sup>2</sup> In South-eastern Asia (2012), the neonatal mortality rate (NMR) was reported 31 deaths per 1,000 live births, while in Indonesia 15 deaths per 1,000 live births.<sup>3</sup>

To date, every year an estimated 4 million babies die in the first year of life and two-thirds died in the first month of life, worldwide.<sup>4</sup> A study reported that the incidence of newborn asphyxia in West Java provincial hospitals was 25.2%, with 41.94% of deaths due to asphyxia in this Indonesian province.<sup>5</sup> An estimated 1 million children who survive after experiencing asphyxia at birth are at higher risk of long-term morbidity (cerebral palsy,

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mental retardation, and learning disabilities).<sup>6</sup> Blood gas analysis remains the gold standard for establishing a diagnosis of newborn asphyxia. Umbilical blood pH with a cut-off value of 7.20 had a good receiver-operating curve (ROC) value in determining the state of newborn asphyxia (ROC 0.74; 95%CI 0.69 to 0.79).<sup>7</sup> Other experts have used the ratio of urinary uric acid to creatinine (UA/Cr) in newborn asphyxia. Chen *et al.* reported that the use of the urinary UA/Cr ratio showed fairly good accuracy in full term and preterm infants with asphyxia. The ratio of UA/Cr urine had sensitivity of 80% and specificity of 71% in full-term newborns with asphyxia, while preterm newborns with asphyxia had sensitivity of 71% and specificity of 70%.<sup>8</sup> Examination of biomarkers in the urine provides optimism in helping the diagnosis of newborn asphyxia. The biomarker tests to detect cellular damage should be readily available, practical, inexpensive, and non-invasive. Blood gas analysis is a routine laboratory examination for newborn asphyxia, but it is invasive and increases the risk of infection. As such, examinations of urinary biomarkers have been developed.<sup>9</sup> The purpose of this study was to assess for a possible correlation between blood pH and urinary UA/Cr ratio in newborns with asphyxia, with the hope of using UA/Cr as a non-invasive method of diagnosis.

## Methods

This was a cross-sectional study conducted from November 2013 to April 2014 in the Neonatology Division at Prof. Dr R.D. Kandou Hospital, Manado, North Sulawesi. The subjects were full-term newborns who fulfilled the inclusion criteria of at least one criteria from the American Academy of Pediatrics (AAP) and the American College Of Obstetricians and Gynecologists (ACOG) guidelines for newborn asphyxia. These criteria were Apgar score  $\leq 3$  at 5 minutes after birth, blood pH  $< 7.00$ , clinical manifestations such as neurological symptoms of seizures; hypotonus, coma, hypoxic-ischemic encephalopathy (HIE), and evidence of multiorgan dysfunction in the neonatal period.<sup>10</sup> Exclusion criteria were congenital anomalies (congenital heart disease, esophageal atresia, diaphragmatic hernia, or gastroschisis), full-term newborns with birth trauma,

suspected sepsis, or caesarean section under general anesthesia. Subjects' parents provided informed consent. This study was approved by the Research Ethics Committee of Sam Ratulangi University Medical School, Manado, North Sulawesi.

Patient demographics and risk factors for asphyxia were described in this study. The urinary UA/Cr ratio was calculated from urinary uric acid and urinary creatinine examinations. The urinary uric acid examination required 5 mL of fresh urine, which was diluted with 0.6 M NaOH until the urine pH was  $> 8$ . For urinary creatinine, only 5 mL of fresh urine was required. For blood gas analysis, blood was collected from the umbilical artery in a 1 mL syringe with heparin. Statistical analysis was performed using Windows SPSS version 22 software. The relationship between blood pH and urinary UA/Cr ratio in newborn asphyxia was analyzed with Pearson's test, with a statistical significance of  $P < 0.05$ . The interpretations for coefficient correlation ( $r$ ) were as follows: very weak (0-0.2), weak (0.2-0.4), moderate (0.4-0.6), strong (0.6-0.8) and very strong (0.8-1).

## Results

**Table 1.** Demographic and laboratory description of subjects

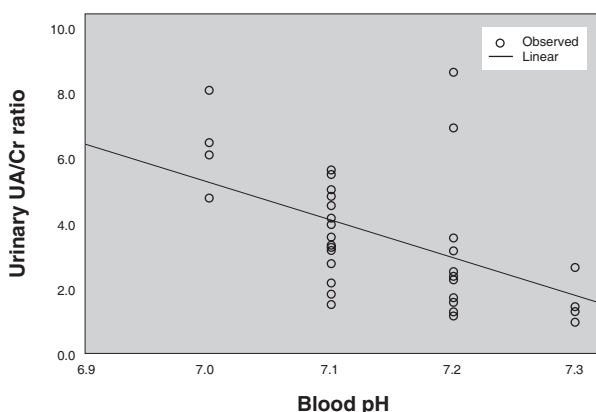
Characteristics	(N=40)
Gender, n	
Male	28
Female	12
Level of father education, n	
Elementary	8
Junior high	19
Senior high	13
Father occupation, n	
Laborers	6
Farmers	15
Fishermen	6
Drivers	1
Entrepreneurs	12
Delivery type, n	
Vaginal delivery	14
Caesarean section	26
Laboratory results	
Mean blood pH (SD)	7.1 (0.1)
Mean urine UA/Cr ratio (SD)	3.7 (1.9)

During the study period, we collected 40 subjects. **Table 1** shows the characteristics of subjects, of whom the predominant gender was male (28 infants). The most common dad's education level was senior high school (19 cases), and most common dad's occupation was farming (15 cases). Most subjects underwent caesarean section deliveries (26 cases) and 12 subjects experienced the risk factor of fetal distress. Subjects' mean blood pH and urinary UA/Cr ratio were 7.1 (SD 0.1) and 3.7 (SD 1.9), respectively.

**Table 2** shows types of risk factors described as: placental, fetal, and maternal factors. For placental factors, we found 1 subject with placenta previa. For fetal factors, 12 subjects had fetal distress. Maternal factors included amniotic fluid mixed with meconium (6 cases), chronic maternal disease (2 cases), severe pre-eclampsia (6 cases), prolonged labor (8 cases), and uterine atonia (5 cases).

**Table 2.** Types of asphyxia risk factors in the newborns.

Risk factors	N
Placenta factor	
Placenta praevia	1
Fetal factor	
Fetal distress	12
Maternal factors	
Amniotic fluid mixed with meconium	6
Chronic maternal disease	2
Severe preeclampsia	6
Prolonged labor	8
Uterine atonia	5



**Figure 1.** Scatter plots of pH blood and urinary UA/Cr ratio in newborn asphyxia.

**Figure 1** describes a moderate negative correlation between blood pH and urinary UA/Cr ratio in newborns with asphyxia ( $r = -0.55$ ;  $P < 0.001$ ). As such, lower blood pH was associated with higher urinary UA/Cr ratios in newborn asphyxia.

## Discussion

Chiabi *et al.* reported that predominantly male newborns had asphyxia, with a male:female ratio of 1.3:1. Socioeconomic status did not affect the incidence of newborn asphyxia.<sup>11</sup> We also observed more males (28/40) with asphyxia than females. The highest level of father education in our subjects was high school in 19 cases, and the most common father occupation was farming (15 cases).

Caesarean section was the most common delivery type in our study. A previous study reported that caesarean section was one of the risk factors for asphyxia (OR 3.78; 95%CI 2.75 to 5.19;  $P < 0.001$ ).<sup>12</sup> Asphyxia is less common in infants delivered vaginally than in those delivered by caesarean section. As the baby passes through the birth canal, force is exerted on the infant's chest wall, causing positive pressure in the chest cavity. In addition, due to uterine contractions during labor (pressure > 80 mmHg), blood flow from the placenta to the baby increases as a compensatory mechanism to prevent hypoxia in the fetus. The rest of the fluid contained in alveoli is pushed into the lymphatic vessels and lung parenchymal tissue when the baby cries. This process occurs as a result of the interruption of transplacental circulation, thus triggering the respiratory center to stimulate crying shortly after birth. Other risk factors for newborn asphyxia are severe preeclampsia, placenta previa, maternal chronic disease, meconium staining, prolonged labor, and dysfunctional uterine contractions.<sup>13</sup>

The most common risk factor for newborn asphyxia was reported by Mohan *et al.* to be fetal distress (58.33%). Other risk factors observed were amniotic fluid mixed with meconium (28 subjects, 23.33%), prolonged labor (16 subjects, 13.33%), preeclampsia, (12 subjects, 10%), and antepartum haemorrhage (8 subjects, 6.66%).<sup>14</sup> In our study, we observed amniotic fluid mixed with meconium in 6 (15%) cases, prolonged labor in 8 (20%) cases, severe preeclampsia in 6 (15%) cases, dysfunctional uterine

contractions in 5 (12.5%) cases, maternal chronic diseases in 2 (5%) cases, and placenta previa in 1 (2.5%) case.

Another study reported significant differences in blood pH in newborns with asphyxia and healthy newborn infant. In the group of newborns with asphyxia, highest levels of blood pH were 7.25 to 7.30 in 17 (34%) cases, whereas in the healthy newborn group, the highest umbilical artery pH was 7.30 to 7.35 in 7 (50%) cases. There was a significant difference in urinary UA/Cr ratio between the newborn asphyxia group and the healthy control group [2.58 (SD 1.09) vs. 0.86 (SD 0.17);  $P < 0.001$ ].<sup>15</sup> In our study, mean blood pH and urinary UA/Cr ratio for neonates with asphyxia were 7.1 (SD 0.1) and 3.7 (SD 1.9). Boskabadi *et al.* reported blood pH in newborn with asphyxia was similar with us [7.1 (SD 0.1)].<sup>16</sup> Based on Pearson's correlation test revealed a moderate negative correlation between blood pH and urinary UA/Cr ( $r = -0.55$ ;  $P < 0.001$ ). It shows the existence of a relationship between blood pH levels with urine UA/Cr ratio in newborn asphyxia. Khaw *et al.* reported that the use of oxygen during resuscitation did not affect blood pH levels in newborns with asphyxia. They compared the administration of 21% oxygen (room oxygen) to 60% oxygen ( $FiO_2$ ), and they found no significant difference in umbilical artery pH levels between groups [7.25 (SD 0.09) vs. 7.24 (SD 0.09), respectively;  $P > 0.05$ ]. In addition, there were no significant differences in blood pH levels within 1 hour of resuscitation of newborns.<sup>17</sup>

Tissue hypoxia triggers the accumulation of  $CO_2$ , causing increased levels of ions ( $H^+$ ) and resulting in decreased blood pH, as compared to healthy babies. In addition, the process of asphyxia causes anaerobic metabolism and lactic acid to form a compound that lowers blood pH such that the patient experiences acidosis.<sup>18,19</sup> Anaerobic metabolic processes increase the metabolism of xanthine to uric acid production, thus increasing serum uric acid levels, to be offset by increased excretion of uric acid in urine as a compensatory mechanism to prevent the buildup of uric acid in the body. On the other hand, serum creatinine in newborns is decreased, due to the relatively small muscle mass compared to the body mass and the absence of an adequate diet in newborns. Serum creatinine formation is derived from the diet and the degradation of muscle mass, with the help of adenosine triphosphate (ATP), whereas uric acid is not affected

by muscle mass. Further decrease of serum creatinine leads to decreased urinary creatinine levels. As such, this condition causes an increase in the urinary UA/Cr ratio in newborns with asphyxia.<sup>20,21</sup>

Badder *et al.* reported a highly significant difference between urinary UA/Cr ratio between asphyxia group and control group [2.06 (SD 1.12) vs. 0.64 (SD 0.48), respectively;  $P < 0.001$ ].<sup>22</sup> The urinary UA/Cr ratio also increased in newborns with hypoxia encephalopathy (HIE): the ratios were 3.18 (SD 0.61) in severe HIE, 2.19 (SD 0.32) in moderate HIE, and 1.53 (SD 0.25) in mild HIE. These differences corresponded to the severity of hypoxia, with higher urinary UA/Cr ratios associated with more severe hypoxia.

To our knowledge, this is the first study to assess for a relationship between blood pH levels and urinary UA/Cr ratios in newborns with asphyxia. Such studies are difficult to conduct as collecting sufficient urine from newborns is challenging. Shashidhara reported that there were significant differences between blood pH levels and urinary UA/Cr ratio with the severity of neonatal hypoxic ischemic encephalopathy ( $P < 0.001$ ).<sup>15</sup> We found a moderate negative correlation between blood pH levels and urinary UA/Cr ratios in newborns with asphyxia. Our hypothesis was based on the theory that blood pH and urinary UA/Cr ratio change during tissue hypoxia. However, Basu *et al.* found no significant relationship between urinary UA/Cr ratio with Apgar scores in newborns with asphyxia ( $r = -0.298$ ;  $P = 0.103$ ).<sup>23</sup>

A limitation of this study was that we did not classify subjects based on the severity of asphyxia (degrees of HIE). Further research is needed on the relationships between urinary UA/Cr ratio and the clinical symptoms in asphyxia. In conclusion, lower blood pH is correlated to higher urinary UA/Cr ratio in newborns with asphyxia.

## Conflict of interest

None declared.

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