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Secondary Tools to Cardiotocography for Fetal Monitoring during Labor

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2021

Document Version:
Publisher's PDF, also known as Version of record

The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: http://www.tandfonline.com/loi/ijmf20

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To cite this article: L. Iorizzo, T. W. Klausen, E. Wiberg-Itzel, F. Ovin & N. Wiberg (2018): Use of Lactate Pro™2 for measurement of fetal scalp blood lactate during labor – proposing new cutoffs for normality, preacidemia and acidemia: a cross-sectional study, The Journal of Maternal-Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2017.1416603

To link to this article: https://doi.org/10.1080/14767058.2017.1416603

Published online: 04 Jan 2018.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE, 2018
https://doi.org/10.1080/14767058.2017.1416603

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Use of Lactate Pro^{TM}2 for measurement of fetal scalp blood lactate during labor – proposing new cutoffs for normality, preacidemia and acidemia: a cross-sectional study

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ABSTRACT

Objective: Measurement of fetal scalp blood lactate is a supplementary tool to cardiotocography in the case of a non-reassuring tracing. Several hand-held lactate meters have been launched, all with differentials in absolute values. Therefore, the reference intervals must be calculated for each device. The internationally accepted reference interval is based on measurement with Lactate Pro^{TM} with recently got out of production. The aim of this study was to propose cutoffs for normality, preacidemia, and acidemia in fetal scalp blood for Lactate Pro^{TM}2 based on the comparison of lactate values measured with Lactate Pro^{TM} and Lactate Pro^{TM}2.

Design: Seven hundred one fetal scalp blood samples were analyzed simultaneously. The conversion equations were retrieved from the linear regression model. On the basis of the cutoffs for Lactate Pro^{TM} cutoffs for Lactate Pro^{TM}2 were calculated.

Results: The conversion equations obtained were Lactate Pro$^{TM} = -0.02 + 0.68 \times$ Lactate Pro^{TM}2 (SD: -0.09–$0.07 \times$ Lactate Pro^{TM}2) and Lactate pro^{TM}2 (LP2) $= 0.03 + 1.48 \times$ Lactate Pro^{TM} (SD: $0.16 + 0.17 \times$ Lactate Pro^{TM}). The correlation to umbilical arterial pH was identical for the two devices ($r = -0.18$), whereas the correlation to umbilical arterial lactate was better for Lactate Pro^{TM} than for Lactate Pro^{TM}2 ($r = 0.38$, respectively, $r = 0.33$). The correlation to umbilical arterial lactate was dependent on time from sampling to delivery.

Conclusion: Proposed reference values for Lactate Pro^{TM}2: scalp lactate <6.3 mmol/L = normal, no indication for intervention; 6.3–7.1 mmol/L = preacidemia, repeated testing has to be considered; >7.1 mmol/L = acidemia, expedite delivery.

ARTICLE HISTORY
Received 29 October 2017
Revised 6 December 2017
Accepted 10 December 2017

KEYWORDS
Fetal blood; fetal surveillance; lactate; point-of-care device

Introduction

The clinical applicability of different tools for fetal monitoring during labor is currently under debate. The most frequently used method is cardiotocography (CTG), although criticized because of low specificity and high interobserver variation [1]. To keep unnecessary interventions to a minimum, complementary methods such as fetal scalp blood sampling (FBS) have therefore been introduced [2,3].

Traditionally pH was analyzed, but in the 1990s, lactate was introduced as an alternative [4,5]. Lactate is the end product of anaerobic metabolism and reflects the degree of metabolic acidemia, whereas pH is dependent on both the respiratory and the metabolic component and, therefore, does not discriminate between the different types of acidemia.

FBS is to a varying degree associated with technical and practical challenges, especially when pH is analyzed [6]. Lactate is shown to be comparable with or even better than pH, in assessment of fetal acidemia and metabolic acidosis without increase in the number of instrumental deliveries [6].

Lactate can be analyzed in only a few seconds by an easy to use point-of-care device (POC), which requires only 0.5–10 μL blood. There are several lactate meters on the market and due to different test characteristics and variations within the POC's, it is important to emphasize that the recommended cutoffs for normality, preacidemia, and acidemia are based on measurements with only Lactate Pro^{TM} (LP) (Arkray, Kyoto, Japan) [7,8].

By the end of LP's production, the same manufacturer launched an updated version, Lactate Pro^{TM}2

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(LP2). Both test strip devices measure the lactate concentration by amperometry with production of a small electric current proportional to the lactate value. The new version has the advantage of shorter analysis time (15 s versus 60 s) and requires only 0.5 μL whole blood. Based on a sample size of 69 a recently published study showed an excellent correlation between the two devices, but with significant differences in absolute lactate values. The study recommended cut-offs for LP2: scalp lactate $<$6.4 mmol/L = normal and $\geq$7.4 mmol/L = acidemia [8]. As a result of the study, these reference values are now recommended by the Swedish obstetrical society (SFOG) if LP2 is used.

The primary aim of this study was to propose cut-offs for normality, preacidemia, and acidemia for LP2. Second, to investigate the correlation of lactate measured by the two devices and to pH and lactate in arterial umbilical cord blood and to show if the time interval from FBS to delivery affects the correlations.

Materials and methods

The study was carried out at Herlev University Hospital, Copenhagen, Denmark, and Soder Hospital, Karolinska Institute, Stockholm, Sweden, from November 2013 to May 2014.

Women in labor fulfilling the inclusions criteria; singleton in cephalic presentation, $>$ 33 weeks of gestational age, no contraindications for FBS, a non-reassuring CTG or a significant event with automated analysis of fetal electrocardiogram (ST-waveform analysis (STAN®, Neoventa Medical, Gothenburg, Sweden)) were included. In case of a non-reassuring CTG or a significant STAN-event, the doctor on call interpreted the CTG tracing and if it was still considered non-reassuring FBS was performed by standard technique according to the clinical guidelines. Solely lactate values measured with LP were used in the clinical management. When indicated, fetal blood sampling was repeated. FBS samples taken within 60 min before delivery were included in the correlation analysis between pH and lactate values in cord blood. Umbilical cord blood samples were taken immediately after delivery on unclamped cord and analyzed within 15 min by a stationary blood gas analyzer (ABL 800, Radiometer, Copenhagen, Denmark). Obstetric and neonatal data were routinely entered into the electronic records (Copenhagen: OPUS, H-EPJ, Sweden: Obstetrix, Siemens AB).

Biochemical analyses

The fetal scalp was carefully wiped and a small incision was made. The scalp blood was collected in heparinized plastic capillaries. From the same capillary, one drop of blood was analyzed bed-side with LP and LP2 simultaneously (Arkary, Kyoto, Japan). It was not allowed to sample further scalp blood in case of insufficient amount of blood for successful analysis with LP2. The results were displayed in 1 min, respectively, in 15 s. The test strips in both devices are based on an amperometric method using an enzymatic reaction and is calibrated for every 25th analysis with a control test strip. According to the manufacturer the SD in adult blood is 0.07 mmol/L and the coefficient of variation (CV) is 3.2% for LP. For LP2, the SD is 0.2–0.7 mmol/L and the CV 2.9–4.3% in adult blood [9]. Repeated analysis of lactate (10 times in the same blood drop within 5 min) was performed from five different cord blood samples with various lactate levels to calculate the CV for LP2 in umbilical cord blood.

Statistics

The correlation between various variables was calculated by linear regression analysis with 95% prediction interval. Bland–Altman plot was used to investigate a possible relationship between the discrepancies between the lactate values by the two devices. Limits of agreement and conversion equations were calculated by performing a linear regression with the difference between the measurements of two methods as dependent variable and the mean value of the methods as independent [10]. Conversion equations between the two methods were calculated from the results of the regression.

From the conversion equations, new reference values for normality, preacidemia, and acidemia for LP2 based on LP were generated. Sensitivity and specificity with 95% CI for normality and acidemia were calculated for comparison between the two devices.

All p values were two-sided and p values below .05 were considered significant. R statistical software version 3.2.3 (SPSS Inc., Chicago, IL) was used for all calculations. The conversion formulas were calculated using the R package "MethComp" (SPSS Inc., Chicago, IL).

The study was approved by the Regional Ethics Committee in Copenhagen, Denmark (H-6-2014-FSP-013), The Danish Data Registry (HEH-2014-075) and from Regional Ethics Committee of Karolinska Institute, Stockholm, Sweden (2016/1723-32).

Results

From March 2013 to December 2014, 466 women in active labor with a non-reassuring CTG were included.

One hundred seven women were included from the Swedish hospital and 359 from the Danish hospital (Table 1). Seven hundred one fetal scalp blood samples were analyzed simultaneously with LP and LP2. LP-lactate values ranged from 0.9 to 10.3 mmol/L (median 2.8) and LP2-lactate values from 1.2 to 13.3 mmol/L (median 4.1) with consistently higher values when measured with LP2 (Figure 1). Absolute values were closely interrelated with a correlation coefficient of $r = 0.92$ (95% CI: 0.91, 0.93, $p < .0001$), although the difference in absolute values increased linearly with increasing lactate concentration (Figure 1). From the linear model and the corresponding regression coefficients, the conversion equations were calculated to (Figure 2):

Relationships between methods:

$$\text{LP2–LP1} = 0.03 + 0.39\ (\text{LP2} + \text{LP1})/2$$
$$\text{LP} = -0.02 + 0.68 \times \text{LP2}$$
$$\text{LP2} = 0.03 + 1.48 \times \text{LP1}$$
$$\text{SD(LP)} = -0.09 - 0.07 \times \text{LP2};\ \text{SD(LP2)} = 0.16 + 0.17 \times \text{LP}$$

By converting the recommended cutoffs for normality and acidemia for LP (using the conversion equation above) to cutoffs for LP2, we found that LP2-lactate <6.3 mmol/L corresponds to LP − lactate <4.2 mmol/L with a sensitivity, respectively, a specificity of 0.789 (95% CI: 0.712, 0.853) and 0.980 (95% CI: 0.965, 0.99). LP2-lactate >7.1 mmol/L corresponds to LP-lactate >4.8 mmol/L with a sensitivity of 0.803 (95% CI 0.691, 0.888) and a specificity of 0.959 (95% CI 0.940, 0.973) (Figure 3). The sensitivity and specificity were calculated on how many normal and pathological values received by LP2 in comparison with LP.

In 327 women, FBS was performed within 60 min before delivery. The correlation between lactate values measured with LP and LP2 to pH in artery umbilical cord blood were significant and equally poor for both devices LP: $r = -0.18$ ($p < .002$, 95% CI: −0.29, −0.07), LP2: $r = -0.18$ ($p < .002$, 95% CI: −0.28, −0.06). There was a positive significant correlation to lactate in umbilical artery cord blood for both devices with a stronger correlation for LP than for LP2 ($r = 0.38$,

Table 1. Maternal and fetal characteristics.

	Study population, $N = 466$	
	Median [range]	Missing values
Maternal age,	31 [18–45]	1
Gestational age in weeks	40 + 3 [33 + 3 − 42 + 5]	1
Time from last FBS to delivery in minutes	27 [0–1201]	5
	N	
Fever ≥38 °C	43	373
5-min AS <7	6	125
Umbilical cord arterial pH <7.05	10	158
Mode of delivery		121
Normal vaginal delivery	199	
Vaginal OD, suspect asphyxia	54	
Vaginal OD, dystocia	26	
Acute caesarean section	66	

FBS: fetal scalp blood sampling, OD: operative delivery.

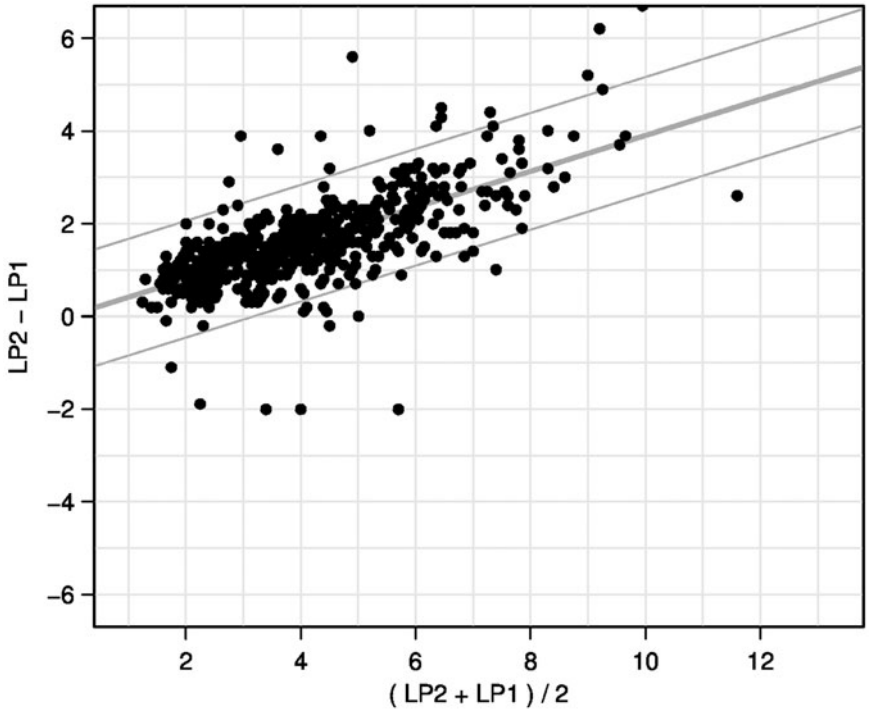

Figure 1. Bland Altman graph showing the agreement between the two methods.

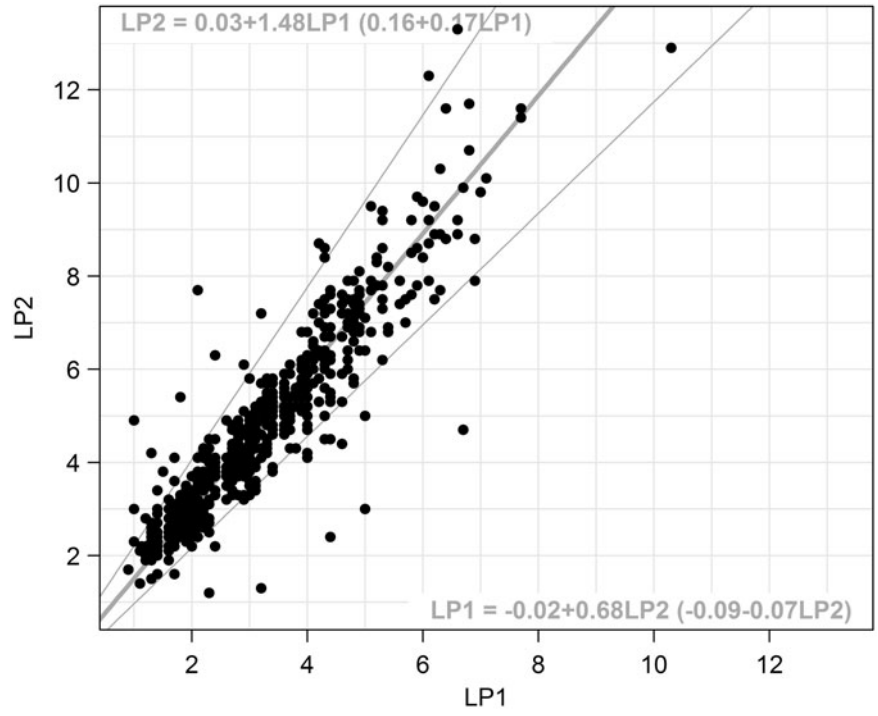

Figure 2. Scatterplott with conversion line and 95% prediction limits between Lactate Pro™ (LP) and Lactate Pro™2 (LP2).

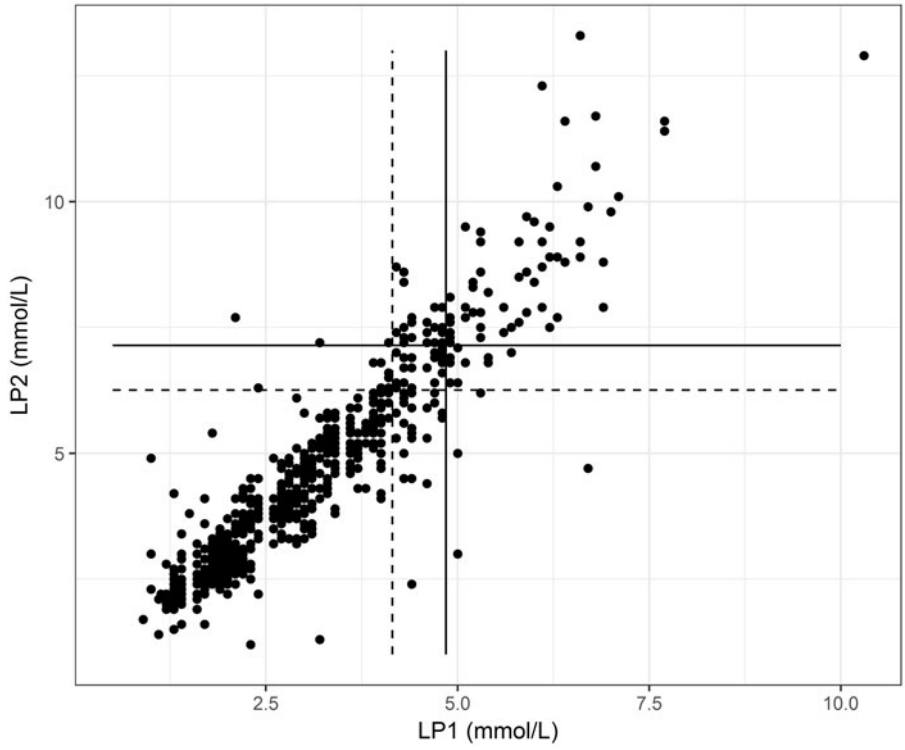

Figure 3. Scatterplott of 701 scalp lactate values measured with LP and LP2. Vertical and horizontal lines showing reference values for normality and acidosis with LP, respectively, LP2.

$p < .0001$, 95% CI: 0.24, 0.50, respectively, $r = 0.33$, $p < .0001$, 95% CI: 0.19, 0.46). The inter-relationship of FBS-lactate measured by LP2 and lactate in umbilical cord blood was dependent on the time from FBS to delivery: within 0−15 min, $r = 0.43$ (95% CI: 0.16, 0.63), 16–30 min, $r = 0.25$ (95% CI: 0.04, 0.43). Between 31 and 60 min, there were too few samples to allow analysis. Values measured with LP1 showed the same tendency (results not shown).

We got coincidental information about the maternal temperature in 93 cases and of those 43 women had a temperature of 38 °C or more. The mean and median scalp blood lactate values measured by LP were 3.6 mmol/L, respectively, 3.4 mmol/L in women with fever compared with 3.9 mmol/L, respectively, 3.6 mmol/L in women without fever ($p = 0.33$). We found a stronger correlation of scalp blood lactate to lactate in umbilical cord blood in women with temperature of 38 °C or more, compared with women without fever. This was true for both devices LP: $r = 0.67$ (95% CI: 0.21, 0.89) versus $r = 0.42$ (95% CI: −0.07, 0.75), LP2: $r = 0.71$ (95% CI: 0.28, 0.90) versus $r = 0.26$ (95% CI: −0.29, 0.68).

The CV for LP2 was calculated from five different cord blood samples with lactate levels ranging from 3.5 to 11.2 mmol/L and varied between 4.2 and 23.4% (Results not shown). For lactate concentration 6.9 mmol/L which is the closest value to the newly recommended cutoff value, the CV was 7.2%.

In 83 cases (12%), the lactate values were over the cutoff for acidemia with use of LP, but only 71 (10%) cases when lactate was measured with LP2. The sensitivity and the specificity for acidemia and normality in comparison with LP were calculated firstly using the algorithms suggested by our group and then using the previous published algorithms [1]. The sensitivity for acidemia calculated by our algorithm was (0.803 (95% CI: 0.691, 0.888) versus 0.761 (95% CI: 0.645, 0.854)) and the specificity with our algorithm (0.959 (95% CI: 0.940, 0.973) versus 0.975 (95% CI: 0.959,0.985)). In regards of normality, there were only small differences in sensitivity, respectively, specificity when calculated with the two formulas (0.789 (95% CI: 0.712, 0.853)) versus (0.775 (95% CI: 0.697, 0.840)), respectively (0.980 (95% CI: 0.965, 0.990) versus 0.986 (95% CI: 0.972, 0.994)), respectively, table not shown.

Discussion

It is highly important to emphasize that lactate meters from different manufacturers and even different models from the same manufacturer measure lactate differently. Introduction of a new lactate meter into clinical management requires testing for its analytical performance. Neonatal intrapartum hypoxia is a rare event emphasizing the need of a large study group. Also, to avoid overseeing an already existing fetal hypoxia, there must be no false negative results.

From our conversion equation, we propose the following cutoff values for LP2: lactate <6.3 mmol/L = normality, lactate >7.1 mmol/L = acidemia. By using our cutoff value for LP2, the number of false negative results in relation to LP was lower compared with previously published cutoffs [8].

Measurement of scalp lactate is regarded as a validated tool for intrapartum fetal monitoring by most of the obstetrical societies. Traditionally, pH was analyzed, but because of the high failure rate due to the relatively large amount of blood needed, as well as the risk of coagulation in the syringe before analyzing the blood with the stationary blood gas analyzer and the common logistics at many delivery departments, measurement of bed-side lactate has become an attractive alternative [6]. Although rarely highlighted, the internationally recommended cutoffs are based on measurement with LP and, for this reason, these reference intervals are only valid for LP. Also, LP and LP2 are designed for the use in adult athletes but adult whole blood and fetal blood have different physiological features. Fetal cord blood has a higher hematocrit value compared with adult blood [11]. The reference range for hematocrit at birth among term neonates is 42–65% as shown in a study which is both a wider range and higher values than adults [12]. Lactate levels measured in whole blood depend on the hematocrit value [13]. In a study by Professor Niels Fogh Andersen, Copenhagen, (unpublished data), three tubes were filled with adult venous whole blood. The hematocrit (%) was manually increased from (1) 47 to 66, (2) 39 to 59, and (3) 43 to 71. When lactate was measured by LP, a decrease was observed. The observed differences were 42%, 34%, and 45%. Consequently, one can fear that measurements of lactate with LP or LP2 can eventually mask a fetal acidemia since a high hematocrit value leads to false low lactate values. Several POC devices have been launched but to our knowledge only one of them adjusts for the hematocrit value [14]. This new device is shown to be reliable with a low failure rate but with discrepancies between the absolute lactate values when measured by a stationary blood gas analyzer [7]. The discrepancies in absolute values may be explained by the fact that the POC analyzes lactate in whole blood with intact erythrocytes whereas the stationary blood gas analyzer analyses lactate in plasma [7,15]. Further studies addressing this specific issue is therefore required.

In our study, the reproducibility of LP2 was low with a coefficient of variation ranging 4.2–23.4% implying a high risk of misinterpretation. For instance, in a clinical situation with a lactate value close to the cutoff for acidemia 6,9 mmol/L the true value can be between 6.4 and 7.4 mmol/L, where both the false too low or too high lactate value can affect further management of labor in a negative way. The correlation

between LP2 lactate within 60 min before delivery and umbilical cord artery lactate was low. Interestingly, but not surprisingly, the inter-relationship of FBS-lactate measured by LP2 and lactate in umbilical cord artery blood was found to be dependent on the time from FBS to delivery with increased correlation the closer FBS was performed to delivery.

Surprisingly we found no significant differences in lactate values in cases with or without fever. Lactate is a marker of the degree of anaerobic metabolism but also a diagnostic predictor for sepsis in both adults and children [16,17]. Thus, if a maternal fever is present, it is, therefore, speculated whether scalp lactate can be used as a reliable predictor for intrapartum hypoxia. Also, we found no significant difference in Apgar scores or umbilical artery pH between cases with and without fever. There was no report of severe infection or sepsis in any of the patients with high temperatures. However, except for a few cases, women with fevers also had epidurals. Numerous studies have shown an association between epidural and maternal/fetal fever, but the causal relationship is not yet understood [18,19]. Fever shifts the oxyhemoglobin dissociation curve to the right and, therefore, could result in less oxygen delivery to the fetal tissues, resulting in an increased anaerobic metabolism and increased scalp lactate as shown in a study by Wiberg and Kallen [20]. Due to the limited number of patients involved in the study, this issue needs to be addressed in the future.

Strengths and limitations

We analyzed a large number of samples simultaneously using both LP and LP2 which improved statistical calculations. The indication for FBS and further obstetrical management were comparable in the two labor wards. Even though we had a large number of paired samples, in a few cases, FBS was repeated on the same fetus, thus the total number of included laboring women was lower $n = 466$. For this reason, the data are insufficient to correlate the scalp blood lactate value to severe neonatal outcomes, such as hypoxic ischemic encephalopathy since it is a rare event. The suggested cutoffs are, therefore, created from the pre-existing cutoffs for LP converted for LP2, thereby passing on the uncertainty from one POC device to another.

Conclusion

We propose the following cutoffs for LP2; scalp lactate <6.3 mmol/L = normal, no indication for intervention; 6.3–7.1 mmol/L = preacidemia, repeated testing must be considered; >7.1 mmol/L = acidemia, expedite delivery. However, LP2 cannot be recommended as a reliable tool to assess intrapartum fetal well-being due to its high coefficient of variation, and since it does not adjust for the hematocrit value. The correlation between LP2 lactate and cord artery lactate was stronger for samples taken closest to delivery. Whether measurement of scalp lactate in case of maternal fever is a reliable method for monitoring the fetus intrapartum needs to be addressed in further studies.

Acknowledgements

The authors are grateful to all the midwives and assistant nurses for their enthusiasms to double analyze and to Medexa AB who kindly provided the LactatePro™2 devices with test strips. The authors are also grateful to professor Nils Fogh Andersen, Copenhagen, who showed the importance of hematocrit interference and gave us his consent to use his unpublished data.

Disclosure statement

The authors declare they have no conflicts of interest to disclose. Medexa AB did not have any influence on the study design, analyzing and interpreting data or on writing the article.

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