European Journal of Obstetrics & Gynecology and Reproductive Biology 236 (2019) 69–74

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Factors associated with neonatal hypoxic ischemic encephalopathy in infants with an umbilical artery pH less than 7.00

Mathilde Barrois[a,*], Juliana Patkai[b], Pierre Delorme[a,c], Clément Chollat[b], François Goffinet[a,c], Camille Le Ray[a,c]

[a] Port Royal Maternity Unit, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, DHU Risks in Pregnancy, Paris Descartes University, Paris, France
[b] Neonatal Intensive Care Unit, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, DHU Risks in Pregnancy, Paris Descartes University, Paris, France
[c] INSERM UMR 1153, Obstetrical, Perinatal and Paediatric Epidemiology Research Team (EPOPé), Centre for Epidemiology and Statistics Sorbonne Paris Cité (CRESS), France

ARTICLE INFO

Article history:
Received 29 July 2018
Received in revised form 1 February 2019
Accepted 6 February 2019

Keywords:
Hypoxic-ischemic encephalopathy
Neonatal encephalopathy
Severe acidosis
Fetal asphyxia
Umbilical pH
Association

ABSTRACT

Objective: Our objective was to identify factors associated with hypoxic-ischemic encephalopathy (HIE) among newborns with an umbilical pH < 7.00.
Study design: Case-control study during a four-year study period in a single academic tertiary-center, including all neonates ≥35 weeks with an umbilical pH < 7.00. Cases were neonates with HIE, regardless of Sarnat classification, and controls were neonates without signs of HIE. We used univariate and multivariate analysis to compare the maternal, obstetric, and neonatal characteristics of cases and controls.
Results: Among 21,211 births, 179 neonates≥35 weeks (0.84%) had an umbilical pH < 7.00. One hundred and forty-seven(82.1%) newborns had severe asphyxia without HIE, 32(17.9%) had HIE and 21(11.7%) needed therapeutic hypothermia. Neonates with HIE were significantly more likely to have 5-minute Apgar score<7(75% versus 15.7% $P < 0.01$), together with a lower mean umbilical arterial pH (6.84 versus 6.95, $P < 0.01$) and lower mean base deficits (-17.0 versus -12.7, $P < 0.01$). Factors significantly associated with HIE were the mother being overweight(28.1% for cases versus 14.3% for controls, adjusted OR=4.6 [1.4–15.2]) or obese(25.0% versus 13.6%, aOR=15.5[1.1–12.5]), smoking(18.7% versus 5.4%, aOR=5.8[1.6–21.2]), a sentinel event as cord prolaps or placenta abruption (34.4% versus 13.6%, aOR=2.7[1.1–7.2]), and decreased fetal heart rate variability(68.7% versus 44.2%, aOR=2.8[1.1–6.9]).
Conclusion: Among neonates with an umbilical cord pH < 7.00, those with HIE had a more severe metabolic acidosis. Maternal factors associated with HIE among newborns with an umbilical pH < 7.00, were being overweight or obese, and smoking, and the associated obstetric factors were a sentinel event and decreased fetal heart rate variability.

Introduction

The combination of metabolic acidosis, determined by a pH less than 7.00 and a base excess less than −12 mmol/L, and poor clinical evaluation, assessed by a 5-minute Apgar score less than 7, defines fetal asphyxia [1]. An umbilical arterial pH less than 7.00 at birth induces anxiety in both parents and physicians, and can induce serious neurologic injuries. Nonetheless, the prognosis of these newborns differs quite sharply. Most of them will recover shortly with a good prognosis, while a subgroup will develop hypoxic-ischemic encephalopathy (HIE) that would require neuroprotective treatment [2]. This is may be treated by neuroprotective hypothermia [3], which sometimes reduces cerebral metabolism and limits the cerebral impairment linked to it [4].Some of the infants with HIE will develop cerebral palsy or long term neurodevelopmental sequelae (25%), and likely few will die (10%) [5,6].

Although many studies have examined neonatal outcomes after HIE or identified the risk factors of neonatal acidosis at birth [7], few have analyzed the ante- and intrapartum risk factors of HIE in cases of neonatal acidosis. Knowledge of these factors could help obstetricians to adapt obstetric management and neonatologists to tailor neonatal decisions for neonatal transfer to an appropriate center for treatment.

Using a case control study of neonates>35 weeks with an arterial pH lower than 7.00,our objective was to identify risk factors for HIE, during pregnancy and labor and at birth.

* Corresponding author at: Maternité Port Royal, 123 boulevard de Port Royal, 75014, Paris, France.
E-mail address: mathilde.barrois@aphp.fr (M. Barrois).

https://doi.org/10.1016/j.ejogrb.2019.02.009
0301-2115/

Material and methods

This case-control study took place at a single academic tertiary center in Paris (France) (5500 births annually). It was conducted during a 4-year study period including all near-term and term neonates (more than 35 weeks)with an umbilical pH less than 7.00 at birth.

From our hospital database, we selected all live births with an umbilical cord pH less than 7.00 in 2012−2015. We excluded births before 35 weeks because no guidelines currently recommend therapeutic hypothermia for encephalopathy treatment for this group.

Umbilical artery pH is measured routinely in our center, sampled into pre-heparinized syringes after cord clamping and within 3 min after birth. The blood samples were analyzed by a blood-gas analyzer in the delivery room (ABL 800 flex, Radiometer, France), which provides a complete analysis with pH, base excess, pO_2, and pCO_2. Blood gases were then routinely rechecked one hour after birth.

All the obstetric and neonatal files of patients with an umbilical pH less than 7.00 were retrospectively reviewed. Each fetal heart rate (FHR) tracing during the last hour of labor was reviewed by an observer (MB) blinded to neonatal outcome. The FIGO classification was used for this FHR analysis [8].

We studied the following potential risks factors:

- Maternal factors, including maternal age, body mass index (BMI) before pregnancy, tobacco use during pregnancy, and any history of diseases, such as diabetes, hypertension, and other chronic diseases.
- Gestational factors such as diseases during pregnancy (e.g., gestational diabetes mellitus and preeclampsia), estimated fetal weight (suspected of being small for gestational age (SGA) when the estimated weight was <10th percentile and large for gestational age (LGA) when it was >90th percentile).
- Women with no history of diabetes, hypertension, or cesarean delivery and no preeclampsia or gestational diabetes in the current pregnancy were considered at low risk.
- Intrapartum factors, including induction of labor, fetal presentation, maternal hypotension requiring intravenous use of vasopressor agents, thick meconium, use of oxytocin, FHR abnormalities, labor duration, type of analgesia, and mode of delivery. Sentinel events during labor, defined by, among others, shoulder dystocia, cord prolapse, placental abruption, uterine rupture, amniotic embolism, Benckiser hemorrhage, intravenous lidocaine injection, maternal cardiac arrest associated with eclampsia, maternal diabetic coma were also recorded.

The National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL n° 1755849) approved this study. Under French regulations, this study is exempt from institutional ethics review because it is an observational study using anonymized data from medical records. Women are informed that their records can be used for the evaluation of medical practices and are explicitly informed that they can opt out of these studies.

HIE was graded, according to the Sarnat and Sarnat classification, based on the infant's clinical presentation, examination findings, the presence of seizures. Routinely used in neonatal units to evaluate newborns, this classification categorizes HIE into 3 stages (1: mild HIE, 2: moderate HIE, and 3: severe HIE). The neonatologists in our center used it to decide on therapeutic hypothermia in cases of moderate to severe HIE.

In our first analysis, "HIE" cases are infants who had HIE at birth, regardless of its Sarnat stage. "No-HIE" controls are all other neonates born with a pH less than 7.00 without signs of HIE, according to the same classification.

In a secondary analysis, we studied the predictive factors of moderate to severe HIE that required therapeutic hypothermia. The "hypothermia"group comprised the newborns with moderate to severe HIE who were determined to need therapeutic hypothermia and the"No hypothermia" group those newborns with umbilical pH less than 7.00 who did not need therapeutic hypothermia.

Characteristics of the two groups were compared by univariate analysis. Then, to study the factors associated with neonatal encephalopathy (HIE of any stage in a first model and HIE requiring therapeutic hypothermia in a second model), we performed multivariate analysis using logistic regression models. The models included all variables associated with neonatal encephalopathy in the univariate analyses, with $P < 0.1$). However, because cesarean delivery is the most frequent option in serious obstetric situations, we chose not to include mode of delivery in the multivariate analyses.

Statistical analyses were performed with Stata software version 11.0. Chi-2 and Fisher exact tests were used to compare categorical variables, and Student t tests and non-parametric tests, appropriately, to compare continuous variables. The multivariate analysis of significant effects was based on a conditional logistic regression analysis. Odds ratios (ORs) and their 95% confidence intervals (CIs) were used to estimate the strength of association of each variable.

Results

Among the 21,211 live births during the study period, 198 (0.93%) newborns had an umbilical artery pH less than 7.00. After we excluded those born before 35 weeks, our study included 179 born after 35 weeks with an umbilical artery pH less than 7.00 (0.84%) (Fig. 1).

Mean gestational age at birth was 38.9 (+/- 1.62 (SD)) weeks of gestation in the HIE group and 39.4 (+/- 1.5) in the group without HIE; it did not differ between the two groups ($P = 0.13$) (Table 1). Newborns with HIE had significantly lower 5-minute Apgar scores and umbilical pH at birth as well as significantly excess base at birth and higher lactate levels at 1 h of life than the group without HIE.

Compared with women whose infants did not have HIE, those whose children did have HIE were more likely to be obese (25% versus 13.6%, $P = 0.02$) and smoke (18.7% versus 5.4% $P = 0.01$) (Table 2). They were also more likely to have had gestational diabetes requiring insulin (12.5% versus 4.8%), but this difference was not significant ($P = 0.19$).The percentage of women at low risk was similar in the two groups – 50% in the HIE group and 59% in the no HIE group.

Women in the HIE group had more frequent cesarean deliveries and particularly emergency cesareans (28.1% versus 5.4%, $P < 0.01$). Maternal hypotension during labor requiring vasopressor agents was twice as frequent in the HIE group ($P = 0.03$). The appearance of a sentinel event during labor was significantly associated with HIE (Table 3). After review of all FHR tracings, only decreased variability was a significant risk factor for HIE.

After adjustment, the factors associated with HIE were the mother being overweight (BMI 25–30 kg/m^2) (adjusted OR 4.6, 95% CI 1.4–15.2) or obese (BMI > 30 kg/m^2 (adjusted OR 15.5, 95%CI 1.1–12.5), smoking during pregnancy(adjusted OR 5.8, 95%CI 1.6–21.2), occurrence of a sentinel event during labor (adjusted OR 2.7, 95% CI 1.1–7.2), and decreased FHR variability (adjusted OR 2.8, 95%CI 1.1–6.9) (Table 4).

For a secondary analysis, we selected the neonates needing hypothermia treatment for the "hypothermia" group (N = 21); the others comprised the "no hypothermia" group (N = 158) (Fig. 1).

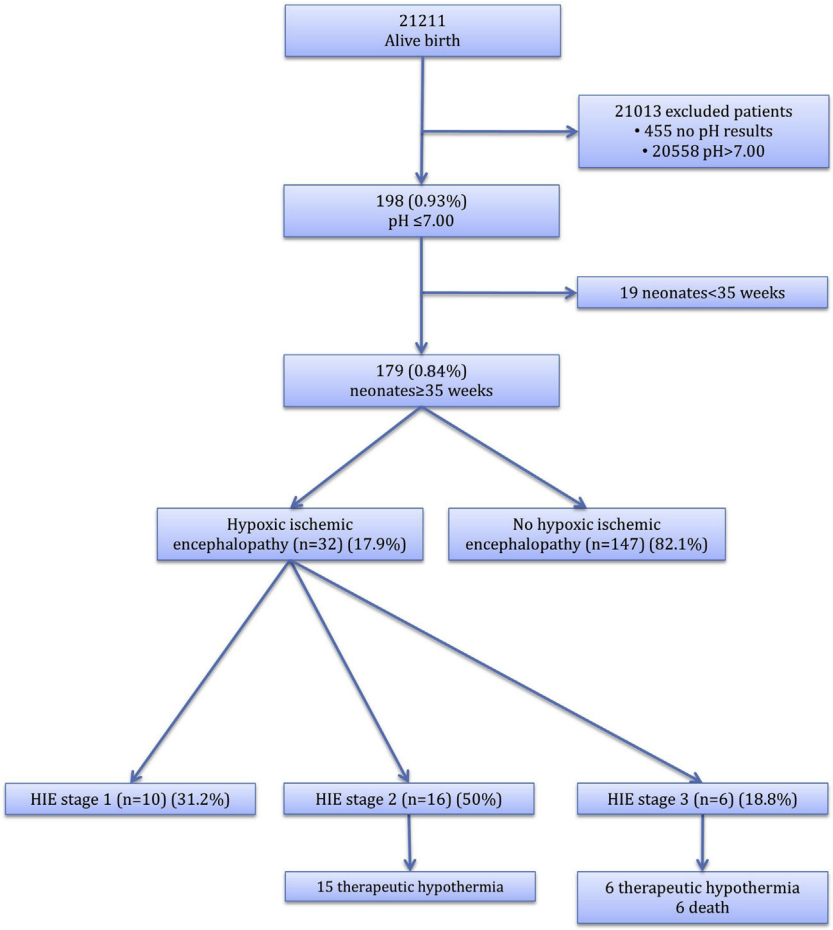

Fig. 1. Population Flow Chart.

Table 1
Comparison of the neonatal characteristics between the groups with and without HIE.

	HIE (N = 32)	No HIE (N = 147)	*P*
Gestational age (in weeks (mean ± SD))	38.9 ± 1.62	39.4 ± 1.5	0.13
Female (n (%))	18 (56.2)	65 (44.2)	0.21
Birth weight (in g (mean ± SD))	3220 ± 634	3193 ± 526	0.79
Percentile of birth weight (mean ± SD)	48 ± 35	41 ± 29	0.2
Birth weight <5th percentile (n (%))	7 (21.7)	29 (19.7)	0.78
5-min Apgar score (mean [min-max])	4 [4–10]	5 [0-10]	<0.01
≤4 (n (%))	13 (40.6)	2 (1.4)	<0.01
≤7 (n (%))	24 (75)	23 (15.7)	<0.01
Arterial umbilical pH (mean ± SD)	6.84 ± 0.14	6.95 ± 0.04	<0.01
Arterial umbilical excess base (mean ± SD)	−17.01 ± 7.22	−12.75 ± 3.63	<0.01
Lactates at 1 hour (in mmol/L (mean ± SD))	15.05 ± 6.72	9.22± 3.3	<0.01

After adjustment, the only factors significantly associated with moderate to severe HIE requiring therapeutic hypothermia treatment were maternal BMI 25–30 kg/m^2 (adjusted OR 5.5, 95% CI 1.2–24.4), and decreased FHR variability (OR 3.5, 95% CI 1.2–10.6) (Table 5).

Discussion

Factors associated with HIE were maternal BMI>25 kg/m^2, smoking during pregnancy, occurrence of a sentinel event during labor, particularly placental abruption and decreased FHR variability.

The frequency of severe acidosis in our population is similar to rates reported in other studies [9], as is the HIE rate in infants with severe acidosis [10]. In accordance with the literature, high maternal BMI were associated with HIE. In their two-year prospective study of 812 women with cesarean delivery during labor, Spain et al. found that neonatal morbidity and severe perinatal asphyxia were higher in cases of maternal obesity [11]. Similarly, Persson et al. found associations between BMI and severe asphyxia-related outcomes in infants born at termin a population-based cohort study of1,764,403 term births, with lower 5-minute Apgar score and more neonatal convulsions among overweight and obese mothers [12]. Moreover, it is well known that obesity maternal BMI > 25 kg/m^2 is a risk factor for prolonged labor, failed cervical ripening in induction of labor, and cesarean delivery during labor, all of which are situations that augment the risk of fetal hypoxia [13,14].

Table 2
Comparison of maternal and gestational characteristics in the groups with and without HIE.

	HIE (N = 32)	No HIE (N = 147)	*P*
Maternal age (mean ±SD)	35.2 ± 5.9	34.64 ± 5.6	0.61
Primiparous women (n (%))	19 (59.4)	72 (48.9)	0.28
Ethnic origin			
European (n (%))	15 (46.9)	97 (66)	
North Africa (n (%))	6 (18.8)	16 (10.9)	
Sub-Saharan Africa (n (%))	8 (25)	25 (17)	
South America (n (%))	0 (0)	2 (1.4)	
Asia (n (%))	2 (6.3)	3 (2)	
DOM TOM (n (%))	1 (3.1)	4 (2.7)	0.21
BMI before pregnancy (kg/m^2)	25.5 ± 5.7	23.9 ± 6.1	0.18
<20 (n (%))	9 (28.3)	39 (26.5)	
20-25 (n (%))	6 (18.6)	67 (45.6)	
25-30 (n (%))	9 (28.1)	21 (14.3)	
>30 (n (%))	8 (25)	20 (13.6)	0.02
Diabetes before pregnancy (n (%))	1 (3.1)	7 (4.8)	1
Hypertension before pregnancy (n (%))	1 (3.1)	11 (7.5)	0.69
Smoking during pregnancy (n (%))	6 (18.7)	8 (5.4)	0.01
Previous cesarean delivery (n (%))	8 (25)	41 (27.9)	0.91
Twin pregnancy (n (%))	1 (0.1)	9 (6.1)	0.50
ART* conception (n (%))	3 (9.4)	13 (8.8)	0.57
Preeclampsia (n (%))	4 (12.5)	11 (7.5)	0.35
Gestational diabetes			
Diet (n (%))	2 (6.3)	8 (5.4)	
Insulin (n (%))	4 (12.5)	7 (4.8)	0.19
Size for gestational age			
SGA/FGR** (n (%))	3 (9.4)	9 (6.1)	
Normal (n (%))	25 (78.1)	124 (84.4)	
LGA† (n (%))	4 (12.5)	14 (9.5)	0.61
Women at low risk (n (%))‡	16 (50.0)	88 (59.9)	0.31

‡ Low risk = no history of diabetes, hypertension, or cesarean delivery, and no preeclampsia or gestational diabetes during pregnancy.
* Assisted reproductive technique.
** SGA small for gestational age/ FGR fetal growth restriction.
† LGA large for gestational age.

Table 4
Predictive factors for HIE: multivariate analysis.

	Adjusted* Odds Ratio	95% confidence interval
BMI before pregnancy		
<20	1.9	0.6–6.2
20-25	1	
25-30	4.6	1.4–15.2
>30	15.5	1.1–12.5
Smoking	5.8	1.6–21.2
Sentinel event	2.7	1.1–7.2
FHR decreased variability	2.8	1.1–6.9

* Adjustment on all variables included in the table.

Maternal smoking was associated with HIE in our first model but not with moderate to severe HIE requiring hypothermia in our second model, perhaps due to lack of power because of the limited number of neonates who needed this treatment. Smoking has previously been reported to increase global perinatal morbidity, especially the risk of IUGR, placental disorders, and placental abruption [15]. Active smoking may cause chronic fetal hypoxia associated with morphological brain modifications [16]. Smoking during pregnancy may stimulate free radical damage in the mother and fetus, related to the augmentation of lipid peroxidation; it also depletes antioxidant potential in maternal plasma and umbilical cord blood [17], thereby contributing to mechanisms of asphyxia that have been linked with brain damage. We cannot definitively conclude that a causal association exists between smoking and encephalopathy, but the physiopathologic hypothesis, the strength of the association, and the chronology suggest that a larger study could evaluate this association and demonstrate a potential dose-effect.

It is possible that high maternal BMI and smoking increase oxidative stress, leading to placental hypoperfusion. This then

Table 3
Comparison of intrapartum characteristics in the groups with and without HIE.

	HIE (N = 32)	No HIE (N = 147)	*P*
Prolonged pregnancy ≥41 weeks (n (%))	5 (15.6)	25 (17)	0.63
Onset of labor			
Spontaneous labor (n (%))	14 (43.7)	96 (65.3)	
Cervical ripening (n (%))	4 (12.5)	24 (16.3)	
Oxytocin induction (n (%))	2 (6.2)	13 (8.8)	
Planned cesarean (n (%))	3 (9.4)	6 (4.1)	
Emergency cesarean (n (%))	9 (28.1)	8 (5.4)	<0.01
Breech presentation (n (%))	2 (6.2)	14 (9.2)	0.74
Thick meconium during labor (n (%))	6 (18.8)	26 (17.7)	0.89
Thick meconium at delivery (n (%))	10 (31.3)	39 (26.5)	0.59
Oxytocin use* (n (%))	15 (75)	79 (59.4)	0.22
Abnormal FHR (n (%))	28 (87.5)	132 (89.8)	0.75
Bradycardia on FHR			
No bradycardia (n (%))	18 (56.2)	73 (49.7)	
Bradycardia>60 (n (%))	9 (28.1)	51 (34.6)	
Bradycardia ≤60 (n (%))	5 (15.6)	23 (15.6)	0.75
Decreased FHR variability (n (%))	22 (68.7)	65 (44.2)	0.01
Manual rotation*(n (%))	5 (25)	19 (14.3)	0.32
Maternal hypotension during labor requiring vasopressives drugs*(n (%))	10 (50)	31 (23.3)	0.03
Total labor duration* (in min (mean ±SD))	236.5±45.3	171.8±12.4	0.08
Second stage duration* (in min (mean ±SD))	74.2±19.2	53.3±5.8	0.21
Expulsive effort duration* (in min (mean ±SD))	13.8±3.9	10.3±1	0.26
Mode of delivery			
Spontaneous delivery (n (%))	2 (6.2)	37 (25.2)	
Operative delivery (n (%))	7 (21.9)	36 (24.5)	
Cesarean delivery (n (%))	23 (71.9)	74 (50.3)	0.04
Sentinel event (n (%))	11 (34.4)	20 (13.6)	<0.01
Shoulder dystocia	1	2	
Uterine rupture	1	4	
Abruptio placentae	4	4	
Cord prolapse	1	8	
Amniotic embolism	1	1	
Others†	3	1	

* Among patients with attempted vaginal delivery: HIE group (N = 20) and no HIE group (N = 133).
† Benckiser hemorrhage, intraveinous lidocaine injection, maternal cardiac arrest associated with eclampsia, maternal diabetic coma.

Table 5
Predictive factors for hypothermia: Multivariate analysis.

	Adjusted* Odds Ratio	95% confidence interval
BMI before pregnancy		
<20	3.5	0.8-14.7
20-25	1	
25-30	5.5	1.2-24.4
>30	2.9	0.6-15.1
Smoking	2.6	0.6-11.9
Sentinel event	2	0.7-6.1
FHR decreased variability	3.5	1.2-10.6

* Adjustment on all variables included in the table.

causes chronic hypoxemia, reflected by the lactate levels in the HIE group, worsening the metabolic status at birth and consequently increasing the risk for HIE.

Among the antepartum maternal factors considered, gestational diabetes mellitus was more frequent in the HIE group, although the difference was not statistically significant. Similarly, Mimouni et al. found a higher rate of perinatal asphyxia among mothers with gestational diabetes mellitus, but they did not study risk factors for HIE in the cases of perinatal asphyxia in this population [18].

Sentinel events are frequently reported in cases of cerebral palsy [19]. Placental abruption has also been associated with adverse neonatal outcomes, especially when accompanied by severe FHR abnormalities [20]. We also found comparable associations in our population of neonates with HIE. Smoking has also been associated with placental disorders, such as abruption [21], but none of our patients with placental abruption was a smoker.

Placental pathology is unfortunately not performed routinely in our population. Pathologic examination of the placenta in the HIE cases could have added interesting information, in particular on the pathophysiological mechanisms leading to HIE. High maternal BMI and smoking during pregnancy can indeed be associated with placental dysfunction and particularly endothelial dysfunction [22,23], and this dysfunction could lead to chronic hypoxemia, and impair neurological neonatal outcomes.

The association we observed between HIE and FHR abnormalities, especially decreased FHR variability, has previously been reported. Milsom et al. showed that abnormal FHR variability, repeated late decelerations regardless of amplitude, and repeated variable decelerations, occasional late or variable decelerations, and no accelerations are all associated with asphyxia [24], and Spencer et al. that decreased FHR variability is associated with a higher encephalopathy rate [25]. It is possible that reduced variability of FHR is a proxy of chronic hypoxemia linked with placental hypoperfusion. Despite the false positives and the poor correlation between FHR and neonatal outcome, the analysis of cord blood gas for each birth remains the best marker for evaluating neonatal acidosis [26,27].

Nonetheless, most newborns with severe acidosis at birth are ultimately healthy and do not need specific neonatal care [2]. The absence of risk factors for HIE and of neurologic manifestations after birth in cases of severe acidosis make it possible to reassure parents and caregivers. Knowledge of these risk factors could help medical staff in decision-making during labor but also at birth when severe acidosis occurs.

Conclusion

Among neonates with an umbilical cord pH < 7.00, those with HIE had a more severe metabolic acidosis. Sentinel events were associated with HIE. Maternal BMI > 25 kg/m^2 and smoking were also associated with HIE, possibly through chronic hypoxia reflected by decreased FHR variability. The mechanisms explaining these associations should be studied further.

Conflicts of interest

The authors did not report any potential conflicts of interest.

References

[1] Zupan Simunek V. Definition of intrapartum asphyxia and effects on outcome. J Gynécologie Obstétrique Biol Reprod 2008;37(February (Suppl. 1)):S7–15.
[2] Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med 2009;361(October (14)):1349–58.
[3] Douglas-Escobar M, Weiss MD. Hypoxic-ischemic encephalopathy: a review for the clinician. JAMA Pediatr 2015;169(april (4)):397–403.
[4] Committee on Fetus and Newborn, Papile L-A, Baley JE, Benitz W, Cummings J, Carlo WA, et al. Hypothermia and neonatal encephalopathy. Pediatrics 2014;133(june (6)):1146–50.
[5] Hankins GDV, Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. Obstet Gynecol 2003;102 (September (3)):628–36.
[6] Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, et al. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev 2013;1:CD003311.
[7] Bouiller J-P, Dreyfus M, Mortamet G, Guillois B, Benoist G. Intrapartum asphyxia: risk factors and short-term consequences. J Gynecol Obstet Biol Reprod (Paris) 2015;27(August).
[8] Ayres-de-Campos D, Spong CY, Chandraharan E. FIGO Intrapartum Fetal Monitoring Expert Consensus Panel. FIGO consensus guidelines on intrapartum fetal monitoring: Cardiotocography. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet 2015;131(October (1)):13–24.
[9] Richardson BS, Czikk MJ, daSilva O, Natale R. The impact of labor at term on measures of neonatal outcome. Am J Obstet Gynecol 2005;192(January (1)):219–26.
[10] Ahmadpour-Kacho M, Zahedpasha Y, Hagshenas M, et al. Short term outcome of neonates born with abnormal umbilical cord arterial blood gases. Iran J Pediatr 2015;25(June (3)):e174.
[11] Spain JE, Tuuli MG, Macones GA, Roehl KA, Odibo AO, Cahill AG. Risk factors for serious morbidity in term nonanomalous neonates. Am J Obstet Gynecol 2015;212(June (6))799 e1–7.
[12] Persson M, Johansson S, Villamor E, Cnattingius S. Maternal overweight and obesity and risks of severe birth-asphyxia-related complications in term infants: a population-based cohort study in Sweden. PLoS Med 2014;11(May (5))e1001648.
[13] Lassiter JR, Holliday N, Lewis DF, Mulekar M, Abshire J, Brocato B. Induction of labor with an unfavorable cervix: how does BMI affect success? J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet 2015;23(November):1–3.
[14] Shaban MM, Bassiouny YA, Elzahaby IM, Hassan AA. Body mass index and labour outcome in Egyptian women. J Obstet Gynaecol J Inst Obstet Gynaecol 2014;34(April (3)):248–50.
[15] Andres RL, Day M-C. Perinatal complications associated with maternal tobacco use. Semin Neonatol 2000;5(3)231–41 août.
[16] Habek D, Habek JC, Ivanisević M, Djelmis J. Fetal tobacco syndrome and perinatal outcome. Fetal Diagn Ther 2002;17(December (6)):367–71.
[17] Chelchowska M, Ambroszkiewicz J, Gajewska J, Laskowska-Klita T, Leibschang J. The effect of tobacco smoking during pregnancy on plasma oxidant and antioxidant status in mother and newborn. Eur J Obstet Gynecol Reprod Biol 2011;155(April (2)):132–6.
[18] Mimouni F, Miodovnik M, Siddiqi TA, Khoury J, Tsang RC. Perinatal asphyxia in infants of insulin-dependent diabetic mothers. J Pediatr 1988;113(august (2)):345–53.
[19] Gilbert WM, Jacoby BN, Xing G, Danielsen B, Smith LH. Adverse obstetric events are associated with significant risk of cerebral palsy. Am J Obstet Gynecol 2010;203(October (4))328 e1–5.
[20] Takano Y, Furukawa S, Ohashi M, Michikata K, Sameshima H, Ikenoue T. Fetal heart rate patterns related to neonatal brain damage and neonatal death in placental abruption. J Obstet Gynaecol Res 2013;39(January (1)):61–6.
[21] Ananth CV, Cnattingius S. Influence of maternal smoking on placental abruption in successive pregnancies: a population-based prospective cohort study in Sweden. Am J Epidemiol 2007;166(August (3)):289–95.
[22] Liong S, Barker G, Lappas M. Placental ras regulates inflammation associated with maternal obesity. Mediators Inflamm 2018 2018:3645386.
[23] Zdravkovic T, Genbacev O, McMaster MT, Fisher SJ. The adverse effects of maternal smoking on the human placenta: a review. Placenta 2005;26(April (Suppl. A)):S81–6.

[24] 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(October (10)):909–17.
[25] Spencer JA, Badawi N, Burton P, Keogh J, Pemberton P, Stanley F. The intrapartum CTG prior to neonatal encephalopathy at term: a case-control study. Br J Obstet Gynaecol 1997;104(January (1)):25–8.
[26] Bogdanovic G, Babovic A, Rizvanovic M, Ljuca D, Grgic G, Djuranovic-Milicic J. Cardiotocography in the prognosis of perinatal outcome. Med Arch Sarajevo Bosnia Herzeg 2014;68(2):102–5.
[27] 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 (March (4)):724–30.