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Analysis of CTG patterns in cases with metabolic acidosis at birth with and without neonatal neurological alterations

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ABSTRACT

Objective: To determine cardiotocographic patterns in newborns with metabolic acidosis, based on clinical signs of neurological alteration (NA) and the need for hypothermic treatment.

Methods: All term newborns with metabolic acidosis in a single center from 2016 to 2020 were included in the study. Three segments of intrapartum CTG (cardiotocography) were considered (first 30 min of active labor, 90 to 30 min before birth, and last 30 min before delivery) and a longitudinal analysis of CTG pattern was performed according to the 2015 FIGO classification.

Results: Three hundred and twenty-four neonates with metabolic acidosis diagnosed at birth were divided into three groups: the first group included all neonates with any clinical sign of neurological alteration, requiring hypothermia according to the recommendation of the Italian Society of Neonatology (group TNA—Treated neurological Alteration, $n=17$), the second encompassed neonates with any clinical sign of neurological alteration not requiring hypothermia (group NTNA—Not Treated neurological Alteration, $n=83$), and the third enclosed all neonates without any sign of clinical neurological involvement (group NoNA—No neurological Alteration, $n=224$). The most frequent alterations of CTG in TNA group were late decelerations, reduced variability, bradycardia, and tachysystole. Unexpectedly, from the longitudinal analysis of the CTG, 49% of all cases with metabolic acidosis never showed a pathological CTG with normal trace at the beginning of labor followed by normal or suspicious trace in the final part of labor, the same as in TNA and NTNA groups (10 and 39%, respectively).

Conclusions: CTG has limited specificity in identifying cases of acidosis at birth, even in babies who will develop NA.

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Hypoxic-ischemic encephalopathy; cardiotocography; metabolic acidosis; neurological alterations; umbilical artery pH

Introduction

Neonatal hypoxic ischemic encephalopathy (HIE) is a short-term neurological dysfunction caused by intrapartum hypoxia and ischemia, which can be associated with perinatal death or the development of long-term neurological outcomes, such as cerebral palsy [1].

There are other non-hypoxic causes of neonatal encephalopathy, and the hypoxic-ischemic nature of this entity needs to be confirmed by the evidence of metabolic acidosis at birth, low Apgar score, early imaging evidence of brain edema, and the appearance of changes in muscular tone or sucking movements, seizures, or coma in the first 48 h of life [1]. Metabolic acidosis is defined as the measurement of a pH ≤ 7.00 and/or a base excess (BE) ≤−12 mMol/L in arterial or venous umbilical cord blood, or in any blood specimen within the first hour of life [2]. The incidence of HIE is 2–3/1000 births; its severity has been clinically graded in three stages (mild, moderate, and severe)

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according to neurological examination within the first hour of life and the consequent clinical score [3,4].

Severe and moderate HIE patterns benefit from the use of therapeutic hypothermia (TH) as neuroprotective treatment to reduce the risk of perinatal death, cerebral palsy, and significant disability [5,6]. Mild forms of HIE are usually not treated with hypothermia, although the opportunity of performing it even for mild HIE is currently under discussion [6–9]. The use of amplitude-integrated EEG (aEEG) can improve the detection of the newborns that could benefit from the treatment [10,11].

The antepartum identification of cases at risk of HIE is certainly one of the objectives of obstetrical research with the aim to reduce newborns with neurological damage. Badawi et al. verified that the neurological damage related to a hypoxic insult occurs exclusively at childbirth only in 4% of cases, while in 69% of cases, the damage occurs during pregnancy, or may be due in 25% to a combination of ante and intrapartum events [12]. Locatelli et al. identified a greater number of intrapartum causes (26% of cases of NE with only antepartum risk factors, 22% with only intrapartum risk factors, and 44% with a combination of the two), probably due to wider use of continuous CTG [13].

Cardiotocography (CTG) is currently the principal method used for the prompt identification of cases developing metabolic acidosis. Unfortunately, cardiotocography is not a perfect approach, as none of the current classifications in use has high sensitivity and specificity in detecting cases of metabolic acidosis [14]. However, many studies correlate specific cardiotocographic features with hypoxia. In particular, late decelerations and prolonged variable decelerations are significantly associated with fetal acidosis [15–17]; some studies correlate late decelerations and reduced variability to neonatal neurological damage [18,19]; fetal bradycardia is characterized by a rapid drop in pH and may predict a sentinel event (placental abruption, uterine rupture, cord prolapse) [20]. Furthermore, all guidelines focus on the frequency of contractions, as the recovery time between contractions is crucial for good fetal oxygenation in labor [21,22].

In this study we analyzed CTG patterns of neonates born with metabolic acidosis, comparing those with NA at birth with those who did not develop the complication, and stratifying newborns according to the severity of NA and the need or not of hypothermic treatment. The aim of the study was to understand if there are any differences in the CTG pattern between cases of metabolic acidosis with and without neurological alterations.

Methods

The study is a retrospective observational cohort study that considered babies born at Sant'Anna Hospital from March 2016 to August 2020 and was approved by the local Ethical Committee (protocol number 240/2021). Informed consent was obtained from all individual adult participants included in the study.

Neonates of gestational age ≥37 weeks, no chromosomal abnormalities or major malformations, who were born with metabolic acidosis, defined as the measurement of a pH ≤ 7.00 and/or a base excess (BE) ≤−12 mMol/L in arterial/venous umbilical cord blood or in any blood specimen within the first hour of life, were included. We have excluded preterm births to eliminate confounding bias of neurological damage related to prematurity. Additional exclusion criteria were: maternal age <18 years, multiple pregnancy, and lack of funicular arterial blood gas analysis at birth. Indications for funicular arterial blood gas analysis in the labor ward of our Center are depressed newborn, suspicious or pathological CTG, maternal fever, meconium-tainted amniotic fluid, instrumental delivery, breech delivery, shoulder dystocia, twin birth, preterm birth or intrauterine growth restriction.

As per the standard protocol used in our institution, which is based on the recommendation of the Italian Society of Neonatology [11], infants who fulfill these criteria undergo a standardized neurological examination within the first hour of life using the Sarnat score modified by the Eunice Kennedy Shriver National Institute of Child Health and Human Development NICHD-NRN (Neonatal Research Network) trial of hypothermia (HT) [23]. The score evaluates six categories: level of consciousness, spontaneous activity, posture, tone, primitive reflexes (suck and Moro), and autonomic nervous system (pupils, heart rate, and respiration).

In all infants with ≥1 abnormal category, the severity of neonatal encephalopathy (NE) was assessed using the amplitude-integrated electroencephalogram (aEEG) as defined by Al Naqueeb et al. [10]. All patients with a "normal trace" were not cooled, while moderately and severely abnormal traces underwent hypothermic treatment.

All infants with ≥3 categories of moderate/severe signs of neurological involvement were first assessed by aEEG (all of them being not normal) and then cooled.

Based on the possible occurrence and severity of NE, all our eligible cases of metabolic acidosis at birth were divided into three groups: (a) Group NoNA—No neurological Alteration: Infants without clinical sign of NA based on a normal neurological examination on admission; (b) Group NTNA—Not Treated neurological

Alteration: Infants with 1 or 2 abnormal categories based on modified Sarnat score and normal aEEG trace; (c) Group TNA—Treated neurological Alteration: Infants with moderate or severe NA based on modified Sarnat score and infants with ≥1 abnormal category and abnormal aEEG trace. Only the third is the hypothermia-treated group.

Two of the authors (R.A., S.P.) analyzed the CTG traces in double, being blinded to neonatal outcome. CTG characteristics were evaluated in accordance with the 2015 FIGO classification (Table 1), adopted and recommended by the Italian Society of Gynecology and Obstetrics (SIGO) [24,25]. Three different CTG periods were analyzed: (a) first 30 min of active labor (period 1); (b) from the 90th minute to 30 min before the end of recording (period 2); (c) last 30 min of the recording (period 3). In each period, the following parameters were noted: reduced variability, variable decelerations and prolonged variable decelerations (lasting more than 3 min according to FIGO classification), late decelerations, bradycardia, tachycardia and tachysystole (≥5 uterine contractions in 10 min, for ≥30 min) [24]. Period 1 was chosen to identify fetuses with chronic hypoxia; the other two periods permitted to analyze the final part of labor, in particular the second stage which is considered the one most at risk of hypoxia.

A longitudinal evaluation of the CTG was also performed to identify the progression of CTG changes during labor, adapting a CTG longitudinal analysis model present in literature, created to include all possible progressive changes of a tracing during labor [26]; similar models exist in neonatal area [27]. Patients were divided into 4 patterns using the longitudinal grouping of CTG patterns illustrated in Figure 1.

Pattern N-S: normal CTG in period 1 followed by normal or suspicious CTG in periods 2 and 3. This is the best condition for the fetus that starts labor with a CTG showing fetal well-being; at the end of labor the CTG remains normal or with slight alterations which may anticipate hypoxia/acidosis;

Pattern S-N: suspicious trace in period 1 followed by normal CTG in at least one of the other two periods. At the beginning of labor, the fetus presents a CTG with alterations that could anticipate a condition of hypoxia/acidosis but it doesn't worsen, indeed in some cases, there is a normalization of the CTG in the 90 min preceding delivery;

Pattern N-P: normal trace in period 1 followed by pathological CTG in at least one of the other two periods. The fetus starts labor in a well-being condition but at the end of labor it exhibits CTG changes that may be associated with hypoxia/acidosis;

Pattern S/P-P: suspicious or pathological CTG in period 1 followed by pathological trace in at least one of the other two periods. This is the worst condition in which the CTG does not appear normal either at the beginning or at the end of labor and it is the situation of greatest risk of acidosis for the fetus.

We have excluded from the longitudinal analysis of the CTGs all cases in which the CTG was interrupted more than 10 min before birth, even in case of cesarean section.

Statistical analysis

Statistical analysis was carried out comparing the three groups of newborns (TNA, NTNA, and NoNA). Quantitative variables were first analyzed for distribution using the Kolmogorov–Smirnov test; then, the differences between the three groups were tested by the *t*-Student or Wilcoxon-Rank tests according to the normal or skewed data distribution. For multiple comparisons, the multiple analysis of variance (MANOVA) was used. For qualitative variables, Chi-square or Fisher tests were applied. Data are presented as mean, median, standard deviation, percentage, Odd Ratio, and 95% Confidence Interval, as appropriate. A p-value <0.05 was considered statistically significant.

Results

From March 2016 to August 2020, 28,344 births took place in our hospital, among which a single, full-term infant with metabolic acidosis at birth was delivered in

Table 1. FIGO 2015 CTG classification.

	Normal CTG	Suspicious CTG	Pathological CTG
Baseline	110–160 bpm	Lacking at least one of the normal characteristics, with no pathological features	<100 bpm
Variability	5–25 bpm	Lacking at least one of the normal characteristics, with no pathological features	Increased or reduced variability, sinusoidal pattern
Decelerations	No repetitive decelerations	Lacking at least one of the normal characteristics, with no pathological features	Repetitive decelerations (late or prolonged) for >30 min (>20 min if reduced variability); one deceleration lasting >5 min
CTG interpretation	No hypoxia or acidosis	Low probability of hypoxia or acidosis	High probability of hypoxia or acidosis

Contractions normal if <5 contractions in 10 min.
Adapted from Ayres-de-Campos et al. [24].

Table 2. Antepartum risk factors in case of newborns with hypoxia at birth.

	All patients ($n=324$)	TNA group ($n=17$)	NTNA group ($n=83$)	NoNA ($n=224$)	p-Value**	p-Value***
Age*	33.49 (5.55)	30.5 (6.96)	34.56 (5.73)	33.12 (5.31)	0.0770	0.1120
Caucasian ethnic group	292/324 (90.12%)	14/17 (82.35%)	70/83 (84.34%)	208/224 (92.86%)	0.1544	0.01
Scholarity					0.0001	0.0001
Elementary	1/216 (0.46%)	1/11 (9.09%)	0/54 (0%)	0/151 (0%)	–	
Middle school	41/216 (18.98%)	1/11 (9.09%)	11/54 (20.37%)	29/151 (19.21%)	–	
High school diploma	101/216 (46.76%)	5/11 (45.45%)	26/54 (48.15%)	70/151 (46.35%)	–	
Graduation	73/216 (33.80%)	4/11 (36.36%)	17/54 (31.48%)	52/151 (34.43%)	–	
Pregravidic BMI*	23.46 (4.95)	24.03 (4.78)	24.49 (4.57)	23.69 (4.33)	0.1290	0.2160
Nulliparous	243/324 (75%)	9/17 (52.94%)	64/83 (77.11%)	170/224 (75.89%)	0.0952	0.5786
MAR	25/324 (7.72%)	1/17 (5.88%)	11/83 (13.25%)	13/224 (5.80%)	0.0905	0.0535
Weight gain in pregnancy*	12.83 (4.89)	12 (4.33)	13 (4.95)	13 (4.63)	0.6730	0.5980
Smoking during pregnancy	22/324 (6.79%)	0/17 (0%)	5/83 (6.02%)	17/224 (7.59%)	0.6490	0.4130
Drinking alcohol during pregnancy	1/324 (0.31%)	0/17 (0%)	0/83 (0%)	1/224 (0.47%)	0.7994	0.5568
Type 1 or 2 diabetes	2/324 (0.62%)	0/17 (0%)	0/83 (0%)	2/224 (0.89%)	0.6381	0.9259
Chronic hypertension	3/324 (0.93%)	0/17 (0%)	0/83 (0%)	3/224 (1.34%)	0.5087	0.7984
Hypothyroidism	36/324 (11.11%)	2/17 (11.76%)	8/83 (9.64%)	26/224 (11.61%)	0.8252	0.6707
Autoimmune diseases	8/324 (2.47%)	0/17 (0%)	2/83 (2.41%)	6/224 (2.68%)	0.7896	0.7162
Asthma	3/324 (0.93%)	0/17 (0%)	1/83 (1.20%)	2/224 (0.89%)	0.8905	0.9259
Thrombophilia	5/324 (1.54%)	0/17 (0%)	0/83 (0%)	5/224 (2.23%)	0.3219	0.4473
Previous myomectomy	2/324 (0.62%)	0/17 (0%)	1/83 (1.20%)	1/224 (0.47%)	0.7121	0.5568
Previous cesarean section	17/324 (5.25%)	2/17 (11.76%)	7/83 (8.43%)	8/224 (3.57%)	0.1101	0.043
IUGR	5/324 (1.54%)	0/17 (0%)	1/83 (1.20%)	4/224 (1.79%)	0.8123	0.5961
Gestational diabetes	45/324 (13.89%)	3/17 (17.65%)	12/83 (14.46%)	30/224 (13.39%)	0.8740	0.6992
Hypertensive diseases in pregnancy	44/324 (13.58%)	1/17 (5.88%)	16/83 (19.27%)	27/224 (12.05%)	0.1654	0.2299
Oligohydramnios	8/324 (2.47%)	1/17 (5.88%)	1/83 (1.20%)	6/224 (2.68%)	0.4931	0.7162
Anaemia at delivery	31/324 (9.57%)	0/17 (0%)	8/83 (9.64%)	23/224 (10.27%)	0.3818	0.515
Beta-hemolytic streptoccocus infection	55/324 (16.98%)	3/17 (17.65%)	21/83 (25.30%)	31/224 (13.84%)	0.0593	0.02

Abbreviations: TNA group, newborns with NA treated using hypothermia; NTNA group, newborns eligible for cerebral function monitoring, not treated with hypothermia; NoNA, newborns without NA; BMI, body mass index; IUGR, intra uterine growth restriction; MAR, medically assisted reproduction.
*Mean (standard deviation).
**p Among all three groups.
***p Between neonates in NoNA group *vs.* those in the other two groups.

324 cases. Of these newborns, 17 developed severe or moderate NA and underwent hypothermic treatment (TNA group), 83 developed mild NA and were eligible for CFM, but did not undergo hypothermic treatment (NTNA group), and 224 were in fairly good clinical conditions at birth and did not develop NA (NoNA group).

In Table 2 are summarized antepartum risk factors in case of newborns with hypoxia at birth, while in Table 3 are resumed intrapartum risk factors and materno-foetal outcomes in case of newborns with hypoxia at birth (Tables 2 and 3).

By analyzing CTG traces, few cases displayed alterations in period 1: late decelerations were found in one case of TNA (1/12–8.3%), one case of NTNA (1/75–1.3%), and no cases in NoNA group ($p=0.04$). In period 2, late decelerations were more frequent in NA cases ($p=0.001$), and also variable decelerations were significantly more frequent in NA cases ($p<0.001$), although this difference was no more significant when only prolonged variable decelerations were considered. In period 2, tachysystole was detected in 54.5% of cases in TNA group *vs.* 18.2% in NTNA group and 19% in NoNA group ($p=0.01$). We investigated whether the higher frequency of tachysystole in the TNA group was iatrogenic. Mantel-Haenszel stratified analysis in the period 2 shows in the TNA group the Relative Risk (RR) of tachysystole with oxytocin *vs.* non-oxytocin is RR 3 (95% CI 0.25–35.33). In the group NTNA + NoNA RR 1.63 (0.27–9.74) with an adjusted RR 2 (0.47–8.52). It turns out that in the NONA group oxytocin was administered in 48.6% of cases, against 67 and 71.4% of the TNA and NTNA groups, respectively.

In period 3, the cases developing NA showed a significantly higher frequency of reduced variability ($p=0.03$) and late decelerations ($p=0.003$); bradycardia was observed in 35.7% of TNA cases, 9% of NTNA cases, and 8.1% of NoNA newborns ($p=0.003$).

In 261 cases, the CTG traces of all three periods were available and a longitudinal evaluation of CTG pattern was performed. Most cases (229/261, 88%) began with a normal pattern at the onset of the active phase of labor (type 1 pattern); 80% of TNA newborns showed a type 3 pattern, but pattern 1 was sometimes observed also in NA cases (1/10, 10% in TNA group, 29/74, 39% in NTNA group).

Discussion

The peculiarity of the present study is to be the first in which a comparative analysis was not performed

Table 3. Intrapartum risk factors and materno-fetal outcomes in case of newborns with hypoxia at birth.

	All patients ($n=324$)	TNA group ($n=17$)	NTNA group ($n=83$)	NoNA ($n=224$)	p-Value**	p-Value***
Induction of labor	136/323 (42.11%)	11/17 (64.71%)	33/83 (39.76%)	92/224 (41.07%)	0.1484	0.2062
Use of antibiotics in labor	111/324 (34.26%)	7/17 (41.18%)	37/83 (44.58%)	67/224 (29.91%)	0.0458	0.0015
Oxytocin	152/324 (46.91%)	8/17 (47.06%)	48/83 (57.83%)	96/224 (42.86%)	0.06546	0.0285
Epidural anesthesia	176/324 (54.32%)	8/17 (47.06%)	51/83 (61.45%)	117/224 (52.23%)	0.2933	0.2586
Meconium-tainted amniotic fluid	86/324 (26.54%)	5/17 (29.41%)	30/83 (36.14%)	51/224 (22.77%)	0.0598	0.0216
Fever during labor	11/324 (3.40%)	1/17 (5.88%)	5/83 (6.02%)	5/224 (2.23%)	0.2239	0.0836
Duration of labor (min)°	245 (20–770)	187 (55–780)	287 (54–741)	230 (24–777)	0.010	0.1310
Labor duration <3 h	105/324 (32.41%)	8/17 (47.06%)	26/83 (31.33%)	71/224 (31.70%)	0.4143	0.6923
Duration of second stage of labor (min)	69.59 (44.36)	76 (55.74)	76 (45.80)	66 (42.94)	0.0420	0.1220
PROM from >18 h	32/324 (9.88%)	5/17 (29.41%)	8/83 (9.64%)	19/224 (8.48%)	0.0204	0.2079
Sentinel event	4/324 (1.23%)	2/17 (11.76%)	1/83 (1.20%)	1/224 (0.45%)	0.0002	0.0545
Increase in flogosis indexes	87/324 (25.85%)	2/17 (11.8%)	22/83 (26.5%)	63/224 (28.1%)	0.3396	0.4389
Mode of delivery					0.0001	0.0001
Vaginal	183/324 (56.48%)	5/17 (29.41%)	35/83 (42.17%)	143/224 (63.84%)	–	
Operative vaginal	116/324 (35.80%)	8/17 (47.06%)	38/83 (45.78%)	70/224 (31.25%)	–	
Elective cesarean section	2/324 (0.62%)	0/17 (0%)	0/83 (0%)	2/224 (0.9%)	–	
Urgent cesarean section	23/324 (7.10%)	4/17 (23.53%)	10/83 (12.05%)	9/224 (4.02%)	–	
Urgent cesarean section + operative vaginal	139/324 (42.90%)	12/17 (70.58%)	48/83 (57.83%)	79/224 (35.27%)		
Gestational age (weeks)*	39.58 (1.37)	39.20 (1.49)	39.89 (1.10)	39.49 (1.43)	0.2370	0.1180
Male newborn	142/324 (43.83%)	6/17 (35.29%)	30/83 (36.14%)	118/224 (52.68%)	0.1650	0.0054
Neonatal weight (gr)*	3236.86 (416.36)	3505 (379.92)	3295 (441.42)	3273 (392.97)	<0.001	0.3760
Neonatal weight <10°percentile (SGA)	30/324 (9.26%)	0/17 (0%)	12/83 (14.46%)	18/224 (8.04%)	0.906	0.2555
Neonatal weight >90°percentile (LGA)	28/324 (8.64%)	2/17 (11.76%)	12/83 (14.46%)	14/224 (6.25%)	0.0676	0.0218
Percentile*	48.21 (28.82)	52 (26.67)	42 (31.41)	44 (27.73)	0.4250	0.8910
APGAR 1°min*	7.01 (2.41)	3.06 (1.95)	5.79 (2.36)	8.5 (1.43)	<0.0001	<0.001
APGAR <7 after 5 min	34/324 (10.49%)	12/17 (70.59%)	18/83 (21.69%)	4/224 (1.79%)	<0.0001	<0.0001
pH umbilical artery°	7.06 (6.60–7.20)	6.91 (7.12–6.60)	7.02 (6.74–7.15)	7.08 (6.8–7.95)	0.06	0.07
BE umbilical artery°	−13.30 (−29.40–22.20)	−16.3 (−29.40–22.0)	−13.7 (−25.6–20.20)	−12.9 (−22.0–17.0)	0.0001	0.0001
SARNAT 0	244/324 (75.31%)	0/17 (0%)	21/83 (25.30%)	223/224 (99.55%)	<0.0001	<0.0001
SARNAT 1	68/324 (20.99%)	6/17 (35.29%)	61/83 (73.49%)	1/224 (0.45%)	–	
SARNAT ≥2	12/324 (3.70%)	11/17 (64.71%)	1/83 (1.20%)	0/224 (0%)	–	
Admission to neonatal intensive care unit	103/324 (31.79%)	16/17 (94.12%)	83/83 (100%)	4/224 (1.79%)	<0.0001	<0.0001
Hospitalization in neonatal intensive care unit (days)*	2.09 (5.91)	9.64 (.25)	4.73(8.62)	0.08 (0.79)	<0.0001	<0.0001
Survival at 7 days	323/324 (99.69%)	16/17 (94.12%)	83/83 100%	224/224 100%	0.0001	0.5567
Placental histological examination available	77/324 (23.77%)	11/17 (64.71%)	35/83 (42.17%)	31/224 (13.84%)	<0.00001	<0.0001
Infection at the placental histological examination	19/77 (24.7%)	2/11 (18.2%)	10/35 (28.6%)	7/31 (22.6%)	0.7377	0.6273

Abbreviations: TNA group, newborns with NA treated using hypothermia; NTNA group, newborns eligible for cerebral function monitoring, not treated with hypothermia; NoNA, newborns without NA.
*Mean (standard deviation).
**p Among all three groups.
***p Between neonates in NoNA group *vs.* those in the other two groups.

between hypoxic babies with HIE and physiological controls but between newborns with metabolic acidosis who developed NA of various degrees and those who did not, and in which the evidence confirmed the low specificity of CTG analysis in depicting HIE.

Actually, the objective of this study was to understand how reliable is CTG in identifying newborns that will develop neurological alterations, and if there are any differences in the CTG pattern between cases of metabolic acidosis with and without neurological alterations.

Regarding CTG analysis, 88% of our cases had a normal CTG at the beginning of labor (period 1), similar to data reported by Murray et al. who observed 69% normal CTGs at admission in babies born with hypoxia [26]. In period 2 (from 90 to 30 min before delivery), all groups had a high percentage of variable decelerations (50% in TNA, 71% in NTNA, and 67% in NoNA), with no significant difference in the occurrence of variable decelerations; however, TNA group more frequently displayed late decelerations (41% of cases *vs.* 3.9% in NTNA group and 1.6% in NoNA group). This suggests a greater metabolic component of acidosis in TNA group, confirmed by blood gas analysis at birth (median BE −16.3 in TNA, −13.7 in NTNA, and −12.9 in NoNA). In period 2, TNA cases showed a much higher frequency of tachysystole than the other groups (54.5% *vs.* 18.2 in NTNA and 10% in NoNA, respectively); it is well known that tachysystole shortens the time available for fetal reoxygenation between a contraction and

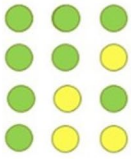
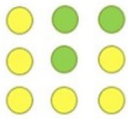
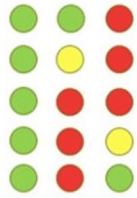
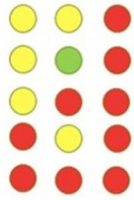
Pattern 1	Pattern 2	Pattern 3	Pattern 4
Normal trace at the beginning of labor and normal or suspicious trace in the other two periods	Suspicious trace at the onset of labor and normal trace in at least one of the other two periods	Normal trace at the onset of labor and pathological trace in the other two periods	Suspicious or pathological trace at the onset of labor and pathological trace in at least one of the other two periods
			

Figure 1. Textual and graphic description of the patterns considered in the longitudinal analysis of CTG, based on the progression of CTG trace in three different periods of labor.

the following. Analyzing the last 30 min of labor, tachysystole was found in more than one-third of cases of TNA *vs.* approximately one-fourth of cases without NA, confirming that tachysystole is a decisive element in modifying the fetal acid-base balance [28]. Interestingly enough we observed that myometrial contractility augmentation with oxytocin was significantly associated with NA development. In period 2, in the TNA group showed a higher risk of tachisysytole in case of oxytocin administration with respect to non-oxytocin (RR 3), while NTNA + NoNA group showed an RR 1.63 and an adjusted RR 2. This finding is in agreement with other studies [29–31] and confirms that sometimes oxytocin administration can lead to tachysystole, in turn linked to neonatal morbidity. Indeed, oxytocin not only causes an increased frequency of contractions but also enhances their strength and duration, leading to a relevant prolongation of the time required for fetal reoxygenation in between.

The CTG trace in the last 30 min of labor (period 3) was characterized by prolonged variable decelerations or late decelerations in 60% of TNA cases *vs.* 40% of all other cases. The higher frequency of sentinel events in TNA cases is confirmed by a higher incidence of bradycardia (35.7% in TNA *vs.* 9% in NTNA and 8% in NoNA) [32].

From the longitudinal analysis of CTG traces, we found that 80% of newborns with TNA had a normal CTG at the beginning of labor, which then became pathological in at least one of the other two periods (pattern 3). Interestingly enough pattern 1, the most reassuring, with minimal alterations during the whole labor, was observed in 52% of newborns who did not develop NA, but also in 10% of newborns in TNA group and 39% of those in NTNA group. This evidence confirmed the widely proven low specificity of CTG analysis in depicting HIE [18,33].

Conclusions

With the limitations of a retrospective analysis, the low incidence of HIE in full-term singleton neonates in our Center (0.6 per 1000 births), and the lack of long-term pediatric follow-up, our study shows that most newborns with metabolic acidosis have a normal CTG at the onset of labor and the CTG pattern during labor is not fully reliable, and only partially identifies also cases that will develop NA. Furthermore, tachysystole in period 2 (90 to 60 min before delivery) and/or in the 30 min before delivery characterizes more than half of the cases with TNA, and should therefore be regarded as a very relevant risk factor, frequently linked to oxytocin use.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the Helsinki Declaration (1964) and later amendments or comparable ethical standards. The study was approved by the local Ethical Committee Azienda Ospedaliera Universitaria Città della Salute e della Scienza of Turin (protocol number 240/2021). Informed consent was obtained from all individual adult participants included in the study.

Author contributions

B.Mo., R.A., and B.Ma. drafted the study and prepared the first and final version of the manuscript. E.V. designed and performed statistical analysis. B.Mo., A.M., C.G., M.Q., and V.C. retrieved the data of the patients and made the figures and the tables. S.P. and R.A. analyzed CTG traces. E.M., I.M., and

B.Ma. reviewed the manuscript. A.R. overviewed the research and reviewed the manuscript. The first two authors equally contributed to the paper; the last two authors equally contributed to the paper.

Disclosure statement

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [A.R.], upon reasonable request.

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