


RESEARCH ARTICLE

Intrapartum Care

Short-term morbidity and types of intrapartum hypoxia in the newborn with metabolic acidaemia: a retrospective cohort study

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Abstract

Objectives: To assess labour characteristics in relation to the occurrence of Composite Adverse neonatal Outcome (CAO) within a cohort of fetuses with metabolic acidaemia.

Design: Retrospective cohort study.

Setting: Three Italian tertiary maternity units.

Population: 431 neonates born with acidaemia ≥ 36 weeks.

Methods: Intrapartum CTG traces were assigned to one of these four types of labour hypoxia: acute, subacute, gradually evolving and chronic hypoxia. The presence of CAO was defined by the occurrence of at least one of the following: Sarnat Score grade ≥ 2 , seizures, hypothermia and death < 7 days from birth.

Main outcome measures: To compare the type of hypoxia on the intrapartum CTG traces among the acidaemic neonates with and without CAO.

Results: The occurrence of a CAO was recorded in 15.1% of neonates. At logistic regression analysis, the duration of the hypoxia was the only parameter associated with CAO in the case of an acute or subacute pattern (odds ratio [OR] 1.3; 95% CI 1.02–1.6 and OR 1.04; 95% CI 1.0–1.1, respectively), whereas both the duration of the hypoxic insult and the time from PROM to delivery were associated with CAO in those with a gradually evolving pattern (OR 1.13; 95% CI 1.01–1.3 and OR 1.04; 95% CI 1.0–1.7, respectively). The incidence of CAO was higher in fetuses with chronic antepartum hypoxia than in those showing CTG features of intrapartum hypoxia (64.7 vs. 13.0%; $P < 0.001$).

Conclusions: The frequency of CAO seems related to the duration and the type of the hypoxic injury, being higher in fetuses showing CTG features of antepartum chronic hypoxia.

KEY WORDS

hypoxic ischaemic encephalopathy, intrapartum CTG, neonatal acidaemia

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Tweetable abstract: This study demonstrates that in a large population of neonates with metabolic acidemia at birth, the overall incidence of short-term adverse outcome is around 15%. Such risk seems closely correlated to the duration and the type of hypoxic injury, being higher in fetuses admitted in labour with antepartum chronic hypoxia than those experiencing intrapartum hypoxia.

1 | INTRODUCTION

Intrapartum fetal hypoxia is a condition of impaired blood gas exchange that may lead to metabolic acidemia of the neonate.¹⁻³

Neonatal acidemia may be clinically unremarkable or associated with a systemic disorder, commonly called neonatal hypoxic-ischaemic encephalopathy (HIE).^{4,5} This can be characterized by persistently reduced vital signs, tone and reflexes as well as multi-organ failure and signs of cerebral injury at early neuroimaging, and represents a major risk factor for neonatal death or adverse perinatal outcome.⁶⁻⁹

It is widely acknowledged that the occurrence of adverse perinatal outcome in neonates with metabolic acidemia is greater when the arterial cord blood pH is below 7.0 or the base excess (BE) exceeds -12 mmol/L.^{1,10-15} However, available evidence suggests that additional intrapartum factors besides the cord blood gases may impact the risk of severe morbidity of acidemic neonates born with the same arterial pH.¹⁶⁻¹⁸

As demonstrated in previous experiments on animal models, the ability of the fetus to cope with intrapartum hypoxia and protect the brain from a severe hypoxic injury is closely correlated to the duration and the type of hypoxia.¹⁹⁻²⁴ Similarly, human fetuses develop different grades of brain injury if exposed to intrapartum hypoxia of different intensity and duration.²⁵

The use of cardiotocography during labour has been widely adopted with the aim to predict the occurrence of intrapartum hypoxic injury based on the morphological features of fetal heart rate. However, all traditional classifications for CTG trace readings have shown a suboptimal performance and a poor specificity in detecting fetal metabolic acidemia or neurological damage.²⁶

In the last few years, a new approach based on physiology has been proposed for the interpretation of intrapartum CTG. The approach relies on the timing and velocity of onset of the hypoxic insult and not on pattern recognition, and has been demonstrated to be associated with the highest sensitivity and specificity in predicting neonatal acidemia.²⁷

Based on such a physiological approach, the following subtypes of fetal hypoxia are claimed to occur prior to or during labour: acute, subacute, gradually evolving and chronic antepartum hypoxia.^{25,28-30} The aim of the present study was to evaluate and compare the labour characteristics and the type of intrapartum hypoxia among acidemic neonates with and without an adverse outcome.

2 | MATERIALS AND METHODS

2.1 | Study design and study population

This is a retrospective cohort study including all the neonates consecutively born with acidemia between January 2015 and October 2020 at three tertiary hospitals (Parma, Varese, Torino). Neonatal acidemia was defined based on a pH ≤ 7.00 and/or a BE of ≥ -12 mmol/L on arterial umbilical cord blood sampling performed at birth.

Only women with singleton pregnancy at a gestational age beyond ≥ 36 weeks who were admitted due to active labour and submitted to continuous CTG monitoring were eligible for this study. Exclusion criteria were represented by elective caesarean section, unsatisfactory or technically inadequate CTG recording, and congenital anomalies detected before or after birth.

The CTG traces were systematically evaluated from labour onset until delivery in terms of baseline, presence of accelerations, cycling, variability and decelerations, by three senior obstetricians (TG, SF, BM) aware of the postnatal confirmation of the metabolic acidemia but blinded with respect to the neonatal outcome. Inconsistencies were discussed by the three obstetricians and in the event of disagreement the final decision was made by the most experienced one (TG).

According to the physiological interpretation of the CTG,²⁸ the fetal heart rate features were used to assign each case to one of the following four subtypes of labour hypoxia: acute, subacute, gradually evolving and chronic (antepartum) hypoxia (Table S1, Figure S1).^{25,28-30}

Demographic and clinical characteristics were retrieved from the medical records. In particular, the occurrence of labour complications including meconium-stained amniotic fluid, intrapartum pyrexia and sentinel event were recorded. Maternal pyrexia was defined as a temperature (oral or auricular) $\geq 39.0^{\circ}\text{C}$ (102.2°F) as a single finding or a temperature between 38.0°C (100.4°F) and 39.0°C (102.0°F), confirmed by two measurements within 30 minutes.³¹ A sentinel event was defined as the occurrence of any of the following: placental abruption, umbilical cord prolapse, uterine rupture or maternal collapse.

Clinical data of each neonate including birthweight, occurrence and severity of HIE, hypothermia and death within 7 days after delivery were collected from neonatal records. The severity of the HIE was assessed by means of the modified Sarnat Score and classified into mild (1), moderate (2) or severe (3) HIE.⁷ The scores were based on the evaluation

of the following items: level of consciousness, activity, neuromuscular control, reflex complexes, autonomic nervous system activity and presence/absence of seizures.

The presence of a short-term Composite Adverse neonatal Outcome (CAO) was defined by the occurrence of at least one of the following: Sarnat Score grade two or three, seizures, hypothermia and/or neonatal death within 7 days after delivery. When available, the results of early postnatal brain imaging (magnetic resonance imaging and/or brain ultrasound) were not used to define or exclude the occurrence of composite neonatal outcome. Newborns with evidence of antepartum brain injury related to stroke and/or congenital malformations were excluded from the study.

The primary outcome of the study was to compare the labour characteristics and the type of intrapartum hypoxia among acidaemic neonates with and without CAO. As a secondary outcome, we aimed to investigate whether the type and the duration of the hypoxic insult on intrapartum CTG is associated with an increased incidence of CAO.

2.2 | Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS), release 21.0. The Kolmogorov–Smirnov test was used to assess the normality of the distribution of the data.

Data were displayed as mean \pm standard deviation (SD) or as number (percentage). Categorical variables were compared using the Chi-square or Fisher exact test. Between-group comparison of continuous variables was undertaken using *t*-test and the Mann–Whitney nonparametric equivalent test. Two-sided *P*-values were calculated and *P*-values <0.05 were considered statistically significant. Comparisons between more than two groups were performed using the Kruskal–Wallis test.

A binary logistic regression analysis was performed to assess the independent predictors of outcome using all covariates that were significantly different at the univariate analysis. Data were expressed as odds ratio (OR) \pm 95% confidence interval (CI).

A survival analysis was used to assess the incidence of neonates without a CAO according to the time and type of intrapartum hypoxia. The study was performed following the STROBE guidelines.³²

This study protocol was approved by the local ethics committee of the participating units.

3 | RESULTS

Overall, 63 990 deliveries were recorded in the participating centres during the study period in the three centres; 513 neonates fulfilling the inclusion criteria were assessed for eligibility. Of these, 76 were excluded for unsatisfactory or technically inadequate CTG recording low-quality CTG registration, one due to evidence of perinatal stroke

at post-natal imaging, one due to missing neonatal outcomes data in the clinical charts and four due to congenital heart defect. A total of 431 neonates with a mean birthweight of 3298 ± 461 g were included in the final analysis (Figure S2). Among these, caesarean section and CAO were recorded in 65 (15.1%) cases each. Death in the neonatal period due to the consequence of the severe HIE occurred in five cases (Table S2).

The comparison of the maternal, labour and neonatal characteristics between cases with or without CAO is shown in Table 1. A higher incidence of sentinel event (7.7% vs. 1.6%; $P = 0.004$), intrapartum maternal pyrexia (18.5% vs. 6.6%; $P = 0.001$), meconium-stained amniotic fluid (49.2% vs. 34.2%; $P = 0.020$) and a longer interval from PROM to delivery (14.6 ± 17.8 vs. 10.1 ± 9.2 h, $P = 0.004$) were recorded in neonates with CAO. Also, neonates with CAO had a lower arterial pH (6.93 ± 0.1 vs. 7.04 ± 0.1 , $P < 0.001$) and a higher BE (-16.3 ± 3.5 vs. -14.2 ± 2.4 , $P < 0.001$) compared with those without CAO.

Table 2 shows the type and the duration of the hypoxic insult between the cases with or without CAO. Cases with CAO had a longer mean duration of acute (20.5 ± 6.0 vs. 14.3 ± 4.6 min; $P = 0.003$), subacute (71.1 ± 34.2 vs. 44.2 ± 17.8 min; $P < 0.001$) and gradually evolving hypoxia (401.0 ± 227.9 vs. 308.9 ± 168.8 min; $P = 0.005$). At logistic regression analysis, the duration of the hypoxic insult was the only parameter independently associated with CAO in those neonates experiencing intrapartum acute and subacute hypoxia (OR 1.3; 95% CI 1.02–1.6 and OR 1.04; 95% CI 1.0–1.1, respectively), whereas the duration of hypoxic insult and the time interval between PROM and delivery were both independently associated with CAO in the fetuses showing features of gradually evolving hypoxia (OR 1.13; 95% CI 1.01–1.3 and OR 1.04; 95% CI 1.0–1.7, respectively) (Table 3).

Overall, the incidence of CAO in fetuses with chronic (antepartum) hypoxia was higher than the cases of intrapartum hypoxia (64.7 vs. 13.0%; $P < 0.001$), as was the incidence of moderate-to-severe HIE (58.9 vs. 12.3%; $P < 0.001$), hypothermia (35.3 vs. 6.0%; $P < 0.001$) and neonatal seizures (29.4 vs. 2.2%; $P < 0.001$) (Table 4). These latter were also more common in neonates with subacute hypoxia than in those who suffered gradually evolving hypoxia (4.5 vs. 1.8%; $P = 0.04$).

The intact survival rates according to the duration and the type of intrapartum hypoxic insult are shown in Figure 1. A 100% intact survival rate was observed below 12 minutes of acute hypoxia, 20 minutes of subacute hypoxia and 145 minutes of gradually evolving hypoxia.

4 | DISCUSSION

4.1 | Main findings

Our study demonstrates that in a cohort of neonates with metabolic acidaemia at birth the overall risk of adverse outcome is approximately 15%. Such risk seems closely

TABLE 1 Maternal, labour and neonatal characteristics between neonates with and without a composite adverse outcome (CAO)

	No CAO <i>n</i> = 366	CAO <i>n</i> = 65	<i>P</i> -value
Maternal age (years)	32.6 ± 5.6	32.6 ± 5.7	0.98
Pre-pregnant BMI (kg/m ²)	24.2 ± 4.7	24.6 ± 5.3	0.56
Gestational weight gain (kg)	12.5 ± 4.9	11.9 ± 5.2	0.37
Caucasian	323 (88.3)	55 (84.6)	0.41
Artificial reproductive technique	28 (7.7)	4 (6.2)	0.67
Nulliparous	310 (84.7)	50 (77.0)	0.12
Hypertensive disorders	2 (0.5)	1 (1.5)	0.29
Gestational diabetes mellitus	2 (0.5)	2 (3.0)	0.05
Prior caesarean section	18 (4.9)	7 (10.8)	0.06
Induction of labour	152 (41.5)	30 (46.2)	0.49
Oxytocin use	198 (54.1)	37 (57.0)	0.67
Epidural analgesia	195 (53.3)	37 (57.0)	0.53
Sentinel event	6 (1.6)	5 (7.7)	0.004
Intrapartum maternal fever	24 (6.6)	12 (18.5)	0.001
Meconium-stained amniotic fluid	125 (34.2)	32 (49.2)	0.020
Mode of delivery			
Vaginal delivery	224 (61.2)	24 (37.0)	<0.001
Operative vaginal delivery	101 (27.6)	17 (26.1)	
Caesarean section	41 (11.2)	24 (36.9)	
Premature rupture of membranes (PROM) at admission	119 (32.5)	23 (35.4)	0.65
Interval time from PROM to delivery (h)	10.1 ± 9.2	14.6 ± 17.8	0.004
Interval time from PROM to delivery (min)	607.3 ± 554.1	874.7 ± 1066.7	0.004
Length of active labour (min)	342.0 ± 188.4	349.5 ± 228.9	0.79

(Continues)

TABLE 1 (Continued)

	No CAO <i>n</i> = 366	CAO <i>n</i> = 65	<i>P</i> -value
Length of second stage (min)	71.7 ± 46.0	72.5 ± 50.9	0.91
Neonatal percentile <10	36 (9.8)	8 (12.3)	0.54
Neonatal percentile >90	36 (9.8)	4 (6.2)	0.35
Arterial pH	7.04 ± 0.1	6.93 ± 0.1	<0.001
Base excess (mmol/L)	-14.2 ± 2.4	-16.3 ± 3.5	<0.001

Note: Numbers are expressed as mean ± SD or *n/N* (%).

correlated to the duration and the type of the hypoxic injury being higher in fetuses admitted in labour with antepartum chronic hypoxia compared to those experiencing intrapartum hypoxia. In this latter case, the duration of the hypoxic insult seems to be the only parameter independently associated with adverse outcome in fetuses with acute or subacute hypoxic pattern, whereas in the case of gradually evolving hypoxia, the duration of the hypoxia and the interval time from PROM to delivery were both independently associated with the occurrence of adverse neonatal outcome. For cases with features of intrapartum hypoxia, the maximum time to achieve an intact survival following the onset of the hypoxic injury according to the type of hypoxia has been estimated.

4.2 | Strengths and limitations

The main strengths of our study are represented by its original design and by the large number of neonates included in the analysis. Additionally, given that all the CTG traces were evaluated by consensus between three senior obstetricians with specialised expertise in the physiological interpretation of the CTG, such evaluation is expected to be reliable. It should be highlighted that the use of physiological guidelines of the CTG interpretation seems more reproducible than the traditional assessment, even though the former approach has not been endorsed by the main international scientific societies, which may represent a matter of controversy.^{26,27,33–36}

The main limitations of our study include its retrospective design and the lack of a long-term neonatal follow-up. In addition, in the cases of gradually evolving hypoxia, we did not analyse the results according to the stage of fetal compensation (e.g. decelerations accompanied by lack of accelerations, and fetal tachycardia) or decompensation (as above plus increased or reduced variability, time at baseline shorter than time at decelerations, and baseline instability) at the time of delivery, as it has been acknowledged that the shift from the compensated to the decompensated phase plays a critical role in affecting perinatal outcome.^{25,28–30} Moreover, the occurrence of uterine tachysystole, the accomplishment of intrauterine resuscitation manoeuvres

TABLE 2 Type and duration of hypoxia between neonates with and without a composite adverse outcome (CAO)

	No CAO <i>n</i> = 366	CAO <i>n</i> = 65	<i>P</i> -value
Type of hypoxia			
Chronic	6 (1.6)	11 (17.0)	<0.001
Acute	34 (9.3)	8 (12.3)	
Subacute	77 (21.0)	12 (18.4)	
Gradually evolving	249 (68.0)	34 (52.3)	
Overall duration of intrapartum hypoxia	224.5 ± 189.3	271.3 ± 248.9	0.11
Duration of acute hypoxia (min)	14.3 ± 4.6	20.5 ± 6.0	0.003
Duration of subacute hypoxia (min)	44.2 ± 17.8	71.1 ± 34.2	<0.001
Duration of gradually evolving hypoxia	308.9 ± 168.8	401.0 ± 227.9	0.005

Note: Numbers are expressed as mean ± SD or *n/N* (%).

TABLE 3 Logistic regression of factors associated with a composite adverse outcome (CAO) according to the subtype of intrapartum hypoxia

	Acute	Subacute	Gradually evolving
Duration of hypoxia	1.3 [1.02–1.6] (min)	1.04 [1.0–1.1] (min) 8.7 [1.4–52.7] (h)	1.002 [1.001–1.004] (min) 1.13 [1.01–1.3] (h)
Sentinel event	4.11 [0.2–85.6]	NA	5.0 [0.4–65.6]
Meconium-stained amniotic fluid	4.4 [0.6–32.8]	1.0 [0.22–4.7]	1.3 [0.6–2.9]
Intrapartum hyperpyrexia	NA	6.7 [0.86–52.0]	2.2 [0.6–6.6]
Duration PROM-delivery (h)	1.03 [0.9–1.1]	1.03 [0.97–1.1]	1.04 [1.0–1.7] <i>P</i> = 0.02

NA, not available (no events in the group of neonates with composite adverse outcome); PROM, preterm rupture of membrane.

Note: Numbers are expressed as OR [95% CI].

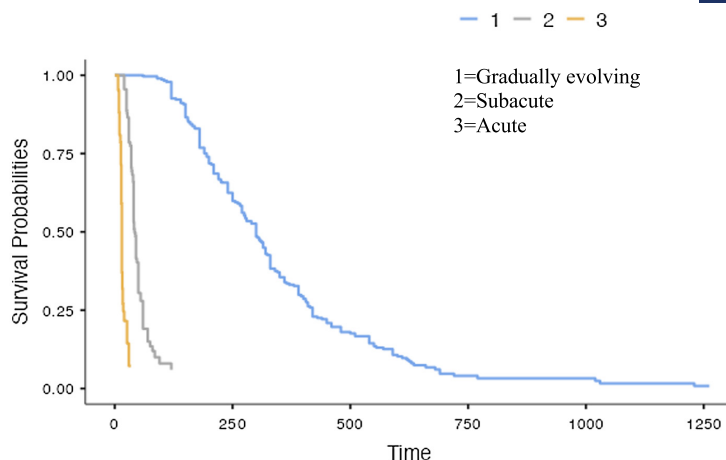
TABLE 4 Composite adverse outcome (CAO) among different types of hypoxia

	Chronic antepartum hypoxia (<i>n</i> = 17) A	Acute hypoxia (<i>n</i> = 42) B	Subacute hypoxia (<i>n</i> = 89) C	Gradually evolving hypoxia (<i>n</i> = 283) D	<i>P</i> -value	Intrapartum hypoxia (<i>n</i> = 414) (B + C + D)	<i>p</i> -value Ante- vs. intrapartum A vs. B + C + D
Composite adverse outcome (CAO)	11 (64.7)	8 (19.0)	12 (13.5)	34 (12)	<0.001 A vs. B <0.001 A vs. C <0.001 A vs. D <0.001	54 (13.0)	<0.001
Sarnat score 2–3	10 (58.9)	8 (19.0)	11 (12.4)	32 (11.3)	<0.001 A vs. B 0.007 A vs. C <0.001 A vs. D <0.001	51 (12.3)	<0.001
Hypothermia	6 (35.3)	4 (9.5)	5 (5.6)	16 (5.7)	<0.001 A vs. B 0.02 A vs. C <0.001 A vs. D <0.001	25 (6)	<0.001
Neonatal seizures	5 (29.4)	0	4 (4.5)	5 (1.8)	<0.001 A vs. B = 0.002 A vs. C = 0.004 A vs. D <0.001 C vs. D = 0.04	9 (2.2)	<0.001
Neonatal mortality ≤7 days	1 (5.9)	2 (4.8)	0	2 (0.7)	0.02 A vs. D <i>P</i> = 0.04	4 (1)	0.06

Note: *P*-value for the single pair comparison are specified below this value in bold.

and the use of uterotonics was not considered.²⁵ Finally, it should be underlined that in the definition of the CAO we focused on the neonatal short-term outcome, as this is

considered a reliable predictor of the long-term outcome; we did not include the results of the post-natal brain imaging because hypoxic–ischaemic brain injury is an evolving



	Median (min)	Range (min)	Time of 100% survival rate (min)
Acute	15	14-17	12
Subacute	42	40-50	20
Gradually evolving	300	275-320	145

FIGURE 1 Intact survival curves according to the subtype of intrapartum hypoxia

process and later investigations may be required to confirm the severity of the brain injury.^{37,38}

4.3 | Interpretation

Current knowledge on the fetal response to intrapartum hypoxic insults has mostly been derived from studies on animal models. Several experimental studies have shown that during intermittent total cord occlusion, the amount of neuronal loss and to the risk of death is related more to the severity of fetal hypotension than to the degree of metabolic acidemia.¹⁹⁻²⁴

Among human newborns at term, a potential relation between the severity of the hypoxic insult, the degree of metabolic acidemia and the risk of brain injury has already been described.^{10,11,25,39} Therefore, it is likely that for the same level of metabolic acidemia, the extent of neuronal damage is greater when intrapartum hypoxia leads to fetal hypotension and subsequent cerebral hypoperfusion.²³ Although we are unable to measure the fetal blood pressure during labour, the consistently proven association between the deceleration area and the risk of brain injury seems to confirm the primary role of hypotension in causing the cerebral damage.^{40,41}

As already reported, in healthy fetuses at term gestation the brain seems to be protected against hypoxic insults by hemodynamic, endocrine and metabolic compensatory mechanisms.^{20,42}

When a hypoxic insult is moderate and occurs over time, the fetus is able to modulate the cerebral blood flow, preserving some brain areas (i.e. brainstem and basal ganglia) at the expense of those regulating non-essential activities (i.e. cerebral cortex and 'watershed areas' of the cerebral hemispheres). Conversely, in the presence of a sudden and severe cerebral hypoperfusion, the compensatory mechanisms are not able to protect the deep grey matter and the brain damage may affect not only the cortex but also the thalami and basal ganglia.⁴³⁻⁴⁵

This latter pattern has been found to be highly predictive of adverse outcome and usually corresponds to the brain damage seen in the experimental animal models characterized by total asphyxia.^{46,47} Notably, in humans, other physiological variables seem to play a role in the onset of the brain injury. Indeed, the coexistence in labour of obstetric factors which may diminish the tolerance towards labour hypoxia or amplify its effects (i.e. placental insufficiency, inflammation, meconium) should also be considered. Moreover, the latency time between the occurrence of the hypoxic event and the delivery is expected to affect the neonatal brain integrity.¹³⁻¹⁵

Our study has shown that among neonates born with a similar degree of metabolic acidemia, the chance of adverse outcome depends on the type and duration of the hypoxic insult. More specifically, the highest incidence of adverse outcome has been found among the acidemic fetuses whose hypoxic injury seemed to start before labour. Conversely,

a similar incidence of adverse neonatal outcome has been reported among fetuses exposed to intrapartum hypoxia irrespective of the type of hypoxic insult (slow vs. rapid). However, it has to be underlined that for each pattern of intrapartum hypoxia in a healthy fetus, there is a specific interval time beyond which the compensatory mechanisms are overwhelmed, hence the resulting cerebral ischaemia and hypotension lead to neuronal injury in line with the acuity and severity of the hypoxic insult. On the other hand, in the event of chronic antepartum hypoxia, the fetus has already exhausted all the compensatory mechanisms during the antenatal period, showing evidence of brain depression before the onset of labour.

The literature data largely agree that umbilical cord pH or BE is not an accurate predictor of the neonatal outcome; even in the presence of severe neonatal acidaemia, the incidence of an adverse neurological outcome is estimated to be around 20%.^{9,11} On this basis, several studies have attempted to test the ability of additional markers to predict the clinical outcome of acidaemic infants.⁴⁸⁻⁵¹ Lactates have been proposed as predictors of the neonatal outcome, as they are produced and released in the umbilical cord when the anaerobic metabolism is activated. Tuuli et al. found that arterial lactates >3.9 mmol/L were significantly more predictive of neonatal morbidity compared with the pH of the cord blood. However, that prospective study was conducted not only on acidaemic neonates but on a large cohort of consecutive deliveries with a much lower prevalence of composite neonatal outcome (1.1%) compared with our series.⁵² A small pilot study by Yatham et al.³³ has previously attempted to assess the correlation between the type of intrapartum hypoxia observed on the CTG traces and the neonatal MRI scan findings. Among 11 neonates with available post-natal MRI, nine showed evidence of intrapartum hypoxia on CTG, but only six demonstrated evidence of brain damage on MRI. Those with acute hypoxia showed abnormalities in the basal ganglia and thalami, and a gradually evolving hypoxia or a subacute hypoxia was associated with lesions in the brain myelination and in the cerebral cortex. Such findings support the association between the type and duration of intrapartum hypoxia and the pattern of brain damage.

In our series, the incidence of adverse outcome was greater among the acidaemic neonates exposed to antepartum hypoxia. This is in agreement with Badawi et al.,⁵³ who first reported that in a population of 164 neonates with moderate or severe HIE, 69% had antepartum risk factors for encephalopathy whereas only 5% had identifiable intrapartum risk factors. Accordingly, a recent large cohort study on 1069 infants with severe cerebral palsy described the features of the fetal heart rate pattern to estimate the timing of fetal brain injury during labour. The authors found that a substantial proportion of cases were suspected to have an antepartum onset of the hypoxia.⁵⁴

To our knowledge, this is the first study evaluating whether and how the type and duration of intrapartum hypoxia as defined according to the criteria for the physiological

interpretation of the CTG, may predict the perinatal outcome among the neonates at risk for brain injury, such as those born with metabolic acidaemia. According to our data, in a neonate with a low blood pH whose CTG features are consistent with chronic antepartum hypoxia, the risk of adverse perinatal outcome is expected to be >50%, irrespective from a prompt delivery of the fetus. On the other hand, in a newborn with metabolic acidaemia showing intrapartum CTG hypoxic features, the type and the duration of the hypoxic insult may contribute to refine the risk of having a moderate to severe HIE.

Furthermore, our observation of a favourable outcome among all acidaemic neonates exposed to acute intrapartum hypoxia and delivered within 12 minutes after the onset of the hypoxic insult, seems to confirm that the previously described '3-6-9-12-15 rule' for the management of these cases of acute intrapartum hypoxia ensures a good neonatal outcome.^{28,55}

In addition, our study has provided the time threshold above which a brain injury is likely to occur in acidaemic neonates exposed to subacute or gradually evolving hypoxia. Such findings, if confirmed, could lead to an improved intrapartum care of such cases. Indeed, the current guidelines recommend an overall decision to delivery interval (DDI) of 30 minutes in the case of suspected fetal compromise and a DDI of 15 minutes in the case of acute hypoxic accident including a sentinel event.⁵⁶ However, most studies failed to demonstrate that expediting delivery within the optimal DDI ensures a good neonatal outcome. Among them, the UK National Sentinel Caesarean Section audit, one of the largest on this subject, assessed 17780 births by emergency CS over a 2-month period. Neonatal outcome (Apgar score at 5 minutes and stillbirths) was compared between babies delivered within a DDI of ≤15 minutes and no differences were noted compared with those delivered between 16 and 75 minutes.⁵⁷ Other studies found that a DDI <30 minutes is paradoxically associated with a worse neonatal outcome.⁵⁸

Of note, most studies addressing the clinical impact of the DDI have enrolled fetuses with abnormal or pathological intrapartum CTG features, not fetuses who turned out to be truly acidaemic at birth. Because of the suboptimal specificity of traditional CTG classification in predicting neonatal acidaemia, some of the traces which were classified as abnormal and prompted an emergency delivery were not in fact associated to severe fetal acidaemia; therefore in such cases the DDI might not have had a substantial impact on neonatal outcome.^{57,58} In addition, it is plausible that those cases with more severe CTG anomalies and potentially with more severe intrapartum hypoxia, have been delivered faster compared with those with less severe CTG anomalies, with the result that a shorter decision to delivery interval is associated with a worse outcome.

We speculate that tailoring the DDI on the physiological classification of intrapartum CTG (type and duration of the intrapartum hypoxia) rather than on the morphological CTG features, may lead to more appropriate obstetric

management of labour hypoxia and to better intrapartum care.

5 | CONCLUSION

Our study has shown that in neonates born with metabolic acidemia, the risk of adverse perinatal outcome and the severity of the neurological injury correlates with the duration and the type of the intrapartum hypoxic insult. Further larger prospective studies evaluating the long-term outcome are needed to confirm our observations.

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CONFLICT OF INTERESTS

None declared. Authors declare no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous 3 years; no other relationship or activities that could appear to have influenced the submitted work. Completed disclosure of interest forms are available to view online as supporting information

AUTHOR CONTRIBUTIONS

All authors have read and approved the manuscript. Study conception and design: TG, SF, TF, B Masturzo. Acquisition of data: A Commare, RA, S Paolucci, A Cromi, CMG, B Montersino. Analysis and interpretation of data: TG, SF, B Montersino, AD, EDP, RA. Drafting of manuscript: TG, EDP, A Commare, AD. Critical revision: TF, FP, S Perrone, B Masturzo, A Cromi.

ETHICS APPROVAL

This study protocol has been approved by our local ethics committee (protocol 555/2020/OSS/AOUPR, 09/10/2020).

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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