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Prediction of Perinatal Hypoxic Encephalopathy: Proximal Risk Factors and Short-Term Complications

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Abstract

Background: To determine the proximal risk factors associated with perinatal hypoxic encephalopathy signs and its short-term complications.

Methods: This is a prospective study conducted in women in labor with medical and obstetrics risk factors at King Abdulaziz University Hospital, Jeddah, Saudi Arabia from May 1, 2010 to May 1, 2011. The abnormal umbilical arterial base deficit levels (≥ 12 mmol/L), compared with a normal base deficit level (< 12 mmol/L) and the neonatal outcomes were studied in both groups.

Results: The frequency of fetal acidosis with a cord pH ≤ 7 or a base deficit level of ≥ 12 mmol/L at birth was 31 (5.6%) versus 59 (10.7%), respectively. The intrapartum proximal risk factors were abnormal fetal heart rate patterns (n = 18, 30.5%); prolonged labor duration, vacuum delivery (n = 12, 20.3%); pregnancy-induced hypertension (n = 10, 17%); fetal growth restriction (n = 4, 6.8%); and abruptio placentae (n = 3, 5.1%). The neonatal encephalopathy signs with an abnormal base deficit and proximal risk factors were umbilical arterial cord blood pH (n = 24, 40.7%); low Apgar score at 5 minutes (n = 10, 17%); admission to the neonatal intensive care unit (n = 20, 33.9%); and intubation (n = 9, 15.3%).

Conclusion: Fetal metabolic acidemia may predict neonatal encephalopathy signs in association with intrapartum proximal risk factors.

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Introduction

Fetal asphyxia or "birth hypoxic encephalopathy" is the inadequate intake of oxygen by the fetus before and/or at the time of labor process or just after birth, which may result in neonatal signs of encephalopathy and appear in first hours or days of life in an infant born at or beyond 35 weeks of gestation [1, 2]. Many investigators indicate that majority of cases of cerebral palsy are due to prenatal causes and the role of perinatal birth asphyxia has been overestimated [3, 4]. In addition, a fetus that has suffered prenatal reduced blood flow and/or oxygenation directed to the tissues may be at an increased risk of a perinatal insult, which could lead to adverse outcomes and/or permanent neurological sequelae.

The fetal surveillance and assessment of well-being can protect the infant by the prediction and early diagnosis of sentinel hypoxic or ischemic event during labor or delivery. The identification of an increased risk of fetal neonatal encephalopathy signs is based on characteristic changes in fetal heart rate (FHR) patterns, low Apgar score at 5 min and fetal hypoxic acidemia, and requires a blood gas analysis to provide evidence of a metabolic acidosis. This is achieved by performing umbilical cord blood gas sampling and acid-base analysis at the time of delivery [2].

The International Neonatal Encephalopathy and Cerebral Palsy Task Force defined acute intrapartum hypoxia as presence of fetal metabolic acidosis at birth in the umbilical arterial cord blood [5]. The pH of umbilical arterial cord blood ≤ 7 and a base deficit ≥ 12 mmol/L has since been suggested as the optimal cut-off to define fetal metabolic acidosis [6-8]. Several studies have highlighted the serious consequences of fetal hypoxia in preterm fetuses [9-12]. For this reason, comprehensive evaluation is needed for assessment of likelihood and can be obtained from all available data of maternal medical history, obstetric antecedents, and intrapartum risk factors predisposed to neonatal encephalopathy. The risk factors that have been traditionally assigned

Table 1. Maternal Characteristics of the Women Included in This Study

Variable	Normal group (n = 493)	Asphyxial group (n = 59)	P
Age	28.8 ± 6.26	27.63 ± 5.9	NS
Primigravida	137 (27.8%)	24 (40.7%)	0.024
Parity	2.24 ± 2.0	1.1 ± 1.4	0.02
BMI	28.15 ± 4.9	28.1 ± 6.1	NS

Mean ± standard deviation (SD); BMI: body mass index.

by general obstetricians are related to maternal medical diseases such as hypertension, diabetes and sever anemia, and/or obstetric risk factors, such as diminished fetal movements, oligohydramnios and post-term delivery [13]. The aims of this study were to determine the proximal risk factors that are associated with perinatal hypoxic encephalopathy and its short-term neonatal complications.

Methods

This is a prospective study conducted at King Abdulaziz University Hospital (KAUH), a tertiary obstetric center in Jeddah Saudi Arabia, for a period of 1 year beginning on May 1, 2010. During this period, all women attending for delivery who fulfilled the inclusion criteria were invited to participate in the study. The study was approved by the Biomedical Ethics Research Committee Human Investigation at King Abdulaziz University (Ref. 331-10).

Sample size estimation was done using a confidence level of 95%, a power of at least 0.8 and a population size estimate of 4,453 deliveries per year to generate a sample size of at least 354 patients. The inclusion criteria were the women with singleton normal pregnancies who were in labor with relevant antepartum and intrapartum complications. The antepartum maternal medical complications included hypertension, diabetes mellitus and other medical diseases, the obstetric complications, including ≥ 1 previous cesarean section (CS), antepartum hemorrhage (APH) and pregnancy-induced hypertension (PIH). The fetal factors included preterm delivery, post-term gestation, premature rupture of membranes (PROM), and fetal growth restriction (FGR). The intrapartum complications included fetal malpresentation, meconium-stained amniotic fluid (MSAF), maternal pyrexia (MP), placental abruption (PA) and cardiotocogram (CTG) abnormalities. Internal or external fetal cardiac monitoring was considered as abnormal (category III) if one or more of the following FHR patterns were present: frequent or repetitive late or severe decelerations; bradycardia < 110 beats/min (bpm) that lasted for at least 2 min or was prolonged (> 10 min); recurrent variable decelerations with reduced or absent variability (< 5 bpm), and persistent tachycardia > 160 bpm [14-16]. All CTG tracings were reviewed at the time of labor and after delivery by expert obstetrician consultants.

For each patient, we recorded the following demographic data: maternal age, gestational age at delivery (based on the last menstrual period and/or early ultrasound), gravid status, parity, and body mass index (BMI) on admission to labor room. We also recorded the time of labor onset and its duration, along with other delivery variables, including mode of delivery, fetal birth weight, and the presence of macrosomia. Relevant antepartum and intrapartum complications were also documented.

We obtained blood samples from the fetal umbilical artery immediately after birth from a clamped segment of the umbilical cord and analyzed blood gas and acid status using the Roche OMNI-S blood gas analyzer (Mannheim, Germany) in the delivery room. Based on previously published data, we defined metabolic acidosis using a base deficit of ≥ 12 as the threshold [6-8]. We identified two groups based on the results: a "normal or non asphyxial" group with a base deficit < 12 mmol/L and an "abnormal or asphyxial" group with a base deficit ≥ 12 mmol/L.

The following neonatal complication markers were studied: fetal umbilical artery acidemia (pH ≤ 7.0, and base deficit greater or equal to 12 mmol/L), the Apgar score at 5 min, the need for intubation and any admission to the neonatal intensive care unit (NICU). Short-term complications in the NICU were recorded, including the development of convulsions, confirmed intraventricular hemorrhage (IVH), neonatal sepsis and neonatal mortality in infants born ≥ 35 weeks and < 35 weeks.

Statistical analysis was performed using SPSS PC version 18 (SPSS Inc., Chicago, IL, USA), as appropriate. The data were presented as numbers (n), percentage (%), means ± SD, with 95% confident interval (CI). Student's *t*-test was used for continuous variables, and the Chi-square test or

Table 2. Medical and Obstetric Risk Factors

Variable	Normal group (n = 493)	Asphyxial group (n = 59)	P
DM	33 (6.9%)	3 (5.1%)	NS
PIH	35 (7.1%)	10 (16.9%)	0.01
Other diseases	20 (4.1%)	2 (3.4%)	NS
Total CS	89 (17.9%)	8 (13.6%)	NS
Previous 1 CS	51 (10.3%)	5 (8.5%)	NS
Previous ≥ 2 CS	38 (7.7%)	3 (5.1%)	NS
PROM	87 (17.6%)	10 (16.9%)	NS
Preterm delivery	67 (13.6%)	12 (20.3%)	NS
Post term ≥ 42	21 (4.3%)	-	
FGR	14 (2.8%)	4 (6.8%)	0.02
Malpresentation	25 (4.8%)	2 (3.4%)	NS
APH	6 (1.2%)	4 (6.8%)	0.02

CS: cesarean section; PROM: prelabor rupture of membranes; FGR: fetal growth restriction; APH: antepartum hemorrhage; PIH: pregnancy-induced hypertension.

Fisher's exact test was used for categorical data. Multinomial logistic reggression analysis (R^2 Nagelkerke) was used to determine the predictors of the risk factors for birth hypoxic encephalopathy. A P-value < 0.05 was considered statistically significant.

Results

A total of 4,453 deliveries were recorded during the study period. Of these 552 women fulfilled the inclusion criteria. Overall, 493 newborns were delivered with a base deficit < 12 mmol/L; they constituted the normal or non asphyxial group. The abnormal or asphyxial group comprised of 59 neonates who were born with a base deficit ≥ 12 mmol/L and low bicarbonate (HCO_3) levels. Forty-seven infants were born at ≥ 35 and 12 were born at < 35 weeks gestational age. The maternal characteristics of both groups are presented in Table 1; the percentage of primigravida and lower parity women was significantly higher in asphyxial group compared to the normal group.

The medical and obstetric risk factors among the two groups are shown in Table 2. The frequency rates of PIH, FGR and APH alone were significantly higher in the asphyxial group, as there were no differences in the other medical and obstetric risk factors analyzed.

The labor outcomes are presented in Table 3. The percentages of abnormal FHR patterns on CTG "category III", and rate of abruptio placentae were both higher in the asphyxial group, compared to the normal group. Furthermore, the mean of labor and the second stage duration was significantly longer and the instrumental delivery with vacuum extraction was significantly more common in the asphyxial group compared to the normal group.

In order to examine the role of gestational age, a comparison of the neonatal morbidities and mortality was performed. In the infants born at ≥ 35 weeks, the frequency rates of neonates with 5-min Apgar score ≤ 5, cord pH ≤ 7, admission to NICU and neonatal sepsis were all higher in the asphyxial group, while there was no increase in other morbidities or mortalities between the two groups (Table 4). For infants born at < 35 weeks, the neonatal morbidities were higher among the asphyxial group and with significantly higher neonatal mortalities (33.3% vs. 1.5%), with the estimated risks (OR 33; 95% CI 3.3 - 333; P = 0.002) compared to the normal group (Table 5).

Multinomial logistic regression analysis was used to determine and predict the intrapartum proximal risk factor

Table 3. Labor Outcomes

Variable	Normal group (n = 493)	Asphyxial group (n = 59)	P
G. age	38.6 ± 3.1	37.8 ± 4.2	NS
Induction	32 (6.5%)	8 (13.6%)	NS
Augmentation	80 (16.2%)	12 (20.3%)	NS
Meconium	220 (44.6%)	23 (39.0%)	NS
Ab. CTG	57 (11.6%)	18 (30.5%)	0.001
Intrapartum pyrexia	6 (1.2%)	2 (3.4%)	NS
Abruption	4 (0.8%)	3 (5.1%)	0.03
Eclampsia	1 (0.2%)	1 (1.7%)	NS
Labor duration (h)	6.3 ± 3.5	8.70 ± 4.5	0.04
D. second stage (min)	26.0 ± 33.7	48.0 ± 40.7	0.001
SVD	307 (62.3%)	29 (49.2%)	NS
Vacuum	26 (5.3%)	12 (20.3%)	0.001
Total CS	160 (32.5%)	18 (30.5%)	NS
Elective CS	33 (6.7%)	2 (3.4%)	NS
Emergency CS	127 (25.8%)	16 (27.1%)	NS
Fetal Wt.	3,010 ± 707.2	2,723 ± 833.1	NS
Macrosomia	20 (4.1%)	3(5.1%)	NS
HS (days)	2.1 ± 1.4	2.5 ± 2.2	0.001

G. age: gestational age; Ab. CTG: abnormal cardiotocogram; SVD: spontaneous vaginal delivery; PPH: post-partum hemorrhage; HS: hospital stay.

Table 4. Neonatal Complications for Infants Born ≥ 35 Weeks

Variable	Normal group (n = 426)	Asphyxial group (n = 47)	P
5-min AS ≤ 5	8 (2%)	4 (8.5%)	0.02
pH ≤ 7	7 (1.6%)	21 (44.6%)	0.001
NICU admission	10 (2.35%)	11 (23.4%)	0.001
Intubation	2 (0.5%)	1 (2.13%)	0.3
Seizures	-	-	
IVH	-	-	
N. sepsis	1 (0.2%)	4 (8.5%)	0.001
NND	1 (0.2%)	1 (2.13%)	0.2

IVH: intraventricular hemorrhage; NICU: neonatal intensive care unit; NND: neonatal death.

Table 5. Neonatal Complications for Infants Born < 35 Weeks

Variable	Normal group (n = 67)	Asphyxial group (n = 12)	P
5-min AS ≤ 5	11 (16.4%)	6 (50%)	0.02
pH ≤ 7	-	3 (25%)	
NICU admission	24 (35.8%)	9 (75%)	0.013
Intubation	10 (15%)	8 (66.7%)	0.001
Seizures	2 (3%)	2 (16.7%)	0.1
IVH	5 (7.5%)	3 (25%)	0.1
N. sepsis	4 (6%)	3 (25%)	0.1
NND	1 (1.5%)	4 (33.3%)	0.002

IVH: intraventricular hemorrhage; NICU: neonatal intensive care unit; NND: neonatal death.

variables for fetal birth asphyxia. The study findings showed that abnormal intrapartum FHR patterns "category III" and a prolonged labor duration are proximal risk factors predictors (OR 4.1; 95% CI 1.7 - 10.04; P = 0.001) of perinatal hypoxic encephalopathy and correlated with increased frequency rates of fetal metabolic acidosis, low Apgar scores at 5 min, NICU admission and neonatal sepsis (Table 6).

Discussion

Fetal hypoxia with prolonged metabolic acidosis carries a higher risk of increased base deficits in comparison with an acidosis of shorter duration (for example, respiratory acidosis). However, prediction and prevention of birth hypoxic encephalopathy and neonatal complications is dependent on the early identification of pregnancies at risk of intrapartum events during labor or delivery with appropriate intervention, in order to prevent the progression of fetal hypoxia to moderate-severe metabolic acidosis [6, 17, 18].

The present study is a hospital-based observational population study, which demonstrated the associations between maternal and fetal risk factors and birth hypoxic encephalopathy. Fetal acidemia is an important variable for predict-

Table 6. Multinomial Logistic Reggression Analysis (R^2 Nagelkerke) Model Summary

Dependent variables/ predictors	M. disease	Ob. risk factors	Ab. CTG	M. delivery	Labor duration
Base deficit (≥ 12 mmol/L)	NS	NS	0.003	NS	0.04
5-min AS	NS	NS	0.001	NS	NS
NICU	NS	0.045	0.001	NS	NS
Intubation	NS	0.001	NS	0.007	NS
Convulsion	NS	NS	NS	0.031	NS
IVH	NS	NS	NS	NS	NS
pH ≤ 7	NS	NS	0.001	NS	0.028
NDD	NS	NS	NS	NS	NS

NICU: neonatal intensive unit; IVH: intraventricular hemorrhage; NDD: neonatal death.

ing neonatal morbidity and mortality [17, 19]. The perinatal proximal risk factors that may identify pregnancies at risk for fetal birth encephalopathy with metabolic acidosis included primigravida mothers, PIH, FGR, PA, abnormal FHR patterns "category III" on CTG, and prolonged labor duration. Recently define the neonatal signs consistent with intrapartum event, if present, had an intrapartum hypoxic component may contribute to neonatal encephalopathy; Apgar score less than 5 at 5 min and 10 min, metabolic acidosis in fetal umbilical cord blood (pH ≤ 7) or acid base deficit of ≥ 12 mmol/L, or both [2, 5, 6, 20, 21]. Pathological fetal acidemia is correlated with an increased risk of neurological deficits and long-term sequelae. However, Low et al [22] demonstrated the limitations of clinical risk scoring, and a proportion of cases of intrapartum fetal asphyxia occur without the presence of clinical risk factors. Therefore, prediction and/or early diagnosis of patients at risk of significant intrapartum fetal asphyxia are the challenging issues.

The correlation between low Apgar scores at 5 min and neurological outcome has previously been reported [23]. The positive predictive value of 20% in the asphyxial group means that 80% babies with a low 5-min Apgar score will be normal on follow-up. The real problem is the low sensitivity of this parameter, as only 10.7% of neonates have an adverse outcome and need follow-up if the Apgar score at 5 min is only the criterion used for prediction. A low Apgar score at 5 min could be a relevant factor in predicting the mortality in preterm infants born between 24 and 28 weeks gestational age. However, very premature infants have a significantly higher risk of mortality compared to term and late preterm infants who have relatively high survival rates [24].

A meta-analysis of cohort and case-control studies found a strong association between cord arterial pH and neonatal complications [25]. Several investigators have found that a cord blood pH ≤ 7 is a significant threshold for fetal acidemia. The risk of neonatal morbidity is inversely related to pH level, and with greater risk when pH ≤ 7 [7, 26-28]. Using a cut-off pH ≤ 7, the frequency of fetal metabolic acidosis in the study was 31 (5.6%) versus 59 neonates (10.7%) with base deficit. The level of bicarbonate is important in defining base deficit and metabolic acidemia develops when the primary buffer, bicarbonate (HCO_3) decreases to a critical level [29]. We found a low fetal serum bicarbonate level in the asphyxial group compared to normal group (OR 2.23; 95% CI 1.87 - 2.67; P = 0.000), which could explain the high prevalence percent of base deficit versus the pH ≤ 7 of all deliveries among study group. The pH is a possible predictive variable in comparison with base deficit, alone or in combination with Apgar scores (OR 4.2, 95% CI 1.5 - 11.8 versus OR 5.1, 95% CI 2.2 - 11.6) respectively.

The FHR monitoring is widely practiced, and useful surveillance test with or without fetal blood gas and acid-base assessment for the prediction and diagnosis of intrapartum fetal hypoxia. Low et al [21] stated that the prediction of fetal hypoxia exposure by FHR patterns is possible, and these are principally observed during the narrow 1-h window before decompensation. Fetal hypoxic exposure must be considered with two or more cycles of minimal baseline variability and late or prolonged decelerations documented in the FHR record [21]. Eighteen (30.8%) out of 59 newborns in this study had an abnormal intrapartum FHR tracing: variable deceleration (n = 1, 1.7%); late decelerations (n = 12, 20.3%); and fetal bradycardia (n = 5, 8.5%). Five out of these 18 cases had a low Apgar score (< 5) at 5 min. The positive predictive values of FHR patterns were low in this study, ranging from 24% alone to 34.5% with a low 5-min Apgar score and pH ≤ 7; these findings were similar to those of Locatelli et al [14]. Difficulties in the interpretation of FHR records complicated with high false-positive FHR patterns can lead to unnecessary interventions, with a consequently increased incidence of CS and instrumental deliveries [23, 30, 31].

Metabolic acidosis at birth has low predictor of perinatal brain damage. Jeffery et al [32] demonstrated that combinations of identified high-risk neonatal signs show a strong relationship with neurological complications. In the study group, three (30%) out of 10 newborns with a low 5-min Apgar score had a low cord blood pH ≤ 7, and they needed intubation in the delivery room before admission to NICU; two of these < 35 weeks neonates developed convulsions and IVH, and one > 35 weeks newborn developed meconium aspiration. However, a low pH level in the cord blood of clinically normal infants was not associated with a higher risk of later neurological complications [28]. Ten (21.3%) out of 47 infants > 35 weeks had a low cord blood pH but were neither admitted to NICU nor developed neurological complications. Therefore, the risk of morbidity and/or mortality is higher in infants that are born at < 35 weeks with metabolic acidosis, particularly before 32 weeks gestational age [9, 10, 12, 24]. In our study, the "asphyxial group" included four neonatal deaths at < 32 weeks gestational age. They were delivered by CS and developed neonatal complications of prematurity. This was compared to one neonatal death > 35 weeks that was associated with intrapartum MP. The neonate was delivered vaginally and developed neonatal sepsis.

The Royal College of Obstetricians and Gynecologists states that the routine measurement of cord blood gas and acid-base balance is essential for all operative deliveries, including CS and instrumental [33]. However, recording blood gas and acid-base assessment may be cost effective for all deliveries, not least as part of important medicolegal evidence of a normal acid-base status at delivery, if the diagnosis of cerebral palsy is made in later childhood. Preterm birth asphyxia carries a high risk of neonatal morbidity and mortality, and should be recognized and managed as early as possible.

A limitation of our study is the definition of the obstetric risk factors that predispose to fetal birth asphyxia or perhaps lack of perinatal dataset risk factors in the literature to allow

better population data collection. We need further an accurate and clear case definition for the role of obstetric risk factors to be evaluated in prospective, randomized studies. In conclusion, fetal metabolic acidemia may predict neonatal encephalopathy signs in association with intrapartum proximal risk factors.

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References

1. Gunn AJ, Bennet L. Timing of injury in the fetus and neonate. Curr Opin Obstet Gynecol. 2008;20(2):175-181.
2. Executive summary: Neonatal encephalopathy and neurological outcome. Obstet Gynecol. 2014;123(4).
3. Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, Pemberton PJ, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. BMJ. 1998;317(7172):1549-1553.
4. Freeman JM. Prenatal and perinatal factors associated with brain disorders. NIH Publication. 1985;1149:13-32.
5. MacLennan A. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. BMJ. 1999;319(7216):1054-1059.
6. Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. Am J Obstet Gynecol. 1997;177(6):1391-1394.
7. Graham EM, Ruis KA, Hartman AL, Northington FJ, Fox HE. A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. Am J Obstet Gynecol. 2008;199(6):587-595.
8. Ross MG, Gala R. Use of umbilical artery base excess: algorithm for the timing of hypoxic injury. Am J Obstet Gynecol. 2002;187(1):1-9.
9. Vergani P, Locatelli A, Doria V, Assi F, Paterlini G, Pezzullo JC, Ghidini A. Intraventricular hemorrhage and periventricular leukomalacia in preterm infants. Obstet Gynecol. 2004;104(2):225-231.
10. Victory R, Penava D, da Silva O, Natale R, Richardson B. Umbilical cord pH and base excess values in relation to neonatal morbidity for infants delivered preterm. Am J Obstet Gynecol. 2003;189(3):803-807.
11. Thorngren-Jerneck K, Herbst A. Perinatal factors associated with cerebral palsy in children born in Sweden. Obstet Gynecol. 2006;108(6):1499-1505.
12. Logitharajah P, Rutherford MA, Cowan FM. Hypoxic-ischemic encephalopathy in preterm infants: antecedent factors, brain imaging, and outcome. Pediatr Res. 2009;66(2):222-229.
13. Milsom I, Ladfors L, Thiringer K, Niklasson A, Odeback A, Thornberg E. Influence of maternal, obstetric and fetal risk factors on the prevalence of birth asphyxia at term in a Swedish urban population. Acta Obstet Gynecol Scand. 2002;81(10):909-917.
14. Locatelli A, Incerti M, Ghidini A, Greco M, Villa E, Paterlini G. Factors associated with umbilical artery acidemia in term infants with low Apgar scores at 5 min. Eur J Obstet Gynecol Reprod Biol. 2008;139(2):146-150.
15. ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol. 2009;114(1):192-202.
16. Royal College of Obstetricians and Gynaecologists. The use of electronic fetal monitoring. The use and interpretation of cardiotocography in intrapartum fetal surveillance. London: RCOG Press; 2001:136 (Evidence-based clinical guidelines; no. 8).
17. Low JA. Intrapartum fetal asphyxia: definition, diagnosis, and classification. Am J Obstet Gynecol. 1997;176(5):957-959.
18. Boog G. [Cerebral palsy and perinatal asphyxia (I--diagnosis)]. Gynecol Obstet Fertil. 2010;38(4):261-277.
19. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Neonatal encephalopathy and cerebral palsy: defining the pathogenesis and pathophysiology. Elk Grove Village (IL): AAP; Washington, DC: ACOG; 2003.
20. Low JA, Panagiotopoulos C, Derrick EJ. Newborn complications after intrapartum asphyxia with metabolic acidosis in the term fetus. Am J Obstet Gynecol. 1994;170(4):1081-1087.
21. Low JA, Victory R, Derrick EJ. Predictive value of electronic fetal monitoring for intrapartum fetal asphyxia with metabolic acidosis. Obstet Gynecol. 1999;93(2):285-291.
22. Low JA, Simpson LL, Tonni G, Chamberlain S. Limitations in the clinical prediction of intrapartum fetal asphyxia. Am J Obstet Gynecol. 1995;172(3):801-804.
23. Ruth VJ, Raivio KO. Perinatal brain damage: predictive value of metabolic acidosis and the Apgar score. BMJ. 1988;297(6640):24-27.
24. Lee HC, Subeh M, Gould JB. Low Apgar score and mortality in extremely preterm neonates born in the United States. Acta Paediatr. 2010;99(12):1785-1789.
25. Malin GL, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: systematic review and meta-analysis. BMJ.

2010;340:c1471.
26. Sehdev HM, Stamilio DM, Macones GA, Graham E, Morgan MA. Predictive factors for neonatal morbidity in neonates with an umbilical arterial cord pH less than 7.00. Am J Obstet Gynecol. 1997;177(5):1030-1034.
27. Victory R, Penava D, Da Silva O, Natale R, Richardson B. Umbilical cord pH and base excess values in relation to adverse outcome events for infants delivering at term. Am J Obstet Gynecol. 2004;191(6):2021-2028.
28. Andres RL, Saade G, Gilstrap LC, Wilkins I, Witlin A, Zlatnik F, Hankins GV. Association between umbilical blood gas parameters and neonatal morbidity and death in neonates with pathologic fetal acidemia. Am J Obstet Gynecol. 1999;181(4):867-871.
29. Nageotte, MP, Gilstrap, LC III. Intrapartum fetal surveillance. In: Creasy, Resnik, Iams, Lockwood, Moore, eds. Creasy & Resnik's Maternal-Fetal Medicine Principles and Practice, 6th ed. Philadelphia, PA: Saunders; 2009:397.
30. Low JA, Pickersgill H, Killen H, Derrick EJ. The prediction and prevention of intrapartum fetal asphyxia in term pregnancies. Am J Obstet Gynecol. 2001;184(4):724-730.
31. Larma JD, Silva AM, Holcroft CJ, Thompson RE, Donohue PK, Graham EM. Intrapartum electronic fetal heart rate monitoring and the identification of metabolic acidosis and hypoxic-ischemic encephalopathy. Am J Obstet Gynecol. 2007;197(3):301 e301-308.
32. Perlman JM, Risser R. Can asphyxiated infants at risk for neonatal seizures be rapidly identified by current high-risk markers? Pediatrics. 1996;97(4):456-462.
33. Royal College of Obstetricians and Gynaecologists; Royal College of Midwives. Towards safer childbirth. Minimum standards for the organisation of labour wards. Report of a joint working party. London: RCOG Press; 1999:22.

