Umbilical cord arterial blood gas analysis in term singleton pregnancies: a retrospective analysis over 11 years

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Objective
Given that the large volume of data on cord arterial blood gas analysis (ABGA) have been rarely addressed in Korean population, we aimed to examine the incidence, associated factors, and neonatal outcomes in cases of low cord pH, and investigate the incidence of cerebral palsy (CP).

Methods
From data of all consecutive term singleton pregnancies delivered in our institution from 2006 to 2016 (n=15,701), cases with cord ABGA (n=14,221) available were included. We collected information on maternal clinical characteristics and delivery outcomes and also examined neonatal and infant outcomes, including neonatal intensive care unit (NICU) admission and CP, in cases with low cord pH, defined as a pH <7.1.

Results
Rates of low Apgar scores at 1 minute (<4) and 5 minutes (<7) were 0.6% (n=79) and 0.4% (n=58), respectively. Rates of cord pH <7.2, <7.1, and <7.0 were 7.1% (n=1,011), 1.1% (n=163), and 0.3% (n=38), respectively. Among cases with low cord pH, 30.1% (n=49/163) were admitted to the NICU and 11.0% (n=18/163) required ventilator support. Ultrasonography of the brain was performed in 28.8% (n=47/163), with abnormal findings observed in 27.7% (n=13/47). Among cases with low cord pH, 1.8% (n=3/163) were subsequently diagnosed with CP, including 2 cases of spastic CP and 1 of ataxic CP.

Conclusion
Although low cord pH was a relatively frequent finding observed in 1 out of every 87 cases, hypoxic-ischemic encephalopathy-related CP was found in only 1 out of 7,111 term singleton deliveries over 11 years in our institution.

Keywords: Umbilical cord; Analysis, blood gas; Term birth; Cerebral palsy

Introduction
While most fetuses experience the physiologic fetal-to-neonatal transition to air breathing after birth at term, 10% of newborns require some degree of active resuscitation to activate breathing and 1% require extensive care [1]. According to the most recent neonatal resuscitation protocol endorsed by the American Academy of Pediatrics (AAP) and supported by published studies, it was reported that approximately 3% of newborns needed positive-pressure ventilation, 2% needed endotracheal intubation, and 0.1% needed cardiac...
compressions or epinephrine administration [2-4].

Difficulty in initiating respiration, and depression of tone and reflexes are common symptoms of neonatal encephalopathy (NE), which is a clinically defined syndrome of disturbed neurologic function in the earliest days of life in babies born at or beyond 35 weeks of gestation manifested by a subnormal level of consciousness or seizures. Historically, the incorrect assumption that most NE results from hypoxia during the intrapartum period has hindered serious research into other possible causes of NE. Recent epidemiologic studies have identified several preconception demographic, and maternal medical conditions (advanced maternal age, family history of seizure, family history of neurologic disorder, maternal thyroid disease, and infertility treatment) and antepartum risk factors (preeclampsia, moderate to severe vaginal bleeding, advancing pregnancy beyond 39 weeks gestation, late or no prenatal care, and low neonatal birth weight percentile) as independent risk factors for NE [5-7]. Of note, it was reported that 70% of NE cases were likely the result of events arising before the onset of labor [8].

Hypoxic ischemic encephalopathy (HIE) comprises a cause-specific subset of all NE. Inaccurate prediction of fetal acidaemia by intrapartum fetal heart rate (FHR) monitoring can lead to the presumptive diagnosis of HIE as the direct cause of depressed neonates in cases that are otherwise unexplained, thereby overestimating the true incidence of HIE. According to the American College of Obstetricians and Gynecologists (ACOG) and the AAP, a low cord arterial blood pH <7.0 and/or a base excess (BE) <=-12 mmol/L are the generally accepted cutoff values for pathological acidosis, which increases the risk of seizures, HIE, and cerebral palsy (CP) [9]. As umbilical cord blood gas and acid-base assessment are the most objective predictors of fetal acidemia [10,11], it is usually recommended by the ACOG to obtain a cord arterial blood gas analysis (ABGA) in certain clinical circumstances such as a low 5-minute Apgar score, severe growth restriction, or abnormal FHR tracing [12,13], although there is no specific guideline in Korea.

Meanwhile, as a tertiary center, our institution has adopted the routine performance of cord blood ABGA at birth for every delivery since 2006 for a variety of reasons, including medicolegal considerations. Surprisingly, we could not find any study with a large volume of data including Korean population regarding cord ABGA at birth and the association analysis between cord pH and other clinical factors such as meconium staining, nuchal cord, and mode of delivery. This led us to initiate a comprehensive analysis of cord blood pH in consecutive singleton pregnancies delivered at term in our hospital population.

The specific questions that we pursued here were as follows. First, what are the distribution of cord blood pH and the incidence of low cord pH? Second, what are the associations between low cord blood pH and clinical factors including the grade of meconium, number of nuchal cord cases, and mode of delivery? Thirdly, among cases with low cord pH defined as a pH <7.1, what is the actual frequency of adverse neonatal outcomes including neonatal intensive care unit (NICU) admission, ventilator support, need for brain ultrasonography, and abnormal sonographic findings? Lastly, how many CP cases were subsequently diagnosed among neonates with low cord pH at term?

Materials and methods

During the study period from January 2006 to December 2016, there were 21,428 deliveries in our institution including 4,855 preterm deliveries, 16,554 term deliveries, and 19 post-term deliveries. Fig. 1 shows the inclusion and exclu-
Table 1. Comparison of clinical characteristics according to cord blood pH at birth

| Clinical variables               | Total (n=14,221) | Cord pH≥7.1 (n=14,058) | Cord pH<7.1 (n=163) | P-value |
|----------------------------------|------------------|------------------------|---------------------|---------|
| Maternal age (yr)                | 32.4±3.8         | 32.3±3.9               | 32.4±3.8            | 0.813<sup>a</sup> |
| Maternal height (cm)<sup>b</sup> | 161.6±5.3        | 161.6±5.3              | 160.6±5.3           | 0.024<sup>a</sup> |
| Maternal weight (kg)<sup>b</sup> | 68.2±9.5         | 68.2±9.5               | 65.9±9.4            | 0.006<sup>a</sup> |
| Maternal BMI (kg/m<sup>2</sup>)  | 26.1±3.3         | 26.1±3.3               | 25.5±3.5            | 0.057<sup>a</sup> |
| Primiparity                      | 7,597 (53.4)     | 7,484 (53.2)           | 113 (69.3)          | <0.001<sup>c</sup> |
| Prior preterm delivery           | 684 (4.8)        | 679 (4.8)              | 5 (3.1)             | 0.199<sup>c</sup> |
| Underlying hypertension          | 185 (1.3)        | 183 (1.3)              | 2 (1.2)             | 1.000<sup>c</sup> |
| Hypertensive disorders<sup>d</sup> | 482 (3.4)        | 473 (3.4)              | 9 (5.5)             | 0.130<sup>c</sup> |
| Overt DM                         | 100 (0.7)        | 99 (0.7)               | 1 (0.6)             | 1.000<sup>c</sup> |
| Gestational DM                   | 926 (6.5)        | 915 (6.5)              | 11 (6.7)            | 1.000<sup>c</sup> |
| GA at delivery (wk)              |                  |                        |                     | 0.369<sup>e</sup> |
| 37.0–37.6                        | 1,415 (10.0)     | 1,394 (9.9)            | 21 (12.9)           |         |
| 38.0–38.6                        | 4,075 (28.7)     | 4,042 (28.8)           | 33 (20.2)           |         |
| 39.0–39.6                        | 4,341 (30.5)     | 4,292 (30.5)           | 49 (30.1)           |         |
| 40.0–40.6                        | 3,378 (23.7)     | 3,335 (23.7)           | 43 (26.4)           |         |
| 41.0–41.6                        | 1,012 (7.1)      | 995 (7.1)              | 17 (10.4)           |         |
| Meconium staining grade          |                  |                        |                     | 0.001<sup>e</sup> |
| None                             | 12,769 (89.8)    | 12,660 (90.0)          | 109 (66.9)          |         |
| +                                | 1,080 (7.6)      | 1,049 (7.5)            | 31 (19.0)           |         |
| ++                               | 223 (1.6)        | 213 (1.5)              | 10 (6.1)            |         |
| +++                              | 113 (0.8)        | 106 (0.8)              | 7 (4.3)             |         |
| ++++                             | 36 (0.2)         | 30 (0.2)               | 6 (3.7)             |         |
| Number of nuchal cord            |                  |                        |                     | 0.002<sup>e</sup> |
| 0                                | 9,894 (69.6)     | 9,801 (69.7)           | 93 (57.1)           |         |
| 1                                | 3,697 (26.0)     | 3,636 (25.9)           | 61 (37.4)           |         |
| 2                                | 546 (3.8)        | 538 (3.8)              | 8 (4.9)             |         |
| 3                                | 73 (0.5)         | 73 (0.5)               | 0 (0.0)             |         |
| 4                                | 11 (0.1)         | 10 (0.1)               | 1 (0.6)             |         |
| Mode of delivery                 |                  |                        |                     |         |
| Elective CS                      | 2,925 (20.6)     | 2,914 (20.7)           | 11 (6.7)            | <0.001<sup>c</sup> |
| Emergent CS                      | 1,809 (12.7)     | 1,779 (12.6)           | 30 (18.4)           | 0.028<sup>c</sup> |
| Spontaneous VD                   | 8,712 (61.3)     | 8,612 (61.3)           | 100 (61.4)          | 0.981<sup>c</sup> |
| Vacuum-assisted VD               | 775 (5.4)        | 753 (5.4)              | 22 (13.5)           | <0.001<sup>c</sup> |
| Male sex of baby                 | 7,276 (51.2)     | 7,185 (51.1)           | 91 (55.8)           | 0.231<sup>c</sup> |
| Apgar score at 1 min <4          | 79 (0.6)         | 53 (0.4)               | 26 (16.0)           | <0.001<sup>c</sup> |
| Apgar score at 5 min <7          | 58 (0.4)         | 39 (0.3)               | 19 (11.7)           | <0.001<sup>c</sup> |
| Neonatal weight (kg)             | 3.24 (1.51–5.19) | 3.24 (1.51–5.19)       | 3.08 (1.68–4.62)    | <0.001<sup>f</sup> |
| SGA                              | 1,559 (11.0)     | 1,523 (10.8)           | 36 (22.1)           | <0.001<sup>c</sup> |
| LGA                              | 1,226 (8.6)      | 1,218 (8.7)            | 8 (4.9)             | 0.089<sup>c</sup> |
| NICU admission                   | 851 (6.0)        | 802 (5.7)              | 49 (30.1)           | <0.001<sup>c</sup> |

Data are presented as the mean±standard deviation or number (%) or median (range). BMI, body mass index; DM, diabetes mellitus; GA, gestational age; CS, caesarean section; VD, vaginal delivery; SGA, small for gestational age; LGA, large for gestational age; NICU, neonatal intensive care unit.

<sup>a</sup>P-value by Student's t-test; <sup>b</sup>Cases unavailable with maternal height (n=3,149), weight (n=2,939), and BMI (n=3,242) were excluded from this analysis; <sup>c</sup>P-value by chi-squared test; <sup>d</sup>Hypertensive disorders include gestational hypertension, mild pre-eclampsia, severe pre-eclampsia, superimposed pre-eclampsia on chronic hypertension, HELLP syndrome (hemolysis, elevated liver enzymes, and a low platelet count), and eclampsia; <sup>e</sup>P-value by linear-by-linear association; <sup>f</sup>P-value by Mann-Whitney U test; P<0.05: statistically significant.
At pediatric or rehabilitation doctors as documented in the medical confirmation was based on the clinical diagnosis made by pediatricians (G80; CP) in our electronic medical system. Case confirmation included heart anomalies, central nervous system anomalies, chromosomal anomaly, specific syndromes, and complications from other major anomaly categories. We also searched for all cases of neonates born with normal cord pH (≥7.1) during the same study period. We also searched for all cases of neonates born with normal cord pH (≥7.1) during the same study period. We also searched for all cases of neonates born with normal cord pH (≥7.1) during the same study period. We also searched for all cases of neonates born with normal cord pH (≥7.1) during the same study period. We also searched for all cases of neonates born with normal cord pH (≥7.1) during the same study period.

In cases of low cord pH, we also examined additional neonatal and infant outcomes including ventilator support, brain ultrasoundographic findings, major anomaly, and CP by thorough review of medical records. The major anomaly category included heart anomaly, central nervous system anomaly, chromosomal anomaly, specific syndromes, and complications from other major anomaly categories.

### Table 2

| Variables | Meconium staining grade | Number of nuchal cord | Mode of delivery |
|-----------|-------------------------|-----------------------|----------------|
|           | None (n=12,769) | + (n=1,080) | ++ (n=223) | +++ (n=113) | ++++ (n=36) | Mean pH | P-value | Mean BE | P-value | pH ≥7.2 | P-value | pH <7.2 | P-value | pH <7.1 | P-value | pH <7.0 | P-value |
|           | 7.28±0.06 | 7.26±0.07 | 7.24±0.08 | 7.24±0.08 | 7.23±0.12 | <0.001 | 7.28±0.06 | 7.28±0.06 | 7.28±0.06 | 7.28±0.05 | 7.25±0.11 | <0.001 | 7.29±0.04 | 7.29±0.06 | 7.28±0.06 | 7.26±0.07 | <0.001 | 7.24±0.02 | <0.001 |
|           | −3.4±2.57 | −3.6±3.03 | −3.5±3.46 | −3.8±3.79 | −3.9±3.11 | <0.001 | −3.5±2.67 | −3.7±2.71 | −3.6±2.80 | −3.6±2.85 | −4.5±4.43 | 0.024 | −2.45±1.92 | −3.16±2.82 | −3.97±2.78 | −5.38±2.88 | <0.001 |
|           | 9.96±8.04 | 9.99±8.35 | 12.05±9.88 | 11.77±8.26 | 11.94±7.26 | <0.001 | 9.34±9.12 | 9.16±8.77 | 9.03±8.26 | 9.01±8.26 | 8.92±7.23 | <0.001 | 2.85±1.95 | 1.69±0.80 | 8.01±0.65 | 6.55±0.91 | <0.001 |
|           | 11.96±8.9 | 9.99±8.35 | 12.05±9.88 | 11.77±8.26 | 11.94±7.26 | <0.001 | 9.34±9.12 | 9.16±8.77 | 9.03±8.26 | 9.01±8.26 | 8.92±7.23 | <0.001 | 2.85±1.95 | 1.69±0.80 | 8.01±0.65 | 6.55±0.91 | <0.001 |

*Data are presented as the mean±standard deviation or number (%).*  
CS, caesarean section; VD, vaginal delivery; BE, base excess.

**P-value by ANOVA;** Cases unavailable with no meconium staining (n=3), 1+ meconium staining (n=1), and 2+ meconium staining (n=2), cord neck 0 (n=5), cord neck 1 (n=1), emergent caesarean section (n=2), spontaneous vaginal delivery (n=1), and vacuum-assisted vaginal delivery (n=3) were excluded from this analysis; **P-value by linear-by-linear association;** P-value by chi-square test; P<0.05: statistically significant; *Cases of cord pH <7.2 include those of cord pH <7.1 or pH <7.0. Cases of cord pH <7.1 include those of cord pH <7.0.*
record. Statistical analysis was done using Mann-Whitney U tests, analysis of variance tests, Student’s t-tests, and linear-by-linear association tests using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA).

**Results**

Table 1 shows a comparison of the clinical characteristics according to cord blood pH at birth. The low cord pH group was characterized by lower maternal height and weight and a higher rate of primiparity. The low cord pH group was associated with a higher grade of meconium staining and higher number of nuchal cord compared to the control group. In terms of the mode of delivery, the low cord pH group showed a significantly lower rate of elective caesarean section and higher rates of emergent caesarean section and vacuum-assisted delivery compared to the control group. Overall, rates of low Apgar scores at 1 minute (<4) and 5 minutes (<7) were 0.6% (n=79) and 0.4% (n=58), respectively. The low cord pH group was also associated with a higher rate of low Apgar scores at 1 minute and 5 minutes and NICU admission compared to the control group. Of note, the low cord pH group showed a lower mean neonatal weight (3.08 [1.68, 4.62] kg vs. 3.24 [1.51, 5.19] kg; \( P<0.001 \)) and a higher rate of SGA compared to the control group (22.1% vs. 10.8%; \( P<0.001 \)).

In our study population of term singleton pregnancies, the mean cord blood pH was 7.28±0.06, ranged 6.75–7.53 and the mean BE was \(-3.63±2.69\). Rates of cord pH <7.2, <7.1, and <7.0 were 7.1% (n=1,011), 1.1% (n=163), and 0.3% (n=38), respectively. Next, we analyzed the mean value and distribution of cord blood pH according to the grade of meconium staining, number of nuchal cord, and mode of delivery (Table 2). There were significant differences in the mean cord pH based on the grade of meconium staining, number of nuchal cord, and mode of delivery (\( P<0.001 \) for all), but all mean values were within the normal range. Severe grades of meconium staining were associated with higher rates of cord pH <7.2, <7.1, and <7.0. The incidence of nuchal cord was also associated with a higher rate of cord pH <7.2 and <7.1 but not with cord pH <7.0. There were also significant differences in the rates of cord pH <7.2, <7.1, and <7.0 according to the mode of delivery.

Fig. 2 shows the clinical course information in cases with low cord blood pH. Among 163 cases, 49 babies (30.1%)...
were admitted to the NICU and 18 (11.0%) needed ventilator support. Ultrasonography of the brain was performed in 28.8% (n=47) of cases, and significant abnormal findings were observed in 27.7% (n=13) as follows: diffuse brain edema (n=7), grade 2 intraventricular hemorrhage (n=2), basal ganglia vasculopathy (n=2), Dandy–Walker complex (n=1), and myelination disorder (n=1).

Table 3 presents detailed clinical information on 3 cases of presumed CP with low cord pH. The baby in the first case was born at 39.0 weeks by prompt emergent caesarean section due to a non-reassuring FHR pattern detected at the time of admission. The neonatal weight was 3.334 kg and the meconium staining grade was 4+. The Apgar scores at 1 minute and 5 minutes were 0 and 4, respectively, but increased to 7 at 10 minutes. Cord blood pH was 7.021, and BE was −15.00 mmol/L. The baby was admitted into the NICU immediately and placed on a ventilator. An ultrasound examination of the brain on the first day of life revealed profound HIE findings, and the baby was diagnosed with moderate-severe cerebral coordination disturbance 1 month later. The baby was discharged 23 days after birth and, unfortunately, was found dead at home 6 months later. The second case was born by emergent caesarean section due to a non-reassuring FHR pattern developed during the second stage. The neonatal weight was 3.392 kg, and meconium staining grade was 1+. The Apgar scores at 1 minute and 5 minutes were 2 and 5, respectively. Cord blood pH was 6.887, and the BE was −18.30 mmol/L. The baby was admitted to the NICU and placed on a ventilator. Magnetic resonance imaging (MRI) of the brain checked on the 9th day showed a selective deep gray or white matter injury probably due to profound asphyxia. The electroencephalogram finding was also suggestive of diffuse cerebral dysfunction. The baby was lost to follow-up but was presumed to have CP. The third baby was born by spontaneous vaginal delivery without any remarkable event in the perinatal period. The baby had routine nursery care and was discharged uneventfully. However, after 4 months, the baby visited the pediatric clinic in our hospital due to difficulty with head tilting. Unfortunately, the baby suffered severe developmental delays and was finally diagnosed with ataxic CP at age 2.5 years, which was not HIE-related CP.

Lastly, we summarized the perinatal characteristics of the CP cases (n=18) with normal cord pH (≥7.1) at birth during

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**Table 3.** CP cases among low cord pH at birth

| Clinical variables | Case 1            | Case 2            | Case 3            |
|-------------------|-------------------|-------------------|-------------------|
| Birth year        | 2006              | 2007              | 2014              |
| Maternal age (yr) | 26                | 29                | 33                |
| GA at delivery (wk) | 39.0             | 41.4              | 40.0              |
| Mode of delivery  | Emergent CS       | Emergent CS       | Spontaneous VD    |
| Weight of baby (kg)| 3.234 (AGA)\textsuperscript{a} | 3.392 (AGA)\textsuperscript{a} | 3.280 (AGA)\textsuperscript{a} |
| Meconium staining grade | 4+               | 1+               | None              |
| Cord blood pH     | 7.021             | 6.887             | 6.969             |
| Cord blood base excess (mmol/L) | −15.00 | −18.30 | −7.30 |
| Apgar score at 1 min | 0               | 2                | 7                 |
| Apgar score at 5 min | 4               | 5                | 9                 |
| Apgar score at 10 min | 7               | NA               | NA                |
| NICU admission    | Yes               | Yes              | No                |
| Ventilator support| Yes               | Yes              | No                |
| Brain USG\textsuperscript{b} | Done            | Done             | NA                |
| Diagnosis of CP   | Yes               | Presumed          | Yes (Ataxic CP)   |
| Mortality         | Yes               | No               | No                |

GA, gestational age; CS, caesarean section; VD, vaginal delivery; AGA, appropriate for gestational age; NA, not assessed; NICU, neonatal intensive care unit; USG, ultrasonography; CP, cerebral palsy.

\textsuperscript{a}Neonatal weight category; \textsuperscript{b}Brain USG performed at perinatal period.
**Table 4.** CP cases among normal cord pH at birth during the same study period

| Case No. | Birth year | Maternal age (yr) | GA at delivery (wk) | Mode of delivery | Weight of baby (kg) | Mecocnium staining grade | Cord blood pH | Cord blood BE (mmol/L) | AS at 1 min | AS at 5 min | NICU admission | Ventilator support | Brain image at diagnosis of CP | Diagnosis of CP | Mortality | Remarks |
|----------|------------|-------------------|---------------------|------------------|---------------------|------------------------|--------------|-----------------------|-------------|-------------|----------------|-----------------|-----------------------------|----------------|-----------|---------|
| 1        | 2006       | 31                | 39.2                | Spontaneous VD    | 3.08 (AGA)          | None                   | 7.285        | −2.7                  | 8           | 9           | N             | N               | Resolving IVH associated with PVL, left, suspected. | Y              | N         | -       |
| 2        | 2006       | 38                | 38.3                | Spontaneous VD    | 3.11 (AGA)          | None                   | 7.331        | −0.9                  | 9           | 9           | N             | N               | Suspected tissue loss and gliosis due to focal old infarction, left frontoparietal area. | Y              | N         | Infantile hemiplegic CP |
| 3        | 2007       | 29                | 39.4                | Spontaneous VD    | 3.39 (AGA)          | None                   | 7.241        | −5.9                  | 9           | 9           | N             | N               | 1. Hemimegalencephaly, left. 2. Suspected white matter injury in right frontal lobe. 3. Left choroid plexus hemorrhage. | Y              | N         | Infantile hemiplegic CP |
| 4        | 2007       | 23                | 37.0                | Spontaneous VD    | 2.62 (AGA)          | None                   | 7.350        | −1.4                  | 7           | 8           | N             | N               | 1. Severe band heterotopia or lissencephaly variant. 2. Numerous cystic white matter lesions of unknown etiology. 3. Ventriculomegaly with suspected deep white matter injury. | Y              | N         | -       |
| 5        | 2007       | 33                | 37.3                | Elective CS       | 2.12 (SGA)          | None                   | 7.279        | −2.6                  | 8           | 9           | N             | N               | 1. Slightly more prominent of posterior aspect, both ventricles without definite parenchymal lesion. 2. Probable a small cyst in right caudothalamic groove. 3. Nonspecific leptomeningeal enhancement. | Y              | N         | Other infantile CP |
| 6        | 2007       | 31                | 37.0                | Emergent CS       | 3.198 (AGA)         | None                   | 7.228        | −7.4                  | 1           | 3           | Y             | Y               | Injury in basal gangia, thalamus, corticospinal tract. | Y              | N         | Uterine rupture |
| 7        | 2007       | 32                | 38.0                | Emergent CS       | 3.06 (AGA)          | None                   | 7.330        | −0.6                  | 8           | 9           | Y             | N               | 1. Diffuse brain atrophy with subarachnoid fluid collection and tissue loss in posterior aspect of bilateral cerebral hemisphere. 2. Diffuse intracerebral hemorrhage along bilateral watershed zone. 3. Interval increased amount of subdural hemorrhage, bilateral. | Y              | N         | PA c VSD type IV → shunt op CP, quadriplegic |
| 8        | 2007       | 24                | 39.1                | Spontaneous VD    | 2.39 (SGA)          | None                   | 7.243        | −2.2                  | 7           | 8           | Y             | N               | Parenchymal change due to previous HIE cannot be excluded. | Y              | N         | Mild CP multiple contracture, ASD, PDA |
| 9        | 2008       | 30                | 41.0                | Emergent CS       | 3.3 (AGA)           | 1                      | 7.338        | −1.6                  | 8           | 9           | N             | N               | 1. RO White matter injury such as brain insult. 2. RO Leukodystrophy. | Presumed N      | RO CP, ro metabolic WM disease → Normal development |
| Case No. | Birth year | Maternal age (yr) | GA at delivery (wks) | Mode of delivery | Weight of baby (kg) | Meconium staining grade | Cord blood pH | Cord blood BE (mmol/L) | AS at 1 min | AS at 5 min | NICU admission | Ventilator support | Brain image at diagnosis of CP | Diagnosis of CP | Mortality | Remarks                           |
|----------|------------|-------------------|----------------------|------------------|-------------------|----------------------|---------------|------------------------|-------------|-------------|----------------|----------------|-------------------------------|----------------|----------|----------------------------------|
| 10       | 2008       | 34                | 38.3                 | Emergent CS      | 1.95 (SGA)        | 1                    | 7.187         | −7.4                   | 8           | 9           | Y              | N              | 1. Curvilinear structure involving right caudate nucleus and putamen of unknown etiology. 2. Partial empty sella. | Y              | N        | R/O Schwartz–Jampel syndrome, Spastic quadriplegic CP |
| 11       | 2008       | 25                | 40.3                 | Spontaneous VD   | 3.06 (AGA)        | None                 | 7.312         | −0.2                   | 9           | 9           | N              | N              | NA                             | Y              | N        | -                               |
| 12       | 2008       | 28                | 40.3                 | Vacuum-assisted VD | 3.17 (AGA)       | None                 | 7.201         | −9.3                   | 5           | 7           | Y              | N              | 1. Infarct in bilateral frontoparietal area. 2. Small amount of SDH along right cerebral convexity, tentorium, and high frontal gyrus. 3. Suspicious steno-occlusive lesion in distal left MCA → Focal embolic infarct cannot be excluded. 4. Subgaleal hemorrhage or cephalohematoma in left parietal area. | Y              | N        | Neonatal stroke, SDH, Skull fracture, Neonatal seizure. |
| 13       | 2010       | 29                | 38.0                 | Spontaneous VD   | 2.74 (AGA)        | None                 | 7.332         | −4.2                   | 9           | 9           | N              | N              | 1. Dysmorphic ventriculomegaly with presumed white matter tissue loss. 2. R/O Arachnoid cyst in the right middle cranial fossa. | Y              | N        | R/O PVL, more likely.            |
| 14       | 2013       | 34                | 41.0                 | Spontaneous VD   | 3.34 (AGA)        | 1                    | 7.247         | −4.9                   | 7           | 9           | N              | N              | NA                             | Y              | N        | Spastic CP                       |
| 15       | 2013       | 31                | 38.6                 | Spontaneous VD   | 2.47 (SGA)        | None                 | 7.341         | 0.6                    | 9           | 10          | Y              | N              | 1. Suggestive of semilobar to lobar holoprosencephaly. 2. Dysplastic cortex and heterotopic gray matter, adjacent to interhemispheric tissue of the frontal lobe. | Y              | N        | Lennox–Gastaut syndrome          |
| 16       | 2014       | 32                | 41.2                 | Spontaneous VD   | 2.85 (AGA)        | 1                    | 7.218         | −5.4                   | 9           | 10          | N              | N              | 1. Suspicion for white matter tissue loss. 2. R/O Basal ganglia vasculopathy. | Y              | N        | Goldenhar syndrome              |
| 17       | 2014       | 29                | 38.3                 | Spontaneous VD   | 3.42 (AGA)        | None                 | 7.305         | 0.1                    | 9           | 10          | N              | N              | 1. Old infarction in left MCA territory. 2. Probable parasagittal injury or PVL. | Y              | N        | Spastic hemiplegic CP            |
| 18       | 2014       | 34                | 40.5                 | Emergent CS      | 2.75 (SGA)        | 3                    | 7.211         | −6.9                   | 6           | 9           | Y              | N              | 1. Schizencephaly. 2. R/O Arachnoid cyst in the extra-axial CSF space, left. | Y              | N        | Seizure (+)                      |

GA, gestational age; BE, base excess; AS, Apgar score; NICU, neonatal intensive care unit; CP, cerebral palsy; VD, vaginal delivery; AGA, appropriate for gestational age; N, No; IVH, intraventricular hemorrhage; Y, Yes; PVL, periventricular leukomalacia; CS, caesarean section; PA c VSD, pulmonary atresia with ventricular septal defect; SGA, small for gestational age; ASD, atrial septal defect; PDA, patent ductus arteriosus; R/O (and r/o), rule out; WM, white matter; NA, not assessed; SDH, subdural hemorrhage; MCA, middle cerebral artery; CSF, cerebrospinal fluid.
the same study period (Table 4). Among 18 cases of CP, there were 4 cases with brain anomalies (hemimegalencephaly, severe band heterotopia, semilobar to lobar holoprosencephaly, and schizencephaly), 3 cases with specific syndromes (Schwartz-Jampel syndrome, Lennox-Gastaut syndrome, and Goldenhar syndrome), 3 cases of old brain infarction, and 1 case with a cardiac anomaly. Overall, SGA was complicated in 6 cases. Of note, the cord pH and BE were all within normal ranges and only 38.9% (n=7/18) of cases had NICU admission during the neonatal period.

Discussion

Our data provided the following clinical information on a large hospital-based patient population over an 11-year study period. First, the mean cord blood pH was 7.28±0.06 among term singleton pregnancies. The rates of cord pH <7.2, <7.1, and <7.0 were 7.1%, 1.1%, and 0.3%, respectively. Secondly, low cord pH (<7.1) was associated with multiple antepartum factors including lower maternal height and weight, a higher rate of primiparity, lower neonatal body weight, and a higher rate of SGA. As for intrapartum factors, the grade of meconium staining, number of nuchal cord, and mode of delivery were associated with low cord pH, though the actual positive rate for low cord pH in the presence of these risk factors was quite low. Thirdly, among cases with low cord pH (<7.1), 30.1% were admitted into the NICU, 11.0% required ventilator support, and 28.8% warranted brain ultrasonography, with significant abnormal findings observed in 27.7% of cases. Lastly, the rate of presumable CP among cases with low cord pH was approximated at 1.8% (3/163), with 2 cases of spastic CP and 1 case of ataxic CP.

Although it is well documented that an umbilical artery pH <7.0 is considered one of the prerequisite criteria for a subsequent diagnosis of HIE [14], some studies on cord pH and FHR monitoring have chosen to use an umbilical artery pH of <7.1 as the critical acid-base level in an effort to identify the predictive risk factors at the stage before injury occurs [15-17]. Similarly, as we aimed to investigate the neonatal outcomes in cases near the critical pH level, we defined “low” cord pH as <7.1 for research purposes. In our study, the mean cord blood pH and BE were 7.28±0.06 and −3.63±2.69 mmol/L, respectively, in term singleton pregnancies, and pathologic fetal acidemia with an umbilical artery pH <7.0 occurred in only 0.3% of cases. In our study population, the NICU admission rate was 6%. These results were quite similar to a previous study from Canada including more than 20,000 singleton infants born at term, in which the mean umbilical artery pH and BE were 7.24±0.07 and −5.6±3.0 mmol/L, respectively, and pathologic fetal acidemia (pH <7.0) occurred in 0.4% of cases with a NICU admission rate of 7.6% [18].

Multiple risk factors, both antepartum and intrapartum, have been reported to be associated with fetal acidemia. Antepartum risk factors include prior cesarean delivery, maternal age 35 years or older, prior neonatal death, single civil status, and short stature [19]. Intrapartum risk factors include the use of oxytocin, tachysystole, meperidine use, uterine rupture, cord complications, clinical indication of chorioamnionitis, meconium-stained amniotic fluid, breech presentation, operative delivery, and abnormal FHR during labor [10,19-24]. Our data also confirmed the antepartum factors of lower maternal height and weight, primiparity, lower neonatal birth weight, and SGA as risk factors for low cord pH.

Many studies have investigated the association between meconium staining and possible fetal acidemia, with conflicting results [25,26]. One study reported a poor correlation between meconium-stained amniotic fluid and acute acidemia [27]. According to another study that included 323 term pregnancies with meconium-stained amniotic fluid, there was no correlation between umbilical cord acid-base measurements and fetal condition at birth [28]. In contrast, other studies have demonstrated that a severe grade of meconium staining is associated with cord blood pH [3,29]. Our study also confirmed that a high meconium staining grade was associated with lower umbilical cord pH. However, the actual frequency of low cord pH (<7.1) was low. In detail, the rate of low cord pH (<7.1) occurred in only 2.87% of cases of meconium staining grade +1 and 16.67% of cases of grade +4. Nuchal cord events increase with gestational age and are found in nearly 25% of deliveries at term [30]. While a nuchal cord is not associated with adverse outcomes in general, a multiple nuchal cord entanglement may be associated with a risk of meconium, abnormal FHR pattern, the need for operative vaginal delivery, mild umbilical artery acidemia at birth, and lower Apgar scores [31,32]. Our data also identified an incidence of nuchal cord about 30% in term singleton pregnancies and showed that a multiple nuchal cord entanglement was associated with low cord pH, as expected. The mode of delivery is a well-known factor
associated with low cord pH. Our data showed that the rate of low cord pH was higher in vacuum-assisted delivery than in any other mode of delivery, reflecting clinical situations requiring prompt delivery in cases of fetal jeopardy. However, the actual incidence of low cord pH (<7.1) was only 2.84%, while that of significant acidemia (<7.0) was exceedingly low (0.65%) in cases with vacuum-assisted delivery.

A population-based study indicated that the incidence of NE was 3.0 per 1,000 live births (95% confidence interval [CI], 2.7–3.3) and that of HIE was 1.5 per 1,000 live births (95% CI, 1.3–1.7) [33]. According to our study, the incidence of significant acidemia (<7.0) was 0.3% and that of umbilical cord pH <7.1 was 1.1%. Our observation that 1.8% of cases with low cord pH (<7.1) were finally presumed to have CP was similar to that of a recent observational cohort study including 51,519 term singleton neonates in which only 2.96% of neonates with cord pH <7.0 had adverse neurologic outcomes, including encephalopathy with seizures and/or death [34]. In their study, the authors concluded that most neonates with neurological morbidity have normal cord pH values, which is consistent with our data showing that most infants with neurodevelopmental disability during the same study period had normal umbilical cord pH levels. Collectively, these population-based studies suggest that variables other than acidemia are influencing the neurologic outcomes of infants.

Our study showed that an ultrasound of the brain was performed in only about one-third (28.8%) of cases with low cord pH, among which an abnormal finding was observed in 27.7%. In fact, diverse findings were identified, including diffuse brain edema, grade 2 intraventricular hemorrhage, basal ganglia vasculopathy, Dandy-Walker complex, and myelination disorder, which reflects the various underlying pathologies among cases of low cord pH. According to an MRI study of children with CP from a cohort of 334,339 infants at ≥36 weeks of gestation, it was demonstrated that only 5% had imaging abnormalities compatible with hypoxic-ischemic brain injury [35]. Other abnormalities included focal arterial infarction (22%), brain malformation (14%), periventricular white matter abnormalities (12%), generalized brain atrophy (7%), intracranial hemorrhage (5%), and delayed myelination (2%). Of note, a normal brain was seen in almost one-third of infants who underwent neuroimaging (31%).

The limitations of our study can be summarized as follows. First, considering the characteristics of a tertiary center where term neonates without NICU admission may not have long-term follow-up, we were unable to obtain complete information on the long-term outcomes of all neonates in this hospital population, especially those with cord pH >7.1, which may have resulted in an underestimation of the total prevalence of CP. Importantly, to overcome this limitation, we tried to search for CP cases among all the infants delivered in our hospital based on ICD-10-CM codes in our electronic medical record system, and we found 18 cases during the same study period that were diagnosed (or presumed) with CP later in life. The average follow-up period for 181 cases (163 cases with low cord pH and 18 cases of CP with normal cord pH) was 3.7 years. As a result, there were 21 CP cases, including 3 cases with low cord pH (2 cases of HIE-related and 1 case of ataxic CP), among 14,221 term singleton deliveries. Collectively, our data indicate that the total prevalence of CP in term pregnancies can be estimated at 1.48 per 1,000 live births, of which HIE-associated CP accounts for 9.5% (2 out of 21). This proportion seems to be similar to our previous study with a different study period (from October 1994 to December 2004) in which perinatal HIE events were evident in 20% of term CP cases [36]. Second, given the relatively higher proportion of high-risk pregnancies in our population, as reflected by the 6% NICU admission rate in term singleton pregnancies, generalizability to low risk population may be also limited. Thirdly, although vanishing twin was one of the criteria for exclusion from our study population, there is a chance that not all vanishing twin cases were ruled out in our population since clinical information in the first trimester may be not completely collected.

One of the strengths of our study is that we included a large number of consecutive deliveries in which the performance rate of cord ABGA was over 90%, thereby precluding intrinsic selection bias from case-control studies. In addition, we presented the objective association between umbilical cord pH and certain intrapartum factors including meconium staining, which is often overestimated in medicolegal disputes. Our data showing a very low incidence of HIE-associated CP even in neonates with low cord pH (1.23%, 2 out of 163) and a relatively high proportion of normal cord pH among total CP cases strongly support the expert opinion that if comprehensive etiologic evaluation is not possible, the term HIE should be replaced by NE, since neither hypoxia nor ischemia can be assumed to have been the unique causal mechanism [14].
Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

The retrospective study was approved by the Institutional Review Board of Samsung Medical Center (IRB file No. 2019-08-028-002) and performed in accordance with the principles of the Declaration of Helsinki.

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