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Research Article

Determination of the Relationship Between Serum Lactate Level and Antenatal Complications and Early Neonatal Outcomes In Hyperemesis Gravidarum Patients

Ezgi Turgut,[1] Ugurkan Erkayiran,[1] Burak Karadag,[1] Vakkas Korkmaz[2]

[1]Department of Obstetrics and Gynecology, Ankara Training and Research Hospital, Ankara, Turkey
[2]Department of Obstetrics and Gynecology, Ankara Zekai Tahir Burak Training and Research Hospital, Ankara, Turkey

Abstract

Objectives: The aim of this study was to evaluate the relationship between pregnancy complications occurring during the gestational weeks of pregnancy with hyperemesis gravidarum and hypoxia by measuring the serum lactate level.

Methods: There were a total of 100 pregnant women included in the study, 50 of whom were diagnosed with hyperemesis gravidarum and 50 of whom were diagnosed as having a healthy pregnancy without hyperemesis gravidarum. All of the patients were followed up until full term, and the pregnancy complications and early neonatal evaluations performed during follow-up were recorded.

Results: In our study, gamma glutamyl transferase levels and the newborn's birth weight in the first trimester, blood gas pH level, and the first minute Apgar score were evaluated as having a positive correlation. Similarly, there was a negative correlation between lactate levels and birth weight, first minute Apgar value, and pH level at birth.

Conclusion: The hypoxia, lactate elevation, and increased oxidant substances that appeared with compensatory metabolic alkalosis in patients with emerging severe hyperemesis gravidarum had negative effects on newborn weight, Apgar score, and blood gas results.

Keywords: Antenatal complications, early neonatal outcomes, gamma glutamyl transferase, hyperemesis gravidarum, lactate

Nausea and vomiting, which reduce the quality of life of pregnant women, constitute a major group of complaints in pregnancy period. Along with the change in the severity, it is a complaint which is seen at pregnants at a rate of 50-70%.[1] In pregnancy, complaints of nausea and vomiting often begin at week 5 from the last menstrual period and it reaches its peak in 8-12 weeks, then it diminishes spontaneously and it disappears before the 16th week. But, these symptoms continue throughout pregnancy at the 10% of the pregnants.[2] In 1-2% of patients, hyperemesis gravidarum (HEG), which is a much more severe clinical picture appears to us. Although a definite diagnostic criteria for HEG is not determined, acid-base balance disorder, electrolyte imbalance, dehydration (blood urea nitrogen, creatinine disorder), hypernatremia, ketonuria and more than 5% weight loss are seen in patients.[3, 4] It has been

Address for correspondence: Ugurkan Erkayiran, MD. Ankara Egitim ve Arastirma Hastanesi, Kadin Hastaliklari ve Dogum Klinigi, Ankara, Turkey
Phone: +90 533 957 28 07 **E-mail:** byugrerk@hotmail.com
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reported that these conditions that are occured in HEG patients may constitute a risk factor in terms of fetal low birth weight, intrauterine growth retardation and fetal anomaly.[5]

Long-term loss of stomach contents in HEG patients causes hypochloremic metabolic alkalosis.[6] In metabolic alkalosis, the respiratory center in acute compensation and the kidneys in chronic compensation move into action. Chemoreceptors that control ventilation during acute compensation reduce ventilation as a responce to the increase in pH, thus the formation of pCO_2 and H+ is increased and the pH is tried to be reduced to normal. For this reason, low oxygen or in other words hypoxia is seen in respiratory acidosis.[7] In the case of hypoxia, nicotinamide adenine dinucleotide (NAD) formation is inhibited, thereby the NADH/NAD ratio and lactate levels increase.[8]

It was stated that there isn't any change in gamma glutamyl transferase (GGT) levels in pregnancy.[9] GGT, which catalyses the transfer of gamma glutamyl residues of amino acids or small peptides, is an enzyme present in serum and on the outer surface of many cells.[10] GGT is responsible for extracellular catabolism of glutathione (GSH), an important antioxidant especially in mammalian cells. The important role of GGT in reductive events such as antioxidant/antitoxic defense and cell proliferation/apoptosis balance in the cell is shown in performed studies.[11] It is asserted that GGT activity may have an increase as response to oxidative stress and besides increased serum GGT activity may be used as an indicator of increased oxidative stres.[12] Increased oxidative stress leads to miscarriage, premature birth, intrauterine growth retardation and preeclampsia in pregnancy.[13]

There develops an oxidative stress in tissues in case of developing hypoxia in patients with HEG. Our study is planned with the aim of observation of the changes in GGT levels in the presence of oxidative stress and the changes in lactate levels which are considered to be indicators of hypoxia, may be predictive of early neonatal findings.

Methods

100 pregnant women, followed up after applying to Obstetrics and Gynecology Clinic between the days May 2015 and May 2016, were included into this study at the first trimester(<14 weeks) as 50 of whom were diagnosed pregnant with HEG and 50 of whom were diagnosed having healthy pregnancy (control group) without HEG. Participant were informed and their consent forms were taken. An approval was taken from Ethics Committee.

Pregnant women who cannot orally be fed due to having nausea and vomiting complaints and having at least 1+ (positive) ketonuria in the spot urine and / or at least 5% weight loss were included into this study gorup. Detailed anamnesis was obtained from the pregnancies in both groups and obstetric examinations were performed. Demographic data (age, gravida, parity, abortus etc.), complaints, daily vomiting, weight loss (if any), last menstrual history and gestational ages were recorded. Patients were asked for complete urine examination, venous blood gas, thyroid function tests, serum lactate level and GGT as oxidative stress markers. Crown to Rump Length (CRL) and fetal heart rate were measured by ultrasonography. All the patients were followed up until full term, and the pregnancy complications and early neonatal evaluations that were seen during the follow-up were recorded. The difference between antenatal complications such as oligohydroamnios, polyhydroamnios, GDM, GHT, intrauterine growth retardation was evaluated between the study group and the control group. Apart from this, the difference between the birth weight of the two groups, the 1st minute apgar score, the 5th minute apgar score and the birth pH was evaluated. During the follow-up, 4 patients were excluded from the study group and 6 patients from the control group were excluded from the study because they could not be reached.

The statistical evaluation of the obtained data was performed with SPSS 17.0 for Windows package program. Continuous variables were expressed as average±standard deviation, and categorical variables as frequency and %. The Kolmogorov-Smirnov test was used to check the normal distribution of continuous variables. Student t test was used for comparison of 2 independent groups with normal distribution, and Mann Whitney U Test was used for variables without normal distribution. The probable relationship between the parameters was evaluated by Pearson correlation analysis method. If p-value is less than 0.05, it is considered signficant for statistical significance.

Results

There were not any statistically significant differences between the groups in terms of demographic characteristics such as age, gravida, parity, abortion, number of curettage, previous type of birth and body mass index.

There was a significant difference between the urine ketone level of the study group and the ketone level of the control group (p=<0.001). There wasn't any significant difference in blood gas pH mean value between the study group and control group (p=0.095). There was a significant difference in the blood gas pO_2 and lactate levels between the study group and control group (both p<0.001). A significant difference was observed in the GGT levels between the study group and the control group (p=0.001). There was not any statistically

Table 1. Laboratory data obtained from the first trimester of the study and control group

	Study group n=46	Control group n=44	p
Urine keton	2 (0-3)	0 (0-1)	<0.001
pH	7.4±0.04	7.38±0.03	0.095
Po_2	36.2±5.43	40.6±4.19	<0.001
Lactate	1.6±0.5	1.19±0.3	<0.001
GGT	25.8±18.4	14.7±12.6	0.001
TSH	1.25±0.8	1.41±0.81	0.347

Table 2. Antenatal complications of the study and control group and forms of delivery

	Study group n=46	Control group n=44	p
Complication N(%)			
No	29 (63)	37 (84.1)	0.320
Oligohidramnios	7 (15.2)	3 (6.8)	
Polihidramnios	2 (4.3)	1 (2.3)	
GDM	2 (4.3)	-	
GHT	2 (4.3)	1 (2.3)	
İUGR	4 (8.7)	2 (4.5)	
Week of Birth	39 (36-41)	38 (34-41)	0.538
Form of Delivery N(%)			
Vaginal delivery	24 (52.2)	24 (54.5)	0.822
Caesarean	22 (47.8)	20 (45.5)	
Caesarean Indication N(%)			
Previous uterine surgery	9 (19.6)	15 (34.1)	0.049
CPD	2 (4.3)	3 (6.8)	
Fetal distress	8 (17.4)	1 (2.3)	
Macrosomia	3 (6.5)	-	
Breech Presentation	-	1 (2.3)	

significant difference between the TSH levels of the study group and TSH levels of the control group (p=0.347) (Table1).

There weren't observed any statistically significant differences between the groups in terms of the complications developed during pregnancy follow-up (p=0.320). There weren't observed statistically significant differences between the groups in terms of delivery forms (p=0.822). There weren't observed any statistically significant differences between the groups in terms of cesarean indications (p=0.049) (Table 2).

When the study and control groups were compared in terms of early neonatal outcomes, there was observed a statistically significant difference in birth weight of newborns (p=0.002). There was observed a significant difference between the 1st minute apgar scores of the control and study groups (p=0.022). No statistically significant difference was observed between the newborns' 5st minute apgar scores of the control and study groups (p=0.769). The average values of pH value of the blood gases which were obtained from newborns were detected as 7.29 (±0.03) in study group and as 7.34 (±0.03) in the control group and with this assessment there was observed a statistically significant difference (p<0.001) (Table 3).

Table 3. Early neonatal outcomes of the study and control group

	Study group n=46	Control group n=44	p value
Birth weight	3050±452.4	3345±439.1	0.002
1st apgar scores	8 (6-9)	9 (6-9)	0.022
5st apgar scores	9 (8-10)	9 (8-10)	0.769
pH	7.29±0.03	7.34±0.03	<0.001

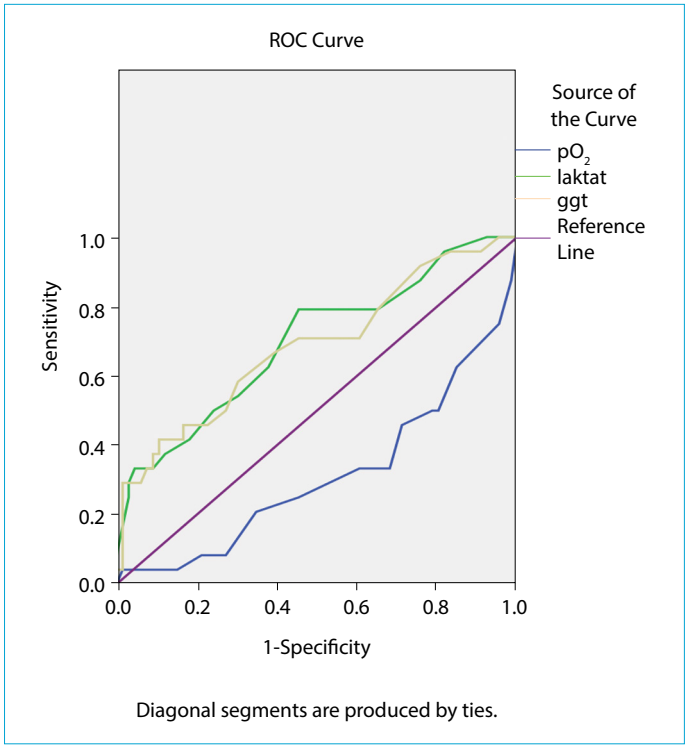

Figure 1. ROC curve adjusted for the pO_2 level, lactate level and GGT level according to complication conditions.

There was a positive correlation between blood gas pH levels and birth weight, first minute apgar value and birth pH of newborns (r=0.189, p=0.074, r=0.409 (p<0.001), r=0.390 (p<0.001)). Positive correlation was observed between the blood gas pO_2 levels of the patients and the birth weight, first minute apgar value and birth pH (r=0.244 p=0.20, r=0.376 (p<0.001), r=0.363 (p<0.001)). A negative correlation was observed between patients' lactate levels and birth weights, first minute apgar values and pH levels of birth (r=-0.085 p=0.426, r=-0.355 p=0.001, r=-0.439 (p<0.001)). There was a negative

Table 4. Correlation coefficients and significance values of the variables in the study and control groups

	Number of vomiting	Weight loss	ketones	pH	Po_2	Laktate	GGT	Birth weight	Apgar 1	Birth pH
Number of vomiting	-	r=0.754 p<0.001	r=0.849 p<0.001	r=-0.567 p<0.001	r=-0.531 p<0.001	r=0.558 p<0.001	r=0.557 p<0.001	r=-0.304 p=0.004	r=-0.410 p<0.001	r=-0.576 p<0.001
Weight loss	r=0.754 p<0.001	-	r=0.772 p<0.001	r=-0.532 p<0.001	r=-0.463 p<0.001	r=-0.444 p<0.001	r=0.488 p<0.001	r=-0.169 p=0.111	r=-0.354 p=0.001	r=-0.349 p=0.001
ketones	r=0.849 p<0.001	r=0.772 p<0.001	-	r=-0.486 p<0.001	r=-0.514 p<0.001	r=0.490 p<0.001	r=0.471 p<0.001	r=-0.303 p=0.004	r=-0.373 p<0.001	r=-0.485 p<0.001
pH	r=-0.567 p<0.001	r=-0.532 p<0.001	r=-0.486 p<0.001	-	r=0.630 p<0.001	r=-0.543 p<0.001	r=-0.570 p<0.001	r=0.189 p=0.074	r=0.409 p<0.001	r=0.390 p<0.001
Po_2	r=-0.531 p<0.001	r=-0.463 p<0.001	r=-0.514 p<0.001	r=0.630 p<0.001	-	r=-0.589 p<0.001	r=-0.478 p<0.001	r=0.244 p=0.020	r=0.376 p<0.001	r=0.363 p<0.001
Laktate	r=0.558 p<0.001	r=-0.444 p<0.001	r=0.490 p<0.001	r=-0.543 p<0.001	r=-0.589 p<0,001	-	r=0.583 p<0.001	r=-0.085 p=0.426	r=-0.355 p=0.001	r=-0.439 p<0.001
GGT	r=0.557 p<0.001	r=0.488 p<0.001	r=0.471 p<0.001	r=-0.570 p<0.001	r=-0.478 p<0,001	r=0.583 p<0.001	-	r=-0.329 p=0.002	r=-0.604 p<0.001	r=-0.303 p=0.004
Birth weight	r=-0.304 p=0.004	r=-0.169 p=0.111	r=-0.303 p=0.004	r=0.189 p=0.074	r=0.244 p=0.020	r=-0.085 p=0.426	r=-0.329 p=0.002	-	r=0.333 p=0.001	r=0.196 p=0.063
Apgar 1	r=-0.410 p<0.001	r=-0.354 p=0.001	r=-0.373 p<0.001	r=0.409 p<0.001	r=0.376 p<0.001	r=-0.355 p=0.001	r=-0.604 p<0.001	r=0.333 p=0.001	-	r=0.284 p=0.007
Birth pH	r=-0.576 p<0.001	r=-0.349 p=0.001	r=-0.485 p<0.001	r=0.390 p<0.001	r=0.363 p<0.001	r=-0.439 p<0.001	r=-0.303 p=0.004	r=0.333 p=0.001	r=0.284 p=0.007	-

correlation between patients' GGT levels and birth weight, 1st minute apgar value and pH levels of birth (r=-0.329 p=0.002, r=-0.604 (p<0.001), r=-0.303 (p=0.004)) (Table 4).

Factors that could be affected in cases with neonatal complications were evaluated by ROC analysis. The relationship between first trimester maternal pO_2, lactate and GGT levels and complication in ROC curve was evaluated. For each of the 3 parameters the area under the curve was defined as meaningful (respectively; AUC=0.313 p=0.007; AUC= 0.696 p=0.005; AUC= 0.067 p=0.008) (Fig. 1).

Discussion

It is generally accepted that the incidence of hyperemesis gravidarum with heavy nausea-vomiting table is generally around 0.5-1%.[14] HEG is a clinical chart with excessive nausea and vomiting and dehydration, ketosis, electrolyte and acid base imbalance, sometimes hepatic and renal insufficiency, leading to weight loss (5% of body weight).[15] This can affect the course of pregnancy and may have negative consequences for mother and fetus.

Prolonged loss of stomach contents in hyperemesis gravidarum leads to hypochloremic metabolic alkalosis.[6] The metabolic alkalosis is the respiratory center in acute compensation and the kidneys in the chronic compensation. Chemoreceptors that control ventilation during acute compensation decrease ventilation in response to the increase in pH, thereby increasing the formation of pCO_2 and H+and attempting to reduce the pH to normal. Compensation is provided by respiratory acidosis. Low oxygen in the respiratory acidosis, ie hypoxia.[7] In the case of hypoxia, nicotinamide adenine dinucleotide (NAD) formation is inhibited, thereby increasing the NADH/NAD ratio and lactate level. [8] In our study, we evaluated the hypoxemia induced by hyperemesis gravidarum and the results of increased hypoxia, increased lactate levels and oxidant substances in the antenatal period and postnatal life. It is thought that

the increase in lactate level may lead to premature neonatal negativities such as newborn weight, apgar score and pH value at birth because it shows that prolonged hypoxic condition is prolonged.

The prognosis of pregnancy in hyperemesis gravidarum is still controversial. Most of the studies reveal that it isn't different from other pregnancies in terms of fetal and maternal morbidity and mortality. When these patients are compared with normal pregnancies, it has been shown that there is no difference in terms of spontaneous abortion, less stillbirths, gestational age, prematurity, congenital anomaly.[7] Conversely, there are studies reporting that there is a negative correlation between symptoms and prognosis.[16] HEG might have a risk factor in terms of fetal low birth weight, intrauterine growth retardation and fetal anomalies.[5] Patients with HEG delivered lower birth weight infants.[17] In another study there was no difference between hyperemesis and normal pregnancies in terms of prematurity frequency and mean gestational age.[15] In our study, there were no significant differences between the study group and the control group in terms of delivery type, birth week, delivery indications with cesarean section, pregnancy complications (oligohydroamnios, polyhydroamnios, gestational hypertension, gestational diabetes mellitus, intrauterine growth retardation). Studies which are performed in patients with HEG are in a quality that support our findings.

NAD formation is inhibited in the case of hypoxia that occurs in patients with HEG, thereby increasing the NADH/NAD ratio and lactate level.[8] Therefore, elevation of the lactate level can be considered as an indicator of hypoxia. There isn't any study comparing the effect of high lactate levels in the early stages of the pregnancy and early neonatal period. In our study, we observed whether this condition in HEG patients was effective in the neonatal period. We assessed the decrease in birth weight with the increase in lactate level, the lowering of the 1st minute apgar score and the lower pH at birth.

GGT is responsible for extracellular catabolism of GSH, an important antioxidant in mammalian cells. Depending on the increased amount of GGT, continuous production of reactive oxygen species causes DNA breaks.[18] Other study suggested that the pathway associated with GSH catabolism of GGT may also lead to the production of prooxidant substances.[19] We observed that the GGT level, which contributed to the reduction of antioxidant production in our study, was higher in the study group than in the control group. In our study, we determined that GGT levels seen at first trimester had negative correlations with newborn birth weight, blood gas pH level and 1st minute apgar score.

Conclusion

Hypoxia, lactate elevation and increased oxidants in patients with hyperemesis gravidarum can be considered as the causes of morbidity in early neonatal period due to low birth weight in newborn, decreased 1st minute apgar score and adverse effects on blood gas. There is a need for new work to be done so that the lactate level seen in patients with HEG can be used as a predictable parameter for early neonatal complications.

Disclosures

Ethics Committee Approval: Permission was obtained from the ethics committee for the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship contributions: Concept – E.T.; Design – V.K.; Supervision – U.E; Materials – U.E, V.K.; Data collection &/or processing – U.E, B.K.; Analysis and/or interpretation – U.E.; Literature search – B.K.; Writing – V.K.; Critical review – E.T.

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