Risk factors for neonatal hypoxic ischemic encephalopathy in Helsinki University Hospital

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Tiivistelmä - Referat – Abstract

Syntymäasfyksia on tila, jossa sikiö tai syntyvä lapsi kärsii hypoksemian lisäksi hiilidioksidiretentiosta ja asidoosista. Se voi johtaa aivotoiminnan häiriöön eli hypoksis-iskeemiseen enkefalopatiaan (HIE), jonka hoitona käytetään vastasyntyneen ruumiinlämmön alentamista 33 asteeseen kolmen päivän ajaksi. Vaikea-asteisessa HIE:ssa mortaliteetti on korkea, ja henkiin jääville lapsille kehittyy usein pysyviä neurologisia vammoja.

Asfyksialle altistavia äidin sairauksia sekä raskauden ja synnytyksen aikaisia riskitekijöitä tunnetaan monia, ja toisaalta suuri osa asfyksiatilanteista tulee yllättäen eikä ole ennakoitavissa. Tämän tutkimuksen tavoitteena oli kartoittaa erityisesti ammattilaisten toiminnalla vältettävissä olevia riskitekijöitä, jotka ovat johtaneet keskivaikeaan ja vaikeaan vastasyntyneen HIE:aan ja vaatineet viilennyshoitoa.

Tutkimus toteutettiin retrospektiivisenä tapaus-verrokkitutkimuksena vuosina 2013 – 2017 Helsingin yliopistollisen sairaalan synnytyssairaaloissa synnyttäneille äideille. Jokaista 88:aa viilennyshoidettua vastasyntynyttä kohden valittiin samaa sukupuolta oleva, samassa sairaalassa ja samalla menetelmällä seuraavaksi syntynyt lapsi. Tiedot äitien terveydentilasta, raskaudesta ja synnytyksestä kerättiin sairaalan potilastietojärjestelmästä. Riskitekijöiden assosiaatiota HIE:n kehittymiseen arvioitiin logistisella regressioanalyysillä. Kaikista kirjallisuuden perusteella valituista todennäköisistä riskitekijöistä monimuuttuja-analyysiin valikoitiin muuttujat, joiden OR yksimuuttuja-analyysissä oli tilastollisesti merkitsevä.

Synnytyksen käynnistäminen (aOR 3.08), äidin tupakointi (aOR 1.45) ja obstetriset hätätilanteet (aOR 3.51), osoittautuivat HIE:n itsenäisiksi riskitekijöiksi. Tutkimusryhmän käynnistetyissä synnytyksissä oli enemmän alatiesynnytyksiä kontrolliryhmään verrattuna (p=0.03). Tutkimustulosten perusteella päivystyskeisarileikkausta tulisi harkita aiempaa herkemmin käynnistettyihin synnytyksiin liittyvissä komplikaatioepäilyissä. Jatkossa tutkimuksia kannattanee suunnata erityisesti sikiön hyvinvoinnin seurannassa käytettävien menetelmien kehittämiseen.

Avainsanat – Nyckelord – Keywords
Obstetrics, Neonatology, Hypoxic-Ischemic Encephalopathy, Asphyxia Neonatorum, Induction of Labor, Labor Complications

Säilytyspaikka – Förvaringställe – Where deposited

Muita tietoja – Övriga uppgifter – Additional information

1 Introduction

1.1 Background

Peripartum asphyxia, generally referred to as birth asphyxia, is one of the main causes of neonatal mortality worldwide (1). Approximately three to five newborns per 1000 live births in developed countries are affected by birth asphyxia (2). It is a condition of hypoxia and acidemia, which develops either gradually during pregnancy, leading to emergency cesarean section when detected, or abruptly, when complications during labour occur (3). The diagnosis of severe birth asphyxia is set when the newborn neonate presents with an Apgar score of 0 to 3 within the first five minutes after birth and a pH of 7 or less in umbilical artery blood sample (4).

The multifactorial antecedents and the pathophysiology of birth asphyxia are well studied and recognized. Extensive effort is made in Finland and countries with comparable health care systems to screen and follow-up with mothers and pregnancies with known obstetric risk factors. These risk factors include maternal health problems such as diabetes mellitus, cholestasis of pregnancy, anemia, and hypertension, as well as fetal conditions like intra uterine growth restriction and infections(5,6).

Hypoxic-ischemic encephalopathy (HIE) is a neurological condition following severe birth asphyxia. According to the severity, it can be divided into mild, moderate and severe categories (7). The signs of mild HIE are quick recovery from asphyxia, normal level of consciousness, mild neurological signs such as irritability, and absence of seizures. The signs of moderate to severe HIE are presence of seizures, multi organ failure, and altered level of consciousness, tone and primitive reflexes. The diagnosis can only be used for neonates aged 36 or more weeks of gestation at birth. (7)

The neurological damage in HIE develops in two phases: at first, in the hypoxic and acidotic phase of birth asphyxia during late pregnancy or labour, cellular hypoxia causes primary neuronal death. The second phase follows with delayed neuronal death hours later. This secondary phase is characterized by the physiological mechanisms such as

hyperemia, edema, and apoptosis in the neonatal brain, and it is associated with encephalopathy and seizure activity. (2) In the most severe cases of birth asphyxia, HIE predisposes the resuscitated neonate to permanent neurologic morbidities such as cerebral palsy, epilepsy, and developmental delays. In term newborn neonates, the medical intervention to reduce brain damage in moderate and severe HIE is to induce cooling of the neonates to around 33 °C for three days (8).

1.2 Finnish antenatal care

Obstetric risk factors are actively screened and systematic efforts to prevent them are made in the Finnish health care system and maternal care. The Finnish maternity health clinics are operated on governmental level and are free for all expectant mothers. Maternity health clinics arrange screening for fetal abnormalities via ultrasound (gestation weeks 12 and 21) and for maternal risks (gestational diabetes, hypertension, proteinuria, anemia). The mother usually meets with a nurse 8 to 15 times and has two routine doctor's checkups during the pregnancy. Data on smoking, alcohol consumption and substance abuse are collected. The mother is weighed, and the growth of the fetus is observed on each visit by tracking the symphysis-fundal height. Maternity health clinics serve as a mode of educating mothers on physical and emotional well-being. Help can also be offered in social issues. High risk pregnancies are referred to tertiary health care in obstetric clinics.

In consequence, comprehensive information on maternal health and possible obstetric risk factors has already been collected upon the mother's admission to the obstetric ward. The information is then transferred to the mother's obstetric records. A spontaneous labour is monitored by a midwife, who consults an obstetrician if the labour calls for an assessment of intervention, based on fetal or maternal well-being.

During labour, especially in the presence of known obstetric risk factors, fetal heart rate and uterine contractions are monitored with cardiotocography (CTG). The analysis of the CTG tracing is based on the assessment of the baseline, variability, accelerations and decelerations of the fetal heart rate, and the changes in these parameters in relation to the

frequency and length of the uterine contractions (9). The interpretation follows the International Federation of Gynecology and Obstetrics (FIGO) guidelines, and midwives as well as obstetricians are trained accordingly. Other ways to assess fetal well-being during pregnancy and labour include ultrasonography, computerized ST analysis of fetal electrocardiography, and determining acidosis from fetal scalp blood sampling. If signs of fetal distress emerge, intervention by cesarean delivery should be achieved immediately.

Despite high-quality maternal care, birth asphyxia and HIE remain a challenge in perinatal care, since many cases of HIE occur unanticipated in low-risk pregnancies. Even in risk pregnancies adverse outcomes are not always preventable, due to the multifactorial nature of fetal distress. (10,11)

1.3 Study objectives

The aim of this study was to assess the importance of the obstetric risk factors identified by previous studies (6), and to study their associations with HIE in neonates delivered at term at the hospitals of Helsinki University area. We particularly focused on management protocols of pregnancy and labour associated with perinatal asphyxia in our clinic. As the first in the field, we also conducted a case-control study where we matched the controls by delivery mode.

2 Subjects and methods

2.1 Setting and obstetric population

This was a retrospective case-control study from January 1, 2013, to December 31, 2017 and performed on patients who gave birth at delivery hospitals in the Helsinki area. Same guidelines for follow up and treatment of pregnancy and delivery were used in all hospitals, but all neonatal intensive care is centralized at the Neonatal Intensive Care Unit (NICU) in Helsinki University Hospital.

2.2 Study design

The study group consisted of the women who gave birth to asphyxiated singleton neonates with moderate or severe HIE. Each neonate was born term or near-term (more than 36 6/7 weeks gestational age), was admitted to the NICU and offered therapeutic hypothermia for neuroprotection. The indications for hypothermia were admitted from the international guidelines (8).

After each delivery with an asphyxiated newborn, the consecutive term singleton delivery was selected as a control. The controls were matched by their delivery hospital, gender of the neonate, mode of delivery (Table 1), and fetal presentation (occipital vs breech). Subgroups were formed based on the onset of labour (spontaneous, section, induction and attempted induction) and mode of delivery (Table 1).

Vaginal delivery, unassisted (ICD-10 code)	**Vaginal delivery, assisted (ICD-10 code)**	**Cesarean section (ICD-10 code)**
Presentation: occiput (O80.0)	Ventouse (O81.4)	Elective (O82.0)
Presentation: breech (O80.1)		Emergency (O81.10)
		Crush (O82.11)

Table 1. Classification according to mode of delivery in the matching process

The data for the study was collected from the hospital database (Siemens Obstetrix). All available obstetric information concerning fetal and maternal well-being was collected, with emphasis on factors previously proven to be independently associated with HIE (6).

The data included information concerning maternal age and health (pregestational BMI, chronic illnesses, medication), substance abuse (smoking, alcohol and drugs), gestation and parity, the information on previous births, the prenatal screening data and the number and reasons of hospital visits during the ongoing pregnancy. Data on admission time and time of birth in relation to work shifts was also obtained. No information on social or economic status is collected of the mothers in the database, which made it necessary to omit socioeconomic, educational and racial factors from the study. We considered and tested all the possible variables that have previously been suggested to increase the risk for HIE or birth asphyxia (12–26), and used the same literature to determine confounding factors.

The study was approved by the Institutional Review Board of the participating hospital (March 3, 2018, 1/2018). According to the Finnish legislation, informed consent from patients is not required for this type of retrospective study.

2.3 Statistical methods

SPSS version 25.0.0 was used to analyse the data. Independent samples t-test and chi-squared test were used to compare continuous and categorical variables, respectively, within subgroups. They were also used to test the independence of the variables and check for multicollinearity. Crude and adjusted odds ratios (OR and aOR respectively) were calculated using logistic regression to estimate associations between independent variables and the outcome. The variables with a p-value < 0,1 in the univariate logistic regression were further explored with two different methods in the multivariate logistic regression analysis.

The first method was used to adjust each independent variable by confounding factors selected according to previous studies (15,18,20,22,26–28). Some variables were used regardless of their high *p*-value in the univariate regression analysis. The second method was used without the assumption of confounding factors. In this model, as many independent variables as possible, with a *p*-value under the selected threshold, were entered into the same model. The variables discovered to have interactions with each other were not used in the same model.

For each model, sensitivity analyses were performed by comparing the pseudo R-squared values and Akaike Information Criterion (AIC) (29). The missing data were imputed for the variables with more than 5% missing data, using the FCS method by linear regression and with maximum iterations of 10 (30). Statistical significance was declared at $p < 0,05$, unless stated otherwise, and the confidence intervals were set to 95%.

3 Results

3.1 General characteristics

During the study period, 73 191 deliveries took place in four study hospitals, the average being 14 638 per year. 112 near-term and term neonates presented with moderate to severe HIE and were admitted to the NICU to receive therapeutic hypothermia. The incidence of moderate to severe HIE in the obstetric population was 1.5/1000.

97 singleton pregnancies resulting in HIE and therapeutic hypothermia made up the original study group. Due to the failure to find matched controls, 9 pregnancies were excluded, leaving us with the final study group of 88 cases.

Altogether, 45% of the neonates (40/88) in the study group were born vaginally, and 65% of these (26/40) were ventouse deliveries. Two neonates were born in breech position. The proportion of elective, emergency and crush cesarean sections were 1.1% (1/88), 15.9% (14/88) and 37.5% (33/88) respectively. Four emergency cesarean sections were preceded by failed trial of instrumental delivery (Figure 1). The mortality of the cooled neonates was 10.2% (9/88). There were no neonatal deaths in the control group.

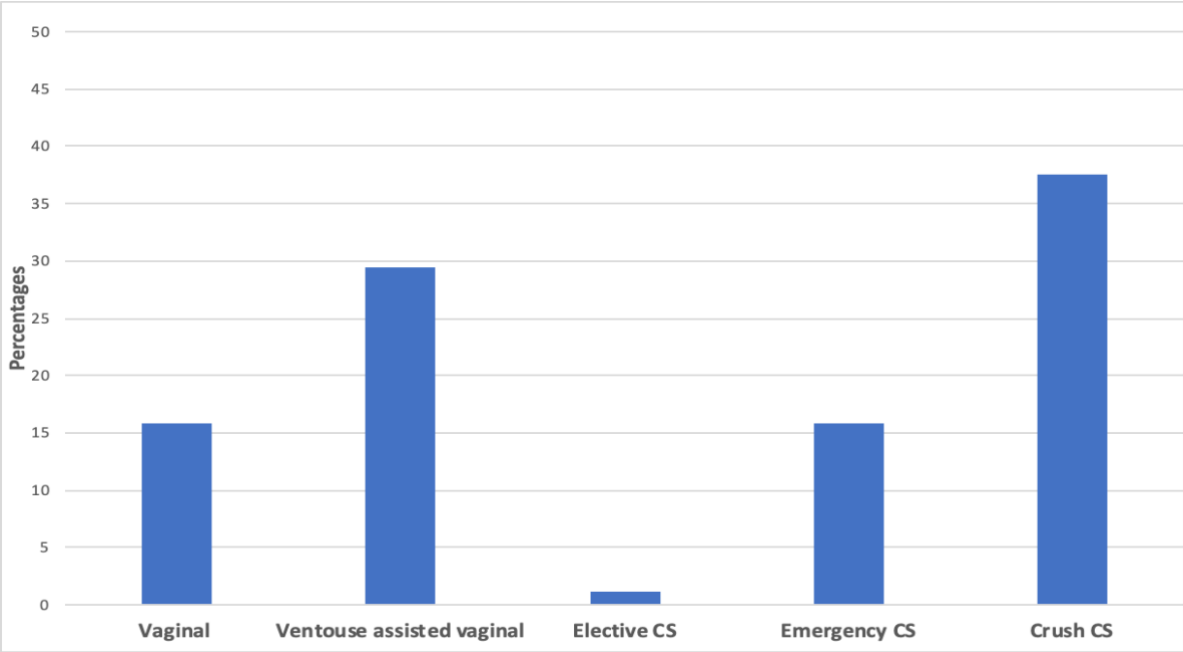

Figure 1. Distribution of delivery modes. CS = cesarean section

3.2 Logistic regression analysis

The maternal and infant characteristics were mostly similar in the study and control groups (Table 2). There were no significant differences in maternal age, nulliparity and maternal BMI. The number of smoked cigarettes per day during pregnancy was significantly larger in the study group.

	Study group	Control group	OR (95% CI)	*p*-value
Maternal characteristic				
Maternal age	31.99 (5.68)	32.96 (5.19)	0.97 (0.92 – 1.02)	0,239
Nulliparity	55 (62.50)	52 (59.09)	1.19 (0.65 – 2.19)	0.576
Maternal BMI*	24.20 (4.52)	23.96 (6.32)	1.02 (0.96 – 1.08)	0.467
Smoking (cigarettes per day)*	1.9 (2.00)	0.4 (1.40)	1.49 (1.16 – 1.76)	0.001
Infant Characteristics				
Gestational age +/- SD	39.89 (1.69)	40.21 (1.38)	0.87 (0.71 – 1.06)	0.160
Post term gestation (≥ 42 GW)	3 (3.41)	12 (13.64)	0.22 (0.06 – 0.82)	0.024
Birth weight	3458.61 (526.62)	3472.33 (506.67)	1.00 (1.00 – 1.00)	0.898

Table 2. Maternal and infant characteristics and their unadjusted odds ratios. Values are presented as number (%) or mean (SD). GW = gestational weeks.

* The data on smoking were missing in 26,1%, and the data on BMI were missing in 14,8% of the mothers. The rest of the data showed less than 5% of missing values and was analyzed as such.

The results of the univariate binary logistic regression for each risk factor are presented at Tables 2 and 3. There were no differences in the incidences of most common antenatal pregnancy complications, such as hypertension or preeclampsia, cholestasis of pregnancy, intrauterine growth restriction, and diabetes. Induction of labour was significantly more common in the study group, increasing the OR of HIE.

Shoulder dystocia was more common in the study group, but no difference was seen in the incidence of other obstetric emergencies. The use of analgetic medication was similar in both groups. Other factors with no significant association with HIE were meconium stained or bloody amniotic fluid and tight nuchal cord (not presented in the tables).

The univariate analysis showed that 9 independent variables were associated with either the presence or absence of moderate to severe HIE (p<0,1): Smoking, post term pregnancy, augmentation of labour by oxytocin, duration of phase II, labour induction, any obstetric emergency, shift change of midwives during active labour, use of nitrous oxide, and delivery during night shift (10 pm. to 8 am.). These variables were further analyzed in the multivariate logistic regression model.

	Study group	Control group	OR (95% CI)	p-value
Antepartum risk factors				
Hypertension/preeclampsia	9 (10.23)	11 (12.50)	0.64 (0.31 – 2.03)	0.797
Cholestasis of pregnancy	3 (3.41)	0	n/a	n/a
IUGR	5 (5.68)	7 (7.95)	0.70 (0.21 – 2.29)	0.552
Diabetes				
DMI	4 (4.55)	3 (3.41)	1.35 (0.29 – 6.21)	0.701
DMII	0	2 (2.27)	n/a	n/a
GDM	12 (13.64)	14 (15.91)	0.84 (0.36 – 1.92)	0.671
Induction (any method)	19 (21.59)	8 (9.09)	2.75 (1.13 – 6.68)	0.025
Failed induction attempt + cs	4 (4.55)	10 (11.36)	0.37 (0.11 – 1.23)	0.106
Suspected chorioamnionitis	7 (7.95)	6 (6.82)	1.18 (0.38 – 3.67)	0.773
Phase II duration	35.44 (28.26)	46.38 (32.13)	0.99 (0.97 – 1.00)	0.098
Any obstetric emergency	18 (20.45)	9 (10.23)	2.57 (1.05 – 6.28)	0.038
Shoulder dystocia	6 (6.82)	0	n/a	n/a
Placental abruption	7 (7.95)	4 (4.55)	1.82 (0.51 – 6.44)	0.356
Uterine rupture	5 (5.68)	5 (5.68)	1.00 (0.28 – 3.58)	1
Medication				
Oxytocin augmentation	24 (27.27)	51 (57.95)	0.27 (0.15 – 0.51)	<0.001
Epidural	50 (56.82)	60 (68.18)	0.61 (0.33 – 1.14)	0.121
Spinal	28 (31.82)	26 (29.55)	1.11 (0.69 – 2.11)	0.744
Opioid	18 (20.45)	21 (23.86)	0.82 (0.40 – 1.67)	0.586
Nitrous oxide	34 (38.64)	47 (53.41)	0.55 (0.30 – 1.00)	0.050
Non-medical risk factors				
Midwife Shift change	40 (45.45)	53 (60.23)	0.55 (0.30 – 1.00)	0.051
Delivery during nightshift (22 - 08)	43 (48.86)	33 (37.50)	1.74 (0.96 – 3.18)	0.070

Table 3. Ante- and intrapartum risk factors, infant characteristics and their unadjusted odds ratios. The values are presented as number (%) or mean (SD). IUGR = intrauterine growth retardation, DM = diabetes mellitus, GDM = gestational diabetes mellitus, CS = cesarean section

In the multivariate regression models (tables 4 and 5), obstetric emergencies, labour induction and smoking significantly increased the odds of HIE. We were able to repeat these results in most of the tried models. Induction of labour had a significant association with HIE in all tried models, but there was no significant association with HIE and any individual induction method (balloon catheter, vaginal misoprostol, amniotomy followed by oxytocin), when entered separately to the regression analysis. Post term pregnancy, oxytocin and nitrous oxide had a significant negative association with HIE. When adjusted with other variables, shift change, duration of the second phase of delivery, and delivery during night shift lost their statistical significance and appeared to be confounding factors (Table 4).

Independent variable	**Study group, N/Mean**	**Control group, N/Mean**	**OR**	**CI (95%)**	***p*-value**
Timing of birth (nightshift 22 - 08)	43	33	1.73	0.88-3.39	0.11
Shift change	40	53	0.70	0.35-1.41	0.32
Post term gestation (≥ 42 gw)	3	12	0.16	0.03-1.00	0.049
Phase II duration	35.44	46.38	0.99	0.97-1	0.12
Any obstetric emergency	18	8	2.59	0.938-7.15	0.07
Oxytocin augmentation	24	51	0.25	0.12-0.52	<0.001
Nitrous oxide	34	47	0.55	0.27-1.11	0.09
Induction (any method)	19	8	3.08	1.18-8.05	0.02
Smoking (cigarettes per day)	1.9	0.4	1.46	1.46-1.14	0.003

Table 4. Multivariate logistic regression analysis, first method. All variables were adjusted by confounding factors (Maternal age, maternal BMI, autoimmune diseases, gestational age, parity, and birth weight).

Independent variable	**Study group**	**Control group**	**OR**	**CI (95%)**	***p*-value**
Oxytocin augmentation	24	51	0.26	0.13-0.53	<0.001
Timing of birth (nightshift 22 to 08)	43	33	1.68	0.86-3.43	0.13
Smoking (cigarettes per day)	1.9	0.4	1.45	1.13-1.87	0.004
Any obstetric emergency	18	8	3.51	1.28-9.60	0.015

Table 5. Multivariate logistic regression model, second method. No assumption of confounding factors. The factors were entered together into the same analysis.

Table 4 had the best AIC score (209) in reference with other models formed with similar method. The model representative of the other method in Table 5 did not fair best in the AIC comparison (AIC=101, compared to lowest of 100), but appeared to better fit the data according to the pseudo R-squared value.

3.3 Subgroup comparison

To reveal any common features in different modes of delivery, results were further analysed in four subgroups: vaginal and ventouse delivery, emergency cesarean and crush cesarean (Appendix 1). We omitted from the crush cesarean subgroup the mothers for whom the section was indicated without preceding active labour or medical intervention. We also made efforts to identify possible common factors between the shoulder dystocia cases. Induction was more common in the study group in vaginal (p=0,016) and assisted vaginal births (p=0,017).

The midwife shift change was significantly more represented in the control groups of the emergency (p=0,008) and crush (p=0,044) caesarian sections and smoking was more common (p=0,017) in the study group of the crush cesarean subgroup. Five of the six cases with shoulder dystocia occurred in the ventouse delivery subgroup (p=0,051). (Appendix 1)

Based on the results of the logistic regression analysis, another subgroup was formed from pregnancies with successful induction of labour (Table 6). Apart from the higher birth weight of neonates in the study group (p=0,03), the induction subgroup showed no significant differences in the characteristics or indications of induction in between the study and control groups cases and controls. Three of the shoulder dystocia cases occurred in the induction subgroup (p=0.529), two of which were ventouse deliveries. None of the instrumentally assisted deliveries in the study group were followed by crush cesarean, while in the control group, there were 3 failed ventouse delivery attempts (p=0,06). Altogether, 84.2% of the induced labours ended in vaginal delivery, while the same number for the control group was 37.5% (p=0.027). (Table 6)

Onset of labour by induction	**Study group (n=19)**	**Control group (n=8)**	***p*-value**
Maternal age	32.2 (5.46)	30.8 (4.28)	0.526
Maternal BMI	24.7 (4.67)	22.2 (1.75)	0.094
Nulliparity	12 (63.16)	6 (75.0)	0.676
Gestational age	39.9 (1.94)	40.6 (1.59)	0.367
Birth weight, g	3790 (509.6)	3314 (424.6)	0.030
Delivery during nightshift (22 to 08)	10 (52.6)	3 (37.5)	0.678
Indication of induction			
DM+macrosomia	4 (21.1)	0 (0)	0.285
Post term pregnancy	6 (31.6)	2 (25.0)	1
Hypertension/ toxemia	4 (21.1)	2 (25.0)	1
Ruptured membranes	1 (5.3)	2 (25.0)	0.201
Other	4 (21.1)	2 (25.0)	1
Duration from induction to birth, hours	24.7 (13.48)	23.9 (19.27)	0.891
Mode of delivery			
All vaginal deliveries	16 (84.2)	3 (37.5)	0.027
Vaginal	6 (31.6)	1 (12.5)	0.646
Ventouse delivery	10 (52.6)	2 (25.0)	0.677
Emergency CS	1 (5.3)	0 (0)	1
Crush CS	3 (15.8)	2 (25.0)	1
Failed ventouse + crush CS	0 (0)	3 (25.0)	0.06
Shoulder dystocia	3 (15.8)	0 (0)	0.529

Table 6. Induced deliveries Subgroup with induced labours. Values are presented as number (%) or mean (SD)

BMI = body mass index, DM = diabetes mellitus CS = cesarean section.

4 Discussion

The purpose of this retrospective case-control study was to find HIE risk factors that could be anticipated and avoided in antenatal care and treatment of delivery. Due to the novel study design and small sample sizes, we saw fit to try out and present two different approaches to the multivariate logistic regression analysis. Surprisingly, only three previously identified risk factors (smoking, obstetric emergency and labour induction), showed significant association with HIE in our logistic regression analysis. Three independent variables (post term pregnancy, oxytocin and nitrous oxide) had a seemingly opposite effect against HIE. Most of the presumed risk factors proved to have an insignificant association or no association to HIE in our study.

4.1 Smoking

There was a significant dose-response association with maternal smoking and HIE. This finding prevailed in the multivariate analysis, although the increase in the odds remained quite small (aOR 1.45 – 1.46). based on previous research, smoking is be strongly associated with fetal growth restriction(31), and increases risk of placental abruption(32), both a repeatedly demonstrated antecedent for birth asphyxia and HIE (6,33). Smoking also increases oxidative stress and reduces endogenous defenses in the fetus, which may play a role in the pathogenesis of a number of diseases in the expectant mother and the fetus(34). While the effect of smoking on the well-being of fetus is quite indisputable, our results all in all were not quite satisfactory for two reasons. First, the proportion of missing data was substantial, and the imputed data may have skewed the results toward HIE. Second, the frequency and cessation or continuity of smoking during pregnancy was self-reported, poorly recorded and susceptible to social desirability bias. Since patients have a tendency to underestimate the frequency of unwanted behavior, it is safe to assume that the effect of smoking on HIE is at least as remarkable as is presented by the unimputed data (OR 1.21, 95%CI 0.99 – 1.46, p=0.06). In the original data, 10 mothers in the study group (11.4%) and 4 (4.5%) in the control group reported of smoking during pregnancy. 38 (43.2%) and 78 (88.6%) mothers, respectively, reported as non-smokers.

4.2 Shoulder dystocia

There were six cases of shoulder dystocia in the study group, but none in the control group, which made the regression analysis inapplicable for this variable. Analyses of all obstetric emergencies (placental abruption, uterine rupture, shoulder dystocia) as a surrogate variable showed a statistically significant association with obstetric emergencies and HIE. The increase in odds of HIE with placental abruption and uterine rupture was insignificant or nonexistent. Aforementioned obstetric emergencies altogether presented an OR of 2.57 and aOR of 3.51 ($p<0.05$). Other obstetric emergencies, such as cord prolapse and eclampsia, were not present in our data.

Shoulder dystocia is a rare, poorly predictable obstetric emergency, and managing it is practiced regularly as case simulations by the obstetricians and midwives of our clinic. The incidence of shoulder dystocia in the study group was 6.8%, while it is approximately 0.7% in the population (35). Fetal macrosomia increases the incidence of shoulder dystocia more than tenfold (35). In these situations, planned delivery at early term has been demonstrated to reduce the risk of shoulder dystocia (36). The association between shoulder dystocia and birth asphyxia is also quite unambiguous, as it results in prolongation of head-to-body delivery, traction of the neck, and birth trauma (37).

4.3 Induction of labour

Induction of labour significantly increased the risk for HIE but was not associated to any particular induction method (vaginal prostaglandin, balloon catheter, or amniotomy-oxytocin combination). In fact, in just 33% of cases only one induction method was used. In addition, there was significant multicollinearity with other supposed risk factors (obstetric emergency, $p=0.084$, oxytocin augmentation, $p=0.02$, shift change, $p=0$, use of nitrous oxide, $p=0.06$ and gestational diabetes, $p=0.007$). The induced labours in the study group ended significantly more frequently in vaginal delivery than in the control group. There were 19 successful induced labours and 4 failed attempts in the study group, whereas for the control group, the respective numbers were 8 and 10. The differences in the induction of labour indications showed no significant differences. When these factors

are weighed in, whether or not induction of labour is an independent risk factor for HIE, is a very complex issue.

In a population-based case-control study, Nelson et al (15) found an association in a bivariate logistic regression between induction of labour and need for whole body cooling. However, induction was ruled out in the forward stepwise multivariate regression model. In our study, forward stepwise regression model was also tested as a reference, and induction was among the first variables in the analysis to enter the equation.

Induction with oxytocin was shown to increase the risk of neonatal encephalopathy in a case-control study in Nepal with OR of 9,09 (10). The same study also found a threefold increase in risk of neonatal encephalopathy when oxytocin augmentation was used. These findings are readily explained by the absence of sufficient fetal and uterine monitoring, as the authors express. According to other studies, induction of labour with oxytocin, oral misoprostol and Foley catheter appear to have similar safety and effectiveness (38,39).

Induction of labour is a subject of ongoing discussion in the HUCH obstetric clinic. The proportion on induced labours has grown over the past decades: In 2007, the IOL rate at our clinic was 17.5%; in 2013, the beginning year of our study period, it was 22.0%, and the rate of 2018 was 27.2% (40). In addition to the increase of labours induced with maternal or fetal indications, elective inductions without medical reason are also increasing (41). Induced labours are a group consisting of mothers with sometimes multiple obstetric risk factors that alone indicate need for close monitoring, and induction of labour only adds to the issue.

4.4 Oxytocin augmentation, nitrous oxide and post term pregnancies

In the study group, there were 23 neonates (26%), who were delivered by cesarean section before the mother went into labour or any intervention was made. The correspondent number in the control group was 7 (8.0%, p=0.002). In other words, almost 1 in 3 mothers in the study group never had an opportunity to have oxytocin administered to them. In addition, the induction of labour was far more frequent in the study group (table 3), and

although oxytocin was used in 40.7% of the labours, it wasn't significantly different in the study and control group. As a result, spontaneous deliveries with oxytocin augmentation was more frequent in the control group. We suggest that the seemingly protective association of oxytocin augmentation in relation to HIE is based on the asymmetric distribution of these different subgroups. The same can be speculated for the administration of nitrous oxide.

Post term pregnancy, too, appeared to decrease the odds of HIE. There are a few elements that could explain this phenomenon. First, there was significant collinearity between post term pregnancy and oxytocin augmentation, midwife shift change and delivery during night shift. Second, since post maturity itself is a moderate risk state compromising fetal well-being with regard to meconium passage and birth asphyxia, high-risk pregnancies are seldom allowed to come post-term.

4.5 Hospital staff and the timing of birth

In a 20-year longitudinal birth register study, Luo et al found two high risk periods for the time of birth: from 5 pm to 1 am, and 9 am, immediately after the beginning of day shift (42). Wu et al declared nighttime to be an independent risk factor of neonatal encephalopathy (43). A German retrospective study observed the incidence of birth asphyxia-related early neonatal mortality in low risk births, and found an increased risk at nighttime between 9 pm and 7 am (RR 3.89, CI 1.51 – 10.03) (44). Knight et al (45) found no difference in presence of perinatal morbidity between neonates born "out-of-hours"(consultant not present at the ward) and "in-hours". Substandard care is the easy answer to the changing of outcome in relation to timing of birth, but biological predisposing factors, such as maternal exhaustion and circadian hormonal rhythm, should be excluded before evaluating standard of care.

In our study, according to the uni- and multivariate analysis, the timing of labour and birth did not have an association with the shifts of the hospital staff. In the subgroup analysis, shift change occurred more often in the control groups, when the delivery mode was cesarean. Our study might have had residual collinearity with the shift change data

and other risk factors. For example, the duration of labour from admission to birth, or medication administered to patients were not observed in relation to the shift change variable. Further studies are required to show whether changing of the responsible professional during active labour effects the outcome of labour.

4.6 Duration of the second phase

Prolonged expulsive efforts of over 60 minutes is declared an indication for obstetric intervention in an otherwise spontaneous delivery. Usual reasons for stalling of delivery at this phase are occipitoposterior position and maternal exhaustion.

Prolonged second phase has been associated with development of birth asphyxia and HIE in several case-control studies(13,19,23–25,46). In a French study (47), it is suggested that under adequate FHR surveillance, the duration of expulsive efforts is not a significant risk of HIE. However, the study observed durations exceeding 15 and 30 minutes as categorical variables, and 30 minutes is still quite short a time, compared to our mean durations of 34 minutes in the study group and 46 minutes in the controls. It is suggested that the reason for the prolonged second stage as a risk factor for birth asphyxia lies in the triggers of the prolonged phase, such as fetal positions (13,48).

4.7 Strengths and limitations

The limitations of this study were the small sample sizes and its retrospective, observational nature. There were some restrictions regarding obtaining data. We didn't have access to primary health care and antenatal outpatient data, and so we relied on the history information of the maternity card and information recorded in the obstetric records upon the mothers' admission to the obstetric clinic or ward. Chronic illnesses, obstetric complications and infections were not always structurally recorded. Some health information such as substance abuse of the mother could be underrepresented. It is, however, unlikely that this has affected our results.

Information on social or marital status is not collected and was mostly not obtainable. Therefore, demographic risk factors had to be excluded. Some previously identified risk

factors (urinary tract and viral infections)(19,26,49,50), had to be excluded because they are treated at the primary health care level.

The strength of this study was in the study setting. To the best of our knowledge, this was the first case-control study pairing the groups by the mode of delivery, sex, hospital and fetal presentation at birth. This could partially explain why our study results differ from the majority of previous similar studies.

In the Finnish population, normal rates for all cesarean sections and emergency cesarean sections are 17% and less than 1%, respectively (51). In our sample, the correspondent rates were 54,5% and 37,5%. This shift in proportions naturally affects the incidence of ante- and intrapartum complications. For instance, 5 to 7% of pregnancies in Finland and worldwide are diagnosed with pre-eclampsia or pregnancy-induced hypertension (52). In our study, the rate was 10,2% for the study group and 12,5% for the control group.

Another aspect that separates our study from many others are our selection criteria for the case group. Although a similar approach with therapeutic hypothermia serving as surrogate outcome for signs of severe birth asphyxia (and sequential HIE) has been used before (15), most case-control studies on the subject rest on a study group of neonates diagnosed with neonatal asphyxia, or neonates with signs of birth asphyxia (low Apgar score and/or signs of acidemia in the peripartum blood samples).(14,16,17,21,25,48,50) In our sample, low Apgar scores and acidic levels of umbilical artery pH and BE were found in both groups. In comparison, the signs of moderate to severe HIE (acidemia and neonatal encephalopathy, extensive need of resuscitation or multi organ failure), would be suggestive of a more severe hypoxic insult (7,53,54), thus making therapeutic hypothermia an outcome more specific than birth asphyxia.

5 Conclusion

Our findings, at best, show that antenatal screening for obstetric risk factors is well performed in our hospital area, and that interventions during pregnancy and labour are made early on. The incidence of birth asphyxia and HIE in the Helsinki University Hospital area, and Finland in general, is commendably low. Regardless, there is always room for improvement, and we believe that training hospital staff by the help of local research is essential to achieve it.

The vast majority of supposed antecedents of HIE appeared insignificant in this study. As it has been previously speculated (6), in most cases HIE is unpredictable or remains beyond the control of the clinicians. Although induction of labour should still be used in situations where it evidently improves the outcome of labour, our results indicate that induced labours are a group that require special vigilance from the obstetric team. Attempts of inducing should be ceased and cesarean be considered if there is any reason to suspect fetal distress.

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Appendix 1.

Cases and matched controls in subgroups by their mode of delivery. BMI = body mass index, GW = gestation week

	Mode of delivery															
	Emergency cesarean n=14				**Crush cesarean (spontaneous or induced onset) n=24**				**Vaginal delivery n=14**				**Ventouse delivery n=26**			
Independent variable	**Study group**	**Control group**	**n** (tot)	***p*-value**	**Study group**	**Control group**	**n** (tot)	***p*-value**	**Study group**	**Control group**	**n** (tot)	***p*-value**	**Study group**	**Control group**	**n** (tot)	***p*-value**
Maternal age	30.07	32.63		0.271	31.67	33.90		0,114	31.28	32.95		0.428	32.49	31.75		0.596
Maternal BMI	23.55	27.61		0.268	24.55	23.21		0.444	22.47	23.65		0.47	24.80	22.75		0.07
Gestational age	40.27	39.82		0.322	40.09	40.61		0.265	40.32	39.84		0.38	40.26	40.29		0.948
Birth weight	3309	3675		0.054	3451	3303		0.390	3762	3360		0.277	3653	3610		0.728
Induction	1	0	1	1	2	5	7	0,696	6	1	7	0.016	10	2	12	0.017
Oxytocin augmentation	2	7	9	0.103	6	16	22	0,178	5	7	12	0.445	11	21	32	0.004
Smoking	1	1	2	0.283	3	2	5	0,039	2	0	2	0.204	1	1	1	0.328
Post term gestation (≥42 GW)	0	1	1	1	1	6	7	0,231	1	1	2	0.759	1	3	4	0.610
Phase II duration	-	-	-	-	19.25	46.50		0.112	42.86	22.58		0.055	33.88	54.65		0.014
Shoulder dystocia	-	-	-	-	-	-	-	-	1	0	1	1	5	0	5	0.051
Delivery during nightshift (22 - 08)	9	5	14	0.131	7	9	16	0,527	10	6	16	0.127	13	11	24	0.578
Midwife shift change	3	10	13	0.008	6	19	25	0,044	11	8	19	0.21	20	15	35	0.139