



Is Serum Lactate Dehydrogenase Level a Good Indicator for Diagnosis of Neonatal Birth Asphyxia?

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Keywords: Neonatal birth asphyxia; Serum LDH; Lactate dehydrogenase; Umbilical cord ABG; pH level; Arterial blood gas.

Abstract

Objective: Neonatal birth asphyxia is a serious health condition. In developing countries, when neonates are referred to Neonatal Intensive Care Units (NICU), sometimes their results for Arterial Blood Gas (ABGs) measurements collected from their umbilical cord blood do not get provided to the NICU. Hence, neonatologists need a proxy parameter to help them detect birth asphyxia. Study aimed to evaluate whether there is an association between umbilical cord ABGs, including pH, PO₂, PCO₂ and HCO₃, and serum Lactate Dehydrogenase (LDH) levels in neonates with birth asphyxia. If there is association, the neonate's serum LDH levels may be used as a proxy for umbilical cord ABG measurements in identifying neonatal birth asphyxia.

Methods: In a cross-sectional prospective study, we evaluated 100 neonates, and their associated mothers, who were admitted to our NICU and were suspected of having birth asphyxia during 2018. Neonates that had abnormal sonography report before birth or were diagnosed with underlying complications such as cardiac or metabolic complications were excluded from the study.

Results: Pearson correlation showed serum LDH levels in neonates had a negative correlation with pH ($r=-0.460$, $p=.000$) and HCO₃ ($r=-0.268$, $p=.008$) and a positive correlation with PaCO₂ ($r=0.276$, $p=.006$) levels from umbilical cord arterial blood but did not associate with maternal age or other characteristics. ANOVA showed from stratified pH levels only pH<7.10 associated with serum LDH levels.

Conclusion: Since acidosis (pH<7.10), which presents with reduced blood pH levels, is associated with increased serum LDH levels, in the absence of umbilical cord ABG measurements, serum LDH levels may be a good indicator for diagnosing neonatal birth asphyxia.



Introduction

Perinatal asphyxia, which may result in hypoxemia or ischemia, is one of the most common causes of morbidity and mortality in neonates [1]. Each year, approximately one million of neonates die due to birth asphyxia worldwide [2]. More than 99% of these deaths occur in developing countries [3,4]. Furthermore, among neonates who survive birth asphyxia, permanent disability is common. Of neonates who survive an episode of hypoxemia or ischemia, 5-10% will suffer from body movement disabilities for the rest of their lives and 20-50% will suffer from neural or cognitive disabilities that last until their teenage years [5,6].

Neonate asphyxia is responsible for 42 million years of life with disability [7,8]. A meta-analysis study showed that among neonates who survived birth asphyxia, at the age of 2-5 years old, 1-18% of them experienced movement and neural or severe learning disabilities, and 40-50% had an abnormal growth rate [5].

In developing countries, the likelihood of birth asphyxia and stillbirth is high, and neonate mortality rates range from 0.2% to 64.4% [9]. Some other studies report that the highest neonate mortality rates are in Asia (39%) and in sub-Saharan Africa (38%), and 70-80% of these neonate deaths are due to diseases that are preventable or curable through simple, low-cost interventions [10,11]. Studies show that insufficient pre-delivery health care services, C-section, meconium-stained amniotic fluid, pre-term birth, pre-eclampsia or eclampsia, and some other delivery factors increase the risk of birth asphyxia [12-14].

Overview: This study aimed to see whether the presence of birth asphyxia in neonates can be determined by measuring serum Lactate Dehydrogenase (LDH) level when the results for umbilical cord Arterial Blood Gas (ABG) measurements are not available. In developing countries like ours, neonates are frequently transferred to referral hospitals without the neonate's history of umbilical cord ABG measurements being provided to the hospital. In those cases, the pediatricians need a proxy measurement to evaluate the presence of birth asphyxia in the neonate to reach to the diagnosis.

Methods

In a cross-sectional prospective study, we evaluated 100 term or late-preterm neonates, and their associated mothers, who were referred to our hospital and were admitted to our Neonatal Intensive Care Unit (NICU) and were suspected of having birth asphyxia during year 2018. ABG parameters were measured either from umbilical cord blood or from the first blood draw from the neonate, and serum LDH was measured within the first 6 hours after birth from the first blood draw after the neonate arrived and was admitted to our NICU. Neonates that had abnormal sonography report before birth or were diagnosed with underlying complications such as inborn errors of metabolism, cardiac or liver disease, or hemolytic diseases were excluded from the study.

Our study sample had all the following characteristics and were clinically suspected of having birth asphyxia: neonates had low Apgar scores of 5 or less at 1 and 5 minutes, neonates with pH values even up to 7.30 in umbilical cord ABG measure-

ments were included when they had Apgar score of 5 or less at 1 and 5 minutes of birth (although pH less than 7 indicates acidosis) [15], and neonates had complications resulting from asphyxia in one or more organs. Examples of end organ damage included mild cardiomyopathy identified by echocardiography, neurological damage such as hypotonia or convulsion, and lung complications presenting as respiratory distress.

The associations between neonates' serum LDH levels and the following measurements were evaluated: ABG measurements (including PaCO₂, PaO₂, pH, and HCO₃); neonate's gender; gestational age; maternal age; gravidity; number of twin or multiple pregnancies; and maternal risk factors such as high blood pressure, diabetes, hypothyroidism, substance use disorders, maternal history of miscarriage or abortion or stillbirth, premature rupture of amniotic membrane, premature delivery, and history of infertility or *In Vitro* Fertilization (IVF).

T-Test or ANOVA were used for associations between quantitative and qualitative parameters. Pearson correlation test was used for quantitative parameters, and chi-square test was used for categorical data. SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) was used to analyze the data. Statistical significance was defined as p value less than 5%. Research was conducted based on approved human research ethics and informed consent was obtained from all the participating mothers (IR.SBMU.MSP.REC.1399.393).

Results

For 100 neonates, the average gestational age was 36.79 weeks (34 - 40 weeks range) and included 42 boys and 58 girls. Mothers' average age was 29 years and 2 months (SD \pm 5.7 years, 18 - 44 years range) and the average for gravidity was 1.540 (SD \pm 1.006, 1-6 deliveries range).

Maternal risk factors are presented in Table 1 and Figure 1. From 100 mothers, 31 of them each had one risk factor. The most common risk factor was hypothyroidism, which affected 9 mothers. Chi-square test did not show any association between gender and presence of maternal risks.

Table 1: Prevalence of maternal risk factors based on the neonates' gender (n = 31/100).

Maternal Risk Factors	Boy (n=15)	Girl (n=16)	Total (n=31)	Pearson Chi-Square 7.014 p value 0.427
Hypothyroidism	4	5	9	
Diabetes	2	4	6	
High Blood Pressure	1	2	3	
Drug Addiction	1	0	1	
Abortion/Miscarriage	6	2	8	
Infertility/IVF	1	1	2	
Premature Rupture of Amniotic Membrane	0	2	2	

IVF: *In Vitro* Fertilization.

Pearson Chi-square could not show any association between maternal risk factors and the neonate's gender.

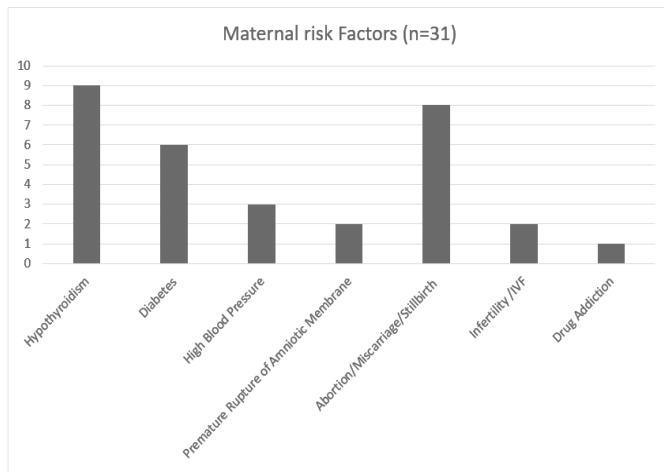


Figure 1: Prevalence of maternal risk factors. (n = 31/100) hypothyroidism was the highest prevalent risk factor among mothers.

IVF: *In Vitro* Fertilization.

The average LDH and ABG measurements for all neonates as well as based on gender are presented in Table 2. As Table 3 presents, Pearson correlation test showed serum LDH level had a negative correlation with pH and HCO₃ levels and had a positive correlation with PaCO₂ levels. Decrease in pH of blood from the umbilical cord was associated with an increase in serum LDH levels in neonates.

Table 2: Averages for LDH and ABG measurements for all neonates as well as based on neonate’s gender (n=100).

	P _a CO ₂ (±SD) kPa	HCO ₃ (±SD) mmol/L	P _a O ₂ (±SD) kPa	pH (±SD)	LDH (±SD) (µkat/L)
Averages for Total Neonates	7.38 (±2.9)	20.79 (±4.92)	7.64 (±3.64)	7.18 (±0.35)	27.57 (±12.62)
Range	3.2 – 21.19	11-38	2.67 – 19.2	6.6 - 7.24	7.80 - 93.58
Averages for Boys	7.04 (±2.13)	20.80 (±5.55)	8.32 (±4.33)	7.19 (±0.12)	28.03 (±11.18)
Averages for Girls	7.62 (±3.34)	20.78 (±4.46)	7.14 (±2.97)	7.17 (±0.14)	27.23 (±13.65)

LDH: Lactate Dehydrogenase; ABG: Arterial Blood Gas.

Mean serum LDH level in conventional unit was 1654 (SD ±757, range 468-5615) U/L. Based on gender, the mean LDH levels were 1682 (SD ±671) U/L in boys and 1634 (SD ±819) U/L in girls.

Table 3: Pearson test evaluated the correlations between serum LDH level and some parameters. (n=100).

Correlation with LDH	pH	P _a CO ₂	HCO ₃	P _a O ₂	Maternal Age	Gravidity	Gestational Age
r (Pearson Correlation)	-0.46	0.276	-0.268	-0.106	0.071	-0.117	-0.138
P value	.000*	.006*	.008*	0.3	0.48	0.25	0.17

*Show statistical significance since p value is less than 0.05.

LDH: Lactate Dehydrogenase.

Pearson correlation test (r) showed serum LDH level had a negative correlation with pH and HCO₃ levels and had a positive correlation with PaCO₂ levels from umbilical cord blood.

For further analysis, the severity of acidosis was divided into three groups based on umbilical cord arterial blood pH levels: severe (<7.10), moderate (≥7.10 and <7.20), and mild (≥7.20 and <7.30) acidosis. ANOVA analyzed the data stratified based on severity of acidosis and showed that only in pH<7.10 an increase in serum LDH was associated with a decrease in pH level.

The level of serum LDH did not show any association with gestational age, maternal age, neonate’s gender, or maternal risk factors. There were no associations between neonates’ gender and any of the ABG measurements including PaCO₂, PaO₂, pH, and HCO₃.

Discussion

This study aimed to evaluate the potential association between serum LDH level and birth asphyxia in our neonate patient population. Our study found that in neonates with birth

asphyxia, there was an association between serum LDH level and umbilical cord ABG levels. In pH<7.10, as pH in umbilical cord blood decreased, the level of neonate’s serum LDH increased. This association may help pediatricians to diagnose birth asphyxia by measuring serum LDH levels whenever the results for umbilical cord ABG measurements are not available. This finding may help in reduction of long-term pathological effects of asphyxia as well as reduction of the cost and duration of neonate’s admission to NICU.

Birth asphyxia is defined as lack of initiation or continuation of breathing at the time of birth [16]. Asphyxia is diagnosed when the neonate has Apgar <5 at 1 or 5 minutes after birth [17]. Presence of acidity in umbilical cord blood can also show the lack of sufficient oxygen in the blood. Birth asphyxia disrupts perfusion in the tissues, and this causes hypoxia and hypercarbia in the organs and extremities [2,18].

A recently published article showed in term neonates, there is an association between serum LDH level measured within the first 24 hours after birth and the presence of birth asphyxia. This association enables clinicians to evaluate the presence of birth asphyxia in neonates referred to their center when they

do not have access to results for umbilical cord ABG measurements [19]. Another study also has shown that the serum LDH level within the first 72 hours after birth is the best indicator for differentiation between neonates who had experienced birth asphyxia and those who had not [20]. A study in hypothermia-treated neonates indicates the serum LDH level has predictive value regarding the outcomes for neonatal asphyxia [21].

Birth asphyxia happens due to various causes which may start during the time of pregnancy or during the time of delivery. Thus, to implement preventive measures, first we need to identify the contributing and risk factors and then eliminate or reduce those factors when possible. Birth asphyxia sometimes even may cause end-organ damage in neonates such as hypoxic-ischemic encephalopathy (HIE). It is important to know that to reduce the chance of those effects, in most cases, even without applying therapeutic hypothermia or other expensive or sophisticated treatments, only simple and effective strategies to provide supportive care for high-risk pregnancies may be sufficient. For example, the presence of a pediatrician alongside the gynecologist at the time of delivery may provide timely resuscitation for the neonate if needed and prevent perinatal asphyxia and reduce the incidence of HIE [22,23].

Birth asphyxia can have detrimental effects on several systems of the body. The degree of neural damage depends on different factors including the gestational age, the start time for the asphyxia (during the pregnancy, during the delivery, at birth, or after birth), the severity, and the time span of asphyxia. Damage to organs like brain, kidneys, or heart can happen. Damage to liver can be evaluated by measuring the levels of hepatic enzymes in the serum like Alanine aminotransferase (ALT) and Aspartate Aminotransferase (AST) and Lactate Dehydrogenase (LDH).

LDH is produced by the liver whenever it is affected by stressors such as hypoxia. While neonatal ABG measurements fluctuate rapidly and therefore need to be collected immediately after birth, LDH levels remain elevated for a longer period of time. Hence, serum LDH levels may be used as a surrogate for umbilical cord ABG levels. Therefore, serum LDH levels can enable pediatricians in referral hospitals to properly identify which neonates had experienced birth asphyxia.

LDH exists in the cytoplasm of neurons and other types of cells. This biomarker is released into extracellular space upon death of cell due to hypoxia or other insults [24]. The importance of our finding is that serum LDH level alongside the clinical picture may help in diagnosis of birth asphyxia. This may also clarify the incidence in relevant disputed legal medicine cases about the hypoxic onset [25].

Study limitations: A larger study sample size and performing this study at multiple health care institutions may further improve the strength of associations between parameters as well as increase generalizability of these findings in other populations.

Conclusion

In neonates with birth asphyxia, decrease in umbilical cord arterial blood pH levels associates with increase in serum LDH levels. This association enables pediatricians to diagnose birth asphyxia by measuring serum LDH levels whenever the results for umbilical cord ABG parameters are not available to them. Unlike ABG levels, serum LDH level has slow fluctuations. When serum LDH level is measured a few hours after birth, that value

may still properly represent its level at the time of birth.

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