Original paper

The evaluation of amniotic fluid lactate level in predicting cesarean delivery and early neonatal acidemia

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Abstract

Aim: Evaluate whether lactate increase in amniotic fluid influences cesarean delivery or correlation of this increase with oxytocin induction and early neonatal blood gas parameters.

Methods: We designed this prospective study of 408 pregnant women. We divided the groups as vaginal delivery (n=184), emergency cesarean (n=46), and planned cesarean delivery (n=178). We evaluated the amniotic fluid lactate values in terms of being associated with labor outcomes and neonatal blood gas parameters.

Results: Amniotic fluid lactate level was different between all three groups. Cord blood pH, lactate values, and maternal age were different between the groups. We analyzed the amniotic lactate and cord blood lactate levels according to acidemia. The group's lactate levels with a pH<7.2 were higher than those with an average pH. In oxytocin-treated groups (n=230), amniotic lactate and cord lactate levels were higher than those that did not receive oxytocin (n=178). Cord blood pH levels were not different in groups. There was an inverse correlation between the lactate and pH levels. However, we found a positive correlation between lactate levels and base gas deficit.

Conclusion: Higher amniotic fluid lactate concentration is associated with oxytocin induction and may increase the risk of early neonatal acidemia.

Key words: vaginal delivery, amniotic fluid, lactic acid, neonatal acidemia

Introduction

Cesarean delivery has been increasing rapidly worldwide in recent years and has become an essential problem in obstetrics[1-3]. The low cesarean rates in undeveloped countries are not always considered a positive indicator, but considering that the maternal mortality rate is high, this may also indicate that access to emergency obstetric care is complicated and inadequate[2,4].

Increase in cesarean rates; many factors have contributed to surgical techniques, improving medical conditions, reducing the risk of complications after

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surgery, demographic and sociocultural factors, safer perception, and desire of patients[5-7].

Labor dystocia is a common obstetric problem worldwide and is one of the main indications for operative labor[8]. Oxytocin is a drug used in pregnant women who develop dystocia, which increases uterine stimulation and contractions, and the American Food and Drug Administration (FDA) approved it for use[9-11].

Myometrium is a non-homogeneous structure composed of myocytes and flat muscle cells arranged in bundles embedded in connective tissue. Inefficient and prolonged muscle activity during labor can lead to uterine muscle hypoxia with progressive lactic acidosis in the tired myometrium[12-14]. The hypoxic environment further reduces the contraction power of the uterine[12-15]. More prolonged or more exposure of oxytocin to hypoxic remaining or tired myometrium tissue may further increase lactic acid production, labor dystocia, and a vicious cycle may prolong the cause. This situation may increase the risk and frequency of cesarean delivery.

A close correlation was found between lactate produced by myometrium and lactate levels in amniotic fluid in some studies[8,16,17]. Pregnancy and labor have a physiologically hypoxic environment. Umbilical cord pH, base deficit, and lactate level analyses appear to be a reliable marker for neonatal problems and functional predictors of adverse neonatal outcomes[18-22.]

The Royal Society of Gynecology and Obstetrics (RCOG) recommends routinely evaluating cord blood parameters in all operative vaginal births and cesarean sections due to foetal causes[23]. Likewise, the American Society of Gynaecology and Obstetrics (ACOG) recommends that the umbilical cord blood analysis be seen in any baby who raises suspicion of foetal metabolic problems[24].

This study's primary purpose is to investigate the relationship between high lactate levels in amniotic fluid and the risk of cesarean delivery. Our study's secondary objectives are to investigate the effect of oxytocin use on amniotic fluid lactic acid (AFL) during labor, the effect of amniotic fluid lactic acid levels on the foetus cord blood parameters, and the correlation of infant birth weight with amniotic fluid lactic acid level.

Materials and methods

We performed this study between December 2019-May 2020 at the Health Sciences University, Bursa Yüksek ihtisas Training, Research Hospital (EAH), Turkey, Obstetrics-Gynecology department.

It was designed cross-sectionally prospectively with the participation of a total of 408 volunteers. The study was approved by the Local Ethics Committee with numbered 2011-KAEK-25 2019/06-27, and participants were informed of the 'Informed Volunteer Consent Form' read and signed.

Determination method of groups

In this study, 230 pregnant women undergoing labor induction constituted the study group. Also, 178 pregnant women who underwent planned cesarean at the 39th week, depending on the history of previous uterine surgery, were included in the study as a control group.

The first group consisted of 184 pregnant women who delivered vaginally. The second group consisted of 46 pregnant women who had labor dystocia or acute foetal distress developed during labor and performed a cesarean delivery. In the third group, 178 pregnant women did not have labor pain, and that we applied for the planned cesarean. All participants in the groups were between 37-41 weeks, above 18 years of age, healthy, single pregnant without foetal or maternal comorbidity with an estimated foetal weight of <4500 grams.

Oxytocin and amniotomy were applied to the study group according to ACOG guidelines and in the same standards[25]. Accordingly, oxytocin was administered at 500 c.c isotonic solutions, with a dose of 5mU per minute, with an increase of 5mU per minute until an adequate uterine contraction activity was established, a condition of increasing to a maximum dose of 30 mU/min.

Data collection method

The labor followed up in three stages based on current data-the first stage, defined as the duration of cervical dilation between 0-10 cm. The second stage of labor is until the baby's birth from 10 cm (full dilation) dilation. We have defined the period in which the placenta is fully separated as the third stage. We considered the latent phase 0-6 cm as the cervical dilatation process and the active phase as the duration between six cm and full dilatation[26]. Cesarean delivery was performed in labor dystocia cases, which we

mentioned in the active phase or the second stage as protraction or arrest[26-28].

The method of collection of amniotic fluid

Sterile speculum examination was performed for each pregnant woman in the study group who entered the active phase. A two c.c fluid sample was collected for lactate determination by penetrating the amniotic membrane with a syringe without contamination and contact. Amniotic samples were transferred to sterile sample tubes and analyzed immediately at the bedside. In the planned cesarean group patients, amniotic fluid collected from the amniotic membrane prolapsed after uterine incision in sterile conditions with the syringe tip.

The lactate concentration measured with the Lactate Scout 4 instrument (SensLab GmbH, Leipzig, Germany), which only needs 0.2 ml of amniotic fluid, is an electrochemical test strip method and analyzes lactate concentration.

Cord blood gas analysis method

In all groups, the umbilical cord was double clamped with 10cm after birth. Then the distal segment was cut, and blood samples were taken from the umbilical artery. A cord blood sample taken with a heparinized syringe analyzed on ABL 800 FLEX blood gas analyzer. Sampling from umbilical artery blood was preferred. Because the umbilical arterial blood mainly reflects foetal metabolism and venous blood mainly reflects placental functions[29-31].

Although different threshold values were there in various publications in terms of blood gas pH value, we accepted umbilical artery average pH values in the range of 7.20-7.28 by considering the Turkish Neonatology Association's infant guide 2016[32].

Statistical analyses

Statistical analysis performed using statistical package SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA). The normal distribution for each continuous variable was checked with Kolmogorov Smirnov and Histograms, and all numerical data expressed as a median (minimum-maximum) or rate. The categoric variables between the groups were analyzed using the Chi-Square test. One Way ANOVA test used for normally distributed data and the Kruskal Wallis test for non-normally distributed data. As the variance analysis was significant, comparisons made using the Post-hoc Tukey test or the Mann-Whitney U test. Correlations tested with Spearman's correlation test. Receiver operating characteristic curves (ROC curves) created, and the areas under the curve (AUC) and sensitivity (sen.), and specificity (spe.) were calculated. Cut-off value determined between the second and third groups lactate levels. P values <0.05 were considered statistically significant.

Results

A total of 408 pregnant women were included in the study and examined in 3 groups: the first group named VD, the second group as CS, and the third group named PCS.

Pregnant women included in the study evaluated according to the mode of delivery. Amniotic fluid lactate (AFL), cord blood pH, cord blood lactate (CBL) value, maternal age ($p<0.001$), and the number of births ($p=0.002$) were statistically different between the groups. When groups were evaluated as binary as post-hoc, no statistically significant difference was found in terms of AFL between VD and CS groups ($p=0,482$). The cord pH values of pcs, vd, and cs groups were 7.33 ± 0.1, 7.28 ± 0.1, and 7.26 ± 0.1 respectively (mean ± SD) and statistically significantly different ($p<0.001$). We determined that the AFL, cord pH value, CBL value of the planned group (PCS) were lower than the other groups (Table 1).

The participants were evaluated according to their acidic status in the baby. When we examined AFL and blood gas lactate value according to acidemia groups, the lactate levels of the group with pH <7.2 (9,1 (1,8-13,4)) found to be statistically higher than those with normal pH (4,6(0,6-12,4)) ($p<0.001$) (Table 2).

When the groups divided into two groups according to whether oxytocin is applied or not, in groups 1 and 2 (n=230) receiving oxytocin, AFL (6.0 (0.6-13.4) mmol/L; 3.2 (0.6-10.5) mmol/L, respectively; $p<0.001$), and CBL levels (2,2 (0,2-8,5) mmol/L; 1,7 (0,1-5,8) mmol/L, respectively; $p<0.001$) were higher and found statistically significant compared to group 3 patients (n=178) without oxytocin ($p<0.001$) (Table 3).

Correlations between variables examined (Table 4). A statistically significant inverse correlation found between AFL and cord blood pH level ($r = -0.35$; $p <0.001$). Accordingly, if the patient's amniotic fluid lactate level increases, the baby's blood gas pH is expected to drop.

A statistically significant positive correlation was found between the AFL and the CBL level and the base gas deficit (r = 0.40 and r = 0.24, respectively, p<0.001). If the patient's amniotic fluid lactate level increases, blood gas lactate level, and base deficit are expected to increase.

There was a statistically significant inverse correlation between cord blood pH level and blood gas lactate level and base deficit (r = -0.57; p<0.001). There was no statistically significant correlation between the baby's blood gas pH level and age, and birth weight (Table 4).

Table 1. Amniotic fluid lactate level (AFL), cord blood gas pH, base deficit and lactate level, age, number of births and birth weight between groups

	VD (n=184)	**CS (n=46)**	**PCS (n=178)**	**P**	**P*$_{VD\&CS}$**	**P*$_{VD\&PCS}$**	**P*$_{PCS\&CS}$**
AFL (mmol/L)	5.9 (0.6-12.4)	6,4 (1,8-13,4)	3,2 (0,6-10,5)	<0.001	0.482	<0.001	<0.001
Cord pH	7.28±0.1	7.26±0.1	7.33±0.1	<0.001	0.197	<0.001	<0.001
Cord Blood Lactate (mmol/L)	2.2 (0.2-8.5)	2.1 (0.3-6.6)	1.7 (0.1-5.8)	<0.001	0.914	<0.001	0.004
Cord Bas Deficit	2.6 (-2.2-10.0)	3.1 (0.1-9.5)	2.3 (-0.3-11.7)	0.085	-	-	-
Age	25.9±5.4	27.1±6.6	29.2±5.8	<0.001	0.354	<0.001	0.085
Parity	1 (0-8)	0 (0-4)	1 (0-7)	0.002	0.081	0.117	0.002
Birth Weight (gr)	3265.0±40 3.8	3285.5±43 0.3	3315.4±40 2.3	0.498	-	-	-

p: OneWay ANOVA (mean±SD); Kruskal Wallis (median(min-max)), p*: Post-hoc tukey; Mann Whitney U test mmol/L: millimoles/liter, gr: gram, AFL: Amniotic fluid lactate

Table 2. Amniotic fluid and cord blood gas lactate levels between groups in terms of cord blood acidemia status

	pH >7.2 (n=361)	**<7.2 (n=47)**	**p**
AFL (mmol/L)	4.6 (0.6-12.4)	9.1 (1.8-13.4)	<0.001
Cord Blood Lactate (mmol/L)	1.8 (0.1-7.0)	4.9 (1.9-8.5)	<0.001

p: Mann Whitney U test (median(min-max)) mmol/L: millimoles/liter, AFL: Amniotic fluid lactate

Table 3. Amniotic fluid lactate level, cord blood lactate and pH levels in groups with and without oxytocin performed

	Oxytocin	Non-Performed Performed (n=230)	p (n=178)
AFL (mmol/L)	6.0 (0.6-13.4)	3.2 (0.6-10.5)	<0.001
Cord Blood Lactate (mmol/L)	2.2 (0.2-8.5)	1.7 (0.1-5.8)	<0.001

p: Mann Whitney U test (median (min-max)) mmol/L: millimoles / liter, AFL: Amniotic fluid lactate

Table 4. Analysis of correlation between variables

		AFL (mmol/L)	Cord Blood pH
AFL (mmol/L)	r	-	-0.35*
	p	-	<0.001
Cord Blood Lactate (mmol/L)	r	0.40*	-0.57*
	p	<0.001	<0.001
Age	r	-0.039	0.14
	p	0.434	0.054
Bas Deficit	r	0.24*	-0.32*
	p	<0.001	<0.001
Birth Weight	r	0.01	-0.002
	p	0.952	0.709
Parity	r	-0.03	0.07
	p	0.503	0.175

Spearman test: p<0.05*, AFL: Amniotic fluid lactate

If the patient's lactate level is> 4.95, the patient is expected to be in emergency cesarean group (second group) with a probability of 76%, 76.1% sensitivity, and 70.2% specificity (AUC = 0.760 (95% CI 0.69-0.83); p<0.001) (Figure 1).

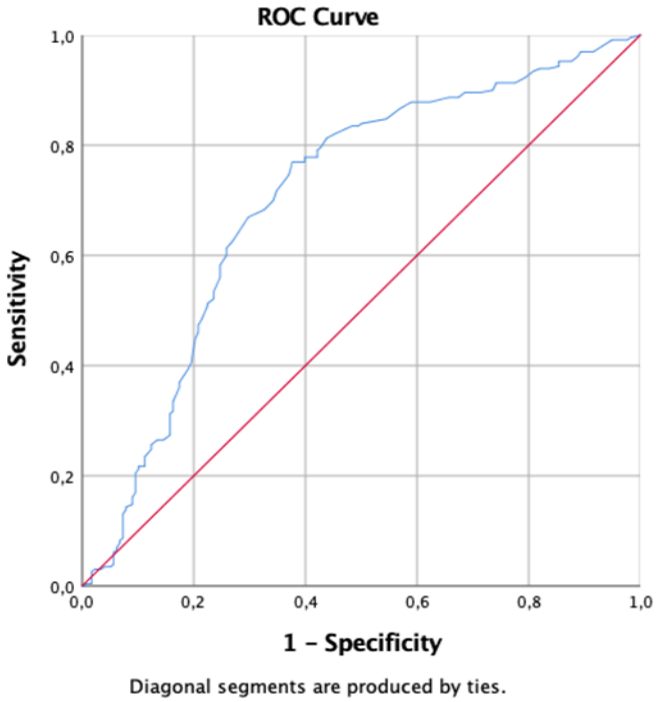

Figure 1. **ROC analyses of amniotic fluid lactate values.**

Discussion

Labor is a physiological process in which pregnancy products (foetus, membranes, umbilical cord, and placenta) are thrown out of the uterus. It is obtained by gradual dilatation of the cervix due to rhythmic uterine contractions' low frequency, intensity, and duration with changes in biochemical connective tissue[28,33].

Due to uterine contractions during labor, lactate is produced, and pH levels in the tissue decrease. Low pH leads to intracellular acidification and inhibition of Ca^{+2} channels in myometrial cells[34]. Decreased intake of Ca^{+2} into muscle means that contraction will be weaker and consequently less active[35]. New studies show a significant relationship between the effect of lactate production, hypoxia, and oxytocin. Lactate level is an essential factor in uterine activity and pathophysiological processes during childbirth[36, 37].

The increased AFL level indicates that a more anaerobic and hypoxic environment develops in the contracted uterus, in line with the increased oxytocin dose. While oxytocin use may be significant in lactic acidemia, neonatal evaluation should be done carefully after prolonged induction, prolonged labor, or foetal distress. In terms of early neonatal lactic acidosis prediction, more large-scale prospective studies are needed in terms of amniotic fluid assessment and the effect of oxytocin induction on this picture. This study suggests that oxytocin should be used with caution in women with high AFL levels at diagnosis.

The effect of the AFL level on labor dystocia has been explained in previous studies with myometrial lactic acidosis[8, 14, 37]. Irregular contraction pattern in prolonged delivery can lead to lactate accumulation in the myometrium. This buildup can reduce uterine contractions and thus contribute to continued reduced progression[8]. In the delivery process, cesarean delivery occurred in 46 of 230 patients due to dystocia or acute foetal distress. Although the AFL level is higher in the emergency cesarean group than the vaginal delivery group, we did not find a statistically significant difference when we performed a post-hoc analysis between both groups (pVD & CS = 0.48). We found the predictive value of AFL low for emergency cesarean delivery. However, in future studies, with more pregnant women, analyzes examining the state of dystocia and foetal distress developed during labor with AFL level can perform.

In the study of Karlsson et al., 61% of cardiotocography records taken 30 minutes before birth was abnormal, while only 9.4% of them found to be associated with adverse neonatal outcomes at birth. This result shows that the cardiotocography record should not be used as the sole means of foetal surveillance during delivery. There is a correlation with other studies showing the low estimate of abnormal cardiotocography on foetal outcome[38, 39]. The need for an alternative method for cardiotocography monitoring occurred during labor. Therefore, a newborn's blood pH or lactate analysis is preferred[40].

In our study, the cord pH values were statistically significantly different between the three groups ($p < 0.001$). When the groups were evaluated bilaterally in post-hoc, there was no significant difference in cord pH values between vaginal delivery and emergency cesarean groups ($p=0.197$). When the planned cesarean group was analyzed in pairs with the other two groups, statistically significant differences were found ($p<0.001$).

Amniotic fluid lactate levels were significantly different between the three groups ($p<0.001$). When the groups were analyzed by binary post-hoc for AFL values, we did not find a significant difference between vaginal delivery and emergency cesarean groups ($p=0.482$). However, statistically, significant differences were detected when the planned cesarean group was analyzed in pairs with the other two groups ($p<0.001$). When we compared the groups in terms of CBL values, we found statistically significant differences ($p<0.001$). When these groups were analyzed by binary post-hoc for CBL, we could not detect a significant difference between vd and cs groups ($p=0.914$). However, when the pcs group analyzed with the other two groups as post-hoc binary, they were detected significant differences statistically ($p<0.001$).

As mentioned above, AFL, cord blood pH, and CBL levels used as evaluation parameters for vaginal delivery, emergency cesarean, and planned cesarean groups were determined clinically and statistically different. The hypoxic environment created by labor, the frequency of contractions with oxytocin induction, pain intensity and frequency, stress, and other psychological factors that childbirth can cause in the mother's room may be the factors that may affect this foetal stress environment. Less exposure of pregnant women and babies in the group we have planned cesarean to hypoxic environment and acidemia can be explained by the factors that we have disabled. However, no statistically significant difference was there in binary analysis between the vd and cs groups. We could explain that the operative delivery was performed quickly after the emergency cesarean decision in pregnant women in labor induction. The foetus was affected by the hypoxic environment for less time.

Neonatal acidemia table is a significant risk factor for early or late neurological morbidity. Early neonatal blood gas parameters, and especially pH values, are essential findings in terms of the development of hypoxic-ischemic encephalopathy and the progression of the table and long-term results[20, 40, 41]. We divided the patients into two groups in terms of neonatal acidemia. Amniotic fluid lactate levels and CBL levels higher in the acidemic group ($pH < 7.2$) ($n=47$) than the group without acidemia ($n=361$) and these differences were statistically significant ($p<0.001$).

Analysis of amniotic fluid lactate levels and some factors affecting this with more detailed and long prospective studies, which we find significant in terms of neonatal acidemia in neurological morbidity, may help predict and prevent some neurological problems that may develop after birth.

In conclusion, the lactate level in the amniotic fluid may be a metabolic marker of uterine contractions during labor. This test is more valuable for early and late neonatal outcomes, especially in pregnant women who received oxytocin. Umbilical artery pH, base deficit, and lactate levels are predictors of adverse neonatal outcomes, and analysis of lactate concentration in amniotic fluid can give meaningful results in terms of these values before birth. There is a need for studies with more volunteers, with longer-term and late childhood outcomes.

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