ORIGINAL ARTICLE

Investigation of the relationship between umbilical cord pH and intraventricular hemorrhage of infants delivered preterm

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SUMMARY

OBJECTIVE: *We measured the level of pH gases in premature infants at birth, and examined the relationship between brain ultrasonography on the third and seventh day after birth. A case-control study conducted at the Neonatal Intensive Care Unit (NICU) of Shahid Akbar Abadi Hospital, Iran, during the years 2016-2017.*

METHODS: *All premature infants who were admitted to NICU were enrolled in the current study. At birth, a blood gas sample was taken from the umbilical cord of the infants. On the third and seventh day after birth, an ultrasound of the brain of each neonate was performed by a radiologist. The umbilical cord was evaluated for blood gases in 72 neonates (mostly boys).*

RESULTS: *Sixty-six newborns had normal sonography, and 16.7% (12 cases) had anomalies. A total of 75% of the 8 infants with intravenous bleeding were girls, which were significantly different from those in the non-hemodynamic group (62.5% male) (P 0.049). However, the type of delivery, mean weight, height, head circumference, the circumference of the chest, and Apgar score did not differ between the two groups. Mean pH, HCO^{3-} and PCO2 in umbilical cord blood gas samples were not significantly different between the two groups with or without intraventricular hemorrhage (IVH). Although it was not related to gender and type of delivery in newborns*

CONCLUSION: *Blood gases do not help in determining the occurrence of IVH in infants. Nevertheless, it is associated with immaturity and fetal age.*

KEYWORDS: *Umbilical cord. Blood gas analysis. Cerebral hemorrhage. Infant, newborn.*

INTRODUCTION

According to the World Health Organization (WHO), preterm labor refers to the onset of uterine contractions after the 20th week and the 37th week of pregnancy, and the infants born of these births are called premature babies.[1] Among preterm infants, most have problems at the gestational age of 23-32 weeks. Although this group accounts for 1%-2% of all premature infants, it consists of 50% of long-term neurological morbidity and 60% of perinatal mortality.[2,3] The prevalence of prematurity in the United States and Europe has been estimated to be 10-8% and 7-5% respectively. Nonetheless, prematurity causes

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60 to 80 percent mortality in infants without anomalies.[4] It is noteworthy that infant mortality decreases by half starting from 25 to 37 weeks of gestation per week.[5] Some of the known risk factors involved in an early delivery include maternal age below 17, smoking, previous preterm delivery, multiple sexes, infection, and other issues such as black ethnicity and low socioeconomic status.[6-8] Preterm babies may present several problems, including intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), cerebral palsy (CP), frequent admissions, infection, apnea, among others. Prevention of early delivery is the best treatment.[9,10] Brain injury and functional disorders of the brain in preterm infants are associated with hypoxia hippocampus, hypoxia hypercapnia, and acidaemia.[11] Disorders of blood gases are more likely to cause brain damage than other factors.[12] For example, in preterm infants, inflammation of the placenta is accompanied by an increase in alveolar pressure of oxygen (PAO2) and the umbilical cord inflammation is linked to a reduction in partial carbon dioxide pressure (PCo2).[13] Intravascular endotoxins cause hypoxemia without acidosis, while chronic vascular disorders associated with pre-birth cause hypoxemia with acidosis in neonates.[14] Severe acidosis at birth is one of the most important predictors of death or neurodevelopmental impairment (NDI) in full-term infants who are suspected of hypoxic-ischemic encephalopathy (HIE), which is correlated with poor prognosis among these patients. However, in preterm newborns, several factors such as organ underdevelopment, IVH, infection, hypoxia due to an absence of lung function, and poor nutrition cause death or NDI. Regarding these combined problems, the role of acidosis and other metabolic disorders in preterm infants is not completely clear.[15] Overall, there are two main causes of neonatal white brain injury: ischemia and re-establishment of cerebral perfusion in preterm infants, which are often associated with cerebral vascular autoregulatory dysfunction and other maternal or fetal bacterial infections that trigger the secretion of various cytokines and lead to brain damage.[16] Bleeding inside the germinal matrix or intracerebral hemorrhages in neonates is associated with a risk of death and complications such as future cerebral palsy. The incidence of these complications is inversely related to gestational age. However, low-grade bleeding is not associated with the risk of developing cerebral palsy. Diagnosis of cerebral hemorrhages before birth and during the first few hours of birth is possible; most bleeding occurs within the first 48 hours, and only 10% occur after the first week of birth.[17]

IVH refers to bleeding into the ventricular system of the brain. Low gestational age and low birth weight, intrauterine infections, vaginal delivery, low Apgar score, acidosis, and sepsis. Additionally, prematurity is considered the main risk factor for this complication. Despite the decline of severe IVH (Grades 3 and 4) in recent decades, IVH has also been associated with high morbidity in preterm newborns, especially with a very low birth weight (ELBW). The disorder in cerebrovascular regulation is known as the most common etiology of these bleedings. On the other hand, hypercapnia during the first 3 days of birth causes cerebrovascular autoregulatory dysfunction and is accompanied by a high incidence of severe IVH. Some studies have shown that the effect of PaCo2 on cerebral circulation was related to the pH of arterial gases. However, most of these studies examined PaCo2 levels regardless of pH and base deficit (BD) levels, or the effect of hypercapnia at > 7.20 pH was evaluated. Therefore, PaCo2 may have its own effect independent of the pH of blood gases in the development of intense IVH.[18,19]

Oxygen is widely used in the regeneration and treatment of pulmonary diseases in premature infants. Additionally, preterm infants are at increased risk of developing hyperoxia due to the sudden increase in oxygen in the environment compared with intrauterine oxygen. This hyperoxia causes bronchopulmonary abnormalities, retinopathy, and apoptosis of the brain cells; therefore, its level of saturation in blood gases is very important.[20] The importance of brain hemorrhage and its complications are not overlooked either at or after admission.

The occurrence of risks such as hydrocephalus, CP, and other complications of cerebral hemorrhage are also very important. In this study, we show it is possible to reduce these risks by demonstrating the importance of analyzing blood gases and its relation as a sign of major risk of neonatal brain hemorrhage. The results will help reduce brain-related complications in neonates.

In this study, the pH of blood gases was evaluated at the birth of premature infants and its relationship with brain ultrasound at the third and seventh day after birth was also investigated.

METHODS

Ethics committee statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and were approved by the Iran University of Medical Sciences Institutional Review Board (Protocol number 2016/2957, October 2016.10.19).

In a case-control study, all preterm infants who were admitted to the Neonatal Intensive Care Unit (NICU) of Shahid Akbar Abadi Hospital during the years 2016-2017 were evaluated. Data from data collection forms were extracted for all premature infants admitted by census method and all those who met the inclusion criteria without any exclusion criteria were included.

Inclusion criteria

Preterm infants (birth with gestational age 20 to 37 weeks) with survival for 3 days after birth.

Exclusion criteria

Term babies; death three days after birth; failure in collecting the sample of arterial gas at birth; incomplete ultrasound reports on the third day

Data collection

Demographic data of patients including gender, gestational age, the type of delivery, family history of anomalies and the presence or absence of other associated anomalies were recorded for each patient in the checklist. On the third and seventh day after birth, a brain ultrasound was performed by a radiologist and observations were finally recorded. A sample of blood gas was taken from the umbilical cord at birth; if sampling was not possible, samples were taken from the peripheral blood vessels and sent immediately to measure the blood gas indexes, HCo3, PCo2, and pH. Information was then recorded in the relevant checklist. On the third day after birth, cerebral ultrasound was performed by a radiologist using Sonosite Model P12163 with a linear probe (made in Malaysia); microcephaly, macrocephaly, ventriculomegaly, and echolucent lesions were subsequently evaluated. On the seventh day after birth, the ultrasound was repeated, and observations from both ultrasound investigations were recorded separately in the checklist for each neonate. A checklist containing patient information was completed. After collecting the data, the obtained results were evaluated statistically. The researchers were committed to the dispositions of the Helsinki Declaration, and all ethical issues were approved by the Ministry of Health of Iran. The names and characteristics of the patients were known only by the researchers.

Statistical analysis

The results of the quantitative variables were presented as mean and standard deviation (mean ± SD), while qualitative and stratified variables were shown as percentages. Quantitative variables were compared using the t-test or, if there was an abnormal distribution, the Mann-Whitney test. The comparison between qualitative variables was also performed using the chi-squared test or the Fisher exact test. Correlations between quantitative variables were investigated using the Pearson correlation coefficient test and Spearman rank correlation. For data analysis, Statistical Package for the Social Sciences (SPSS) software version 20 was used. The significance level was considered to be < 0.05.

RESULTS

The study consisted of 72 preterm infants, 42 boys (60.9%) and 27 girls (39.1%), born at a mean gestational age of 31.03 ± 2.87 weeks (Figures 1A and B). The frequency of infants based on the age groups is shown in Table 1. The age group of 32-36 weeks was determined to be the most frequent. (Table 1 and Figure 1C). Moreover, 74% (n = 52) of neonates were born via cesarean delivery, while 25.7% (n = 18) via normal delivery (Figure 1D). The weight of all neonates at birth was between 570 and 3450 grams (mean 1515 ± 1601.6 g) and the height varied from 33 to 54 cm (with a mean of 42.74 ± 4.83 cm), head circumference (29.02 ± 2.72cm) and circumference of the breast (26.63 ± 4.6), (Figures 5 to 8, 10, 11; Table 3). The mean of pH, HCo3, and PCo2 in umbilical cord blood samples were determined as 7.22 ± 0.8 mmHg, 20.78 ± 4.02 mEq/L, and 52.42 ± 11.22 mmHg, respectively (Figures 1D, 1E, 1F, 1G, 1H 1I and Figures 2A, 2B, 2C, 2D, 2E). Furthermore, pH, HCo3, and PCo2 were compared in terms of umbilical cord blood gases between two groups of infants with and without IVH, which was not significantly different (P = 0.5; P = 0.9; P = 0.7; Table 4; Figures 2F, 2H, 2G, 2I and Figures 3A, 3B). A correlation coefficient between fetal age and pH of cord blood gases from the umbilical artery was determined as +0.299, indicating a positive correlation between these two variables; indeed, the pH slightly increased with fetal age. Also, these two variables had a significant relationship between them (P = 0.01; Figure 3C). Based on the results of the pH of the cord blood gases from the umbilical artery presented here, preterm infants with IVH and/or without IVH have no significant difference regarding gender and type of delivery (Tables 5 and 4-6). Based on the finding presented here, pH levels in infants without IVH and cerebral anomalies were lower than other groups, to whom these values were statistically significant. (P = 0.03; 7.16 ± 0.07 versus 7. 23 ± 0.08; Table 7). The correlation between the pH and fetal age in the group of infants without intravenous hemorrhage was defined as 0.3, which indicates that there is a moderate positive correlation between these two variables (P = 0.01). However, no significant relationship was found between fetal age and cord blood pH in neonates with IVH (Pearson correlation coefficient: 0.29 and P = 0.4), (Figures 3D and 3E).

DISCUSSION

In this case-control study, the umbilical cord was evaluated for blood gases in 72 neonates (mostly boys) with an average fetal age of 31.03 ± 2.87 and with a mean weight of 1515.6011.66 grams. Of the 72, 74.3% (52 subjects) were born through cesarean section. Sixty-two neonates were diagnosed as normal using ultrasound, whereas 16.7% (12 subjects) had cerebral anomalies that included: IV in 5 subjects (6.9%), GMH in 6 neonates (8.3%), and hydrocephaly in 1 infant (1.4%). Unfortunately, 2 infants died. A total of 4.2% (3 individuals) had presented IVH grade (1 in the third-day ultrasound), while 1.4% (1 subject) presented Grade 3.

Furthermore, on the seventh day, 8.2% (2 subjects) presented IV (Grade 1), followed by 2.8% (2 subjects) IVH (Grade 2), 8.2% IVH (Grade 3), and 1.4% (1 subject) grade 2 to 3. On the other hand, 75% of 8 infants had IVH, which showed a significant difference compared with the group of infants without IVH (62.5% male), (P = 0.049). However, the type of delivery, mean weight, height, head and breast circumference, and Apgar score (first minute) did not differ between the two groups.

In this study, blood gases were compared between two groups and the mean pH, HCo3, and PCo2 in umbilical cord blood samples of neonates were determined as 7.2 ± 0.8 mmHg, 20.78 ± 4.02 mEq/L, and 52.42 ± 11.22 mmHg, respectively, which revealed no significant difference between the two groups with/or without IVH. The results did not show a significant relationship between gender and type of delivery in neonates. The pH increased slightly with gestational age, in which its relation to fetal age was significant (P = 0.01). Lower pH was observed in the umbilical cord of infants who did not have IVH but had cerebral anomalies (P = 0.03). In infants without intravesical hemorrhage, pH was associated with fetal age (P = 0.01), while this issue was not associated with the age of infants suffering from IVH (P = 0.4). A study by Sajjadian et al.[21], in Tehran, showed that 64% of preterm infants had Intraventricular-germinal matrix hemorrhage, of which 40% had grade I, 11% grade II, 25.7% grade III, 2.8% grade VI, which is about four times the value determined by the present study. The difference between the mean fetal age justifies this issue in two studies. The frequency of GMH has been reported to be 28% in a prospective study which, unlike the present study, did not differ between the two sexes but was related to the type of delivery, weight, and fetal age.[22]

Stewart et al.[23], have shown that the frequency of IVH (18.2%) was slightly higher than that of the current study (16.7%), which can be due to the very low birth weight (VLBW) of neonates investigated in our study. Another study in Nigeria indicated that 22% of infants presented mild IVH, followed by moderate to severe IVH (7.5%), and periventricular leukomalacia (PVL, 23%), with a 3.5-fold increase in IVH.[24] Our results are consistent with some studies.[15,19]

In the present study, there was no significant difference in blood gases (mean pH, HCo3 and PCo2) between the two groups with/without IVH. However, in the group without cerebral hemorrhage, acidosis decreased with fetal age (P = 0.01), and no relationship was found regarding gender and type of delivery. Furthermore, in infants with interventricular hemorrhage, acidosis was not found to be associated with fetal age. Leviton and colleagues observed that the disruption of each of the blood gas indexes, including pH, PCo2 and Pao2, alone could not increase the risk of brain damage. However, it may indicate an insufficiency or severity of brain disease when there is an interruption of more than one of these indexes.[15] Randolph et al.[25] also found that perinatal acidosis is significantly associated with death or NDI in infants with very low birth weight. This study mentioned that although perinatal acidosis is uncommon in these infants, it was important in predicting mortality and/or NDI as well as other factors.[25] Locatelli et al.[15] demonstrated that severe acidosis at birth, the most important predictor of death or neurodegenerative disorders, in term neonates suspected of hypoxic/ischemic encephalopathy was a predictor of prognosis. Conversely, in preterm infants, acidosis has not played a role due to several pitfalls caused by premature status, such as acidosis and other metabolic disorders. The inverse effect of umbilical cord pH and BE on the outcome events for infants delivered preterm was demonstrated by Victory et al.[26]. Zayek et al.[27], who reported that the risk of severe IVH was elevated with higher Paco 2 and BD, but pH was the only predictor of severe IVH. A higher acidity level during the first 48 hours of life has been correlated with an increased occurrence of IVH.[27]

CONCLUSION

The measurement of umbilical cord blood gases as a non-invasive evaluation method can provide appropriate data for decision-making, treatment and prognosis; however, blood gases do not help determine the occurrence of IVH in infants. Nevertheless, it is associated with immaturity and fetal age. Checking the condition of the umbilical cord pH during the first hours after childbirth is very beneficial in the hospital, where it can provide important information about the respiratory, metabolic, and brain statuses, as well as specialized care setting.[28-31]

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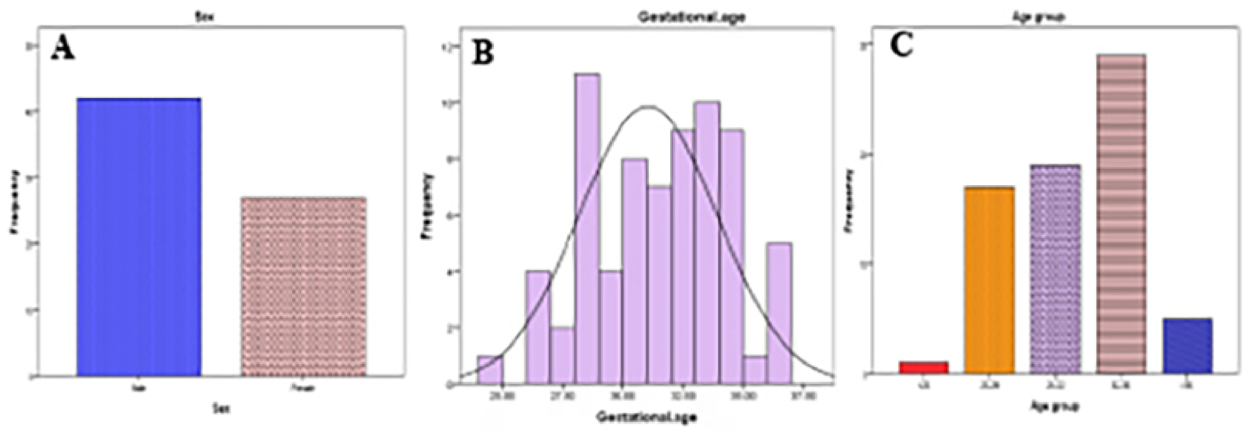
Conflict of interest

None

Authors' contributions

AM, MM, NKH, LYA, and MK carried out the statistical analysis, helped draft the manuscript, collected, analyzed and interpreted the clinical data, conceived, designed, and coordinated the study and wrote the manuscript. All authors read and approved the final manuscript.

FIGURE 1. A) THE FREQUENCY OF SEX IN INFANTS; B): HISTOGRAM OF FETAL AGE; C): FREQUENCY OF INFANTS IN TERMS OF AGE GROUPS; D): FREQUENCY OF PATIENTS PER TYPE OF DELIVERY; E): BIRTH WEIGHT HISTOGRAM; F): HISTOGRAM OF THE HEIGHT; G): HISTOGRAM OF THE HEAD CIRCUMFERENCE; H): HISTOGRAM OF THE BREAST CIRCUMFERENCE; I): NEONATAL ABNORMALITIES CHART BASED ON ANOMALY



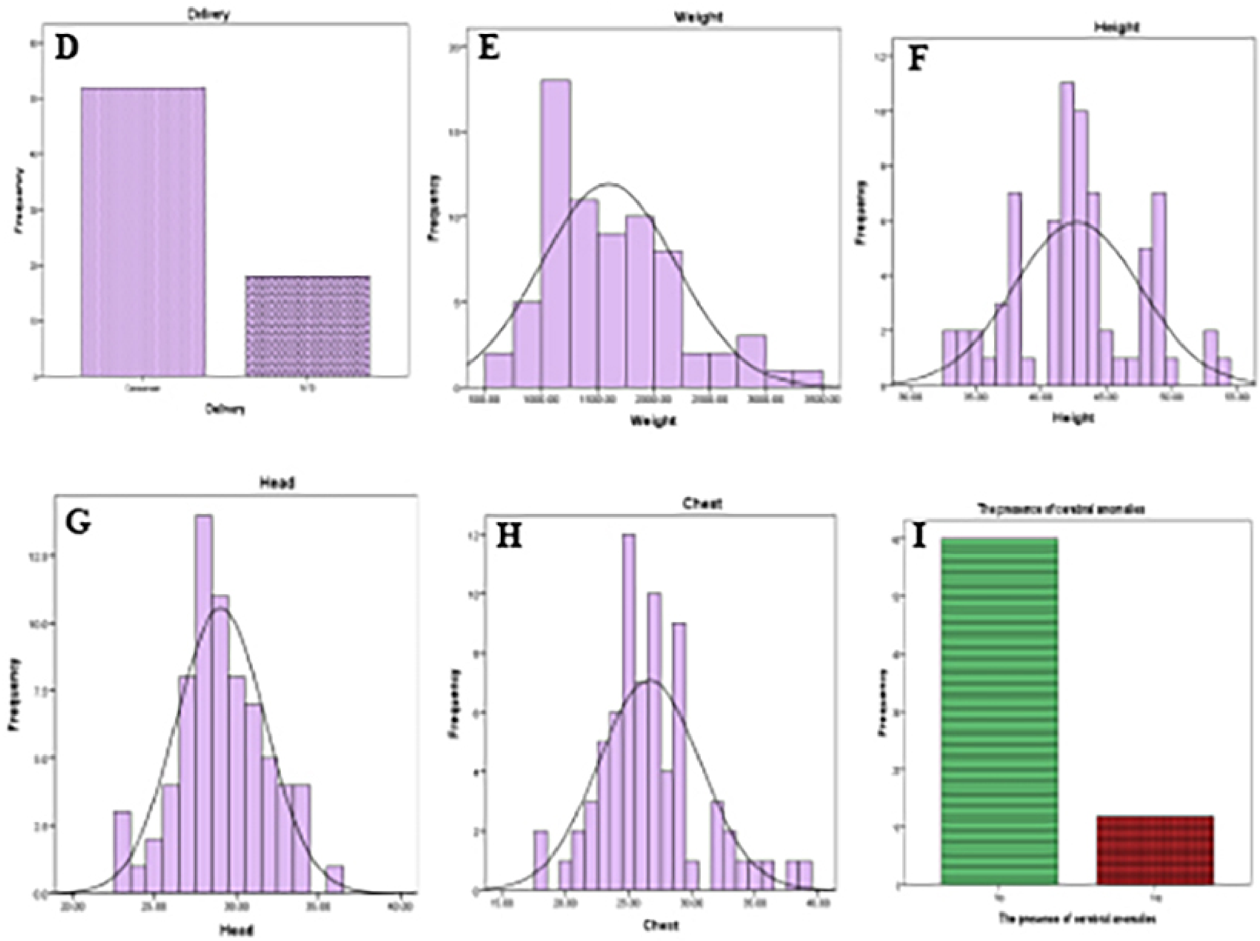
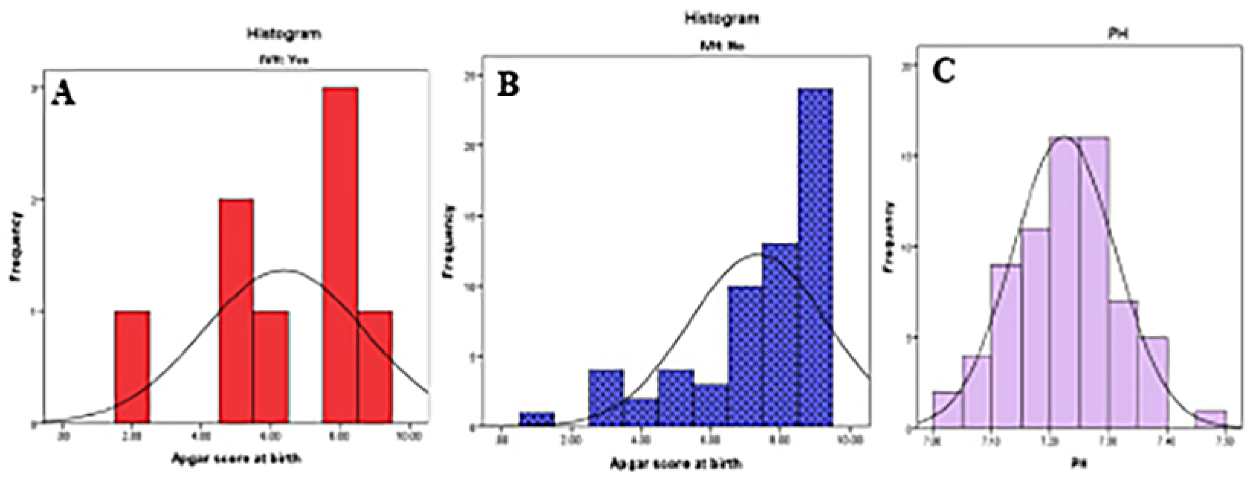


FIGURE 2. A) HISTOGRAM OF APGAR SCORE IN THE FIRST MINUTE IN THE GROUP OF INFANTS WITH INTRAVENTRICULAR HEMORRHAGE; B): HISTOGRAM OF APGAR SCORES IN THE FIRST MINUTE IN THE GROUP OF INFANTS WITHOUT INTRAVENTRICULAR HEMORRHAGE; C): pH LEVELS OF NEONATES' BLOOD; D): THE LEVEL OF HCo3 IN THE NEONATES' BLOOD; E): Pco2 LEVELS IN INFANTS' BLOOD; F): pH HISTOGRAM OF NEONATAL BLOOD AMONG INFANTS WITH INTRAVENTRICULAR HEMORRHAGE; G): BLOOD pH LEVEL IN INFANTS WITHOUT INTRAVESICAL HEMORRHAGE; H): HISTOGRAM OF BLOOD Pco2 LEVEL IN INFANTS WITH INTRAVENTRICULAR HEMORRHAGE; I): HISTOGRAM OF BLOOD Pco2 LEVEL IN INFANTS WITHOUT INTRAVENTRICULAR HEMORRHAGE.



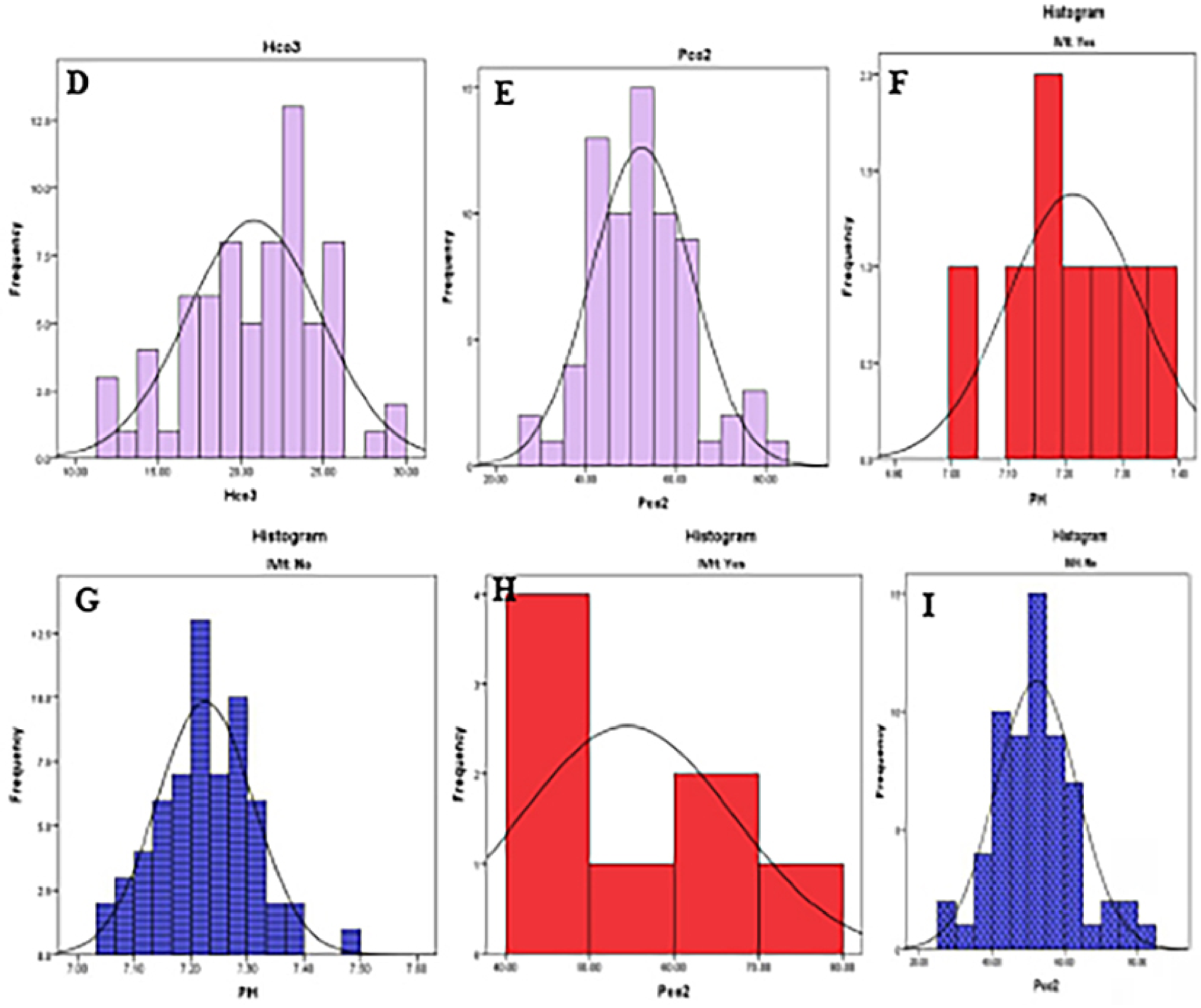
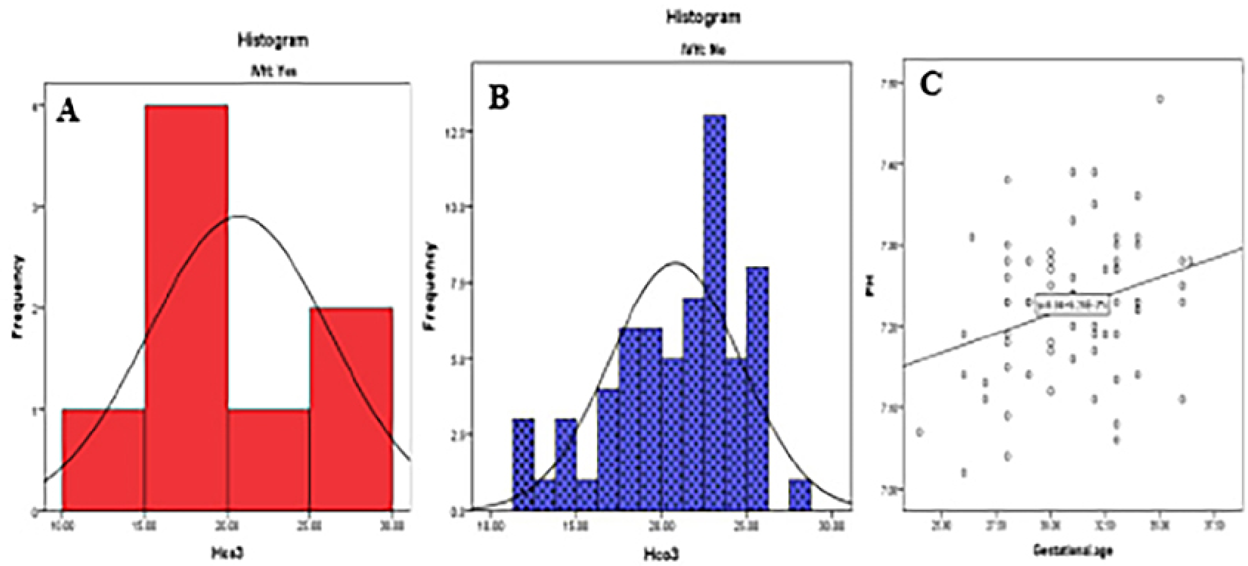


FIGURE 3. A) HISTOGRAM OF BLOOD HCo3 LEVEL IN INFANTS WITH INTRAVENTRICULAR HEMORRHAGE; B): HISTOGRAMS OF BLOOD HCo3 IN INFANTS WITHOUT INTRAVENTRICULAR HEMORRHAGE; C): DISTRIBUTION OF FETAL AGE BASED ON pH IN ALL INFANTS; D): DISTRIBUTION OF EMBRYONIC AGE REGARDING pH IN INFANTS WITH INTRAVENTRICULAR HEMORRHAGE; E): DISTRIBUTION OF FETAL AGE PER WEEK REGARDING pH IN INFANTS WITHOUT INTRAVENTRICULAR HEMORRHAGE.



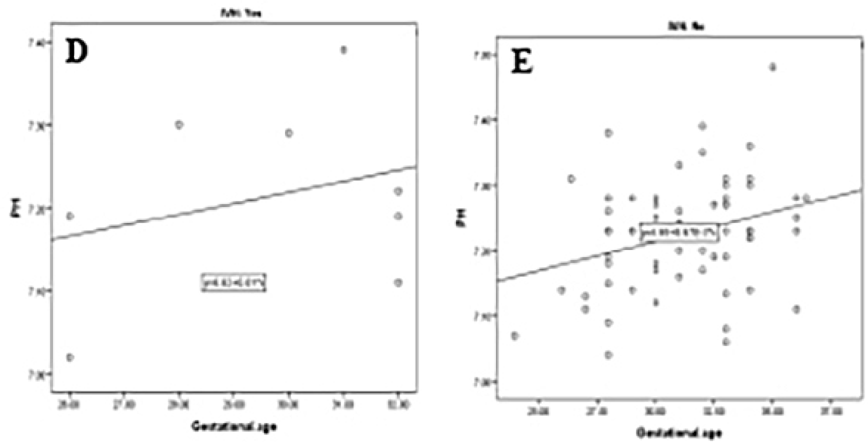


TABLE 1. FREQUENCY OF DISTRIBUTION OF INFANTS PER AGE GROUPS

Age group (weeks)	Frequency
25 ≥	1 infant (4/1%)
29-25	17 infants (9/23%)
32-29	19 infants (8/26%)
36-32	29 infants (8/40%)
36 ≤	5 infants (7%)
Missing	1 infant (4/1%)
Total	72 infants (100%)

TABLE 2. NEONATAL CHARACTERISTICS BASED ON INTRAVENTRICULAR HEMORRHAGE

Variable group	Sex		Type of delivery	
	Male	Female	Cesarean	Natural
Intraventricular hemorrhage	2Neonatals (25%)	6 Neonatals (75%)	6	2
Without intraventricular hemorrhage	40 Neonatals (5/62%)	21Neonatals (4/34%)	46	16
P-value	049/0 *		000/1	

*The statistical test was chi-square and the significance level was 0.05.

TABLE 3. NEONATAL CHARACTERISTICS ACCORDING TO INTRAVENTRICULAR HEMORRHAGE

	Intraventricular hemorrhage	Without intraventricular hemorrhage	P-value
Weight	96/330 ± 25/1416	326/625±37/1621	3/0
Height	46/2 ± 50/27	71/2 ±21/29	09/0
Round the head	64/3±12/41	95/4±94/42	3/0
Round the chest	4/4 ±56/26	05/4 ±64/26	9/0
Apgar Score	32/2 ±37/6	99/1 ±36/7	2/0

TABLE 4. COMPARISON OF CORD BLOOD GASES BASED ON THE INTRAVENTRICULAR HEMORRHAGE

Variable Group	pH	PCo2	HCo3
Intraventricular hemorrhage	11/0 ±21/7	61/12 ±43/54	50/5±71/20
Without intraventricular hemorrhage	08/0 ±22/7	12/11 ±17/52	86/3±79/20
P-value	7/0	5/0	9/0

TABLE 5. COMPARISON OF THE pH OF THE UMBILICAL CORD BLOOD PER PRESENCE OF INTRAVESICAL HEMORRHAGE

Type of delivery Group		Cesarean	Natural	P-value
pH	Intraventricular hemorrhage	09/0 ±23/7	19/0 ±16/7	4/0
	Without intraventricular hemorrhage	07/0 ±22/7	12/0 ±23/7	6/0

TABLE 6. CORD BLOOD pH ACCORDING TO GENDER

Sex Group		Male	Female	P-value
pH	Intraventricular hemorrhage	14/0 ±29/7	10/0 ±18/7	3/0
	Without intraventricular hemorrhage	07/0 ±23/7	08/0 ±22/7	4/0

TABLE 7. pH OF THE UMBILICAL CORD IN THE PRESENCE OF ANOMALIES

P-value	No	Yes	Anomaly Group	
7/0	10/0 ±23/7	13/0 ±20/7	Intraventricular hemorrhage	pH
03/0 *	08/0 ±23/7	07/0 ±16/7	Without intraventricular hemorrhage	

*The statistical test was chi-square and the significance level was 0.05.

RESUMO

OBJETIVOS: *Medimos o nível de gases de pH em bebês prematuros, no nascimento dos neonatos, e examinamos a relação entre a ecografia cerebral no terceiro e no sétimo dia após o nascimento. Um estudo de casos e controles realizados na Unidade de Cuidados Intensivos Neonatais (UCIN) do Hospital Shahid Akbar Abadi durante os anos de 2016-2017, Irã.*

MÉTODOS: *Todos os recém-nascidos prematuros que deram entrada na UCIN foram inscritos no estudo atual. Ao nascer, foi retirada uma amostra de gás em sangue, do sangue do cordão umbilical dos bebês. No terceiro e sétimo dia após o nascimento, um radiologista realizou uma ecografia do cérebro de cada neonato. O cordão umbilical foi avaliado para detectar gases no sangue em 72 neonatos (em sua maioria do sexo masculino).*

RESULTADOS: *Sessenta e seis recém-nascidos tinham ecografia normal e 16.7% (12 casos) tinham anomalias. 75% das 8 crianças com hemorragia intravenosa eram meninas, que foram significativamente diferentes das do grupo não hemodinâmico (62.5% homens) (P.0.049). Contudo, o tipo de parto, o peso médio, a altura, o perímetro cefálico, a circunferência do tórax e a pontuação de Apgar não foram diferentes entre os grupos. O pH médio, HCO3 e PCO2 nas amostras de gás no sangue do cordão umbilical não foram significativamente diferentes entre dois grupos com ou sem hemorragia intraventricular (Hiv). Apesar de não estar relacionado com o gênero e o tipo de parto em recém-nascidos.*

Conclusão: os gases sanguíneos não ajudam a determinar o aparecimento de Hiv nos bebês. Contudo, está associado com a imaturidade e idade fetal.

PALAVRAS CHAVE: *Cordão umbilical. Gasometria. Hemorragia cerebral. Recém-Nascido.*

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