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(RESEARCH ARTICLE)

The prevalence, consequences, and outcome of perinatal asphyxia in term and late preterm live-born neonatesA A case-control study from Iran

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Abstract

Background: Despite several investigations reporting the prevalence of asphyxia in developed and developing countries, very few studies from Iran have demonstrated the rate of neonatal asphyxia and its affecting factors. Objectives: This study aimed to determine the prevalence of asphyxia, its consequences, and neonatal outcomes among Iranian term and late preterm live-born neonates.

Methods: A case-control study was conducted in three hospitals; Vali-e-Asr, Yas, and Ziaean from April 2019 to March 2020. The case group included neonates with a history of perinatal asphyxia. Twice gestational age-matched subjects without such a history also entered the study as the control group. All maternal and neonatal data were collected from participants' medical records. Determining the prevalence of neonatal asphyxia was the primary outcome of the present study.

Results: Totally 48 subjects as the case and control groups were included and 16 asphyxiated cases were observed equal to 3.3 per 1000 live-born neonates. Concerning the type of delivery, cesarean section in the control group and vaginal delivery in the case group were the most frequent types of delivery (p=0.041). Comparing neonatal variables, the results showed a significant difference regarding the groups' genders (p=0.036). Apgar scores in the case group were also significantly lower than the control group (p=0.0001). More cases also required PPV compared to the controls (12 vs. 0; p=0.0001). Hypoxic-ischemic encephalopathy (HIE) grade 1 was also significantly more frequent in the case group than the controls (p=0.0001). The means of pH and base excess in the case group were significantly lower than the control group (p=0.0001).

Conclusion: The results showed the prevalence rate of asphyxia among term and late preterm participants was 3.3 cases per 1000 live-born neonates. Apgar scores<5 accompanied with metabolic acidosis, HIE, and requirement of PPV could be predictive variables for perinatal asphyxia. Observing such clinical risk factors may indicate the need of early diagnosis and timely interventions to improve neonatal outcomes.

Keywords: Asphyxia; Hypoxic ischemic encephalopathy; Neonatal death; Apgar score

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1. Introduction

Perinatal asphyxia is a condition with disturbed blood flow, gas exchange, and oxygen deprivation at any time of gestation, delivery, and post-natal. Perinatal asphyxia is a leading cause of hypoxemia, hypercapnia, and metabolic acidosis. It is a contributing factor for hypoxic-ischemic encephalopathy (HIE), multiple organ failure, or end-organ sequelae [1, 2]. The rate of perinatal asphyxia is about 1.5% among live-born neonates with acceptable prenatal healthcare facilities [3]. Asphyxia accounts for about 20% of perinatal deaths and is the second cause of neonatal mortality after infections [4]. The prevalence of asphyxia inversely correlates to the neonate's gestational age and birth weight [5, 6].

Perinatal hypoxia-ischemic event can result in lowering Apgar scores, fetal umbilical artery acidemia and base deficit, evidence related to acute brain injury, manifestations related to multiple organ failure (MOF) due to HIE, encephalopathy, hypotension, seizures, and lack or weakness of sucking [7, 8]. Maternal, fetal, placental, and neonatal complications like hypo/hypertensive disorders, hypoxia induced by cardiopulmonary diseases, anemia, diabetes, persistent epilepsy, the placenta or umbilical cord accidents, congenital anomalies, chorioamnionitis, and infections are the main risk factors of asphyxia [1, 4, 5].

Despite several investigations reporting the prevalence of asphyxia in developed and developing countries [5, 6, 9, 10], very few studies from Iran [11-13] have demonstrated the rate of neonatal asphyxia and its affecting factors. Hence, considering neonatal asphyxia as an important cause of mortality and morbidity, this study aimed to determine the prevalence of asphyxia, its consequences, and neonatal outcomes among Iranian term and late preterm live-born neonates.

2. Material and methods

A case-control study was conducted in three hospitals affiliated with Tehran University of Medical Sciences; Vali-E-Asr, Yas, and Ziaean from April 2019 to March 2020. The case group included neonates with a history of perinatal asphyxia. Twice gestational age-matched subjects without such a history also entered the study as the control group. Inclusion criteria for the case group were gestational age≥34 weeks and a positive history of asphyxia. Criteria for asphyxia were the presence of at least one of the following clinical characteristics; Apgar scores<5 at 5 and 10minutes, fetal umbilical artery pH<7.0 or base deficit≥12 mmol/L, evidence related to acute brain injury and hypoxia-ischemia according to imaging examination, and MOF signs due to HIE [14].

The exclusion criteria were congenital anomalies, neurological disorders due to metabolic diseases, medication administration, sepsis, and meningitis. Neonates with incomplete data were also exited from the study.

All maternal and neonatal data were collected from participants' medical records and recorded in a checklist. These data composed of maternal age, body mass index (BMI), parity, literacy level, type of delivery (cesarean section, instrumental or vaginal delivery), any history of prenatal complications such as diabetes, hypertensive disorders, heart disease, anemia, chorioamnionitis, placental and umbilical cord accidents, antenatal hemorrhage, abnormal amniotic fluid volume, uterine tetanus, uterine rupture, prolonged delivery, dystocia, fetal presentation, fetal bradycardia, meconium passage, the prolonged rapture of the membrane (PROM>18h), neonate's gender, gestational age, birth weight, umbilical artery abnormalities, meconium aspiration syndrome, Apgar scores, the results of blood gas test, neonatal death during hospital admission, RDS, pneumonia, pneumothorax, the requirement of respiratory support and mechanical ventilation. In determining a neonate's HIE, the findings of the imaging examination were interpreted. The criteria for HIE and its stages were determined according to Sarnat's criteria [15].

The present study was approved by the Institutional Review Board of the Tehran University of Medical Sciences according to the Helsinki Declaration (IR.TUMS.MEDICINE.REC.1398.879). Participant's information was considered confidential and no cost was imposed on patients.

Determining the prevalence of neonatal asphyxia among term and late-preterm neonates born in three Iranian hospitals was the primary outcome of the present study. The possible influencing factors on perinatal asphyxia were also assessed as the secondary outcome.

2.1. Statistical analysis

The collected data were recorded and analyzed using the SPSS version 22 database; the significant level was considered p-value<0.05. Qualitative data for both groups were expressed by absolute and relative frequencies. Quantitative variables were also demonstrated by Mean±stand ard deviation. Analytical statistics were performed using the ANOVA

and Kruskal-Wallis tests to compare the groups' quantitative variables with and without normal distribution, respectively. The Chi-square test was also used to compare qualitative data between the groups. As the Kolmogorov-Smirnov test showed non-normal distribution, the Mann-Whitney test was implemented to compare all quantitative variables between the two groups.

3. Results

Totally 48 subjects as the case and control groups were included. The means of maternal age, gestational age, and birth weight were 28±5.9 years, 37.98±1.2 weeks, and 3205±490.2 grams, respectively. No participants received antenatal corticosteroid therapy. Umbilical cord prolapse was observed in 2 (4.2%) and the placental accidents were found in 3 subjects (6.3%). Breech presentation and shoulder dystocia were reported in 2 neonates. Uterine rupture was not observed and all participants had normal amniotic fluid volume. No cases showed chorioamnionitis, oligo/hydramnios, uterine tetanus, and rupture. PROM was reported in one and 3 neonates had the history of meconium-stained amniotic fluid.

Of all 4902 deliveries during a year; 2410 were reported from Yas hospital, 850 from Ziaean, and 1642 from Vali–E-Asr. Totally 16 asphyxiated cases were observed equal to 3.3 per 1000 live-born neonates. The frequency of asphyxia in different hospitals was 4(2.4 per 1000 live-born neonates) in Vali-E-Asr Hospital; 5 (5.9 per 1000) in Ziaean Hospital; and7 (2.9 per 1000) in Yas Hospital. Thirty–two live-born neonates also entered into the study as the control group. Of all included neonates, 29 (60.4%) were male. Grade 3 HIE was not observed in any case, one case showed grade 2 and the others had grade 1 HIE. No neonatal death was reported during neonates' hospital admission.

Table 1 Comparison of maternal variables between the case and control groups

Maternal variables	Case Group	Control Group	P value
Educational level (n%) <Diploma ≥Diploma	3(18.8) 13(81.3)	12 (37) 20(62.5)	0.161
Maternal age (Mean±SD)	29.8±5.1	28.3±6.4	0.290
Mother's BMI (Mean±SD)	28.3±2.2	28.1±3.3	0.16
Number of parity (Mean±SD)	1.4±1.4	2.2±1.4	0.06
Diabetes (n%)	4(25)	4(12.5)	0.242
Receiving prenatal care (n%)	14(93.3)	32(100)	0.326
Hypertensive disorders (n%)	2(12.55)	1(3)	0.254
Infectious diseases (n%)	0	2(6.3)	0.44
Type of delivery (n%) C/S NVD	5(31) 11(69)	20(62.55) 12(37.5)	0.041

C/S: Cesarean section, NVD: Normal vaginal delivery

Analyses of data showed no significant differences between the groups regarding several maternal variables like the means of age (p=0.290), BMI (p=0.16), and number of parity (p=0.06). Concerning the type of delivery, the results showed a significant difference between the groups (p=0.041); cesarean section in the control group and vaginal delivery in the case group were the most frequent types of delivery. Of all mothers, 45received prenatal care in which all the controls' mothers received prenatal care while 93.3% of cases' mothers received prenatal care (p=0.326). Although the history of prenatal hypertensive disorders and diabetes were more frequent among the cases' mothers than the controls'; the differences were not significant (p=0.254and p=0.242). Comparing maternal infectious diseases between the groups, the results showed no significant difference (2 vs. 0; p=0.44). Detailed data are shown in Table 1.

Comparing neonatal variables, the majority of cases were male (81%) while female and male ratios in the control group were equal. The results showed a significant difference regarding the groups' genders (p=0.036). The Apgar scores at 5 and 10 minutes in the case group were also significantly lower than these values in the control group (p=0.0001). HIE

grade 1 was also significantly more frequent in the case group than the controls (p=0.0001). No significant differences were observed in means of gestational age (p=0.385) and birth weight (p=0.751) between the groups. More cases also required positive-pressure ventilation (PPV) compared to the controls (12 vs.0; p=0.0001). The analyses of the results related to umbilical arterial blood gas tests showed statistically significant differences in pH and base excess (BE) levels between the groups. The means of factors in the case group were significantly lower than the control group (p=0.0001). The mean level of PCO_2 in the case group was higher than this value in the control group; however, the difference was not significant (p=0.178). Although neurologic sequel was more frequent in the case group than the control group, the difference was not significant (p=0.132). There were also no significant differences between the groups concerning the growth parameters, frequency of advanced resuscitation, mechanical ventilation, and positive history of pneumonia and pneumothorax or the presence of neurogenic sequel (p>0.05) (Table 2).

Table 2 Comparison of neonatal variables between the case and control groups

Neonatal Variables	Case group	Control group	P value
Gender (n%) Male Female	13(81) 3(19)	16(50) 16(50)	0.036
Gestational age(week; Mean±SD)	38.1±1.5	37±92	0.385
Birth weight(g; Mean±SD)	3194±550	3210±467	0.751
Birth height (Cm; Mean±SD)	50.78±4.68	50.18±2.16	0.571
Birth head circumference (Cm; Mean±SD)	34.53±1.69	34.43±1.12	0.466
Apgar score at 5 minutes(Mean±SD)	4.3±3.3	8.6±0.6	0.0001
Apgar score at 10 minutes(Mean±SD)	6.7±1.8	9.4±0.6	0.0001
Results of Blood gas test pH HCO_3 (meq/l; Mean±SD) Base Excess (Mean±SD) P CO_2 (mmHg; Mean±SD)	 7.10±0.13 11.3±7.1 -11.6±7 48.2±16	 7.31±.10 17.8±6.0 1.4±5.9 37.6±14.6	 0.0001 0.0001 0.0001 0.178
Requirement of positive-pressure ventilation (n %)	12 (75)	0	0.0001
Requirement of advanced resuscitation (n %)	1 (6)	0	0.333
Requirement of mechanical ventilation (n/%)	2 (12.5)	1 (4)	0.308
History of pneumonia (n %)	3 (19)	3 (11)	0.394
History of pneumothorax (n %)	1 (6)	0	0.372
Neurologic sequel (n %)	2 (12.5)	0	0.132
Hospitalization period (day; Mean±SD)	11.42±11.18	5.6538±3.35	0.106
HIE grade 1	7 (43.8)	0	0.0001
Neonatal death	0	0	-

4. Discussion

Regarding definition of perinatal asphyxia, different studies reported different criteria. For instance, based on the American College of Obstetrics and Gynecology Report, all criteria including low umbilical blood pH, low Apgar score (0-3) at 5 minutes, neurologic sequel, and MOF are needed for diagnosis of asphyxia [16]. Another study defined asphyxia with at least two of following criteria; Apgar scores ≤5 at 10minutes, resuscitation attempts in the first 10 minutes of life, and blood academia (pH<7 or BE>12) [10]. The evidence of perinatal asphyxia was considered pH<7 or BE>12 and HIE presentations by the other study [17]. Neonates with 3 of following characteristics including pH<7.2, 5 minutes Apgar score<6, requirement of PPV, and any sign of fetal distress were also considered as asphyxiated cases in

the other investigation [18]. In the present study, we included each case with any criterion of asphyxia to show the most frequent criteria among our target population.

The present study investigated the prevalence and associated consequences of neonatal asphyxia among live-born neonates in three hospitals. Of 4902 live-born deliveries, 16 asphyxiated neonates were reported. The prevalence of asphyxia among our participants was 3.3 cases per 1000 live-born neonates. According to the world health organization (WHO) report, the prevalence of asphyxia varies from 2 to 10 per 1000 term newborns worldwide depending on the availability of medical facilities [19]. The prevalence rate of asphyxia in the present study was lower than the other reported rate from Iran; Khodaparast et al. (Bojnurd, Iran; 2013-15) showed that after implementing a health improvement program, the prevalence rate of asphyxia decreased from 10.5 to 5.4/1000 [20]. Another study from Iran (Isfahan) demonstrated birth asphyxia in about 0.3% of neonates born in 2013 and 2014 [21]. The results of two investigations from Zambia and Ethiopia also demonstrated higher rates of perinatal asphyxia by 23% and 18% among NICU-admitted neonates, respectively [22, 23]. This discrepancy in the results may correlate to study design, definitions of asphyxia, number of sample size, earlier diagnosis, and improved interventions.

The rate of asphyxia in one of the included hospitals (Ziaean Hospital) was almost two times higher (5.9 cases per 1000 live-born neonates) than in other centers (2.9 per 1000 in Yas Hospital and 2.4 per 1000 in Vali-E-Asr Hospital. As Ziaean Hospital is not a neonatal tertiary center, it seems that this higher rate of neonatal asphyxia correlates to the lack of medical facilities in the NICU ward. This finding shows the significant role of a tertiary hospital with well-trained staff and equipped NICU services in decreasing of adverse neonatal outcomes like asphyxia [24].

Based on the results, no neonatal death was reported among our subjects during hospital admission. Based on WHO, birth asphyxia is responsible for 4,000,000 neonatal deaths annually [19]. Comparing mortality rates due to asphyxia, studies demonstrated that asphyxia was responsible for about 0.1% of neonatal deaths in developed countries and 4 to 26 per 1000 live births in developing countries [5, 22].

According to our results, there was a significant relationship between the occurrence of asphyxia and normal vaginal delivery. In other words, 69% of the case group (vs. 37.5% in the control group) experienced vaginal delivery. This finding indicates that timely awareness and interventions should be implemented during vaginal delivery to prevent birth asphyxia in our centers. Considering asphyxia-related risk factors, tightly monitoring the progress of labor and cardiotocogram, as well as the availability of emergency cesarean section are some of the measures that improve neonatal outcomes [25]. Concerning the effect of type of delivery on the prevalence of asphyxia, the results of the literature are contradictory. Consistent with our results, Uwingabireet al. showed that normal vaginal delivery was a significant influencing factor for Asphyxia; more asphyxiated cases were born vaginally than cesarean section (47.3 vs. 24.6%; p=000) [26]. Sunny et al. reported that of 341 asphyxiated cases, about 60%, 13%, and 28% were born by spontaneous vaginal delivery, instrumental vaginal delivery, and cesarean section, respectively. The authors found that instrumental vaginal delivery was the significant predisposing factor for the developing of asphyxia [27]. Ahmed et al. by a Systematic Review and Meta-Analysis study showed that cesarean section was a significant risk factor for perinatal asphyxia (OR=4.4; 95% CI; 3.1 to 6.2) [28]. This finding was confirmed by Kune et al. (cesarean delivery was a risk factor for asphyxia OR=3.67; 95% CI: 1.31 to 10.23) [29]. On the other hand, a Cochrane Review showed that there was no significant difference in the rate of birth asphyxia between 2 groups of planned immediate cesarean section and planned vaginal delivery (OR= 1.63, 95% CI; 0.84 to 3.14; one trial, 12 women) [30].

In accordance with other studies [22, 31, 32], the analyses of data showed a significant relationship between male gender and perinatal asphyxia. This finding may relate to the protective effect of additional X chromosome in females against perinatal asphyxia [33].

According to the results, Apgar scores <5 at 5 and 10 minutes were also significantly more frequent in the case group than the control group. Other investigations also pointed at low Apgar scores as appropriate predictor of asphyxia. Daliliet al. considered the Combined-Apgar scores at minutes1, 5, and 10 as the high sensitivity (97%) and specificity (99%) factor in prediction of asphyxia [34]. Uwingabire et al. also demonstrated that 5th minute Apgar score<5was a risk factor for asphyxia [26]. It should be also noticed that in the present study, the 5th and 10th minutes Apgar scores<5 were considered as diagnostic values of asphyxia, while other studies like a study by Nayeri et al. from Iran considered the Apgar scores<6 as the risk factor [11].

Consistent with other studies, the results related to analyses of arterial blood gas showed that pH, bicarbonate, and BE levels in our cases were statistically lower than the controls. Acidosis is one of the important criteria for asphyxia and the relationship between the severity of acidosis and subsequent complications associated with asphyxia is well-documented. For instance, Kelly et al. and Younus et al. showed a dose-dependent correlation between the degree of

acidosis within the delivery and the possibility of adverse neonatal and neurodevelopmental outcomes [35, 36]. Boskabadi et al. through a 2-year cohort study (Mashhad, Iran) assessed the risk factors of asphyxia. Their results showed that 110 out of 260 neonates experienced neonatal asphyxia and acidosis was one of the main prognostic factors related to neonatal asphyxia [37]. Bijari et al. also demonstrated that neonatal parameters like pH and bicarbonate levels were lower in the asphyxiated neonates than in their healthy counterparts [38].

According to the results, more asphyxiated cases required PPV compared to the controls. This finding shows the necessity of respiratory support to reverse the asphyxia process [37, 39].

Consistent to other investigations [40, 41], our findings showed that HIE was significantly more frequent in the case group than the controls. In accordance to our results, Gonzalez de Dios et al. demonstrated that the rate of grade 1 HIE was higher than grade 2 and 3 (30 vs. 10 cases) among156 asphyxiated term neonates [42].

It should be noted that our study hadseverallimitations. The sample size was small and the study was conducted in only three centers. Furthermore, our study was a retrospective study and data were collected from medical records. Future cohort studies with larger sample sizes and longer follow-up periods would provide more complementary information.

5. Conclusion

The results of present study showed the prevalence rate of asphyxia among term and late preterm participants was 3.3 cases per 1000 live-born neonates. The results also delineated that Apgar scores<5 at 5 and 10 minutes accompanied with metabolic acidosis, HIE, and requirement of PPV could be predictive variables for perinatal asphyxia. Observing such clinical risk factors may indicate the need of early diagnosis and timely interventions to improve neonatal outcomes.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

Statement of ethical approval

The present study was approved by the Institutional Review Board of Tehran University of Medical Sciences according to the Helsinki Declaration. The data were confidential, and no extra costs were imposed.

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Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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