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Lactic Dehydrogenase in Umbilical Cord Blood in Healthy Infants after Different Modes of Delivery

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Abstract

Background: LDH may be a valuable marker for some of the most important diseases in newborns, and umbilical cord blood is a non-invasive and easy way to obtain blood for analysis. Aims of this study were to define interval for LDH in arterial and venous cord blood at delivery in truly healthy newborns.

Method: a prospective observational study was performed at Soder Hospital, Stockholm, Sweden during 2011-2012. Umbilical cord blood was collected at delivery, and value of LDH was analysed in 549 healthy infants >37 weeks of gestation, born after an uncomplicated pregnancy from a healthy mother.

Results: The 2.5th and 97.5th percentile for arterial LDH was 162-612 u/L and 252-636 u/L for venous LDH. Instrumental delivery and acute caesarian section showed significantly higher intervals and elective caesarian section significantly lower than vaginal delivery. Haemolysis (>0.3 g/l) disqualified a 13-41% of the samples.

Conclusion: Reported LDH levels are in accordance with earlier studies and appear to be a sensitive marker for intrapartal stress factors. The absence of an arterial/venous difference makes the sampling of cord blood easier but frequent haemolysis is a problem when using the standard method of analyses.

Keywords: Healthy newborn; Asphyxia; Reference intervals; Lactate dehydrogenase

Introduction

Lactate Dehydrogenase (LDH) increases early in newborns in several critical conditions, and the LDH activity correlates well with the severity of diseases such as asphyxia [1-4] respiratory distress and Necrotizing Enterocolitis (NEC). In newborns subjected to fetal distress and/or asphyxia, plasma LDH in the first hours of life seems so far to be the best chemical predictor of Hypoxic Ischemic Encephalopathy (HIE) and its postnatal outcome in hypothermia-treated infants. Further, LDH at admission to a neonatal intensive care unit has been shown to be a good predictor of the need for intensive care procedures.

Cord blood is easily accessible immediately after birth, but reference values have only been reported for a limited number of healthy infants in which the means of excluding factors that might affect LDH in plasma are not described [3-5].

Before cord blood LDH can be considered as a new marker of severe intrapartum asphyxia and other critical conditions in obstetrical and neonatal care, reliable 95% confidence intervals in a healthy population are needed.

The aim of the present study was to provide such an interval for LDH in arterial and venous cord blood at delivery in "truly" healthy newborns.

Material and Methods

A prospective observational study of LDH in cord blood was performed at Soder Hospital of Stockholm, Sweden, during 2011. Umbilical cord blood samples were collected from all healthy deliveries during the first three months of the study. In total, 549 full-term healthy neonates (>37 weeks) born after an uncomplicated pregnancy to a healthy mother were consecutively included (see flowchart).

A healthy woman was defined as a woman without any chronic disease and with a normal, uncomplicated pregnancy. A healthy newborn at delivery was defined as a newborn delivered from a healthy pregnancy with a birth weight and length within ± 2 SD for gestational age, Apgar score >7 at 5 min after delivery, umbilical artery pH>7.10, and no need for resuscitation or transmission to the Neonatal Care Unit.

If any other ICD-10 diagnosis besides Z00.1 (routine child health examination without abnormal findings) that theoretically could influence the LDH value was given to the infant before discharge, the infant was excluded from the study (see discussion). Further, infants readmitted to hospital during the first two weeks after birth for any condition known to affect LDH were also excluded from the study.

An arterial and a venous cord blood sample were drawn from the double-clamped segment of the cord before the new-born's first cry and acid-base values were analysed immediately (ABL 800 flex®, Radiometer, Copenhagen, Denmark) according to the well-established routine of the ward. In addition, a sample of 0.4 ml of arterial (aLDH) and of venous (vLDH) blood from the cord was collected in lithium heparin tubes for the analysis of LDH. The blood samples were

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transported within five minutes to the department of clinical chemistry at the hospital, where the analysis was performed within 10 minutes of sampling. Finally all included infants were stratified due to mode of delivery to investigate if the LDH activity was increased in infants delivered by caesarian section or other intervention due to intra partum signs of fetal distress. The stratification was also performed to make sure that the reference interval was calculated solely form infants without fetal distress even in the mildest form.

Laboratory Methods

LDH can be separated into five isoenzymes, each with a different capacity for the forward and reverse reaction between pyruvate and lactate respectively, all normally found in serum. Total LDH activity is measured in routine clinical practice, and was therefore measured in this study; in this paper this is referred to as LDH. LDH was analysed by the accredited clinical laboratory at Soder Hospital of Stockholm, Sweden, using the standard procedure. The tubes were centrifuged and analysed according to the hospital protocol on the Hitachi Modular P800 instrument with LDH, IFCC reagents from Roche Diagnostics. The reaction used was: Pyruvate + NADH + H+ → Lactate + NAD+, which is the most common in routine determination of LDH activity. The initial rate of NADH oxidation is directly proportional to LDH activity in the sample. Activity is determined by photometrically measuring the absorbance. The analytic range for the equipment is 5-1000 U/L with a between-days coefficient of variation (CV) of 2.3%.

All samples were checked for the presence of haemolysis, icterus and lipid index. The haemolysis index was determined by the absorbance of the plasma used for analysis. The cut-off for clinically significant haemolysis was set at 0.3 g/L free haemoglobin in plasma in line with standard laboratory practice. All samples where these parameters exceeded the routine limits set by the department of clinical chemistry were excluded.

Statistical analyses were performed using SPSS 20.0 (SPSS Inc. Chicago, Illinois, USA), and the statistical Package Statistica for Windows, version 11.0 (Stat Soft, Tulsa, Oklahoma, USA). Background data for the mothers and their newborn were presented as frequencies (%), medians and range. Comparison between two continuous variables was tested using the Mann-Whitney U- test. Proportions were compared with the Chi-square test and in expected frequencies <5, Fisher´s exact test was used. Logistic regression was used to study the association between high levels of LDH (>=612 u/l) and each of the independent factors: parity, smoking, maternal weight, maternal age, gestational age, and way of delivery (normal vaginal, vacuum, planned cesarean section or acute cesarean). Model strategy: unadjusted associations with each factor were studied.

The difference between arterial and venous LDH in the individual cases was calculated using a Bland-Altman plot (Figure 1). Written informed consent for participation in the study was obtained for all participants. The study was approved by the Karolinska Institute Human Research Ethics Committee (file record: 2011/218-32).

Results

During the study period, 549 infants fulfilling the inclusion criteria were enrolled in the study. Hemolysis in the venous or the arterial sample was frequently seen and LDH values were available for analysis from 70.1% (385/549) arterial and 79.4% (436/549) venous samples. After excluding deliveries with haemolysis in both samples (n=63), 486 remaining deliveries, with at least one sample of LDH, constituted our material for the study (Figure 2).

The background characteristics of the population are presented in Tables 1 and 2. 83% (455/549) of the deliveries included had a spontaneous vaginal delivery; 8% (45/549) were delivered by vacuum extraction and 9% (49 /549) by caesarean section, 11/49 had a planned caesarean section, and 38/49 were delivered with an acute caesarean section during ongoing labor. The two most common reasons for acute operative intervention (abdominal or vaginal) were labor dystocia in 43% (41/95) and non-reassuring cardiotocographic (CTG) patterns [6-9] in 37% (35/95). During the study period, 279 elective caesarean sections were performed for various reasons, but LDH was

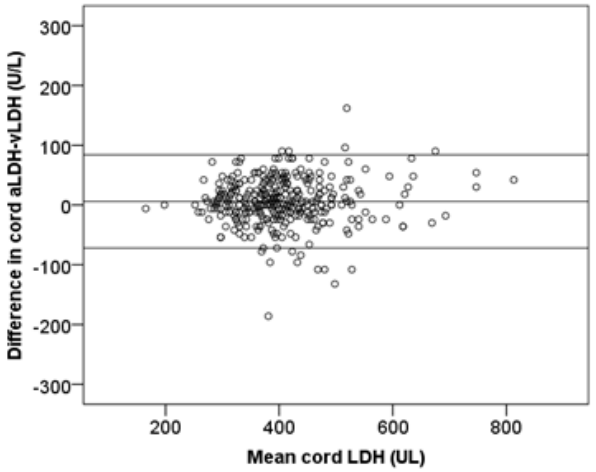

Figure 1: Bland Altman plot of individual differences between arterial and venous cord blood LDH.

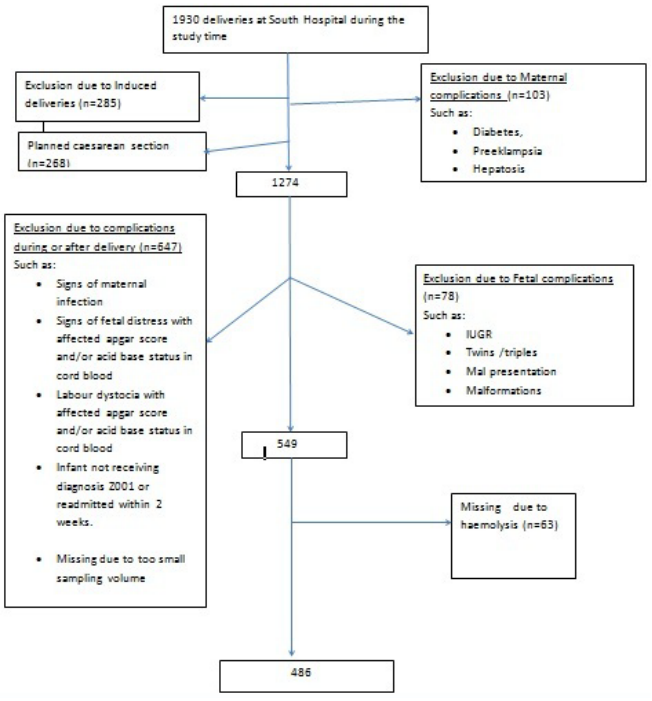

Figure 2: Flow chart.

	LDH obtained (n= 486)	Haemolysis (n=63)	p-value*
Age (years)	33 (19-48)	32 (17-41)	0.4
Nullipara (%)	238 (49.0)	40 (63.5)	0.04
Smokers (%)	56 (11.5)	11 (17.5)	0.02*
Weight (kg)	62 (41-136)	67 (48-105)	<0.001*
Height (cm)	167 (150-185)	167 (153-192)	0.4
* P-value <0.05 is considered as statistically significant difference			

Table 1a: Characteristics of the 486 mothers of newborns with haemolysis under 0.3g/L free Haemoglobin in plasma in at least one sample (LDH obtained) respectively, compared to 63 mothers of newborns with haemolysis over 0.3g/L in both samples (LDH obtained). Values in medians and ranges or %.Values are numbers (%) or medians (range).

	Low levels of LDH (<612u/l, n= 470)	High levels of LDH (>= 612u/l, n=16)	p-value
Age (years)	33.0 (20-48)	32.0 (19-45)	0.8
Nullipara (%)	229 (48.7)	9 (56.3)	0.6
Smokers (%)	55 (11.7)	1 (6.3)	0.5
Weight (kg)	62 (41-136)	63.5 (51-99)	0.5
Height (cm)	167 (150-185)	167 (156-178)	0.7
* P-value <0.05 is considered as statistically significant difference			

Table 1b: Characteristics of the 486 mothers of newborns with high/low values of LDH in cord blood at delivery. Values in medians and ranges or %.

	LDH obtained (n= 486)	Haemolysis (n=63)	p-value*
Gender, male (%)	253 (52.0)	33 (53.4)	0.8
Gestational age (days)	281 (252-296)	282 (261-295)	0.09
Birth weight (gram)	3610 (2360-4815)	3577 (2625-5055)	0.9
Height (cm)	51 (45-56)	51 (46-56)	0.7
Head circumference (cm)	35 (32-39)	35 (31.5-38)	0.8
Presentation (Occiput anterior %)	453 (98.5)	62 (98.4)	0.6
* P-value<0.05 is considered as statistically significant difference			

Table 2a: Characteristics of the 486 newborns with haemolysis under 0.3g/L free Haemoglobin in plasma in at least one sample (LDH obtained) respectively, compared to 63 mothers of newborns with haemolysis over 0.3g/L in both samples (LDH obtained). Values in medians and ranges or %.

	Low levels of LDH (<612u/l, n= 470)	High levels of LDH (>=612u/l, n= 16)	p-value*
Gender, male (%)	247 (52.5)	9 (56.3)	0.8
Gestational age (days)	281 (252-296)	283 (275-293)	0.1
Birth weight (gram)	3610 (2360-4815)	3717 (2925-4215)	0.3
Height (cm)	51 (45-56)	51 (50-52)	0.8
Head circumference (cm)	35 (32-39)	35 (33-38)	0.5
Presentation (Occiput anterior %)	439 (93.4)	14 (87.5)	0.3
*P-value <0.05 is considered as statistically significant difference			

Table 2b: Characteristics of the 486 newborns with a high or low values of LDH I cord blood at delivery. Values in medians and ranges or %.

only determined in 11 where the indication for caesarian section was maternal anxiety regarding a vaginal delivery in a healthy mother and fetus (Tables 1 and 2).

The median value of aLDH among all included deliveries was 403 u/l and 402 u/l for vLDH. The 2.5th and 97.5th percentile for aLDH was 162-612 u/L and 252-636 for vLDH (Table 3). A high LDH was set to 612 u/l in our calculations according to the value of 97.5th percentile (Table 3).

Significantly higher intervals for aLDH were shown in cord blood from infants delivered by acute caesarian section (Table 3) compared to vaginal deliveries (Table 3). In the group delivered by vacuum extraction both aLDH and vLDH were increased compared to spontaneous vaginal deliveries (Table 3, p <0.001) and elective caesarian section, but no difference between acute caesarian section and vacuum extraction was found (Table 3, p=0.2). A clinically significant lower LDH activity was found in the group of infants delivered by elective caesarian section compared to the other groups (Table 3). There was no difference in aLDH or vLDH between the infants with Apgar score 7-8 vs.9-10 (p=0.5) or between infants with pH (a) in cord blood between 7.10 to 7.20 and pH >7.20 (p=0.8).

In the total material a Bland-Altman analysis showed a mean difference between aLDH and vLDH of 5.2 U/L with the limits of agreement set between -74.1 and 84.4 U/L (Figure 1). The plot shows that there is no increase in difference with increasing LDH.

Factors Associated with High Levels of LDH

No significant association was shown between the different maternal och fetal factors tested in the logistic regression and a high level of LDH in cord blood at delivery (Table 4). High LDH value (>612 u/l) associated only with the way of delivery. In the group delivered by cesarean section a high level of LDH was 5.1 times more common (OR 5.1, 95% CI; 3.9-6.2) compared to the group without operative intervention (Table 4).

Method of delivery	Mean value (SD)	Median value (range)	Lower limit (2.5th)	Upper Limit (97.5th)	Frequency of haemolysis
Values of LDH in the total group (n=549)					
Arterial cord blood	403 u/L(100u/l)	396 (84-834)	162 u/L	612 u/l	29.9% (n=164)
Venous cord blood	402 u/L (97u/l)	390 (81-828)	252 u/l	636 u/l	20.6% (n=113)
Spontaneous vaginal deliveries* (n=455)					
Arterial cord blood	401 u/L (81 u/L)	396 u/L	270 u/L (162-684 u/L))	600 u/L	41% (n=227)
Venous cord blood	399 u/L (86.5 u/L)	384 u/L (168-828 u/L)	267 u/L	612 u/L	34.4% (n=189)
Vacuum extraction* (n=45)					
Arterial cord blood	469 u/L (118 u/l)	456 u/L (300-774 u/L)	300 u/L	774 u/L	37.7% (n=17)
Venous cord blood	455 u/L (102 u/L)	456 u/L (276-732 u/L)	276 u/L	732 u/L	13.3% (n=6)
Caesarean Section (n=38)*					
Arterial cord blood	465 (119)	423 (330-834)	330	834	36.8% (n=14)
Venous cord blood	437 (119)	414 (264-792)	264	792	23.7% (n=9)
Elective caesarean section (n=11)*					
Arterial cord blood	145 (89)	96 (84-348)	84	348	0
Venous cord blood	183 (116)	159 (81-413)	81	413	27.3% (n=3)
* A statistically significant difference in LDH values between normal deliveries and other way of delivery is shown					

Table 3: Intervals for LDH in cord blood among healthy newborns according to method of delivery. Values are presented as means (SD), median (range), 2.5th or 97.5th percentile (U/L).

Risk factors for a high level of LDH at delivery**	High level of LDH/total**	OR (95% CI)
Parity		
Multipara	7/248 (2.8)	Ref
Primipara	9/238 (3.8)	1.3(0.3-2.4)
Smokers***		
Yes	1/56 (1.8)	Ref
No	14 /417 (3.4)	1.9 (0.1-3.9)
Maternal weight >65 Kg***		Ref
No	8/271 (3.0)	1.1 (0.04-2.2)
Yes	6/183 (3.3)	
Maternal Age		
>= 30 years	11/352 (3.1)	Ref
<30 years	5/134 (3.8)	1.2 (0.1-2.3)
Gestational age ***		
< 41+0 Weeks	10/359 (2.8)	Ref
>=41+0 Weeks	5/116 (4.3)	1.6 (0.5-2.7)
Normal vaginal delivery		
Yes	9/401 (2.3)	Ref
No	7/85 (8.2)	3.9 (2.9-4.9)*
Vacuum/Forceps delivery		
No	13/445 (2.9)	Ref
Yes	3/41 (7.3)	2.6 (1.3-3.9)*
Acute Cesarean section		
No	12/453 (2.7)	Ref
YES	4/33 (12.1)	5.1 (3.9-6.2)*
Planned Cesarean section		
No	16 /476 (3.4)	-
Yes	0/11	
*P values<0.05 were considered as statistically significant **Haemolysis/missing samples n=63 ***missing data		

Table 4: Associations between possible risk factors and a high level of LDH (>612 U/l) at delivery. Values are expressed as Odds Ratio (OR) with corresponding 95% confidence intervals (CI). *p<0.05 (n=549).

Discussion

This is the first time LDH values from cord blood is presented in a population where truly healthy infants are included solely. Still, the LDH values found in the present study are very similar to previous reports [9,10] which make comparisons with previous studies meaningful. Further, the differences between the individual venous and arterial samples are small offering the possibility of using data collected from one umbilical cord vessel without correctly identifying the artery/vein. This will make sampling easier, compared to blood gases where differences in results are seen between the arterial and venous side, if this method is used in clinical practice in the future.

The ICD-10 diagnosis Z00.1A is given to newborns without abnormal findings and with an uneventful hospital stay before discharge. However, hospital stay is normally short and newborn infants sometimes show very vague signs during the first days even in the event of significant disease. In the present study, we tried to minimise the risk of including non-healthy newborns by selecting infants of healthy mothers with healthy pregnancies, and infants delivered healthy with a normal acid-base status at delivery and an Apgar score of seven or more at five minutes. Infants readmitted for disease that could influence their LDH value, such as infections, malformations causing local or general circulatory insufficiency, serious convulsions etc, were consequently excluded. We included infants born after caesarean section and vacuum extraction but also analyzed them separately based on previous research showing increased LDH in infants with fetal distress and asphyxia [10-12]. The rationale for stratifying the groups in this study was to investigate whether any potential difference in LDH between this group and normal deliveries could be detected even if the most frequently used biomarkers Apgar and/or pH in cord blood were normal, the infant was considered as healthy and most of these infants normally receive the diagnosis Z00.1. We found small but statistically significant increases in LDH after acute caesarian section as well as vacuum extraction. Our suggestion is that there might be a low grade of transitory asphyxia even in these cases, which is not mirrored in the acid-base status in cord blood at delivery. This is supported by the finding that the LDH values found in the 11 infants born after elective caesarian section are low compared with the infants delivered the other means. This result probably reflects the stress of vaginal birth and/or the reason for the vacuum extraction and acute caesarian section respectively. The 97.5th percentile value in the elective caesarian group is less than the median value in the other groups. A comparison with lactate or pH would be misleading since only infants with pH >7.10 were included. Similar results are also reported by Mongelli et al. [9]. In an on-going study we are further exploring the relationship between cord LDH and more pronounced levels of fetal distress.

The major reason for excluding samples in the present study was in-vitro haemolysis, a common finding in samples from children, especially newborns [13,14]. All laboratories and most commercially available analysis equipment have haemolysis cut-off limits for not presenting the results to the clinician; in our hospital this level is set rather low, at 0.3 g/L free haemoglobin in plasma. The reddish hue found in haemolysed plasma together with LDH leakage from erythrocytes does have a great impact on the LDH results if analysed using the routine methods of today. Lippi et al. showed that a haemolysis degree of 0.6 g/L did increase LDH by 34 per cent compared to samples without haemolysis [15]. The high proportion of haemolysed samples in our study could be explained by: a) blood with high haematocrit being sucked into the syringe from the vessel and then being transferred to the sample tube causing mechanical haemolysis, arteries being less accessible than veins, and b) the rather short delay between sampling and analysis at the laboratory. The implication of haemolysis below 0.3 g/L (maximal increase 17 ± 2%) [16] for the present results would be a small overestimation of the LDH median and percentile values.

Haemolysis was significantly higher in smokers than non-smokers. This is well known from studies of non-pregnant women and the explanation given is that cigarette smoke contains oxidative compounds which destabilise the erythrocyte membrane [17,18]. Haemolysis was also higher in infants born to obese mothers. An increased sensitivity to peroxidation and different lipid composition of the erythrocyte membrane has been described in obese women [19], but we have not found evidence in the literature to indicate whether this also holds for their fetuses and infants.

In spite of the increased values seen after instrumental/operative delivery in this study, the levels of LDH are low compared to values seen in newborns subjected to severe asphyxia [3,20]. In critically ill asphyxiated newborns, depending on the time of blood collection after the insult, the LDH values are 2 to 5-fold increase compared to the 97.5th percentile in the present study. The 97.5th percentile of approximately 612 U/L (10.2 ukat/L) cut-off seems to be clinically useful also in other conditions that cause illness in the neonatal period [21-23].

In this study we have provided 95% confidence intervals on cord artery and vein LDH in a group of healthy newborns. LDH seems a

robust biomarker with a reproducible, but rather wide, interval in spite of the conditions discussed above. Our speculation is that LDH might be a more sensitive and accurate biomarker of fetal distress than methods currently used in clinical practice.

Conclusion

LDH <612 U/L is normal in cord blood in the newborn term population. LHD reflects minor distress during the delivery of the infants even in the absence of acidosis at birth and/or Apgar reduction. Frequent in-vitro haemolysis is a challenge for further use of LDH in clinical routine calling for alternative sampling and analysis procedures.

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