Association between Marked Fetal Heart Rate Variability and Neonatal Acidosis: A Prospective Cohort Study.

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RESEARCH ARTICLE

Intrapartum care

Association between marked fetal heart rate variability and neonatal acidosis: A prospective cohort study

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Abstract

Objective: To assess the association between marked variability in fetal heart rate (FHR) and neonatal acidosis.

Design: Bicentric prospective cohort study.

Setting: From January 2019 to December 2019, in two French tertiary care maternity units.

Population: Women in labour at ≥37 weeks of gestation, with continuous FHR monitoring until delivery and with the availability of umbilical arterial pH. Women with intrauterine fetal death or medical termination, multiple pregnancies, non-cephalic presentation or planned caesarean delivery were excluded.

Methods: The exposure was marked variability in FHR in the 60 minutes before delivery, defined as a variability greater than 25 beats per minute, with a minimum duration of 1 minute. To assess the association between marked variability and neonatal acidosis, we used multivariable modified Poisson regression modelling. We then conducted subgroup analyses according to the US National Institute of Child Health and Human Development (NICHD) category of the associated fetal heart rate.

Main outcome measures: Neonatal acidosis, defined as an umbilical artery pH of ≤7.10.

Results: Among the 4394 women included, 177 (4%) had marked variability in fetal heart rate in the 60 minutes before delivery. Acidosis occurred in 6.0% (265/4394) of the neonates. In the multivariable analysis, marked variability was significantly associated with neonatal acidosis (aRR 2.30, 95% CI 1.53–3.44). In subgroup analyses, the association between marked variability and neonatal acidosis remained significant in NICHD category-I and category-II groups.

Conclusions: Marked variability was associated with a twofold increased risk of neonatal acidosis.

KEYWORDS
fetal heart rate, marked variability, neonatal acidosis, neonatal morbidity

1 | INTRODUCTION

Intrapartum electronic fetal monitoring has become a standard of care in the assessment of fetal well-being during labour.[1] Despite extensive research on fetal heart rate (FHR) analysis, its interpretation is subject to low specificity and high interobserver variability,[2] and its effectiveness in reducing perinatal mortality and cerebral palsy remains

controversial.[3–6] Therefore, it seems necessary to reach a more evidence-based approach to FHR interpretation to optimise its performance.

Fetal heart rate (FHR) variability is a pattern of major importance in FHR analysis. Normal FHR variability generally ensures a normal fetal acid–base status.[7] Reduced variability can reflect decreased autonomic activity, in situations such as fetal acidosis,[8] or the administration of some maternal medications.[9,10] On the other hand, research on marked variability is limited and its pathophysiology is incompletely understood.[1,11] In the National Institute of Child Health and Human Development (NICHD) system for categorising FHR patterns,[1,12,13] marked variability is classified into category II, which refers to 'indeterminate patterns'. The risk of acidosis associated with these patterns is uncertain and their clinical management is challenging.[14] Therefore, the NICHD specifically targeted observational studies on indeterminate patterns as subjects of highest priority for research.[1]

Fetal heart rate (FHR) variability is mainly determined by the autonomous nervous system,[15] and marked variability could reflect fetal autonomic instability resulting from impaired fetal oxygenation.[11] A recent review stated that marked variability can indicate fetal compromise and highlighted the need for further research on this pattern.[16]

Our aim was to assess the association between marked variability in FHR patterns during labour and neonatal acidosis.

2 | METHODS

2.1 | Study design and population

This bicentric prospective cohort study was conducted from 1 January 2019 to 31 December 2019 in two French tertiary care maternity units (Toulouse and Poissy). We included women in labour at ≥37 weeks of gestation, with continuous FHR monitoring until delivery. Women with intrauterine fetal death or medical termination, multiple pregnancies or non-cephalic presentation were excluded. Women who met the inclusion criteria were consecutively enrolled when admitted for delivery. Women with caesarean deliveries were excluded because they did not have continuous FHR monitoring until delivery. Indeed, acute events leading to neonatal acidosis could occur after the interruption of the FHR monitoring, inducing potential bias in our results. We also excluded women with missing umbilical arterial pH. Both hospitals practiced continuous intrapartum FHR monitoring and the measurement of umbilical arterial pH, whatever the level of risk for the women and the neonate.

2.2 | Exposure

The exposure of interest was marked variability in FHR patterns in the 60 minutes before delivery, defined as fluctuations in the baseline with an amplitude greater than 25 beats per minute,[1,11] with a minimum duration of 1 minute. We chose this duration because it has been suggested that marked variability lasting 1 minute was associated with adverse neonatal outcomes.[17] FHR patterns of the 60 minutes before delivery were interpreted by two trained assessors who were blinded to clinical information and outcomes. The interpretation was performed using strict definitions from the NICHD criteria and its three-tiered category system.[1] A second interpretation of the FHR was performed by a maternal–fetal medicine specialist who was an expert in FHR for a random sample of 251 tracings (5.6%), to estimate interobserver agreement.

2.3 | Outcomes

The primary outcome was neonatal acidosis, defined as an umbilical artery pH of ≤7.10, obtained after delivery from a clamped segment of the umbilical cord. Secondary outcomes were severe acidosis, Apgar score of <7 at 5 minutes, respiratory distress, neonatal intensive care unit admission, neonatal infection and neonatal death. Severe acidosis was defined as an umbilical artery pH of ≤7.0, and respiratory distress was defined as the need for respiratory support for an unspecified duration of time.

2.4 | Statistical analyses

The sample size calculation was based upon the assumption that marked variability would occur in 6% of the FHR tracings and that 5% of the neonates would have neonatal acidosis in the non-exposed group.[18] We hypothesised that marked variability would be associated with a twofold increased risk of neonatal acidosis. We estimated that the inclusion of 3778 women would give 80% power to detect a difference in the prevalence of neonatal acidosis at a two-sided alpha level of 5%.

We described the characteristics of the women, pregnancies, deliveries, FHR patterns and neonates of our cohort, and compared women with marked variability against women without marked variability, using χ^2 for categorical variables and the Student's *t*-test for quantitative variables.

Potential confounding factors determined from previous literature and included in the multivariable analysis were: maternal age, maternal body mass index, parity, previous caesarean delivery, gestational age at delivery and birthweight.[19] The NICHD category of associated FHR and mode of delivery were not considered as confounding factors. We considered that the NICHD category was a consequence of fetal acid–base status and that the mode of delivery was considerably influenced by the suspicion of fetal acidosis. Therefore, we did not include them in the multivariable analysis to avoid overadjustment.[20] Qualitative variables were categorised as shown in Table 1. Maternal age, birthweight

TABLE 1 Maternal, pregnancy, labour and delivery characteristics

Characteristics	Overall population (*n* = 4394)	Marked variability (*n* = 177)	No marked variability (*n* = 4217)	*p*
Age (*n* = 4393)				
<30 years	1852 (42.2)	76 (42.9)	1776 (42.1)	0.714
30–35 years	1546 (35.2)	67 (37.9)	1479 (35.1)	
35–40 years	795 (18.1)	27 (15.3)	768 (18.2)	
≥40 years	200 (4.6)	7 (4.0)	193 (4.6)	
BMI before pregnancy (*n* = 4362)				
<18.5 kg/m^2	276 (6.3)	14 (8.0)	262 (6.3)	0.199
18.5–24.9 kg/m^2	2463 (56.5)	96 (54.6)	2367 (56.6)	
25.0–29.9 kg/m^2	1019 (23.4)	34 (19.3)	985 (23.5)	
≥30.0 kg/m^2	604 (13.9)	32 (18.2)	572 (13.7)	
Parity (*n* = 4394)				
Nulliparous	1951 (44.4)	111 (62.7)	1840 (43.6)	<0.001
Parous without previous caesarean	2181 (49.6)	52 (29.4)	2129 (50.5)	
Parous with previous caesarean	262 (6.0)	14 (7.9)	248 (5.9)	
Pre-existing diabetes (*n* = 4394)	38 (0.9)	1 (0.6)	37 (0.9)	0.660
Pregnancy complications				
Pre-eclampsia (*n* = 4394)	60 (1.37)	3 (1.7)	57 (1.4)	0.700
Gestational diabetes (*n* = 4391)	577 (13.1)	17 (9.6)	560 (13.3)	0.155
GA at birth (weeks) (*n* = 4394)	39.5 (1.2)	39.8 (1.2)	39.5 (1.2)	0.002
Induction of labour (*n* = 4394)	1338 (30.5)	68 (38.4)	1270 (30.1)	0.019
Fetal heart rate characteristics (*n* = 4394)				
Tachycardia	269 (6.1)	14 (7.9)	255 (6.1)	0.311
Bradycardia	16 (0.4)	0 (0)	16 (0.38)	0.412
Repeated variable decelerations	1126 (25.6)	68 (38.4)	1058 (25.1)	<0.001
Repeated late decelerations	486 (11.1)	11 (6.2)	475 (11.3)	0.036
NICHD category[a]				
I	2119 (48.2)	62 (35.0)	2057 (48.8)	<0.001
II	1746 (39.8)	103 (58.2)	1643 (39.0)	
III	528 (12.0)	12 (6.8)	516 (12.2)	
Mode of delivery (*n* = 4394)				
Spontaneous vaginal delivery	3614 (82.3)	126 (71.2)	3488 (82.7)	<0.001
Assisted vaginal delivery	780 (17.8)	51 (28.8)	729 (17.3)	
Epidural analgesia (*n* = 1911)	1899 (99.4)	70 (100.0)	1829 (99.4)	0.498
Birthweight (g) (*n* = 4383)	3346.1 (424.8)	3319.2 (435.1)	3347.2 (424.4)	0.389

Note: Categorical variables: *n* (%). Continuous variables: mean (SD).

Abbreviations: BMI, body mass index; GA, gestational age.

[a]NICHD category of the associated FHR.

and gestational age were transformed into second-degree fractional polynomials because their relationship with neonatal acidosis was not linear. The relationship between maternal body mass index and neonatal acidosis was linear. There were 4350 (99.0%) women with no missing data for covariates included in the multivariable model. Therefore, we performed our multivariable analysis on complete cases. Characteristics of the women with full data were similar to those of women with missing data (data not shown).

To assess the association between marked variability and neonatal acidosis, we used univariable then multivariable modified Poisson regression modelling with a robust variance, and then estimated relative risks and their 95% confidence intervals. We then performed subgroup analyses according to the NICHD category of the associated FHR. The NICHD classification has three categories: category-I FHRs are normal; category-II FHRs are indeterminate; and category-III FHRs are abnormal.[1] Indeed, marked

variability must be interpreted in the context of other FHR patterns and these analyses are meant to help the clinician assessing the risk of neonatal acidosis. After that, we described the duration of marked variability and we assessed the association between the duration of marked variability and neonatal acidosis.

Finally, we performed two sensitivity analyses. First, we assessed the association between marked variability and neonatal acidosis in a population of women with spontaneous vaginal deliveries. Indeed, it has been suggested that marked variability could be induced by instrumental delivery through increased intracranial pressure.[21] Therefore, this analysis aimed to verify that the association remained unchanged in a population where marked variability cannot be a consequence of an instrumental delivery. In the second sensitivity analysis, we defined marked variability as fluctuations with an amplitude greater than 25 beats per minute, with a minimum duration of 2 minutes (instead of 1 minute in the main analysis).

All tests were two-sided with p-values of ≤0.05 defined as statistically significant. All analyses were performed with STATA 15.1. Graphics were created with R 4.0.4.

2.5 | Ethics and funding

The ethical review committee Comité d'éthique de la recherche en Obstétrique et Gynécologie approved this study (CEROG 2019-OBST-1003). This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

There was no patient and public involvement in this study.

3 | RESULTS

During the study period, 5024 women gave birth in Toulouse Hospital and 3986 women gave birth in Poissy Hospital. After exclusions, our study population included 4394 women (Figure 1). Four percent (177 neonates) had marked variability in FHR patterns in the 60 minutes before delivery. The median duration of marked variability was 2 minutes. Interobserver agreement on the assessment of marked variability was high, with a kappa statistic of 0.81. Examples of FHR recordings with marked variability are shown in Figure S1.

Women with marked variability in FHR patterns, compared with women without, were more often nulliparous, and had higher rates of labour induction and assisted vaginal deliveries (Table 1). FHR tracings with marked variability more often exhibited patterns of repeated variable decelerations and less often patterns of repeated late decelerations compared with FHR tracings without marked variability (Table 1).

The prevalence of neonatal acidosis in our study population was 6.0%: 15.3% in neonates with marked variability in FHR patterns and 5.6% in neonates without marked variability (crude relative risk, RR 2.70, 95% CI 1.82–4.02). After adjustment for confounding factors, marked variability was significantly associated with neonatal acidosis (adjusted relative risk, aRR 2.30, 95% CI 1.53–3.44) (Table 2). Nearly 15% of neonates with marked variability had respiratory distress, compared with 7.9% of neonates without marked variability (aRR 1.73,

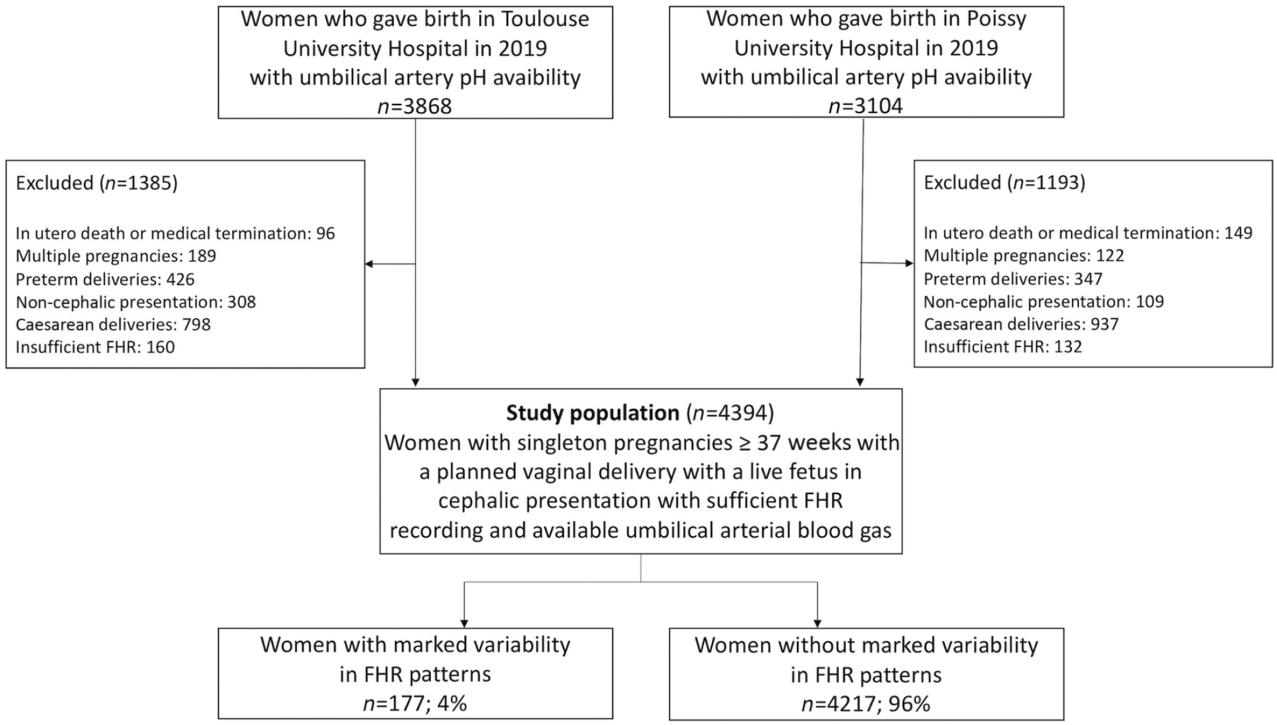

FIGURE 1 Flow chart for study

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TABLE 2 Association between marked variability and neonatal outcomes

Outcomes	Marked variability (n = 177)	No marked variability (n = 4217)	Crude RR (95% CI)	Adjusted RR (95% CI)[a]
Neonatal acidosis[b]	27 (15.3)	238 (5.6)	2.70 (1.82–4.02)	2.30 (1.53–3.44)
Severe neonatal acidosis[c]	3 (1.7)	29 (0.7)	2.46 (0.75–8.09)	2.10 (0.63–6.98)
Apgar <7 at 5 minutes	2 (1.1)	55 (1.3)	0.87 (0.21–3.55)	0.40 (0.05–2.89)
Respiratory distress[d]	26 (14.7)	333 (7.9)	1.86 (1.25–2.77)	1.73 (1.15–2.58)
NICU admission	8 (4.5)	144 (3.4)	1.32 (0.65–2.70)	1.35 (0.70–2.76)
Neonatal infection	4 (2.3)	41 (1.0)	2.32 (0.83–6.49)	1.99 (0.71–5.59)
Neonatal death	0 (0)	4 (0.1)	–	–

Note: Categorical variables: *n* (%).

Abbreviations: NICU, neonatal intensive care unit; RR, relative risk.

[a]Multivariable Poisson regression model including maternal age, maternal body mass index, parity, previous caesarean, gestational age at delivery and birthweight.

[b]Defined as an umbilical artery pH of ≤7.10.

[c]Defined as an umbilical artery pH of ≤7.00.

[d]Defined as the need for respiratory support for unspecified duration of time.

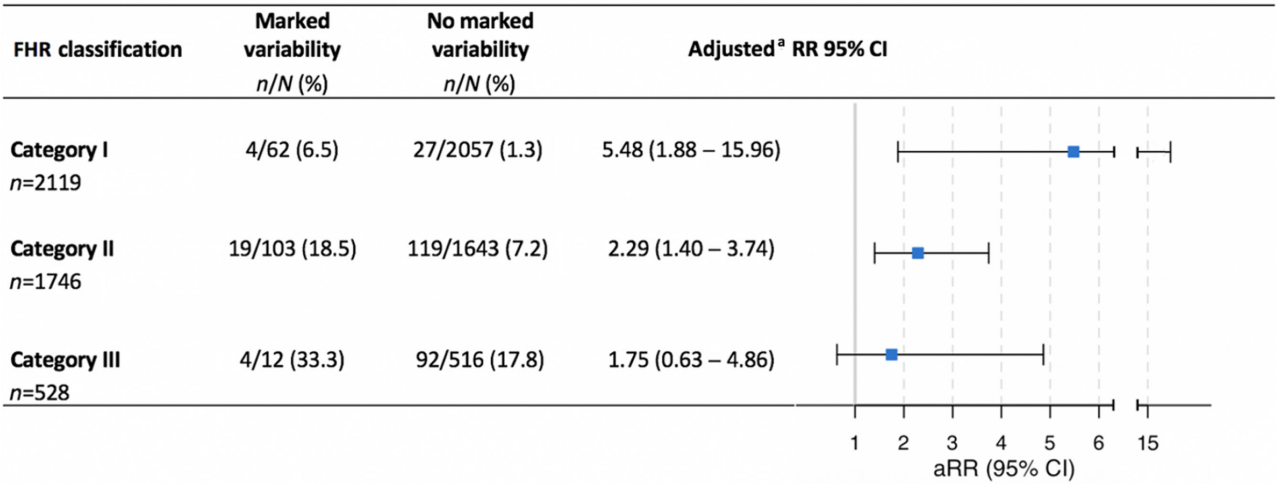

FIGURE 2 Association between marked variability and neonatal acidosis. Subgroup analysis according to NICHD category of the associated FHR. [a]Multivariable Poisson regression model including maternal age, maternal body mass index, parity and previous caesarean delivery, gestational age at delivery and birthweight

95% CI 1.15–2.58). Other secondary outcomes had very low prevalence and were not significantly associated with marked variability (Table 2).

After stratification by NICHD category of the associated FHR, the association between marked variability and neonatal acidosis remained significant in category-I and category-II groups. (Figure 2). In the subgroup category I, 62 neonates (2.9%) had marked variability in FHR patterns, and among them, 6.5% had neonatal acidosis. The risk of neonatal acidosis was significantly higher in neonates with marked variability in FHR, compared with neonates without (aRR 5.48, 95% CI 1.88–15.96). In the subgroup category II, 103 neonates (5.9%) had marked variability, among which 18.5% had neonatal acidosis. The risk of neonatal acidosis was significantly higher in neonates with marked variability in FHR (aRR 2.29, 95% CI 1.40–3.74). In the subgroup category III, 12 neonates (2.3%) had marked variability in FHR patterns. The prevalence of neonatal acidosis was 33.3% in neonates with marked variability and 17.8% in neonates without. After adjustment, we found no significant association between marked variability and neonatal acidosis in neonates with category-III FHR (aRR 1.75, 95% CI 0.63–4.86).

In the first sensitivity analysis on the population of women with spontaneous vaginal delivery, 126 neonates (3.5%) had marked variability in their FHR patterns (Table S1). In this analysis, the prevalence of neonatal acidosis was 5.3%: 13.5% in neonates with marked variability and 5.0% in neonates without. As in the main analysis, the risk of neonatal acidosis was significantly higher in neonates with marked variability than in neonates without (aRR 2.18, 95% CI 1.31–3.61). In the second sensitivity analysis, defining marked variability with a minimum duration of 2 minutes instead of 1 minute in the main analysis (Table S2), the estimation of the adjusted relative risk was close to the main analysis but did not reach statistical significance (aRR 1.53, 95% CI 0.81–2.88).

4 | DISCUSSION

4.1 | Main findings

In this prospective cohort study, marked variability in FHR patterns occurred in 4% of the neonates in the hour before birth. Neonates with a prenatal marked variability had a twofold increased risk of acidosis.

In category-I FHR tracings, marked variability was associated with a fivefold increased risk of neonatal acidosis. However, the absolute risk remained low in this subgroup, with only 6.5% of neonates with marked variability developing neonatal acidosis. In category-II FHR tracings, neonates with marked variability had a twofold increased risk of neonatal acidosis and the absolute risk was high: 18.5% of neonates with marked variability developed neonatal acidosis. The risk of neonatal acidaemia was high for neonates with category-III FHR tracings, at nearly 20%, and marked variability did not significantly increase this risk.

4.2 | Strengths and limitations

The strengths of our study include its prospective cohort design, with the consecutive enrolment of all women meeting the inclusion criteria. All FHR tracings were assessed using the strict definitions from the NICHD criteria and its three-tiered category system, enabling the generalisability of our results. Moreover, as poor interobserver agreement is an important limitation of FHR interpretation, we rigorously evaluated interobserver variability. Interobserver agreement on the assessment of marked variability was excellent. It could mean that marked variability is easier to identify, and then probably more useful in clinical practice, than some other FHR patterns with much higher interobserver variability.[2] Finally, marked variability is a poorly investigated FHR pattern, and a very limited number of clinical studies have focused on this characteristic. Contrary to previous studies on this pattern, we took into account the other FHR patterns by performing subgroup analyses according to the NICHD category of the associated FHR. These results allow a more accurate assessment of the fetal risk of acidosis and are particularly valuable in clinical practice.

The main limitation of this study is its observational design. Indeed, marked variability could have influenced the decision to expedite the delivery. This could have led to underestimating the prevalence of acidosis in neonates with marked variability, and then to underestimating the strength of association between marked variability and neonatal acidosis. Also, we excluded women with caesarean deliveries because they did not have continuous FHR monitoring until delivery. Indeed, acute events leading to neonatal acidosis could occur after interruption of the FHR monitoring, inducing potential bias in our results. Caesarean deliveries are associated with higher risks of neonatal acidosis and should be considered separately. These exclusions, although necessary to assess the association between marked variability and neonatal acidosis, could be responsible for selection bias. Finally, neonatal acidosis is an intermediate outcome. Hypoxic ischaemic encephalopathy or cerebral palsy would be more clinically relevant outcomes. However, these events are fortunately very rare and would require the inclusion of a significant number of women. Moreover, the association between an umbilical artery pH of ≤7.10 and encephalopathy is well documented in large cohort studies,[22,23] and therefore neonatal acidosis remains a relevant outcome.

4.3 | Interpretation

Our results are consistent with other studies on marked variability. In a unicentric cohort study conducted by Liu et al.,[23] marked variability was associated with increased respiratory morbidity in term neonates. Neonatal acidosis was not reported in this study. In a unicentric cohort study conducted by Polnaszek et al.,[24] marked variability occurred in 4.5% of neonates before delivery and was associated with increased risks of respiratory distress and abnormal arterial blood gas. Finally, the association between marked variability and neonatal acidosis is also supported by experimental studies. The regulation of FHR is dependent on the autonomic nervous system and its variability reflects sympathetic/parasympathetic balance. Acute progressive asphyxia triggers an immediate activation of the sympathetic system, which results in increased FHR variability.[25–27]

This study has important implications: it may help clinicians to assess the risk of fetal acidosis. We found that marked variability was associated with an increased risk of neonatal acidosis. In subgroup analyses, this association remained significant in neonates with category-I or category-II FHR tracings. In neonates with category-I tracings, the risk of neonatal acidosis was low, even in the case of marked variability. However, in neonates with category-II FHR tracings, these results may have important clinical implications. Category-II tracings occur in more than 80% of fetuses during labour.[28] This category combines many different FHR patterns, its significance is indeterminate and its management remains the most challenging issue in the field of FHR monitoring. Therefore, it is necessary to better characterise category-II tracings to identify fetuses at high risk of neonatal acidosis. Clark et al. proposed an algorithm for the management of category-II FHR patterns.[29] It did not take marked variability into account, probably because of the lack of evidence about this pattern. Our study suggests that marked variability is associated with an increased risk of neonatal acidosis in neonates with category-II FHR patterns. Therefore, this pattern should be considered in FHR interpretation and integrated into algorithms to improve the performance of electronic fetal monitoring.

5 | CONCLUSION

We found that marked variability was associated with an increased risk of neonatal acidosis. Therefore, this pattern should be considered in FHR interpretation to optimise intrapartum fetal surveillance.

AUTHOR CONTRIBUTIONS

Conceptualisation: PG, CG and PB. Methodology: PG, CG, PB, LL, MA and CV. Formal analysis: LL, PG and AM. Supervision: PG, CG and PB. Writing – original draft: LL, PG and AM. Writing – review and editing: CV, MA, CG and PB.

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FUNDING INFORMATION

No funding.

CONFLICT OF INTERESTS

None declared. Completed disclosure of interests form available to view online as supporting information.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL

The ethical review committee Comité d'éthique de la recherche en Obstétrique et Gynécologie approved this study (CEROG 2019-OBST-1003).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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