

Assessment of Risk Factors and Prognosis in Asphyxiated Infants

Hassan Boskabadi¹; Farah Ashrafzadeh¹; Hassan Doosti²; Maryam Zakerihamidi^{3,*}

¹Department of Pediatrics, School of Medicine, Mashhad University of Medical Sciences, Mashhad, IR Iran

²Department of Biostatistics and Epidemiology, School of Health, Mashhad University of Medical Sciences, Mashhad, IR Iran

³Department of Midwifery, School of Medicine, Tonekabon Branch, Islamic Azad University, Tonekabon, IR Iran

*Corresponding author: Maryam Zakerihamidi, Department of Midwifery, School of Medicine, Tonekabon Branch, Islamic Azad University, Tonekabon, IR Iran. E-mail: maryamzakerihamidi@yahoo.co.nz

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Background: Asphyxia is considered an important cause of morbidity and mortality in neonates. This condition can affect many vital organs including the central nervous system and may eventually lead to death or developmental disorders.

Objectives: Considering the high prevalence of asphyxia and its adverse consequences, the present study was conducted to evaluate the risk factors for birth asphyxia and assess their correlation with prognosis in asphyxiated infants.

Patients and Methods: This two-year follow-up cohort study was conducted on 260 infants (110 asphyxiated infants and 150 healthy neonates) at Mashhad Ghaem Hospital during 2007 - 2014. Data collection tools consisted of a researcher-designed questionnaire including maternal and neonatal information and clinical/laboratory test results. The subjects were followed-up, using Denver II test for 6, 12, 18, and 24 months (after discharge). For data analysis, t-test was performed, using SPSS version 16.5. P value ≤ 0.05 was considered statistically significant.

Results: Of 260 neonates, 199 (76.5%) and 61 (23.5%) cases presented with normal neonatal outcomes and with abnormal neonatal outcomes (developmental delay), respectively. Variables such as the severity of asphyxia ($P = 0.000$), five-minute Apgar score ($P = 0.015$), need for ventilation ($P = 0.000$), and severity of acidosis at birth ($P = 0.001$) were the major prognostic factors in infants with asphyxia. Additionally, prognosis was significantly poorer in boys and infants with dystocia history ($P = 0.000$).

Conclusions: Prevalence of risk factors for developmental delay including the severity of asphyxia need for mechanical ventilation, and severity of acidosis at birth, dystocia, and Apgar score were lower in surviving infants; therefore, controlling these risk factors may reduce asphyxia-associated complications.

Keywords: Asphyxia; Hypoxic-Ischemia Encephalopathy; Risk Factors; Denver II Test; Neonatal

1. Background

Perinatal asphyxia is a significant cause of neonatal mortality and neurological complications (1). Although the majority of these disorders are transient, the long-term consequences of asphyxia may affect the central nervous system (CNS), which can ultimately lead to cerebral palsy, epilepsy, and learning disabilities (2, 3).

There is considerable controversy over the definition and diagnosis of asphyxia. Apgar score, arterial blood gas, and signs of hypoxic-ischemic encephalopathy (HIE) are among the current criteria for the diagnosis of severe asphyxia. However, there is no correlation between patients' prognosis and the diagnostic criteria for asphyxia. About 25% of surviving asphyxiated newborns is likely to present with neurological problems. Annually, 4,000,000 babies are born with asphyxia, of whom 800,000 die and 800,000 suffer from the associated complications (2, 4, 5).

The incidence of asphyxia is 1 - 6 per 1000 births in developed countries and 5 - 10 per 1000 births in developing countries (6). According to statistics by world health or-

ganization (WHO), in developing countries 3% of infants (3.6 million people) suffer from moderate to severe asphyxia, of whom 23% (840,000) die, and almost the same number suffer from the associated consequences (2). Examination of the causes of neonatal mortality in Bushehr revealed that 22% of deaths are due to perinatal asphyxia (7).

Apgar score can be helpful in identifying newborns with fetal distress, intrauterine asphyxia, airway obstruction, CNS depression, and impaired airways. However, low Apgar score does not necessarily indicate fetal asphyxia, since other factors (e.g. prematurity, use of narcotics and sedatives) are also associated with reduced Apgar scores. Thus, Apgar score is not a predictive factor for consequent cerebral palsy in infants (5).

Klinger et al. (8) in a 5-year study on 244 children with HIE reported 64 deaths and 63 cases of severe neurodevelopmental disorders. Moreover, a retrospective study (1999 - 2000), which aimed to examine the risk factors for neonatal HIE in 17,706 Thai patients, showed that 84

infants were born with asphyxia. As the results indicated, 1- and 5-minute Apgar scores, male gender, umbilical cord prolapse, post mature birth, and instrumental delivery were among the risk factors for HIE, although only 5-minute Apgar score was statistically correlated with HIE (9).

Parents of surviving asphyxiated infants are greatly concerned about the future of their newborns. Despite the vast advances in the pathophysiology of asphyxia, no definite criteria have been determined for identifying the long-term prognosis in these patients. Despite the extensive worldwide research on this condition, less attention has been paid to the long-term prognosis of asphyxiated infants in Iran.

2. Objectives

Considering the high incidence of asphyxia and its adverse consequences, we aimed to perform a cohort study to evaluate the risk factors and prognosis in asphyxiated infants.

3. Patients and Methods

In this prospective study, we aimed to compare prognosis in asphyxiated and healthy newborns. The current cohort study was conducted on 260 infants, selected via available sampling at Mashhad Ghaem Hospital during 2007 - 2014.

The subjects were divided into case and control groups. The case group consisted of infants with asphyxia ($n = 110$) and the control group included healthy infants ($n = 150$). Ghaem Hospital is a tertiary referral hospitals in which approximately 2,000 children are born annually. This hospital is equipped with neonatal intensive care unit (NICU) (with 12 beds), a maternity care department (care level 1, 50 beds), and level 2 care (12 beds).

Infants with at least two of the following symptoms were allocated to the case group:

- 1) Signs of fetal distress (heart rate less than 100 bpm, lack of heart rate variability, and late deceleration);
- 2) Meconium-stained amniotic fluid plus hypotonia or bradycardia, or respiratory depression,
- 3) 1-minute Apgar score < 4 and/or 5-minute Apgar score < 7 ;
- 4) More than 1 minute of resuscitation with positive-pressure ventilation (PPV) and oxygen in the delivery room, and
- 5) $\text{pH} < 7.2$ or Base Excess (BE) > -12 during the first hour of life.

The exclusion criteria were as follows: 1) congenital malformations; 2) metabolic disorders; 3) congenital and prenatal infections; 4) signs of chorioamnionitis (body temperature $> 38^{\circ}\text{C}$, foul-smelling amniotic fluid, leukocytosis, and fever); 5) urinary tract infection during childbirth; and 6) parents' lack of cooperation.

Umbilical blood samples were collected immediately after birth. A single neonatologist performed examinations. Neurological function of the neonate at birth, and

on the second and 7th day of life was evaluated. This included a systematic assessment of mental status (level of alertness), function of cranial nerves and the motor and sensory systems, in particular spontaneous movement and muscle tone. Posture and resistance of muscles to passive movement were used to assess active tone. The infants with perinatal asphyxia were divided according to whether HIE developed within the first 7 days after birth. According to the criteria of Sarnat, HIE was classified as mild (Grade 1) if hyperexcitability, hyperalertness or hyper-reflexia persisted without seizures for at least 24 hour after birth; as moderate if the infant was lethargic, had hypotonia, weak primitive reflexes, pupil miosis and seizures; and as severe if the infant had apnea, flaccid weakness, frequent seizures, decelerated posture, or coma.

The outcome was classified as favorable (normal development) or adverse (developmental delay). A favorable outcome was defined as normal neurologic and good general condition at the end of 24 months. Adverse outcome was defined as the presence of at least delay in one domain of Denver test.

Patients were followed-up for 6, 12, 18, and 24 months after discharge, using Denver II test. Denver II is a tool for screening of developmental milestones between 0 - 6 years. The test screens the child in four areas: personal, social, fine and gross motor, and language. The Denver II is a revision and update of the DDST. Its interpretation was slightly modified from the DDST giving greater emphasis on the child's performance. The scale reflects what percentage of a certain age group is able to perform a certain task. Denver Scale is not a tool of final diagnosis, but a quick method to process large numbers of children in order to identify those that should be further evaluated. The tests cover four general functions: personal social (such as smiling), fine motor adaptive (such as grasping and drawing), language (such as combining words), and gross motor (such as walking). If the child has a delay in one domain, this is considered to be a mild developmental, if in two areas this is classified as moderate developmental delay and if in 3 or more domains, this was considered severe developmental delay (10).

Data collection tools included interview sheets and information forms including demographic, pregnancy, and childbirth-related data. The obtained results were described by tables and statistical charts and compared between the groups, using Chi-square, t-test, and Mann-Whitney (if necessary). For data analysis, SPSS version 16.5 was utilized. In addition, for determining the predictive factors, regression models were applied. P value < 0.05 was considered statistically significant.

4. Results

Of approximately 11,347 infants born during the study period, 110 infants presented with asphyxia, which accounted for about 1% of births. Overall, 260 infants were divided into control (150 healthy infants, 56.90%) and case (110 asphyxiated infants, 43.10%) groups.

Statistical analysis showed that 41.96% of asphyxiated infants with normal outcome were male and 58.04% female. Also, 64.40% of asphyxiated infants with abnormal outcome were male and 35.60% female.

There was a significant difference between the two groups in terms of first-hour pH ($P = 0.000$), 1-minute Apgar score ($P = 0.000$), 5-minute Apgar score ($P = 0.000$), and BE ($P = 0.000$); the values were lower in infants with asphyxia.

t-test results showed that 1-minute Apgar score ($P = 0.008$), 5-minute Apgar score ($P = 0.000$), urea level ($P = 0.016$), and serum creatinine level ($P = 0.032$) were significantly different between asphyxiated neonates with normal and abnormal outcome. There was no statistically significant difference between these two groups in terms of maternal age ($P = 0.095$) (Table 1).

Regarding the arterial blood gas changes in asphyxiated infants, the results showed no significant difference between the two groups in terms of 24-hour pH ($P = 0.346$), 48-hour pH ($P = 0.117$), 24-hour BE ($P = 0.511$), 48-hour BE ($P = 0.131$), 48-hour HCO_3^- ($P = 0.117$), partial pressure of carbon dioxide during the first hour (PCO_2) ($P = 0.087$), 24-hour PCO_2 ($P = 0.325$), or 48-hour PCO_2 ($P = 0.806$).

However, there was a significant difference between the two groups of asphyxiated infants regarding first-hour pH ($P = 0.000$), first-hour BE ($P = 0.000$), first-hour HCO_3^- ($P = 0.013$), and 24-hour HCO_3^- ($P = 0.040$); these variables

had lower values in asphyxiated infants with consequent abnormal outcomes (Table 2).

The neonatal outcomes were re-evaluated 6, 12, 18, and 24 months after birth. Of 110 asphyxiated cases, 50 (45.5%) had normal development, 29 (26.3%) passed away, and 31 (28%) presented with developmental delay including 13 (8.11%) patients with mild, 7 (4.6%) with moderate, and 11 (10%) with severe developmental delay.

In this study, a statistically significant association was observed between HIE severity and patients' prognosis; i.e., with increased severity of HIE, incidence of developmental delay increased. In the control group, 14 (32.55%) cases had no HIE, 26 (40.46%) presented with HIE grade I, and 3 (6.97%) were identified with HIE grade II. In the case group, 1 (1.69%) case had no HIE, 7 (11.86%) cases presented with HIE grade I, 27 (45.76%) were identified with HIE grade II, and 25 (42.37%) had HIE grade III.

Overall, 38 infants with poor and 5 infants with good prognosis were ventilated ($P < 0.001$). Dystocia was identified in 35 with poor and in 5 infants with good prognosis, ($P < 0.001$). Chi-square test results showed a significant difference in terms of sex ($P = 0.003$) and obstetric complications ($P = 0.000$) between asphyxiated neonates with normal and abnormal outcomes. However, mode of delivery ($P = 0.161$) and pregnancy-related complications ($P = 0.081$) were not significantly different between these two groups (Table 3).

Table 1. Comparison of Maternal and Neonatal Parameters in Asphyxiated Infants With Normal and Abnormal Outcomes^a

| Parameters | Asphyxiated Infants With Normal Outcomes (n = 50) | Asphyxiated Infants With Abnormal Outcomes (n = 60) | Significance Level (t-Test) |
|----------------------|---|---|-----------------------------|
| Maternal age, y | 27.83 ± 6.02 | 26.47 ± 5.45 | 0.095 |
| Urea, mg/dL | 18 ± 7.83 | 50.30 ± 25.97 | 0.016 |
| Creatinine, mg/dL | 0.53 ± 0.22 | 0.88 ± 0.49 | 0.032 |
| 1-minute Apgar score | 5.17 ± 1.84 | 4.28 ± 1.50 | 0.008 |
| 5-minute Apgar score | 7.73 ± 1.61 | 5.98 ± 1.68 | 0.000 |

^a Data are presented as mean ± SD.

Table 2. Arterial Blood Gas Characteristics in Asphyxiated Infants With Normal and Abnormal Outcome^a

| Parameters | Sampling Time | Asphyxiated Infants With Normal Outcomes (n = 50) | Asphyxiated Infants With Abnormal Outcomes (n = 60) | Significance Level (t-Test) ^b |
|--------------------|-------------------------------|---|---|--|
| pH a | within the first hour of life | 7.24 ± 0.09 | 7.10 ± 0.14 | 0.000 |
| pH b | 24 hours after birth | 7.31 ± 0.04 | 7.29 ± 0.10 | 0.346 |
| pH c | 48 hours after birth | 14.37 ± 17.22 | 9.45 ± 9.74 | 0.361 |
| BE a | within the first hour of life | -10.09 ± 5.23 | -12.76 ± 7.25 | 0.047 |
| BE b | 24 hours after birth | -5.24 ± 2.61 | -5.93 ± 5.52 | 0.511 |
| BE c | 48 hours after birth | -0.23 ± 10.90 | -5.84 ± 6.84 | 0.131 |
| HCO_3^- a | within the first hour of life | 17.38 ± 2.64 | 13.14 ± 4.93 | 0.018 |
| HCO_3^- b | 24 hours after birth | 20.49 ± 3.59 | 18.01 ± 5.61 | 0.040 |
| HCO_3^- c | 48 hours after birth | 22.26 ± 8.02 | 17.66 ± 7.38 | 0.117 |

^a Data are presented as mean ± SD.

^b P value < 0.05 was considered significant.

According to data analysis by regression models, variables such as 5-minute Apgar score ($P = 0.015$), use of ventilators ($P = 0.000$), and first-hour pH ($P = 0.001$) were important factors for determining prognosis in infants with asphyxia. One-minute Apgar score ($P = 0.929$) was not a reliable criterion for determining prognosis in patients. Moreover, 5-minute Apgar score was not associated with first-hour pH ($P = 0.000$) (Table 4).

In 89.9% of cases, the risk of developmental delay can be determined based on variables such as severity of HIE, ventilation, one-minute Apgar score, and 5-minute Apgar score (Table 5).

5. Discussion

In this study, approximately 26% of infants with asphyxia died and 28% presented with developmental delay during a 2-year follow-up. The severity of HIE, need for ventilators, first-hour pH, and 5-minute Apgar score were important predictive factors for long-term neonatal complications. Our results showed that about a quarter of infants died

from asphyxia and a larger number suffered from developmental delays. Overall, the mortality rate associated with asphyxia varies between 16% and 72%, according to previously conducted studies (6, 7). In a study by Klinger et al. (8) on 244 children with HIE, 26% of the subjects died, and 25% presented with neuro-motor dysfunctions, results which are almost similar to the present findings.

HIE is seen as an important cause of morbidity and mortality in infants. Given the fact that Ghaem Hospital, affiliated to Mashhad University of Medical Sciences, is one of the two main centers for high-risk pregnancies in Mashhad city, increased incidence of birth asphyxia can be related to the increased number of high-risk pregnancies, women's late referral to hospital, and poor surveillance, resuscitation, and transfer systems. Prenatal and childbirth care, proper monitoring during labor, presence of a resuscitation team in the delivery room, appropriate resuscitation and stabilization, and proper transfer of the infant to the ward can reduce the associated infant mortality (11).

Table 3. Comparison of Maternal and Neonatal Parameters Between the Two Groups of Asphyxiated Infants With Normal and Abnormal Outcomes

| Parameters | Asphyxiated Infants With Normal Outcomes (n = 50), ^a | Asphyxiated Infants With Abnormal Outcomes (n = 60), ^a | P Value (Chi-Square) ^b |
|--------------------------------------|---|---|-----------------------------------|
| HIE severity | | | 0.000 |
| Without HIE | 14 (32.55) | 1 (1.69) | |
| HIE grade I | 26 (60.46) | 7 (11.86) | |
| HIE grade II | 3 (6.97) | 27 (45.76) | |
| HIE grade III | 0 (0) | 25 (42.37) | |
| Normal development | 50 (100) | 0 (0) | 0.000 |
| Mild developmental delay | 0 (0) | 13 (11.8) | 0.000 |
| Moderate developmental delay | 0 (0) | 7 (6.4) | 0.000 |
| Severe developmental delay | 0 (0) | 11 (10) | 0.000 |
| Neonatal mortality | 0 (0) | 29 (26.4) | 0.000 |
| Male | 21 (35) | 38 (64.40) | 0.003 |
| Female | 29 (65) | 21 (35.60) | 0.003 |
| Natural delivery | 13 (26) | 21 (40.38) | 0.117 |
| Cesarean section (emergency) | 37 (74) | 31 (59.62) | 0.117 |
| Normal delivery | 35 (89/74) | 10 (41/66) | 0.000 |
| Abnormal delivery^c | 4 (10/26) | 14 (50) | 0.000 |

^a Values are presented as No. (%).

^b P value < 0.05 was considered significant.

^c Placental abruption, placenta praevia, impaired monitoring during labor, and dystocia.

Table 4. Some Prognostic Factors in Infants With Asphyxia, According to the Regression Model

| Some Prognostic Factors | P Value |
|-----------------------------|---------|
| Severity of HIE | 0.000 |
| 5-minute Apgar score | 0.015 |
| Use of ventilators | 0.000 |
| First-hour pH | 0.001 |

Table 5. Evaluation of the Risk of Developmental Delay, Based on the Severity of HIE, Use of Ventilators, First-hour pH, and 5-Minute Apgar Score

| Step | Log-Likelihood | Cox and Snell R-Square | Nagelkerke R-Square | Percent Correct (Overall Percentage) |
|------|---------------------|------------------------|---------------------|--------------------------------------|
| 1 | 37.394 ^a | 0.608 | 0.819 | 89.9 |

^a Hosmer and Lemeshow Test (P = 0.698).

In our study, higher incidence of asphyxia in infants with dystocia indicates the significance of maternal complications during pregnancy and childbirth. Therefore, the severity of consequent complications can be reduced by proper interventions, appropriate monitoring during labor, the presence of a pediatric specialist at the mother's bedside before delivery, and preparedness for a risky childbirth.

Based on the results, 1- and 5-minute Apgar scores in the control group were significantly lower than those reported in patients with asphyxia. However, comparison between the two subgroups with normal development and developmental delay showed that 5-minute Apgar score is significantly helpful in predicting children's development (P = 0.015) and can be among the most important prognostic factors for asphyxiated infants.

Furthermore, a statistically significant association was found between 1- and 5-minute Apgar scores and first-hour pH (P = 0.000). Similarly, In Toh's study (12), low 5-minute Apgar score, use of adrenaline, and low initial arterial pH were significant risk factors for asphyxia. Kaveh et al. (13) showed a significant correlation between Apgar score and arterial blood gas within the first hour of life, i.e. arterial pH in infants with low Apgar score was lower. There was also a direct correlation between low Apgar score and asphyxia. Hence, infants born with low Apgar scores may suffer from acidosis, alkaline deficiency, asphyxia, and require special treatment. On the other hand, in other studies, Apgar score in infants with consequent cerebral palsy was shown to be normal, and incidence of cerebral palsy was low in infants with low Apgar score (5-minute Apgar score: 0 - 3) (13, 14). Therefore, Apgar score cannot be the sole criterion for the identification of infants with birth hypoxia and asphyxia.

The present study indicated a statistically significant association between HIE severity and long-term prognosis in infants, i.e. with increasing severity of HIE, incidence of developmental delay increases. In fact, 19% of infants with HIE grade I, 58% with HIE grade II, and 100% with HIE Grade III had developmental disorders. Shireen et al. (6) also indicated that the incidence of developmental delay in infants with asphyxia increases with problems such as prematurity, low birth weight, and increased severity of HIE. In this regard, Soleimani and colleagues (15) indicated a relationship between delayed motor development and asphyxia.

Hatami et al. (7) examined the impact of moderate to severe HIE in neonates in Bushehr, Iran during five years. They showed that among 17 surviving infants, 5 (30.4%) cases suffered from developmental disorders (2 and 3 pa-

tients developed mild and severe cerebral palsy, respectively) and 12 (6.70%) cases were healthy. Thus, a surviving infant with moderate to severe asphyxia needs proper planning and care. Overall, evaluation of nutritional status, vision and hearing examinations, treatment of seizures, cognitive skill assessment, and language development evaluation are required for these patients (16).

In terms of sex, there was a statistically significant difference between asphyxiated infants with normal development and those with developmental delays (P = 0.003), i.e. 64% of infants with developmental delay were male. In a study by Mohamed and Aly (17), African-American ethnicity and male gender were significantly correlated with neonatal asphyxia. Moreover, Hussein et al. (18) evaluated the relationship between sex and cerebrospinal fluid levels of interleukin-8 (IL-8) and antioxidants in 32 asphyxiated neonates (19 boys and 13 girls). They found that male infants were more vulnerable to brain damage, compared to female newborns, since IL-8 and antioxidant levels and pro-oxidant-antioxidant balance in cerebrospinal fluid of female infants are higher (18).

In the current study, delivery-related complications were important risk factors for birth asphyxia. Majeed et al. (19) found that lack of prenatal care, poor nutritional status, prenatal bleeding, and maternal toxemia increased the incidence of asphyxia.

Utomo (3) found that prepartum hemorrhage, pre-eclampsia, preterm birth, post term birth, and low birth weight were among the risk factors for neonatal asphyxia. Hence, understanding the risk factors and promoting prenatal care can reduce the incidence of neonatal asphyxia and mortality rates.

Mode of delivery was among the evaluated variables in the present study. The results showed that this factor plays no major role in the incidence of birth asphyxia. However, Onyearugha and Ugboma (20) showed the (7.3 times) increased risk of neonatal asphyxia by cesarean section. In addition, Utomo (3) showed that cesarean section was a risk factor for asphyxia. Lack of association between mode of delivery and neonatal outcomes in our study may be related to delayed referral of women with obstetric complications and improper monitoring during labor.

In our study, neonatal asphyxia had no association with maternal age, which was consistent with findings of Shireen et al. (6). The results showed that pH, BE, and HCO₃ within the first hour and 24 hours after birth were different between asphyxiated newborns with normal development and those with developmental delays. In other words, the values of these variables in asphyxiated

neonates with developmental delay were lower than those reported in infants with normal development. Therefore, pH, BE, and HCO₃ changes during the first hour increase the possibility of poor prognosis in infants. Additionally, in case changes of HCO₃ persist into the next day, possibility of future complications increases. Kaveh et al. (13) also emphasized the relationship between arterial blood gas (including pH and BE) and Apgar score and showed that 90% of infants with Apgar scores < 7 had BE < -10, while 75% of newborns with Apgar scores > 7 had the same amount of BE. Fetal asphyxia is a condition in which blood gas variations lead to hypoxia, hypercapnia, and metabolic acidosis. Thus, detection of this condition during labor is needed to assess blood gas and blood's acid-base (21). Long-term follow up of infants, not checking the CT scan results and also lack of motivation in some parents of neonates were the limitations of this study.

Based on our findings, incidence of long-term complications in newborns with HIE is high and is directly associated with the severity of asphyxia. Risk factors for developmental delay in surviving asphyxiated infants included the severity of asphyxia, need for mechanical ventilation, severity of acidosis at birth, dystocia and obstetric labor complications, and low 5-minute Apgar score. Therefore, it seems that with proper care during pregnancy, fetal control and surveillance during labor, and proper resuscitation and stabilization, the associated adverse outcomes can be reduced. Finally, special attention should be paid to the prognosis of infants with moderate or severe HIE, metabolic acidosis, and those requiring mechanical ventilation.

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