Risk factors for hypoxic–ischemic encephalopathy in cases of severe acidosis: A case–control study

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Original Research Article

Introduction: The aim of the study was to identify the obstetric risk factors for hypoxic–ischemic encephalopathy (HIE) in infants with asphyxia at birth.

Material and methods: This multicenter case–control study covered the 5-year period from 2014 through 2018 and included newborns ≥36 weeks of gestation with an umbilical pH at birth ≤7.0. Cases were newborns who developed moderate or severe HIE; they were matched with controls with pH ≤7.0 at birth over the same period without moderate or severe HIE. The factors studied were maternal, gestational, intrapartum, delivery-related, and neonatal characteristics. A multivariable analysis was performed to study the maternal, obstetric, and neonatal factors independently associated with moderate or severe HIE.

Results: Our review of the records identified 41 cases and 98 controls. Compared with controls, children with moderate or severe HIE had a lower 5-min Apgar score, lower umbilical artery pH, and higher cord lactate levels at birth and at 1 h of life. Obstetric factors associated with moderate or severe HIE were the occurrence of an acute event (adjusted odds ratio [aOR] 6.4; 95% confidence interval [CI] 1.8–22.5), maternal fever (aOR 3.5; 95% CI 1.0–11.9), and thick meconium during labor (aOR 2.9; 95% CI 1.0–8.6).

Conclusions: HIE is associated with a lower 5-min Apgar score and with the severity of acidosis at birth and at 1 h of life. In newborns with a pH <7.0 at birth, the occurrence of an acute obstetric event, maternal fever, and thick meconium are independent factors associated with moderate or severe HIE.

Keywords: acidosis, encephalopathy, hypoxic–ischemic, intrapartum asphyxia, umbilical pH

Abbreviations: FHR, Fetal heart rate; HIE, Hypoxic–ischemic encephalopathy.
1 | INTRODUCTION

Intrapartum asphyxia results from the impairment of uteroplacental gas exchanges leading to dysfunctional cell metabolism and then metabolic acidosis. It is defined by an umbilical artery pH ≤7.0 and a base deficit ≥12 mmol/L at birth. Intrapartum asphyxia is associated with severe short-term neonatal outcomes: multiorgan failure, hypoxic-ischemic encephalopathy (HIE), and death.

HIE stages have been classified by clinical criteria, in accordance with Sarnat and Sarnat. Its prevalence is estimated at between 1.5 and 2.5 per 1000 livebirths. Among infants with moderate and severe HIE (stages 2 and 3), 30% die and 30% of the survivors have major neurodevelopmental disabilities.

Several studies in the general population have identified risk factors for intrapartum asphyxia and HIE, including in particular intrapartum discharge of thick meconium, fetal heart rate (FHR) anomalies, chorioamnionitis, and the occurrence of an acute obstetric event. Nonetheless, only about 10–20% of children born with intrapartum asphyxia develop HIE or die, and why some children with severe acidosis develop HIE whereas others do not remains unknown.

From a physiological perspective, it is possible that some contributing factors increase the risk of HIE in cases of neonatal asphyxia. For example, an acute obstetric event leading to asphyxia without the possibility of fetal adaptation may be associated with the occurrence of HIE. Moreover, some fetuses that are known to be more vulnerable (post-term pregnancy, small-for-gestational-age fetus) may be more likely to develop HIE. Similarly, other maternal and obstetric factors such as age, smoking, diabetes, and fever during labor might affect fetal brain adaptation to acidosis. The objective of our study was to identify risk factors for HIE in newborns with an umbilical artery pH ≤7.0.

2 | MATERIAL AND METHODS

This retrospective case-control study took place in Trousseau hospital in Paris, which is a tertiary referral center. In addition to the cases of HIE that occurred in infants born at Trousseau, all cases of HIE referred there for controlled hypothermia from four other Paris hospitals during calendar years 2014–2018 were included.

Inclusion criteria were an umbilical artery pH ≤7.0 at birth, a gestational age ≥36 weeks, and a moderate or severe HIE (stage 2 or 3 according to Sarnat and Sarnat) managed by controlled hypothermia. Exclusion criteria were missing umbilical artery pH data, chromosomal abnormality, and neurologic trauma (cerebral hemorrhage, spinal cord injuries). Control children were those with an umbilical artery pH ≤7.0 who did not have moderate or severe HIE born in Trousseau hospital during calendar years 2014–2017.

The data were extracted from medical records in the maternity wards and neonatal units and included four categories of factors. The first comprised maternal variables: age, ethnicity, health insurance, body mass index, medical and surgical history (diabetes, hypertension, chronic diseases), parity, and obstetric history (cesarean delivery, in utero fetal death, gestational hypertension, and history of small-for-gestational-age fetus). The gestational factors were gestational diabetes, gestational hypertension, preeclampsia, intrahepatic cholestasis of pregnancy, and small-for-gestational-age fetus (estimated weight <10th percentile for gestational age). The intrapartum factors were induction of labor, maternal fever during labor (defined by a temperature ≥38 °C, measured in the ear and systematically recorded every 2 h during labor), thick meconium (defined by dark green viscous fluid with “pea soup” characteristics), use of oxytocin, and occurrence of an acute event (placental abruption, uterine rupture, cord prolapse, bleeding from vasa previa, shoulder dystocia, fetomaternalt hemorrhage, and amniotic fluid embolism).

The last 2 h before birth of all FHR traces were reviewed and classified as either normal, suspicious, or pathologic according to the International Federation of Gynecology and Obstetrics (FIGO) 2015 classification. Finally, the delivery factors considered included cesarean delivery (emergency or planned), decision-to-delivery interval for emergency cesarean deliveries, spontaneous or operative vaginal delivery, duration of pushing (expulsive efforts), and FHR during pushing. We also recorded neonatal characteristics: umbilical artery pH and lactate level at birth, 5-min Apgar score, birthweight, sex, and pH and lactate level measured at 1 h of life.

2.1 | Statistical analyses

Characteristics of the two groups were first compared using a univariate analysis. Chi-squared and Fisher’s exact tests were used to compare categorical variables, and Student’s t test was used to compare the continuous variables. The statistical significance threshold was set as a p value <0.05.

A multivariable analysis was used to study the independent factors associated with HIE. The first model investigated the risk factors for HIE in the overall population. A second model studied the association between labor characteristics and HIE in a subpopulation after exclusion of the women with cesarean deliveries before labor. The variables included in the models were those associated with HIE in the univariate analysis with a p < 0.2, maternal age and parity. Mode of delivery was not included in the multivariable analysis models because birth by cesarean or operative vaginal delivery is more frequent in severe obstetric situations; it is therefore an intermediate factor.

The population source of the cases was Trousseau hospital and four other centers referring cases to it for controlled hypothermia. All control patients were born in Trousseau hospital. Because that
could have biased the comparison of women’s characteristics between cases and controls, a sensitivity analysis was performed on a population restricted to infants born at Trouseau hospital to analyze the maternal characteristics associated with HIE.

Statistical analyses were performed with Stata 13 software (TX, USA).

2.2 | Ethical approval

The study received a favorable opinion from the Committee for Ethics and Research in Obstetrics and Gynecology on March 9, 2021 (n°CEROG 2020-OBS-1203).

3 | RESULTS

During the study period, 73 infants admitted to Trouseau hospital’s neonatal intensive care unit were treated with therapeutic hypothermia for moderate or severe HIE. After exclusion of 15 with missing data for umbilical artery pH at birth and 17 with umbilical pH >7.0, 41 neonates with an umbilical pH ≤7.0 made up the case group (HIE group). Among them, 28 (68.3%, 95% confidence interval [CI] 54.1–82.5) had moderate HIE and ten (24.4%, 95% CI 11.3–37.5) had severe HIE.

Among the 14 001 children born in Trouseau hospital between 2014 and 2017, 115 had an umbilical pH artery ≤7.0 (0.82%; 95% CI 0.68–0.99). Among them, 98 did not have moderate or severe HIE and constituted the control group (Figure 1).

The two groups did not differ for the women’s individual characteristics or obstetric history (Table 1). The sensitivity analysis restricted to infants born in Trouseau hospital yielded similar results (Table 2).

Rates of preexisting or gestational diabetes, preexisting or gestational hypertension, or preeclampsia during pregnancy were also similar between the two groups (Table 1). There were significantly more diagnoses of intrahepatic cholestasis of pregnancy in the HIE group (7.3 vs 0%, p = 0.02) as well as significantly fewer spontaneous vaginal deliveries and more emergency cesareans before labor.

Compared with the control group, the case group had a higher rate of maternal fever ≥38 °C during labor and of thick meconium discharge during labor. An acute event occurred in 14 (32.1%) women in the HIE group vs nine (9.2%) in the control group (p < 0.001) (Table 1).

Among the 23 acute events, 17 (73.9%) had pathological FHR according to the FIGO classification,20 and four (17.4%) had suspicious FHR. The one (4.3%) event with normal FHR was shoulder dystocia.

After exclusion of the women with a cesarean delivery before labor (emergency or planned), 32 (78.0%) and 81 (82.7%) women in the case and control groups, respectively, gave birth after labor. In this population, factors associated with HIE were the use of oxytocin and the mode of delivery (Table 3).

The case group also had lower umbilical artery pH levels and higher lactate levels at birth and 1 h after birth as well as a lower 5-min Apgar score (Table 4).

Factors independently associated with HIE in the overall population were the occurrence of an acute event (adjusted odds ratio [aOR] 6.4; 95% CI 1.8–22.5), a maternal temperature ≥38 °C at delivery (aOR 3.5; 95% CI 1.0–11.9), thick meconium at delivery (aOR 2.9; 95% CI 1.0–8.6), and a low umbilical artery pH (Table 5). In the subpopulation of women who underwent labor, only a low umbilical artery pH and an acute event were still associated with HIE.

4 | DISCUSSION

In this case–control study, the risk factors for stage 2 and 3 HIE in newborns with an umbilical artery pH ≤7.0 were the occurrence of an acute event, a maternal temperature ≥38 °C at delivery, thick meconium, and the degree of acidosis at birth.

The selection of patients with umbilical artery pH ≤7.0 is one of the strengths of our study. The pH threshold at birth of 7.0 is frequently used to define infants with asphyxia at birth because the risk of short- and long-term complications increases sharply below this
Specifically, the risk of severe neonatal complications, including encephalopathy, convulsions, or death, is six times higher in newborns with a pH ≤7.0 than in those with a pH between 7.01 and 7.05. A systematic review including ten studies and 386 newborns with a cord pH <7.0 found neurological morbidity among 5–30% of them. Therefore, an umbilical artery pH <7.0 is one of the criteria.

### Table 1
Comparison of maternal and obstetric characteristics between the case (stage 2 and 3 hypoxic–ischemic encephalopathy) and control groups

| Characteristics                                      | Cases n = 41 (%) | Controls n = 98 (%) | p   |
|------------------------------------------------------|------------------|---------------------|-----|
| Age (years, mean ± SD)                              | 31.4 ± 5.3       | 32.3 ± 9.1          | 0.43|
| Age ≥35 years                                       | 15 (36.6)        | 41 (41.8)           | 0.57|
| BMI (kg/m²) ≥30                                     | 13 (31.7)        | 23 (23.5)           | 0.31|
| Origin                                               |                  |                     |     |
| European                                             | 20 (50.0)        | 46 (63.0)           | 0.56|
| North Africa                                         | 7 (17.5)         | 10 (13.7)           |     |
| Sub-Saharan Africa                                   | 11 (27.5)        | 15 (20.6)           |     |
| Other                                                | 2 (5.0)          | 2 (2.7)             |     |
| Missing data                                         | 1                | 25                  |     |
| Health insurance                                     |                  |                     |     |
| Has health insurance                                 | 32 (78.0)        | 82 (83.7)           | 0.36|
| Has no health insurance                              | 9 (22.0)         | 15 (15.3)           |     |
| Missing data                                         | 0                | 1                   |     |
| Previous cesarean delivery                           | 9 (22.0)         | 24 (24.5)           | 0.75|
| Hypertension before pregnancy                        | 0 (0.0)          | 4 (4.1)             | 0.32|
| Diabetes before pregnancy                            | 1 (0.6)          | 1 (1.0)             | 0.50|
| Obstetric history                                    |                  |                     |     |
| Previous SGA, preeclampsia                           | 0 (0.0)          | 5 (5.1)             | 0.32|
| Previous in utero fetal death                        | 1 (2.4)          | 2 (2.0)             | 1   |
| Nulliparity                                          | 26 (63.4)        | 56 (57.1)           | 0.49|
| Multiple pregnancy                                   | 4 (9.8)          | 6 (6.1)             | 0.48|
| Gestational hypertension or preeclampsia             | 3 (7.3)          | 18 (18.4)           | 0.10|
| SGA                                                  | 3 (7.3)          | 15 (15.3)           | 0.20|
| Gestational diabetes                                 | 9 (22)           | 12 (12.2)           | 0.15|
| Intrahepatic cholestasis of pregnancy                | 3 (7.3)          | 0 (0.0)             | 0.02|
| Gestational age of birth                             |                  |                     |     |
| 37–41 weeks                                          | 30 (73.2)        | 81 (82.7)           | 0.46|
| <37 weeks                                            | 2 (4.9)          | 3 (3.1)             |     |
| >41 weeks                                            | 9 (22.0)         | 14 (14.3)           |     |
| Vaginal delivery                                     | 14 (34.2)        | 42 (42.9)           | 0.33|
| Instrumental vaginal delivery                        | 13 (31.7)        | 23 (23.5)           | 0.31|
| Cesarean section                                     | 27 (65.9)        | 56 (57.1)           | 0.34|
| Planned cesarean section                             | 2 (4.9)          | 13 (13.3)           | 0.23|
| Emergency cesarean section before labor              | 7 (17.1)         | 4 (4.1)             | 0.02|
| Emergency cesarean section during labor              | 18 (43.9)        | 39 (39.8)           | 0.65|
| Temperature ≥38 °C at the time of delivery           | 10 (24.4)        | 11 (11.2)           | 0.05|

### Table 1 (Continued)
Comparison of the maternal characteristics of women in the case (stage 2 and 3 hypoxic–ischemic encephalopathy) and control groups who gave birth at Trouseau hospital (sensitivity analysis)

| Characteristics                                      | HIE n = 17 (%) | No HIE n = 98 (%) | p   |
|------------------------------------------------------|----------------|------------------|-----|
| Age (years, mean ± SD)                               | 31.3 ± 18.1    | 32.3 ± 9.1       | 0.46|
| Age ≥35 years                                        | 6 (35.3)       | 41 (41.8)        | 0.79|
| BMI (kg/m²) ≥30                                      | 3 (17.7)       | 23 (23.5)        | 0.76|
| Origin                                               |                |                  |     |
| European                                             | 9 (52.9)       | 46 (63.0)        | 0.76|
| North Africa                                         | 2 (11.8)       | 10 (13.7)        |     |
| Sub-Saharan Africa                                   | 5 (29.4)       | 15 (20.6)        |     |
| Other                                                | 1 (5.9)        | 2 (2.7)          |     |
| Missing data                                         | 0              | 25               |     |
| Health insurance                                     |                |                  |     |
| Has health insurance                                 | 16 (94.1)      | 93 (94.9)        | 0.74|
| Does not have health insurance                       | 1 (5.9)        | 4 (4.1)          |     |
| Missing data                                         | 0              | 1                |     |
| Previous cesarean delivery                           | 4 (23.5)       | 24 (24.5)        | 0.93|
| Hypertension before pregnancy                        | 0 (0.0)        | 4 (4.1)          | 1   |
| Diabetes before pregnancy                            | 0 (0.0)        | 1 (1.0)          | 1   |
| Obstetric history                                    |                |                  |     |
| Previous SGA, preeclampsia                           | 0 (0.0)        | 5 (5.1)          | 1   |
| Previous in utero fetal death                        | 1 (5.9)        | 2 (2.0)          | 0.38|

Abbreviations: BMI, body mass index; SD, standard deviation; SGA, small for gestational age.
set by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics to establish a causal relation between neonatal encephalopathy and intrapartum asphyxia. We did not include HIE stage 1 in this study as we considered moderate or severe HIE—the condition requiring management with controlled hypothermia—to be more clinically relevant.

Our study had some limitations. Cases and controls did not come from exactly the same population, which might have biased the comparison of women’s individual characteristics. However, the sensitivity analysis restricted to women who gave birth in the same hospital provided similar results. A second weakness was the power of the study. Although quite large for such a rare event, the sample size in our study provided a power of 90% to detect a difference of 2.5-fold for a risk factor present in 20% in the control group and a power of only 60% for a 2-fold difference. It was therefore possible that we failed to identify some factors associated less strongly with HIE.

After searching the MEDLINE and Embase databases with adequate medical subject heading terms, we found only one published study that examined the risk factors for HIE stage 2 and 3 in cases of pH ≤7.0. The design was similar to ours but included only half the number of cases with HIE stages 2 and 3; it reported an association between decreased FHR variability and HIE and renal, cardiac, and pulmonary dysfunction in 129 term newborns with pH <7.0.

Abbreviations: FHR, fetal heart rate; FIGO, International Federation of Gynecology and Obstetrics.

**TABLE 3** Comparison of labor characteristics between the case (stage 2 and 3 hypoxic–ischemic encephalopathy) and control groups

| Characteristics                  | Cases n = 32 (%) | Controls n = 81 (%) | p   |
|----------------------------------|------------------|---------------------|-----|
| Onset of labor                   |                  |                     |     |
| Spontaneous                      | 19 (59.4)        | 55 (67.9)           | 0.39|
| Induction                        | 13 (40.6)        | 26 (32.1)           |     |
| Oxytocin use                     | 20 (62.5)        | 31 (38.3)           | 0.02|
| FHR 2 h before birth (FIGO)     |                  |                     |     |
| Normal                           | 3 (9.4)          | 6 (7.4)             | 0.48|
| Suspicious                       | 6 (18.8)         | 9 (11.1)            |     |
| Pathological                     | 23 (71.9)        | 66 (81.5)           |     |
| Mode of delivery                 |                  |                     |     |
| Vaginal delivery                 | 1 (3.1)          | 23 (28.4)           | 0.01|
| Operative vaginal delivery       | 13 (40.6)        | 23 (28.4)a          |     |
| Cesarean                         | 18 (56.3)        | 39 (48.2)a          |     |

Abbreviations: FHR, fetal heart rate; FIGO, International Federation of Gynecology and Obstetrics.

*aFour cesarean sections for failure of operative delivery.*

**TABLE 4** Comparison of neonatal outcomes between the case (stage 2 and 3 hypoxic–ischemic encephalopathy) and control groups

| Outcomes                              | Cases n = 41 (%) | Controls n = 98 (%) | p   |
|---------------------------------------|------------------|---------------------|-----|
| Male                                  | 27 (65.9)        | 50 (51.0)           | 0.11|
| Weight (g, mean ± SD)                 |                  |                     |     |
| SGA                                   |                  |                     |     |
| Umbilical pH (mean ± SD)              |                  |                     |     |
| <7.0                                  | 6.87 ± 0.086     | 6.93 ± 0.053        | <0.001|
| [6.90–7.00]                           | 17 (41.5)        | 80 (81.6)           | <0.001|
| [6.85–6.90]                           | 9 (22.0)         | 8 (8.2)             |     |
| [6.80–6.85]                           | 12 (29.3)        | 10 (10.2)           |     |
| <6.80                                 | 3 (7.3)          | 0 (0.0)             |     |
| Umbilical lactate level (in mmol/L, mean ± SD) |                  |                     |     |
| <5                                    | 11.2 ± 3.3       | 9.3 ± 1.7           | <0.001|
| [5–10]                                | 14 (34.2)        | 64 (68.8)           | <0.001|
| [10–12]                               | 15 (36.6)        | 22 (23.7)           |     |
| ≥12                                   | 12 (29.3)        | 7 (7.5)             |     |
| Missing data                          | 0                | 5                   |     |
| 5-min Apgar score (mean ± SD)         |                  |                     |     |
| 7–10                                  | 4.1 ± 2.4        | 8.6 ± 2.0           | <0.001|
| 4–6                                   | 7 (17.1)         | 83 (84.7)           | <0.001|
| 0–3                                   | 17 (41.5)        | 12 (12.2)           |     |
| pH at 1 h (mean ± SD)                 |                  |                     |     |
| <7.0                                  | 7.10 ± 0.16      | 7.22 ± 0.09         | <0.001|
| [7.10–7.20]                           | 6 (23.1)         | 23 (25.3)           |     |
| [7.00–7.10]                           | 5 (19.2)         | 7 (7.7)             |     |
| [6.00–7.00]                           | 7 (26.9)         | 1 (1.1)             |     |
| Missing data                          | 15               | 7                   |     |
| Lactate level at 1 h (in mmol/L, mean ± SD) |                  |                     |     |
| <5                                    | 13.5 ± 11.4      | 8.5 ± 7.9           | <0.001|
| [5–10]                                | 1 (4.0)          | 12 (13.3)           | <0.001|
| [10–15]                               | 5 (20.0)         | 48 (53.3)           |     |
| ≥15                                   | 9 (36.0)         | 28 (31.1)           |     |
| Missing data                          | 10 (40.0)        | 2 (2.2)             |     |

Abbreviations: SD, standard deviation; SGA, small for gestational age.

HIE and neonatal complications. Moreover, we found that the degree of acidosis is independently associated with HIE. In a retrospective cohort of 504 newborns with a pH <7.0, Kelly et al. found a dose-dependent association between acidosis and adverse neonatal outcomes, including HIE and later neurodevelopmental outcome. Goodwin et al. showed a correlation between the degree of umbilical artery acidemia and HIE and renal, cardiac, and pulmonary dysfunction in 129 term newborns with pH <7.0.
Women in labor

Blood lactate, a hallmark of anaerobic metabolism, has been traditionally employed as a surrogate marker for tissue hypoxia and/or ischemia. Monitoring lactate could be useful for assessing HIE severity.25 Furthermore, a study seeking to correlate serum and brain lactate concentration during HIE reported a correlation between serum and cerebral lactate and severity of insult during perinatal asphyxia.26 A study seeking to correlate serum and brain lactate concentration during HIE found that a longer time to serum lactate normalization was related to the severity of encephalopathy on electroencephalogram and with seizure burden.27 Blood lactate, a hallmark of anaerobic metabolism, has been traditionally employed as a surrogate marker for tissue hypoxia and/or ischemia. Monitoring lactate could be useful for assessing HIE severity.26

We also found that the newborns with moderate or severe HIE had lower arterial pH and higher lactate levels at 1 h of life. The severity of acidosis at 1 h of life is poorly documented. One previous retrospective study of 1690 infants showed worse prognosis for infants born with acidemia that persisted at 1 h of life.24 Furthermore, a prospective study including 50 infants with HIE found that a long-term survival is associated with neonatal encephalopathy. Fever during or after an anoxic-ischemic episode is known to enhance the extension of brain lesions.34,35 Some authors suggest that the short-term outcomes of children with HIE treated with hypothermia after an identifiable intrapartum acute event are worse than for the same population with no such identifiable event.36

The univariate analysis showed significantly more diagnoses of intrahepatic cholestasis of pregnancy in the HIE group. We could not include this variable in the multivariable analysis because the control group had no diagnosis of intrahepatic cholestasis. Gestational cholestasis is associated with both a worse neonatal prognosis and intrapartum asphyxia, especially for bile acid levels above 40 μmol/L.40,41 It is therefore possible that gestational cholestasis worsens the prognosis of neonates with asphyxia. However, because we cannot rule out the possibility that this finding was observed by chance, it should be confirmed by other studies.

We found no difference between the two groups according to FHR. It must be noted that most of the FHR tracings were not among the subgroup of neonates with an umbilical artery pH <6.85 at birth.42

TABLE 5 Predictive factors for hypoxic–ischemic encephalopathy: Multivariable analysis of all women and women in labor

| Factors                      | Overall population | Women in labor |
|------------------------------|--------------------|----------------|
|                              | Crude OR[95% CI]   | Adjusted OR[95% CI] | Crude OR[95% CI] | Adjusted OR[95% CI] |
| Age                          | 1.0 [0.9–1.0]      | 1.0 [0.9–1.1]   | 1.0 [0.9–1.0] | 1.0 [0.9–1.1]       |
| Nulliparity                  | 1.3 [0.6–2.8]      | 2.3 [0.8–6.4]   | 0.9 [0.4–2.1]  | 1.7 [0.5–5.2]       |
| Hypertension, preeclampsia, SGA | 0.5 [0.2–1.3]   | 0.3 [0.1–1.4] | 0.4 [0.1–1.2]  | 0.3 [0.1–1.8]       |
| Gestational diabetes         | 2.0 [0.8–5.2]      | 3.3 [0.9–12.1]  | 1.8 [0.6–5.7]  | 1.8 [0.4–8.3]       |
| Acute event                  | 5.1 [2.0–13.1]     | 6.4 [1.8–22.5]  | 5.5 [2.0–15.2] | 6.6 [1.6–27.2]      |
| Thick meconium at delivery   | 3.2 [1.4–7.5]      | 2.9 [1.0–8.6]   | 2.7 [1.1–6.7]  | 2.9 [0.9–9.3]       |

Abbreviations: CI, confidence interval; OR, odds ratio; SGA, small for gestational age.

Hypertension, preeclampsia, SGA, age, and intrapartum asphyxia, especially for bile acid levels above 40 μmol/L, 40,41 are independent risk factors for HIE. However, it is possible that maternal fever has a direct negative impact on the fetal brain. According to Blume et al., 38 chorioamnionitis and isolated maternal fever are independently associated with neonatal encephalopathy. Fever during or after an anoxic-ischemic episode is known to enhance the extension of brain lesions, and fetal temperature rises as maternal temperature rises.39
pathological, which appears logical given that all children had a pH ≤ 7.0 at birth. Moreover, FHR may not be a good predictor of HIE. In a case–control study comparing FHR 1 h before the birth of neonates with or without HIE treated with hypothermia, Graham et al. 42 found no difference between the groups in the tracing categories according to the American College of Obstetricians and Gynecologists classification. Another study found that experienced clinicians assessing FHR blinded to perinatal outcome detected 75% of neonates who were subsequently diagnosed with HIE and recommended expedited birth in nearly half of those cases. 43 Nonetheless, FHR has very low specificity for predicting HIE because of the high frequency of FHR abnormalities in neurologically normal newborns and the low prevalence of HIE.

5 | CONCLUSION

This study shows that the degree of acidosis at birth is associated with an increased risk of stage 2 and 3 HIE. Moreover, for a given pH at birth, the presence of an acute event, maternal fever at delivery, and thick meconium is associated with a higher risk of HIE. It provides new insight about the pathophysiology of HIE. After birth, for a given pH, these obstetric factors may help pediatricians to identify neonates who need specific care to prevent long-term neurological sequelae.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design, processing of data, interpretation of data, drafting of the article, critical revision, and final approval. PL and EG contributed to the data collection, and PL and GK to the statistical analysis of the data.

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**How to cite this article:** Lorain PP, Bower A, Gottardi E, et al. Risk factors for hypoxic–ischemic encephalopathy in cases of severe acidosis: A case–control study. *Acta Obstet Gynecol Scand*. 2022;101:471–478. doi: 10.1111/aogs.14326