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Abstract: INTRODUCTION Umbilical artery cord blood provides information about the intrauterine metabolism during labor. Umbilical artery lactate is a useful parameter in predicting neonatal morbidity, but data on normal values are limited. We aimed to provide reference ranges of umbilical artery lactate values across the combination of gestational age and mode of delivery. METHODS A single-center retrospective observational study of liveborn infants born between 23 and 42 completed weeks gestation was conducted. Lactate, base deficit (BD), and pH from arterial cord blood were assessed between June 2018 and November 2020 and compared across gestational ages and modes of delivery. RESULTS Overall, there were 3,353 infants with evaluable data. Lactate values at the 50th, 90th, and 97th percentile were 3.4, 7.0, and 9.0 mmol/L. Lactate was inversely correlated with pH ($r = -0.77$, $p < 0.001$) and positively correlated with BD ($r = 0.63$, $p < 0.001$). Lactate values changed significantly across gestational age (Kruskal-Wallis test, $p < 0.001$) which was attributable to an increase in lactate at 39-41 weeks gestational age. Also, lactate values were different across modes of delivery (Kruskal-Wallis test, $p < 0.001$) with lowest values in elective CS and highest values in vaginal instrumental deliveries. Comprehensive reference ranges across modes of delivery and gestational ages could be established. DISCUSSION Mode of delivery and gestational age contribute to lactate levels with highest values occurring in vaginal instrumental deliveries and between 39 and 41 weeks gestational age. Based on these observations, we provide detailed reference ranges for clinical use.

Reference Values for Umbilical Artery Lactate by Mode of Delivery and Gestational Age: A Retrospective Observational Study

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Abstract

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Introduction

Umbilical artery cord blood provides information about the intrauterine metabolism during labor [1]. Acidosis is defined by a pH < 7.35 while base deficit (BD), partial pressure of carbon dioxide (pCO_2), and lactate indicate the origin of the acidosis [2]. The acid-base status is useful to ensure appropriately focused interventions in case of severe acidosis (i.e., pH < 7.00 and/or BD of ≥16.0 mmol/L) and to predict increased morbidity and mortal-

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ity [3]. Lactate was superior to pH in predicting neonatal morbidity in case-control and prospective cohort studies [4–6], and sensitivity and specificity of umbilical artery lactate for neurological sequelae were 70% and 93%, respectively [7, 8]. Reference ranges of lactate values in newborn infants would be useful in distinguishing infants who may need additional clinical examination, laboratory work, or intensive care monitoring.

Umbilical artery lactate after vaginal delivery increases gradually from 34 weeks gestational age onward [9]. In a small population of term infants, lactate values were highest in vaginal instrumental deliveries (VID) and lowest in elective cesarean section (eCS) [10]. However, increased umbilical artery lactate may reflect infant pathologies such as an incipient sepsis or cardiac anomalies. Comprehensive reference ranges across the combination of mode of delivery and gestational age may assist clinicians to integrate lactate values into clinical considerations.

Thus, we aimed to (1) assess the umbilical artery acid-base status and (2) provide combined reference ranges for umbilical artery lactate by gestational age and mode of delivery. We expected higher values in vaginal deliveries and emergency cesarean sections as well as an increase in lactate in more mature infants. Finally, we intended to (3) show the distribution of lactate values for healthy term infants separately who are cared for on the regular postnatal ward.

Methods

Data Collection

This was a retrospective observational study at the Department of Obstetrics and the Department of Neonatology of the University Hospital Zurich, a tertiary referral center with approximately 3,000 births per year. Umbilical artery cord blood is drawn as a routine measurement at our hospital for decades. In June 2018, our clinic started to store values electronically. Immediately after delivery, a midwife drew blood from the umbilical artery in a pre-heparinised syringe (safePICO Aspirator; Radiometer Medical ApS, Brønshøj, Denmark), and the blood was analyzed within 10 min using the ABL815 FLEX blood gas analyzer (Radiometer Medical ApS, Brønshøj, Denmark). Lactate, pH, and pCO_2 were measured directly by using the blood gas analyzer while BD was calculated based on the Henderson-Hasselbalch equation and the Siggaard-Andersen acid-base chart algorithm. Lactate was measured via amperometry using an electrode coated with lactate oxidase which converts lactate to pyruvate and hydrogen peroxide, and the resulting hydrogen peroxide is measured amperometrically [11]. Obstetric and neonatal data were collected and stored using the local patient management system and anonymized before analysis. All infants who were born between June 2018 (beginning of digital data collection) and November 2020 in the University Hospital Zurich were eligible for inclusion in the analysis. Infants were included if arterial cord blood data were available and mothers had provided a written informed general consent to allow use of their clinical and laboratory data for research purposes.

Data Analysis

First, we extracted values of acid-base status for all infants. Second, we assessed correlation between lactate, pH, and BD. Third, we assessed lactate values for completed weeks of gestation (between 23 and 42 weeks). Fourth, we evaluated changes in lactate values across different modes of delivery. We predefined the following modes of delivery: spontaneous vaginal delivery, VID (i.e., forceps or vacuum extraction), eCS without prior contractions, and unplanned or emergency cesarean section after the onset of uterine contractions (uCS). We then assessed the correlation of arterial cord lactate with cardiotocogram (CTG) readings (based on the 2015 FIGO intrapartum CTG classification) in the opening and the expulsion stage of labor to evaluate the potential influence of prenatal factors. Fifth, for the calculation of reference ranges, infants were separated into generally acknowledged age groups (extremely preterm infants [$\leq 27^{6/7}$ weeks], very preterm infants [$28^{0/7}-31^{6/7}$ weeks], moderately preterm infants [$32^{0/7}-33^{6/7}$ weeks], late preterm infants [$34^{0/7}-36^{6/7}$ weeks], and term born infants [$\geq 37^{0/7}$ weeks]), and we calculated percentiles for each combination of gestational age groups and mode of delivery. Finally, we calculated percentiles for healthy term infants separately. We categorized infants as healthy if they did not receive additional monitoring during their hospital stay after assessment and examination by a pediatrician. Infants with a pH < 7.0 were always admitted to the neonatal unit and thus excluded from this subgroup.

Statistical Analysis

We calculated percentiles, including median and interquartile range (IQR), for each group of infants. Differences over gestational age groups and within the different modes of delivery were assessed using a Kruskal-Wallis test for the overall difference. In case of a significant global difference, we performed post hoc comparisons between separate groups (i.e., gestational age or mode of delivery) using pairwise Wilcoxon tests with Bonferroni-Holm correction for multiple testing. Correlation between separate parameters was assessed using Pearson's correlation. A p-value <0.05 was considered statistically significant.

Results

Population

Overall, 6,136 infants were born alive during the study period. Of these, 52 had to be excluded as no cord blood values were available and for 2,731 infants there was no general consent available, leaving 3,353 infants for primary analysis. Demographics and descriptive statistics of the population are provided in Table 1.

Acid-Base Status

Median (IQR) values for pH, lactate, and BD are provided in Table 1. Across all infants, lactate values at the

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Table 1. Population characteristics including arterial cord blood values in all infants and in clinically healthy term infants

	Included infants (N = 3,353)
Population characteristics, median (range)	
Gestational age, weeks + days	$38^{6/7}$ ($24^{0/7}$–$42^{1/7}$)
Birth weight, g	3,200 (450–4,870)
Male sex, N (%)	1,719 (51.3)
Obstetric information: mode of delivery, N (%)	
Spontaneous vaginal	1,368 (40.7)
Vaginal instrumental	341 (10.2)
Elective cesarean section	909 (27.1)
Unplanned cesarean section	735 (21.9)
Perinatal infant characteristics	
Apgar at 1 min	8 (0–10)
Apgar at 5 min	9 (1–10)
Apgar at 10 min	9 (1–10)
Arterial cord pH	7.29 (6.76–7.54)
Arterial cord lactate, mmol/L	3.4 (0.1–22.0)
Arterial cord base deficit, mmol/L	2.3 (−12.1 to 27.8)

Where not otherwise specified, median and range are provided.

3rd, 10th, 90th, and 97th percentile were 1.0, 1.8, 7.0, and 9.0 mmol/L, respectively. Mean (±1z) lactate was at 4.0 (±2.3). There was a strong inverse correlation between lactate and pH ($r = -0.77$, $p < 0.001$) as well as BD and pH ($r = -0.58$, $p < 0.001$) while lactate and BD correlated positively ($r = 0.63$, $p < 0.001$; Fig. 1).

Lactate Values across Gestational Age

Lactate values changed significantly across gestational age (Kruskal-Wallis test for overall difference: $\chi^2 = 480$, $p < 0.001$; Fig. 2). Post hoc analyses revealed that differences were mainly due to an increase in lactate at 39–41 weeks gestational age (online suppl. Table 2; see www.karger.com/doi/10.1159/000518748 for all online suppl. material).

Lactate Values across Mode of Delivery

Lactate values were significantly different between each of the 4 modes of delivery (Kruskal-Wallis test for overall difference: $\chi^2 = 1,241$, $p < 0.001$; Fig. 3). Lowest lactate values were seen in eCS and highest values in VID (all $p < 0.001$ in post hoc analyses; online suppl. Table 1). The range of lactate values was the highest in uCS reaching values >20 mmol/L. Lactate values were highly correlated with CTG readings during the expulsion stage ($r = 0.33$, $p < 0.001$) but not during the opening stage of labor ($r = 0.03$, $p = 0.13$).
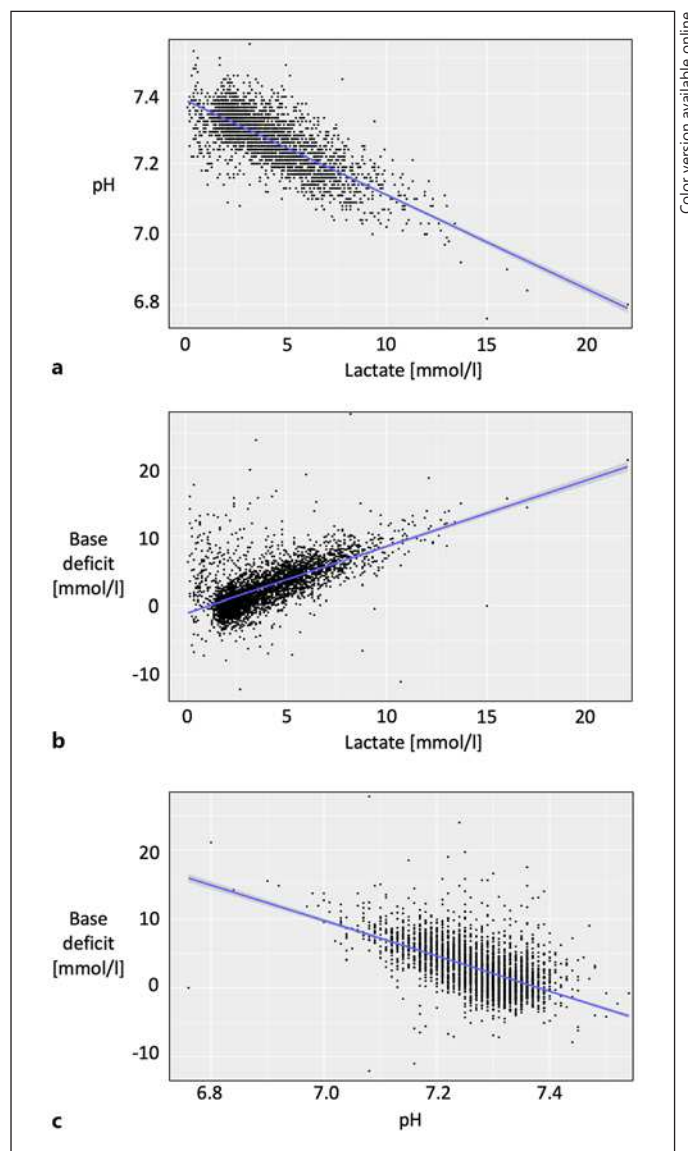

Fig. 1. Correlation between pH, lactate, and base deficit. Dots indicate single patients. The blue line shows the linear regression line with standard errors plotted as gray error lines.

Reference Ranges across Mode of Delivery and Gestational Age

Table 2 provides reference ranges by predefined gestational age groups as well as birth mode, and Figure 4 illustrates the changes.

Lactate Values in Healthy Term Infants

After exclusion of preterm infants and infants who were admitted to the neonatal ward, 2,656 infants remained for subgroup analysis of healthy term infants. For those infants, the lactate values at the 3rd, 10th, 90th, and
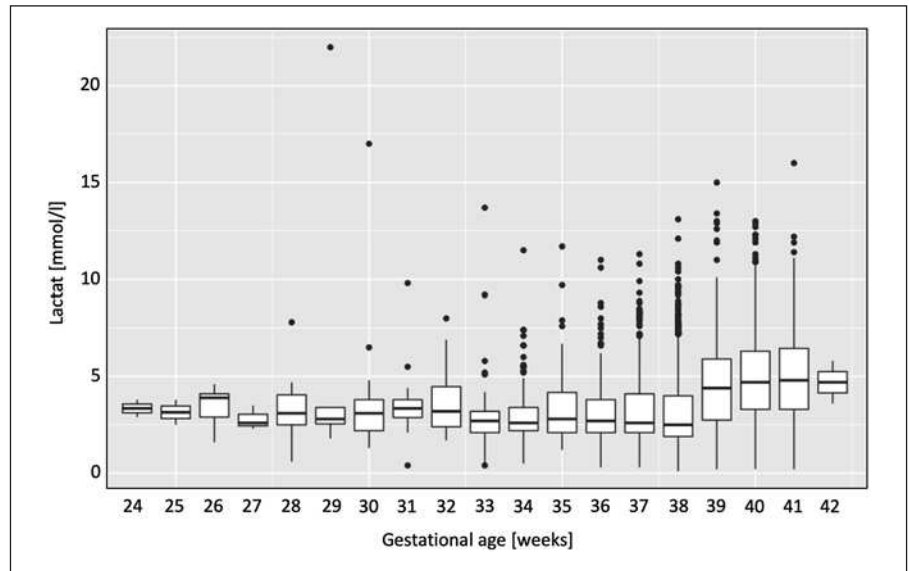
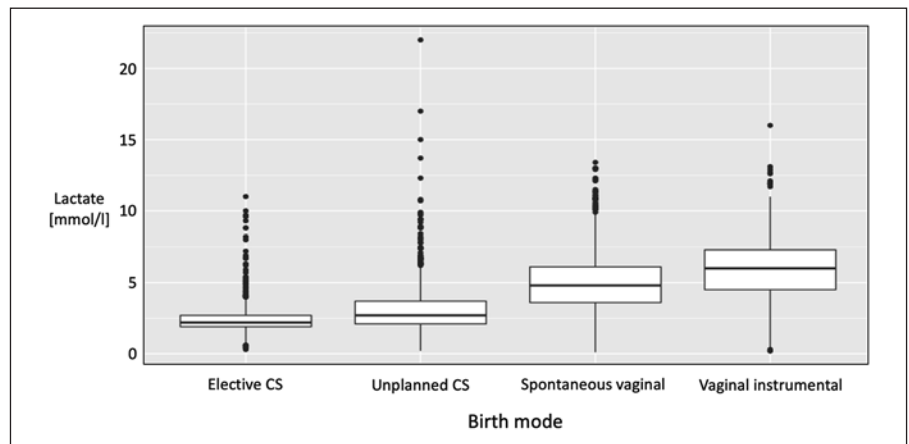**Fig. 2.** Umbilical artery lactate values across weeks of gestational age.

Fig. 3. Umbilical artery lactate values across different modes of delivery. All comparisons between single modes of delivery were significantly different (all $p < 0.001$). CS, cesarean section.

97th percentile were 1.0, 1.7, 7.2, and 9.0 mmol/L, respectively, and the mean ($\pm 1z$) was 4.1 (± 2.2). For term infants admitted to the neonatal unit ($N = 191$), the lactate values at the 3rd, 10th, 90th, and 97th percentile were 0.8, 1.8, 7.4, and 10.8 mmol/L, respectively, and the mean ($\pm 1z$) was 4.3 (± 2.8).

Discussion

This study comprehensively assesses umbilical artery lactate across gestational age as well as mode of delivery. We saw that lactate values were influenced by gestational age and mode of delivery: highest lactate values were seen in VID and in infants born between 39 and 41 weeks gestation. We provided detailed combined reference ranges for gestational age groups and modes of delivery for clinical use.

Increasing gestational age is associated with a mixed metabolic acidosis after birth [12]. Wiberg and colleagues [9] showed a gradual increase in umbilical artery lactate from 34 completed weeks gestation onward in vaginal deliveries. Opposed to these findings, we showed that the increase in lactate values is restricted to infants born between 39 and 41 completed weeks gestation. This difference may be due to the inclusion of VID in our study. Indeed, we demonstrated that lactate values in eCS remain comparable across gestational age, and thus the increased risk of metabolic acidosis in full term infants may be mostly due to mode of delivery.

We demonstrated that lactate values vary across different modes of delivery with an incremental increase from

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Table 2. Percentiles of lactate values across gestational age groups and mode of delivery

Group	N	Percentile					z-scores		
		3rd	10th	50th	90th	97th	−1z	mean	+1z
Extremely preterm	14	1.8	2.2	3.6	4.2	4.5	2.3	3.3	4.2
Elective CS	5	1.7	2.0	2.6	4.3	4.5	1.8	3.0	4.2
Unplanned CS	9	2.1	2.3	3.7	4.0	4.2	2.6	3.4	4.1
Spontaneous vaginal	0	–	–	–	–	–			
Vaginal instrumental	0	–	–	–	–	–			
Very preterm	53	1.0	2.1	3.2	5.4	13.0	0.4	3.9	7.4
Elective CS	19	0.5	1.6	2.7	3.8	4.6	1.6	2.7	3.8
Unplanned CS	31	2.0	2.3	3.4	7.8	17.5	0.3	4.6	9.0
Spontaneous vaginal	3	–	–	–	–	–			
Vaginal instrumental	0	–	–	–	–	–			
Moderately preterm	63	0.8	1.6	2.8	5.4	8.2	1.2	3.3	5.4
Elective CS	15	2.1	2.1	2.8	4.1	5.1	2.0	3.0	3.9
Unplanned CS	41	0.6	1.2	2.8	5.2	7.7	0.9	3.2	5.5
Spontaneous vaginal	6	2.1	2.3	4.3	8.1	8.9	2.0	4.9	7.7
Vaginal instrumental	1	–	–	–	–	–			
Late preterm	374	1.5	1.8	2.7	5.8	7.5	1.5	3.3	5.0
Elective CS	119	1.4	1.7	2.4	3.5	4.6	1.6	2.6	3.6
Unplanned CS	172	1.5	1.8	2.5	3.8	5.8	1.7	2.7	3.8
Spontaneous vaginal	72	2.0	2.8	5.0	7.5	8.5	3.1	5.0	7.0
Vaginal instrumental	11	3.5	3.9	6.1	11.0	11.5	4.2	7.1	9.9
Term born	2,847	1.0	1.7	3.7	7.2	9.1	1.8	4.1	6.4
Elective CS	751	1.4	1.6	2.2	3.3	5.2	1.3	2.4	3.6
Unplanned CS	482	1.1	1.8	2.8	5.5	8.3	1.5	3.3	5.2
Spontaneous vaginal	1,285	0.8	2.4	4.8	7.6	9.3	2.8	4.9	7.0
Vaginal instrumental	329	1.1	3.3	6.0	8.8	11.0	3.5	6.0	8.4

The 3rd, 10th, 50th, 90th, and 97th percentile as well as z-scores are shown. Only percentiles for groups of at least 5 infants are shown. All values are shown as millimoles per liter. CS, cesarean section.

eCS via unplanned CS and spontaneous vaginal to VID where lactate values were the highest. This is comparable to recent findings from smaller studies [10, 13]. We propose 2 mechanisms for these findings: first, delayed cord clamping contributes to increased lactate by prolonging the time until blood sampling [13, 14], which may have contributed to higher values in vaginal deliveries. Second, various peripartal risk factors (e.g., uterine rupture, placental abruption, chorioamnionitis, and pre-eclampsia) may have contributed to higher lactate values. Indeed, this is substantiated by the correlation of arterial cord lactate with CTG readings during expulsion stage. Third, uterine contractions contribute to a surge in stress hormones [15], which is thought to assist in clearing fetal lung liquid thereby improving neonatal transition [16]. eCS is associated with less fetal stress, as indicated by the lowest lactate values in our cohort. However, the lack of uterine contractions may be associated with a higher risk for admission to NICU, mostly due to respiratory distress

[17]. This suggests that low lactate values are not necessarily desirable, and limited perinatal stress may be beneficial for the infant. In fact, there is an ongoing trial examining whether inducing mild fetal stress by administering oxytocin before eCS may reduce the admission rate of newborns [18]. However, trial results need to be awaited before firm conclusions of the potential benefit of mild fetal stress can be drawn.

Higher lactate values during instrumental vaginal and unplanned cesarean delivery may be explained by fetal distress during obstructed labor [19]. Interestingly, lactate values in unplanned CS were very variable with the upper range exceeding 20 mmol/L. A permissive approach to managing the second stage of labor reduced the rate of CS at the cost of an increased rate of maternal (third- and fourth-degree lacerations) and neonatal (shoulder dystocia, admission to the NICU, and arterial cord pH < 7.00) morbidities [20]. Our data may provide some guidance for decision-making during labor based
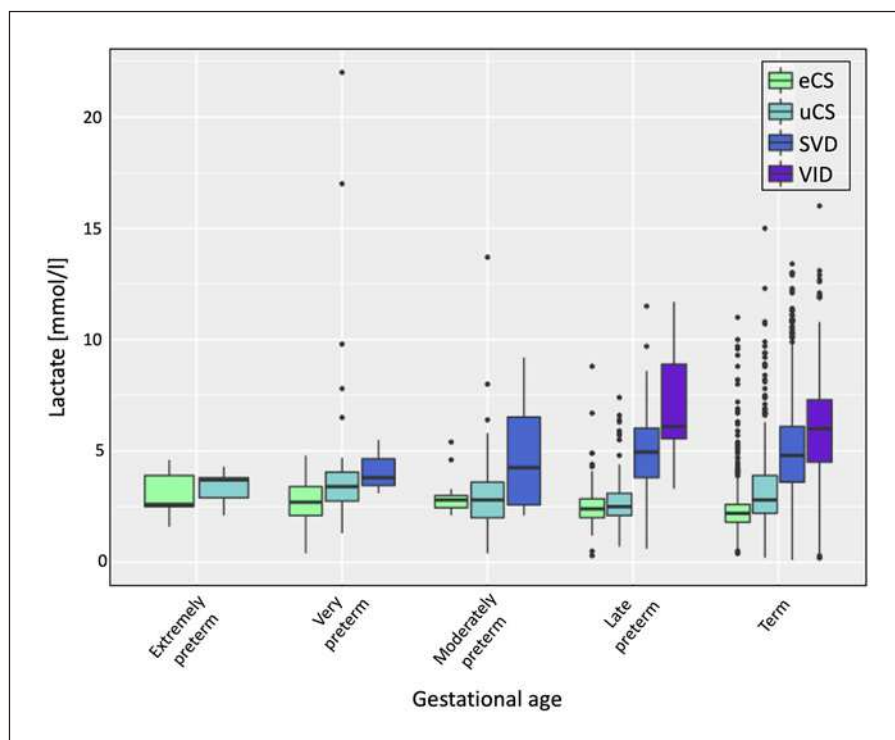
Fig. 4. Lactate values by gestational age and birth mode across all infants. The *x*-axis shows different gestational age groups, and colored boxplots indicate different modes of delivery as described in the legend in the upper right corner. Boxplots show median and interquartile range. eCS, elective cesarean section; uCS, unplanned or emergency cesarean section; SVD, spontaneous vaginal delivery; VID, vaginal instrumental delivery.

on fetal blood sampling. However, the results cannot be directly extrapolated, and the infant's and mother's situation during labor has to be evaluated carefully to assess the necessity of additional interventions.

Recently, it was argued that the definition of neonatal lactic acidosis should be based on gestational age-dependent values [9, 21]. In this study, we outlined reference values for lactate by simplified and generally acknowledged gestational age groups and across modes of delivery thereby providing simple reference tables for clinical use. As increased lactate values may reflect various infant pathologies, these reference ranges may be helpful to integrate umbilical artery lactate into clinical considerations. It is important to note that lactate is not just an alternative measure of the pH, but due to its metabolic involvement, its clinical significance is also dependent on the respective tissue, as well as oxygen tension and blood flow [22]. Clinically, it has been shown that lactate is superior to pH in predicting intrapartum asphyxia [6]. We suggest to re-evaluate all infants with a lactate value above their respective gestational age and mode of delivery specific 90th percentile by clinical examination and blood gas analysis within the first hour after birth. However, our study was not designed to assess sensitivity and specificity of these specific cutoff values, and subsequent prospective studies are needed.

Healthy term infants are not regularly examined by a pediatrician after birth. In this large observational study, healthy infants had median lactate values of approximately 3.5 mmol/L, and the 97th percentile was 9 mmol/L, indicating that some infants can recuperate well from perinatal stress if their transition to extrauterine life after birth is smooth. However, it has to be noted that some infants may deteriorate further after birth, emphasizing the necessity for a thorough clinical assessment of infants with acidotic metabolism during labor. Arterial cord lactate of infants admitted to the neonatal unit was similar to values of healthy infants. As there are various reasons for admission to the NICU, this finding demonstrates further that lactate values alone are insufficient to guide neonatal interventions, and laboratory evaluations need to be accompanied by a thorough clinical examination.

This study has several limitations: First, in a retrospective observational study, it is impossible to draw causal conclusions. In the absence of clear guidelines, we speculate that clinical consequences to lactate values were little (except for pH values <7.00), thus strengthening the value of this study. There are various perinatal factors contributing to lactate levels in newborns. However, the description of lactate values in a large dataset provides detailed reference ranges which will help clinicians to guide decision-making and interventions irrespective of the under-

lying cause of elevated lactate levels. Second, the number of infants in separate gestational age groups was limited, particularly for extremely and very preterm infants. Therefore, we pooled the data by generally acknowledged age groups to increase reliability and clinical usability. Also, percentiles generated using this dataset may be most relevant for more mature infants (i.e., late preterm and term infants) which can be cared for on the regular postnatal ward. For these groups, the number of infants is sufficient to provide reliable results. Third, we only had general consent present for just over half of all infants born during the study period. While a higher number of included infants would have been preferable, there is no reason to assume systematic error based on the presence of a general consent. Fourth, this was a single-center study, and we cannot be certain that values can be extrapolated to other departments due to differing guidelines. Fifth, time of cord clamping was not recorded in our hospital. As the general relationship between cord clamping and arterial cord lactate has already been described [13, 14], our study now complements previous data by showing variations in lactate values across different modes of delivery. Finally, we did not assess clinical outcomes such as short- and long-term neurological outcome or mortality. The association of lactate with short-term neurological outcome has already been demonstrated [7], and the scope of this study was to provide reference ranges of lactate values across gestational age and modes of delivery.

Conclusion

In this retrospective observational study, we evaluated lactate values across modes of delivery and gestational ages. Both factors contribute to lactate levels with highest values occurring in instrumental vaginal deliveries and between 39 and 41 weeks gestational age. Based on these observations, we provide detailed reference ranges for clinical use.

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