

Maternal amylase, lipase, lactate dehydrogenase, creatine kinase levels at preterm delivery, and the effect of tocolysis

Simten Genc¹, Melike Eren¹, Sadik Kukrer², Arzu Yurci³, Basak Cingillioglu¹, Elif Dilasa Pala Kose¹, Orhan Sahin¹, Hicran Acar Sirinoglu¹, Veli Mihmanli¹

¹ Obstetrics and Gynecology Department
Okmeydani Training and Research Hospital
Istanbul, Turkey

² Obstetrics and Gynecology Department,
University of Health Sciences Adana City
Training and Research Hospital

³ Memorial Kayseri Hospital IVF Center,
Gynecology Obstetrics & Reproductive Medicine,
Kayseri, Turkey

ORCID ID of the author(s)

SG: 0000-0003-4446-4467
ME: 0000-0002-5134-6082
SK: 0000-0001-8465-3225
AY: 0000-0003-4808-9019
BC: 0000-0002-1666-8588
EDPK: 0000-0003-2898-5430
OS: 0000-0002-7216-3816
HAS: 0000-0003-4100-3868
VM: 0000-0001-8701-8462

Corresponding Author

Simten Genc
Darulaceze Cad. No:25, Okmeydani, Sisli, 34384,
Istanbul, Turkey
E-mail: simtengenc@yahoo.com.tr

Ethics Committee Approval

Approval was granted by the Ethics Committee of the University of Health Sciences, Okmeydani Training and Research Hospital (Date 15/02/2021, No:48670771-514.10/16).

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest

No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Preterm labor is one of the main obstetric problems and the leading cause of neonatal mortality and morbidity. Some pregnant women at risk of preterm labor receive tocolytic therapy, but the agents used can affect maternal blood parameters and enzyme levels. Physiological changes that occur during pregnancy may cause changes in enzymatic activities. Maternal amylase, lipase, lactate dehydrogenase (LDH), and creatine kinase (CK) levels should be followed throughout pregnancy to assess any increase. This study aimed to examine maternal amylase, lipase, creatine kinase, and lactate dehydrogenase levels in pregnant women who gave term and preterm birth and determine the physiological changes that may occur with gestational age and tocolysis.

Methods: The records of patients over their 24th gestational week who gave birth at the Gynecology and Obstetrics Department of Okmeydani Training and Research Hospital between July-December 2018 were reviewed in this retrospective cohort study. Their clinical findings, maternal and obstetric outcomes were noted. A total of 548 pregnant women were included in the study, who were divided into three groups: Group 1- Preterm delivery without tocolysis, Group 2- Preterm delivery with tocolysis, Group 3- Term delivery

Results: The maternal age, gravidity, history of abortion, fetal gender, amylase, and lipase values were similar between the groups ($P>0.05$ for all), while delivery types and cesarean section indications significantly differed ($P=0.009$, and $P<0.001$ respectively). The mean LDH value of Group 2 was significantly higher than those of Groups 1 and 3 ($P=0.006$, and $P=0.024$, respectively). The mean CK value of Group 3 was also higher than those of Groups 1 and 2 ($P=0.021$, and $P<0.001$, respectively), and that of Group 1 was significantly higher than that of Group 2 ($P=0.021$). LDH, amylase, lipase, and CK levels were not correlated with gestational age and fetal weight in the premature birth groups. In Group 3, a significant negative correlation was observed between fetal weight and amylase ($r=-0.136$ $P=0.02$). Among all patients, gestational week and LDH ($r=-0.117$, $P=0.006$) and fetal weight and LDH ($r=-0.107$, $P=0.012$) were negatively correlated, while fetal weight and lipase ($r=0.095$ $P=0.027$) and gestational week and CK were positively correlated ($r=0.085$ $P=0.047$) (Table 2, Figures 2 and 3).

Conclusion: Maternal enzyme levels may change with gestational week and as fetal weight increases. It is necessary to differentiate between pathological and physiological changes. These enzymes are also affected by tocolytic agents. Since our study was conducted in a healthy pregnant group without any systemic diseases, we think that the changes caused by gestational age and fetal weight gain are physiologically acceptable. However, any sudden elevation in these enzymes should be thoroughly investigated throughout pregnancy.

Keywords: Amylase, Creatine kinase, Lactate dehydrogenase, Lipase, Nifedipine, Tocolysis

Introduction

Physiological changes that occur during pregnancy may alter enzymatic activities. Amylase is mostly secreted from the pancreas and salivary glands. Lipase, on the other hand, is mainly found in the pancreas, with small amounts in the stomach, liver, and intestinal mucosa. Its serum level stays higher for longer periods. However, in conditions such as acute pancreatitis, which is rare and may progress with maternal and fetal mortality and morbidity, a significant increase is observed in both amylase and lipase values [1].

Lactate dehydrogenase (LDH) is found in various tissues such as the heart, the liver, skeletal muscle, and the kidney, and elevated values have nonspecific clinical significance [2]. Creatine kinase (CK) is important in the regulation of high-energy phosphate metabolism [3]. The changes which may occur in these enzymatic activities during normal pregnancy have not been fully elucidated. Maternal enzyme activities should be thoroughly assessed in healthy pregnant women, and their elevations should be investigated, just as in non-pregnant women.

Preterm labor, one of the main problems of obstetrics, is the leading cause of neonatal mortality and morbidity. The respiratory, gastrointestinal, renal, and neurological systems of preterm babies are at elevated risk for various complications. Some pregnant women at risk of preterm labor receive tocolytic therapy [4]. However, the agents used can affect maternal blood parameters and enzyme levels.

This study aimed to examine the maternal amylase, lipase, creatine kinase, and lactate dehydrogenase levels in pregnant women who gave term and preterm birth and to determine the physiological changes that may occur with gestational age and tocolysis.

Materials and methods

The records of the patients over their 24th gestational week who were admitted to the Gynecology and Obstetrics Department of Okmeydani Training and Research Hospital to deliver a baby between July and December 2018 were retrospectively analyzed, and clinical findings and maternal and obstetric outcomes were noted. A total of 548 pregnant women were included in the study. Pregnant women under 18 years of age, smokers, those with systemic diseases, gestational diabetes, preeclampsia, multiple pregnancy, maternal TORCH group infections, chorioamnionitis, fetal death, and fetal anomaly were not included in the study.

Vaginal examinations were performed in all patients at the time of their admission to the hospital, and the presence of cervical effacement and dilatation were recorded. Uterine contractions were followed with external monitoring, and obstetric ultrasonography was performed to observe fetal development. Transvaginal ultrasonography was performed to determine the length of the cervical canal in the preterm delivery group. The gestational age was calculated per the last menstrual date or the ultrasonographic findings obtained before 20 weeks of gestation. Age, gravida, parity, number of miscarriages, gestational age, birth weight, fetal sex, and the delivery type were noted. The patients were divided into 3 groups: Group 1

included the patients who had preterm delivery without tocolysis (n=199), Group 2 patients had preterm delivery and received tocolysis (n=56), and Group 3 included those who gave term deliveries (n=293).

Preterm delivery is defined as the progressive dilatation of the cervix before 37 weeks of gestation with uterine contractions. In our study, the diagnostic criteria of preterm labor were the presence of effective (45-50 mmHg) uterine contractions, occurring 4 times in 20 minutes or 6 times in 60 minutes, as well as a cervical dilation of 2 cm or observation of cervical changes during physical examination. All pregnant women between their 24th-34th gestational weeks received 12 mg of betamethasone at their time of admission and an additional dose after 24 hours for fetal lung maturation.

The nifedipine tocolysis protocol was started on the pregnant women whose contractions persisted despite bed rest and hydration. For tocolysis, the American College of Obstetricians and Gynecologists (ACOG) recommends a loading dose of 30 mg of nifedipine administered orally, followed by 10 mg to 20 mg every 4 to 6 hours [5], which we followed. In our clinic, nifedipine 10 mg capsule was administered orally for a loading dose, repeated every 20 minutes for 3 doses. The maintenance treatment was continued with 10 mg of nifedipine administered in the form of 2 capsules, 4 times in 48 hours. The treatment was discontinued after 48 hours in pregnant women without uterine contractions. In those whose contractions continued after 48 hours, maintenance treatment was continued until the contractions ceased. We observed no side effects, such as maternal tachycardia, hypotension, or chest pain, therefore, did not need to cease treatment early. Pregnant women giving preterm labor over their 34th gestational week or giving birth immediately did not receive tocolysis. Maternal amylase, lipase, creatine kinase, and lactate dehydrogenase levels were studied by obtaining blood samples from all pregnant women before delivery. The normal range for these enzymes in our hospital is as follows: Amylase: 28-100 U/L, lipase: <67 U/L, creatine kinase: 0-145 U/L, and LDH: <248 U/L.

Statistical analysis

All statistical analyses were performed using the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) package program. Data were presented with descriptive statistical methods (mean, standard deviation, median, interquartile range), and the distribution of variables was examined with the Shapiro-Wilk normality test. One-way analysis of variance (ANOVA) and Tukey multiple comparison tests were used to compare normally distributed groups and subgroups, respectively. Non-normally distributed groups and subgroups were compared with the Kruskal-Wallis test and Dunn's multiple comparison test, respectively. The chi-square test was used for the comparison of qualitative data, and the Pearson correlation test was employed to determine the relationships between the variables. A *P*-value of <0.05 was considered significant.

Ethics approval

This study was performed per the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Health Sciences, Okmeydani

Training and Research Hospital (Date 15/02/2021 No:48670771-514.10/16).

Results

The maternal age, gravidity, history of abortion, fetal gender, amylase, and lipase values were similar between the groups ($P>0.05$ for all) (Table 1), while delivery types and cesarean section indications significantly differed ($P=0.009$, and $P<0.001$ respectively). The rates of failure to progress, cephalopelvic disproportion, and macrosomia were higher in Group 3, while malpresentation and placental disorders were more frequent in Group 2.

Table 1: Demographic characteristics, obstetric outcomes, and maternal enzyme levels

		Group 1 Tocolysis (-) n=99	Group 2 Tocolysis (+) n=56	Group 3 ≥37 weeks n=293	P-value
Age (years)	Mean(SD)	27.63 (6.66)	28.2 (7.3)	27.17 (5.54)	0.449 ^a
Delivery	Vaginal	96 48.24%	24 42.86%	175 59.73%	0.009 ^b *
	Cesarean	103 51.76%	32 57.14%	118 40.27%	
Gender	Female	84 42.21%	28 50.00%	151 51.54%	0.121 ^b
	Male	115 57.79%	28 50.00%	142 48.46%	
Gravida	Mean(SD)	2.9 (1.79)	2.61 (1.79)	2.51 (1.18)	0.074 ^c
	Median (IQR)	3 (2-4)	2 (1-3)	2 (2-3)	
Parity	Mean(SD)	1.6 (1.53)	1.29 (1.52)	1.25 (1.01)	0.022 ^c
	Median (IQR)	1 (1-2)	1 (0-2)	1 (0.5-2)	
Abortus	Mean(SD)	0.3 (0.75)	0.32 (0.66)	0.26 (0.61)	0.540 ^c
	Median (IQR)	0 (0-0)	0 (0-0.75)	0 (0-0)	
Gestational age (weeks)	Mean(SD)	35.62 (1.13)	32.11 (2.65)	39.12 (1.2)	<0.001 ^a
Fetal weight (g)	Mean(SD)	2734.65 (456.41)	1967.16 (648.13)	3311.14 (555.3)	<0.001 ^a
Maternal lactate dehydrogenase (U/L)	Mean(SD)	257.18 (86.88)	310.93 (127.6)	261.49 (73.9)	0.019 ^{**}
	Median (IQR)	239 (206-288)	264 (216.25-359.5)	249 (213-292.5)	
Maternal amylase (U/L)	Mean(SD)	70.72 (24.97)	67.73 (30.16)	70.91 (24.88)	0.428 ^c
	Median (IQR)	68.85 (50.36-83.46)	63.4 (48.54-80.68)	66.85 (53.60-84.27)	
Maternal lipase (U/L)	Mean(SD)	18.99 (11.9)	17.72 (9.64)	20.61 (15.01)	0.279 ^c
	Median (IQR)	16.78 (11.44-24.5)	16.42 (10.38-24.17)	17.14 (12.35-24.64)	
Maternal creatine kinase (U/L)	Mean(SD)	94.27 (72.64)	75.98 (54.66)	109.24 (121.54)	<0.001 ^a
	Median (IQR)	68 (50-115)	53.5 (37.25-100.25)	82 (59.5-115.5)	

a One-way analysis of variance, b Chi-square test c Kruskal Wallis test *Statistically significant

The three groups had comparable amylase and lipase values ($P=0.428$, and $P=0.279$, respectively). The mean LDH value of Group 2 was significantly higher than those of Groups 1 and 3 ($P=0.006$, and $P=0.024$, respectively). The mean CK value of Group 3 was also higher than those of Groups 1 and 2 ($P=0.021$, and $P<0.001$, respectively), and that of Group 1 was significantly higher than that of Group 2 ($P=0.021$).

LDH, amylase, lipase, and CK levels were not correlated with gestational age and fetal weight in the premature birth groups. In Group 3, a significant negative correlation was observed between fetal weight and amylase ($r=-0.136$ $P=0.02$) (Figure 1). Among all patients, gestational week and LDH ($r=-0.117$ $P=0.006$) and fetal weight and LDH ($r=-0.107$ $P=0.012$) were negatively correlated, while fetal weight and lipase ($r=0.095$ $P=0.027$) and gestational week and CK were positively correlated ($r=0.085$ $P=0.047$) (Table 2, Figures 2 and 3).

Table 2: Correlation of gestational age and fetal weight with maternal enzymes

Group	Enzyme	Gestational age	Fetal weight
Group 1, Tocolysis (-)	LDH	r	-0.055
		p	0.442
	Amylase	r	0.066
		p	0.357
	Lipase	r	0.001
		p	0.992
CK	r	0.024	
	p	0.740	
Group 2, Tocolysis (+)	LDH	r	0.017
		p	0.902
	Amylase	r	0.038
		p	0.782
	Lipase	r	0.101
		p	0.458
CK	r	0.034	
	p	0.804	
Group 3, Term	LDH	r	-0.068
		p	0.249
	Amylase	r	-0.033
		p	0.569
	Lipase	r	0.001
		p	0.992
CK	r	-0.04	
	p	0.496	
All groups	LDH	r	-0.117
		p	0.006
	Amylase	r	0.031
		p	0.464
	Lipase	r	0.072
		p	0.093
CK	r	0.085	
	p	0.047	

Pearson correlation test

Figure 1: Correlation between amylase level and fetal weight

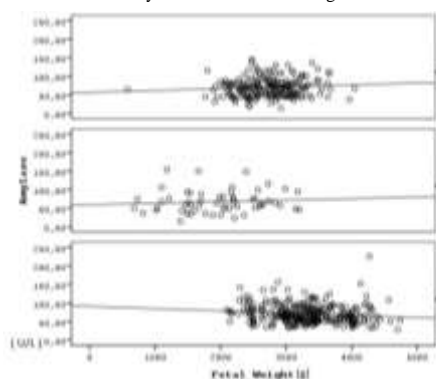


Figure 2: Correlation between maternal enzyme levels and gestational age

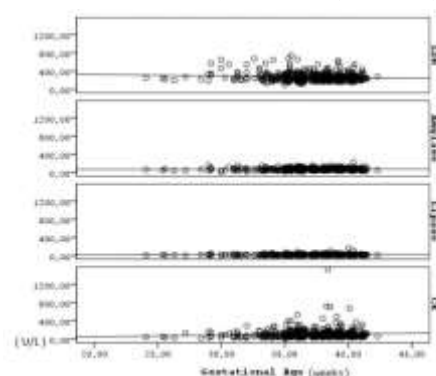
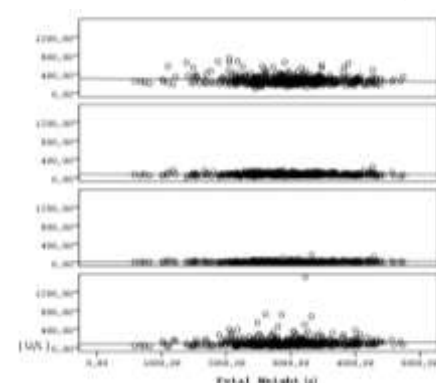


Figure 3: Correlation between maternal enzyme levels and fetal weight



Discussion

Physiological changes can occur in maternal enzyme levels throughout the pregnancy. Since our hospital is a reference center, many patients are admitted to the emergency department to give birth. Therefore, unlike many studies, our study group consisted of a large number of patients. We think that we can better understand the changes that may occur with the advancing gestational weeks and the effects of tocolysis since healthy pregnant women without any systemic disease were included as a control group in our study.

Amylase is produced mainly by the pancreas and salivary glands and is one of the main enzymes of the digestive system. Salivary alpha-amylase is an indicator of sympathetic nervous system activity [6]. Today, salivary and serum amylase tests are widely used in obstetrics and gynecology. Cases of ruptured ectopic pregnancy can also lead to an increase in serum lipase and amylase levels, mimicking acute pancreatitis [7]. Psychological or physical stress, and acute stress conditions during delivery, such as spinal anesthesia in cesarean section, may increase α -amylase levels [8, 9]. As our patient group was treated under observation in the hospital, these patients may have been exposed to stress. In the study of Nava et al., the authors stated that amylase levels did not change with gestational age [10], similar to our results.

Prematurity is one of the leading causes of neonatal mortality and morbidity. Various agents are used for tocolytic therapy. Many centers aim to postpone the delivery with tocolytic agents for 48 hours to ensure the maximum effectiveness of corticosteroids and the transfer of the pregnant women to reference centers. There is no consensus on the first-line agents [11]. Ritodrine has been used for many years as a beta-agonist for tocolysis, but it may cause hyperamylasemia. Although the effect of this agent on serum amylase activity is not fully known, it was shown to cause excessive secretion of salivary type amylase in approximately one-third of pregnant women [12]. In the study of Nakajima et al. on the analysis of the umbilical cord of premature fetuses, amylase levels did not differ between the group receiving and not receiving ritodrine and did not change with birthweight and gestational age [13]. In our study, we used nifedipine as a tocolytic agent. Nifedipine is a calcium channel blocker globally administered via the oral or sublingual route for tocolysis [4]. It exerts its activity by preventing the free calcium ion from entering the cell through the calcium channels in the plasma membrane. It decreases uterine vascular resistance, contractile activity, and the basal tonus of myometrium, as well as the amplitude, and tonus of contractions. In a meta-analysis in which nifedipine was compared with β adrenergic agents, nifedipine was more effective and better tolerated [14]. In our study, no significant difference was found in the amylase values of the pregnant women who gave premature birth when compared with those that did and did not receive tocolytic therapy. However, in women with term pregnancies, fetal weights increased, and amylase values decreased. Xydas et al. [15] obtained several blood samples from healthy pregnant women who did not receive tocolytic therapy to determine whether a change occurred in their serum amylase and lipase values, but no significant change was found in amylase and lipase values with advancing gestational weeks, similar to

our results. Tocolytic therapy did not affect these enzymes, also. Acute pancreatitis during pregnancy is a rare condition that can lead to maternal and fetal mortality and high serum amylase and lipase levels are just as important findings in pregnant women as in non-pregnant women. However, a thorough knowledge of the physiological changes during pregnancy in detail will prevent delays in diagnoses [16]. Serum lipase is a better biomarker than serum amylase to evaluate a diagnosis of acute pancreatitis [17]. In a prospective study by Karsentine et al. [18], pregnant women were examined in all three trimesters and compared with the non-pregnant group with no differences found in amylase levels. However, significantly lower serum lipase activity was observed in the first trimester compared to the third trimester and non-pregnant women. The serum lipase activity of pregnant women in their second and third trimesters and non-pregnant women were similar. Lipase levels remained below the normal upper limit. While diagnosing acute pancreatitis, these physiological modifications during pregnancy should also be considered. In our study, lipase levels increased with fetal weight. However, tocolytic therapy did not play a role in this increase.

There was no significant difference between serum amylase and lipase levels and amylase-creatinine clearance ratio (Cam: Ccr%) in pregnant and non-pregnant women. There is no published data regarding the effect of tocolytic therapy on serum lipase activity, which is considered one of the most sensitive, and specific indicators of pregnancy, and pancreatitis [19]. Under normal conditions, moderate increases in Lactate dehydrogenase (LDH) are observed in cord blood associated with the onset of labor and changes in acid-base status. Its levels also increase in advancing gestation. The increase in LDH levels with pregnancy is more dependent on pH values than on gestational age [20]. In a study conducted with pregnant women who had a preterm delivery, blood samples taken during the 2nd trimester were examined and the average maternal LDH levels were insignificantly higher [21]. In our study, LDH values of the tocolysis group were significantly higher than the LDH values of the preterm group that did not receive tocolytic therapy and the term group. In another study, LDH levels measured in mid-trimester amniocentesis material and preterm delivery were significantly related [22]. One of the most interesting results in our study was that in all patient groups, LDH levels decreased with advancing gestational weeks.

Plasma creatine kinase (CK) activity measured in early pregnancy was associated with blood pressure during pregnancy and severe gestational hypertension diagnosed before 34 weeks of gestation, but no relationship was found between creatine kinase levels and other hypertensive diseases [23]. In the study conducted on women who gave preterm deliveries and received tocolytic therapy with ritodrine for more than 1 week, the cord blood CK concentration was significantly higher than the group that did not receive tocolytic therapy. Additionally, CK was significantly associated with gestational age and birth weight. However, in the same study, no change was detected in LDH levels associated with tocolysis, and tocolytic therapy was not significantly associated with gestational age and birth weight [13]. In another study, if tocolytic therapy was continued for longer than a week, CK levels rose above the normal range in nearly a quarter of these patients [24]. Adamcov et al. [25]

reported that CK levels correlated with gestational age or birth weight. In our study, as the gestational week increased, CK levels also significantly increased.

Maternal enzyme values may vary during pregnancy. In most studies, ritodrine and magnesium sulfate were used for tocolysis. In our study, tocolysis was performed with nifedipine, and we observed that LDH values were higher in the preterm group that underwent tocolytic therapy. However, CK values were higher in the preterm delivery group that did not receive tocolytic therapy. No significant difference was found between these groups in terms of amylase and lipase values. There was no significant correlation between LDH, amylase, lipase, and creatine kinase values, gestational week, and fetal weight in the premature delivery groups. Besides, tocolytic therapy did not change the levels of these enzymes. In pregnant women with term deliveries, as fetal weight increased, amylase values decreased. In the entire patient group, as the gestational week advanced, LDH decreased, but CK increased. As fetal weight increased, LDH decreased, but lipase increased.

Conclusion

Maternal enzyme levels may change with gestational week and as fetal weight increases. It is necessary to distinguish between pathological and physiological changes. Enzymes are also affected by the agents used in tocolysis. Since our study was conducted in a healthy pregnant group without any systemic diseases, we think that the changes caused by gestational age and fetal weight gain can be physiologically acceptable. However, multicentered prospective studies with a greater number of patients are needed to distinguish between the pathological and physiological values accurately.

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