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BLOOD AMMONIA LEVELS IN PREMATURE AND FULL-TERM INFANTS*

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Hyperammonemia is one of the metabolic disorders which shows a severe clinical picture in the neonatal period. There are many reports which point out the grave prognosis of this condition in the immediate newborn period [1-5].

The clinical symptoms of hyperammonemia are various and similar to those of other metabolic disorders [1,4,6]. Clinical manifestations usually are not diagnostic and correct diagnosis must be confirmed by laboratory investigations.

For these reasons, it is very important to know the normal level of blood ammonia in the newborn. Previous studies are limited, and contradictory results have been reported [7-9].

The purpose of this study is to determine blood ammonia levels in a random group of premature and full-term newborns and to evaluate the relationship of the levels with various parameters such as gestational age, birthweight and asphyxia. The findings are compared with those in the literature.

Material and Methods

The study was carried out on 20 premature and 20 full-term randomly-selected infants born at the Hacettepe University Hospital between January 1979 and January 1980. Blood ammonia levels were determined by the Müller-Beissenhirtz method [10].

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Vital signs of the infants were evaluated with the Apgar scoring system[11] at 1 and 5 minutes following birth. Gestational ages of the infants were assessed by the Dubowitz method[12] in cases where the mother's last menstrual period (LMP) was unknown.

The infants were grouped according to Lubchenco's[13] classification of prematurity, as follows:

1. Extremely premature: those under 30 weeks,
2. Moderately premature: those between 30 and 34 weeks, and
3. Slightly premature: those between 34-38 weeks of gestational age.

Intrauterine growth of all infants by weight and gestational age was evaluated according to Lubchenco's classification[14].

During the study, all infants were fed on a diet containing approximately 2 gm/kg protein per day. After an appropriate amount of protein intake was provided, fasting blood ammonia levels were determined in every infant at 72 hours of life. Because of technical difficulties in taking blood samples from infants, the ammonia level was measured on only one occasion. Blood samples had been taken from the external jugular vein because free flowing blood may be most satisfactory. For the statistical analysis, Student's t test and the Mann-Whitney u test were used.

Findings

Twelve of the 20 premature infants were male and 8 were female, giving a male-to-female ratio of 3:2. Half of the 20 full-term infants studied were male and the other half female, giving a male-to-female ratio of 1:1.

The type of delivery and birthweight characteristics of all infants are shown in Table I.

TABLE I

TYPE OF DELIVERY AND BIRTHWEIGHT CHARACTERISTICS OF PREMATURE AND FULL-TERM INFANTS

	Type of delivery		Birthweight		
Infants	Cesarean section	Vaginal	Lower	Upper	Mean
Premature	4	16	1280	2600	1993.5
Full-term	11	9	2750	3650	3283
Total	15	25	1280	3650	

The gestational ages of the premature infants were between 32 and 37 weeks. Birthweights ranged from 1280 gm to 2600 gm in premature infants and from 2750 gm to 3650 gm in full-term infants.

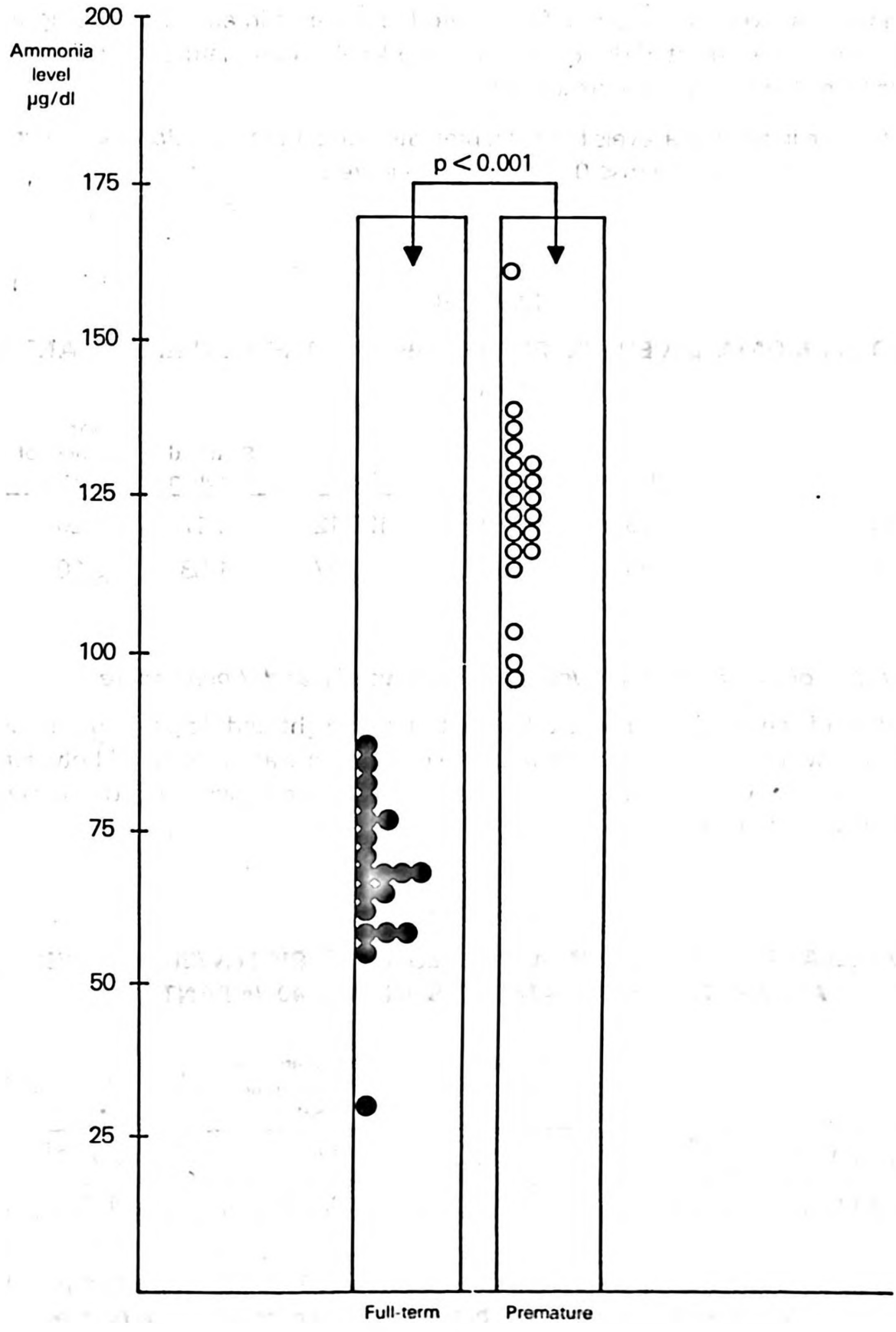

Figure 1

Relationships of ammonia levels in premature and full-term infants.

Blood ammonia levels in full-term infants were the same as in adults according to the method used in the study[10]. Blood ammonia levels in premature infants were found to be higher than in full-term infants.

The difference in ammonia levels between premature and full-term infants was very significant at 72 hours of life ($p < 0.001$, Table II, Figure 1).

TABLE II

BLOOD AMMONIA LEVELS IN PREMATURE AND FULL-TERM INFANTS (µg/dl)

	Lower	Upper	Mean	Standard deviation	Number of cases
Premature	96	160	123.12	14.17	20
Full-term	33.8	87.6	73.87	11.53	20

Relationship of blood ammonia level and birthweight and Apgar score

Correlation of the blood ammonia values with birthweight and Apgar score in all infants is shown in Table III. A close negative correlation was established between birthweights and ammonia levels in all infants. Blood ammonia levels decreased when birthweights increased.

TABLE III

CORRELATION OF AMMONIA VALUES WITH BIRTHWEIGHT AND APGAR SCORE PARAMETERS IN ALL 40 INFANTS

Parameters	Correlation ratio (r)	Standard error of correlation ratio (Sr)	t
Birthweight	−0.819	0.093	−8.803
Apgar score	−0.547	0.153	4.032

The ammonia levels and Apgar scores of all infants at 1 minute were compared. A close negative correlation was established between these two parameters ($r: -0.547$, $p < 0.01$, Table III, Figure 2). When ammonia levels increased, Apgar scores decreased.

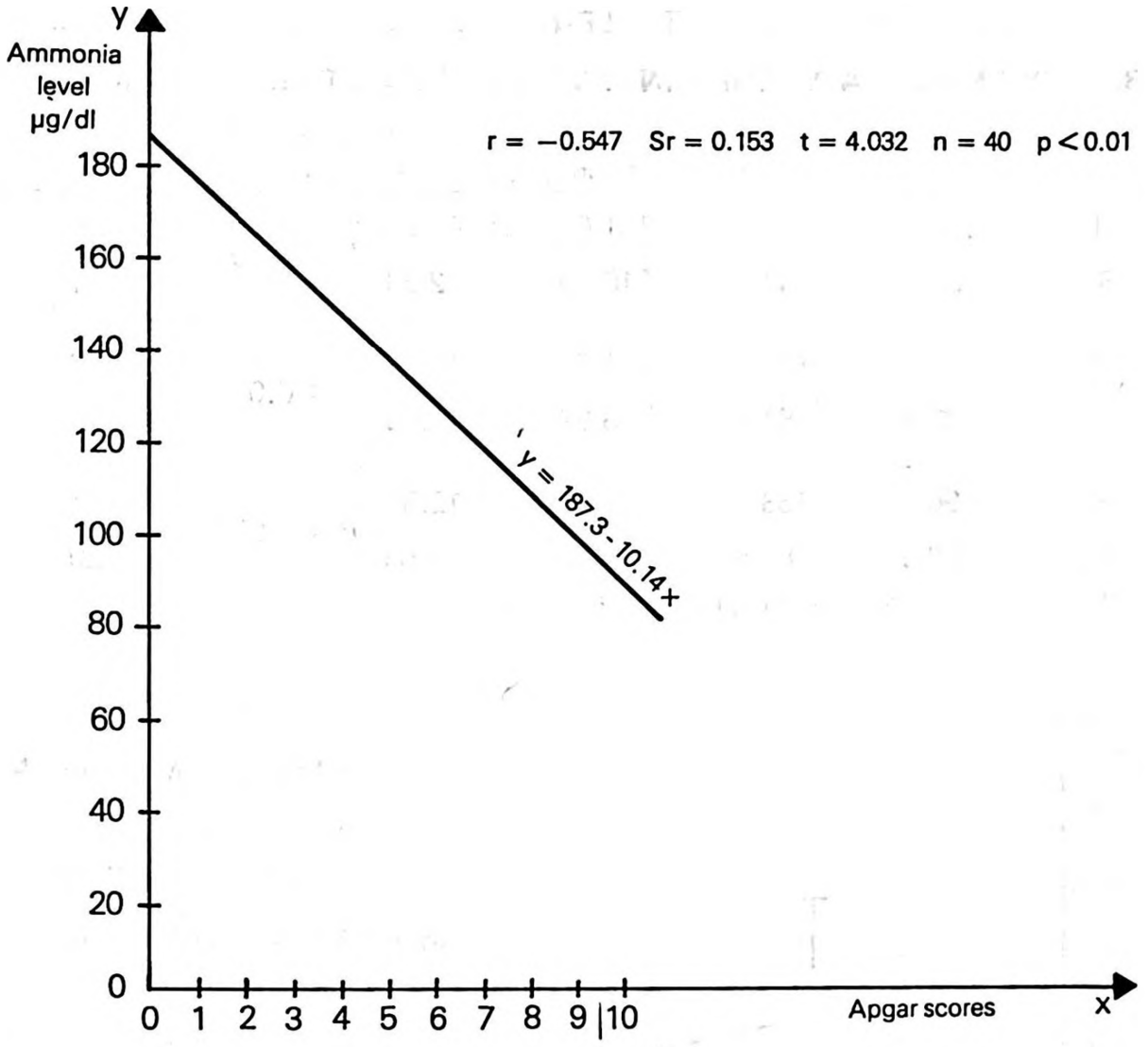

Figure 2

Reverse correlation between Apgar scores and ammonia levels.

Ammonia level in various infant groups

Using Lubchenco's system[13], none of our cases fell into the first category, so our premature infants were classified as two groups: moderately prematures (between 32 and 34 weeks of gestational age), and slightly prematures (between 35 and 37 weeks of gestational age).

There was a significant difference in ammonia value between moderately and slightly premature infants, and also between full-term infants and both premature groups ($p < 0.05$), as shown in Table IV, Figure 3, below.

TABLE IV

BLOOD AMMONIA VALUES IN VARIOUS INFANT GROUPS (μg/dl)

Infants	Lower	Upper	Mean	Standard deviation		Number of cases
M	120	160	131.62	11.78	$P < 0.05$	9
S	96	133	116.16	12.34		11
M	120	160	131.62	11.78	$P < 0.05$	9
F	33.8	87.6	73.87	11.53		20
S	96	133	116.16	12.34	$P < 0.005$	11
F	33.8	87.6	73.87	11.53		20

(M: Moderately premature, S: Slightly premature, F: Full-term)

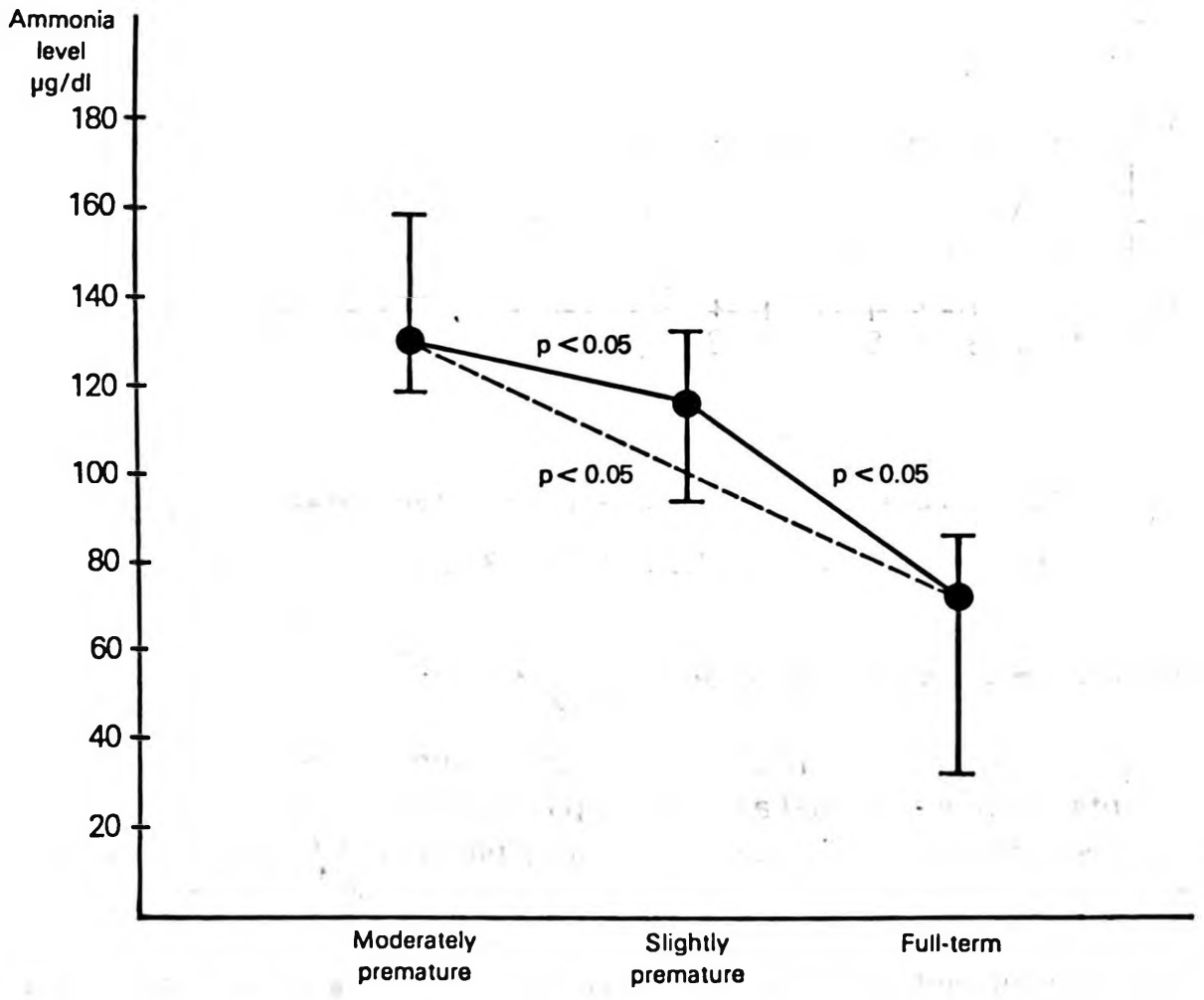

Figure 3

Relationship between ammonia levels of full-term and premature infant groups.

Mean ammonia values of premature infants showed that the ammonia values increased as gestational ages decreased (Table V).

TABLE V

MEAN AMMONIA VALUES (µg/dl) OF PREMATURE INFANTS AT VARIOUS GESTATIONAL AGES

Gestational age (weeks)	Number of cases	Lower	Upper	Mean
32	4	127	160	137.25
33	2	124.3	138	131.15
34	3	120	128	124.43
35	4	116.6	129	123.3
36	4	98	133	116.65
37	3	96	119	106

Ammonia levels and sex

There was no significant difference in ammonia values according to sex ($p > 0.05$), either in premature or in full-term infants.

Ammonia levels and intrauterine growth retardation

All the full-term infants were found to be of appropriate size for gestational age. Four of the premature infants were found to be small for gestational age, and the others were appropriate for gestational age.

In premature infants there was no significant difference in ammonia levels between those appropriate for gestational age and those small for gestational age ($p > 0.05$).

Discussion

Previous studies to determine blood ammonia levels in newborn infants are limited and noteworthy for their contradictory results. Moreover, normal values of ammonia vary according to the technique of measuring.

Clemmens et al[8] measured blood ammonia levels in full-term infants at three days of life and described values ranging from 38 to 162 µg/dl, with a mean value of 99 µg/dl. Using this method, the upper limit of the adult level was 100 µg/dl, with a mean value of 77 µg/dl. In the same study, the authors also reported no significant difference or correlation between ammonia levels and birthweights and sex. In our study, the ammonia levels of full-term infants were found to be the same as adult ranges (Table II). We also confirmed that there was no sex predilection. However, a

significant negative correlation was established between ammonia values and birthweights (r: −0.819). Ammonia levels increased as birthweights decreased.

Anderson and Miller[7] also described high ammonia levels in normal full-term infants at 48-96 hours of life. Oral intake of neomycin of these infants during the first 6 days of life has been shown to prevent an increase in blood ammonia.

Both Anderson and Miller[7] and Clemmens et al[8] suggested that the factors which affect blood ammonia levels in newborn infants might be due to hepatic and renal immaturation, changes in liver vascularization (such as patent ductus venosus), and the contribution of intestinal bacteria formation after birth.

As in our study, Rubaltelli et al[9] found adult ammonia levels in normal full-term infants. However, the same authors reported that ammonia levels in intrauterine growth-retarded infants were significantly higher than in normal infants. They suggested that the high ammonia levels seen in those infants were due to increased protein catabolism and placental insufficiency of clearing formed ammonia. Howewer, this latter idea is doubtful since Holzman et al[15] recently reported that ammonia formation occurred in the human placenta in vitro and suggested that this was due to a deficiency of active urea cycle in the human placenta.

In our study, all the full-term infants were appropriate for gestational age. In the premature group, four were small and the others were appropriate for gestational age. There was no significant difference of ammonia level between the infants who were small for gestational age ($p > 0.05$). Although this finding does not seem to correlate with the findings of Rubaltelli et al[9] the difference in results may be due to the unequal sizes of the two premature groups. However, when all the infants were evaluated according to intrauterine growth, there was a poor negative correlation between ammonia levels and Lubchenco percentiles (r: −0.292) and this result supports the findings of Rubaltelli et al.

In recent years, comparable studies have been undertaken to determine blood ammonia levels in premature and full-term infants. Batshaw and Brusilow[16,17] measured the blood ammonia levels in full-term infants and found them similar to adult levels at three days of life. But in premature infants, ammonia levels were very high compared to those of full-terms, and the difference was significant. They also found a close correlation between birthweights and ammonia levels, with no sex predilection. Our results confirmed their findings (Tables II, III).

Batshaw and Brusilow suggested that the cause of hyperammonemia in premature infants may be due to the immaturation of urea cycle enzymes or substrate deficiency in the urea cycle. This suggestion was confirmed by our results, since we found increased levels of ammonia as the gestational ages of premature infants decreased (Table V). Moreover, a comparison between the moderately and slightly premature groups showed the former group to have significantly higher levels.

Hyperammonemia in premature infants was clinically asymptomatic in Batshaw and Brusilow's cases. It is proposed that perhaps hyperammonemia may contribute to late neurologic abnormalities seen in premature infants. Hyperammonemia in our cases was also clinically asymptomatic.

Vital signs of the newborn were evaluated by the Apgar scoring system[11] at 1 and 5 minutes following birth. Apgar and James[18] reported that the one-minute score after birth was a prognostic criterion for neonatal mortality. This finding was supported by other reports and showed that the five-minute score was also a good criterion for the rate of neonatal mortality and late neurologic sequelae for those who survive[19-21]. In recent years, in addition to the above known complications of perinatal asphyxia, hyperammonemia has also been reported[22,23]. In our study, a significant correlation was established between one-minute Apgar scores and ammonia levels in all infants (r: −0.547). Ammonia levels increased as Apgar scores decreased.

In the cases of Goldberg et al[23] Apgar scores were 5 at 1 and 5 minutes following birth. In our cases the five-minute scores were normal but the one-minute scores were lower in premature than in full-term infants. However, these scores were also within normal limits. The close correlation between ammonia levels and Apgar scores may be due to the lower scores found in premature infants. This finding also supports that perinatal asphyxia may be a contributing factor in transient hyperammonemia of the preterm infant[24].

Summary

Ammonia levels of 20 premature and 20 full-term randomly-selected infants were measured.

In full-term infants, the blood ammonia levels were found to be within the range of adult levels.

In premature infants, ammonia levels increased as gestational ages decreased. Asymptomatic hyperammonemia occurred in the prematures. A significant reverse correlation was found between hyperammonemia and Apgar score indicating the role of perinatal asphyxia in transient hyperammonemia of premature infants.

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