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Image	200	No abstract	3	No table	3

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ORIGINAL ARTICLE

Predictors of pediatric non-alcoholic fatty liver disease (NAFLD) in obese children and adolescents: Is serum ALT level sufficient in detecting NAFLD?

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ABSTRACT

Objective: The prevalence of obesity and related comorbidities is increasing in children and adolescents. This study aimed to specify the prevalence of non-alcoholic fatty liver disease (NAFLD) in obese children and adolescents and to identify the predictive factors associated with NAFLD.

Material and Methods: Obese children and adolescents aged 6 to 18 years were included in the study. The presence and degree of hepatosteatosis were evaluated using liver US. The groups with and without NAFLD were compared in terms of demographic, anthropometric, and biochemical parameters.

Results: One hundred fifty-five obese children and adolescents with a median age of 13.8 (4.93) years (43 males, 131 pubertal) were included in the study. We found that 57.4% of obese cases had NAFLD. In the group with NAFLD, serum ALT level, AST level, HOMA-IR, and triglyceride level were significantly higher ($p<0.001$, $p<0.001$, $p=0.015$, $p=0.021$, respectively), and serum HDL-C level was significantly lower ($p=0.001$) compared to the group without NAFLD. In the binomial logistic regression analysis, age ($\beta=0.213$, OR=1.23, $p=0.040$) and serum ALT level ($\beta=0.047$, OR=1.04, $p=0.011$) were determining factors for hepatosteatosis. The diagnostic accuracy of elevated serum ALT level in detecting NAFLD was found to be 65.8% with a sensitivity of 77.3% and a specificity of 57.3% (+LR 1.81 and -LR 0.40).

Conclusion: The prevalence of NAFLD determined with US in obese children and adolescents was 57.4%. Age and serum ALT level were found to be predictive factors for hepatosteatosis. Increased ALT alone shows insufficient performance in detecting NAFLD.

Keywords: Adolescents, children, hepatosteatosis, non-alcoholic fatty liver, obese, predictors, prevalence.

Cite this article as: Özer Y, Yapar Gümüş C. Predictors of pediatric non-alcoholic fatty liver disease (NAFLD) in obese children and adolescents: Is serum ALT level sufficient in detecting NAFLD? Zeynep Kamil Med J 2024;55(2):59–66.

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INTRODUCTION

Pediatric non-alcoholic fatty liver disease (NAFLD) is described as chronic hepatic steatosis in children and adolescents that is not due to secondary causes such as infection, genetic/metabolic disorder, malnutrition, or steatogenic drug use. Non-alcoholic fatty liver is defined as the presence of hepatosteatosis in the absence of hepatocellular injury, and non-alcoholic steatohepatitis (NASH) is defined as hepatosteatosis associated with inflammation and hepatocellular injury.[1,2] NAFLD is a relatively benign condition, but it may progress to end-stage liver disease because of oxidative stress and inflammation.[3]

Non-alcoholic fatty liver disease is mostly associated with obesity, insulin resistance, diabetes, and dyslipidemia.[1,2] With the dramatic increase in childhood obesity, NAFLD is currently one of the most important health problems. As is known, the prevalence of obesity-related comorbidity increases in parallel to obesity.[4] In a meta-analysis study published in 2015, the prevalence of NAFLD was shown to be 34.2% in the clinically obese population and 7.6% in the general population in children and adolescents aged 1 to 19 years.[5] In the USA, NAFLD is the most common cause of chronic liver disorder in children and adolescents.[1]

Because NAFLD is often asymptomatic, screening for NAFLD in obese children and adolescents is more important.[1,6,7] Unfortunately, there is currently no consensus on screening strategies for NAFLD in children and adolescents who are at risk. While the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommends NAFLD screening with serum alanine aminotransferase (ALT) (ALT >45 IU/L) and abdominal US,[8] the North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) recommends NAFLD screening with ALT level (ALT >52 IU/L for boys and ALT >44 IU/L for girls).[1] In the consensus statement of the European Society of Endocrinology and the Pediatric Endocrine Society (ESPE) published in 2017, it was recommended that children and adolescents with a body mass index (BMI) ≥ the 85th percentile should be evaluated with ALT (ALT >25 U/L for boys and ALT >22 U/L for girls) in terms of NAFLD.[6] Although liver biopsy is the gold standard for the diagnosis of NAFLD, its use in children is limited. Therefore, biochemical markers and abdominal US in NAFLD screening will help clinicians in making decisions.[3]

In obese children and adolescents, measurements of body composition such as BMI and trunkal fat index, fasting glucose, fasting insülin, ALT, γ-glutamyltranspeptidase (γGT), uric acid levels and dyslipidemia have been reported to be predictors of NAFLD.[3,7,9–11] This study aimed to specify the prevalence of NAFLD in obese children and adolescents with US and to determine predictive factors for NAFLD. In addition, it was also aimed to compare the diagnostic accuracy of serum ALT level with the NAFLD screening results specified with liver US.

MATERIAL AND METHODS

Children and adolescents aged between 6 and 18 years, who were diagnosed as having obesity at the pediatric endocrinology outpatient clinic between July 1, 2022, and June 31, 2023, were evaluated retrospectively. Data related to age, anthropometric measurements, pubertal status, biochemical parameters, and presence of hepatosteatosis according to US results were recorded from the files of the subjects whose BMI values were above the 95th percentile for age. The subjects who had congenital anomalies, syndromic obesity, endocrine disorders, psychiatric disorders, and diseases known to cause steatosis (viral hepatitis, a history of parenteral nutrition, drug use, and autoimmune and metabolic liver diseases) were not included in the study.

In all subjects, physical examination and pubertal staging were performed by the same pediatric endocrinologist (YÖ). Weight measurements were performed using a calibrated 100 g sensitivity digital scale, and height measurements were performed using a wall-mounted stadiometer (SECA, model 220, Hamburg, Germany). The body mass index was computed by dividing weight by the square of height (kg/m²). Obesity was defined as a BMI value of > the 95th percentile according to the reference curves prepared for the Turkish children and adolescents.[12] This study was approved by the Ordu University Clinical Researches Ethics Committee (2023/177), and informed consent was not required due to the retrospective design of the study. The study was conducted following the ethical guidelines set forth in the Declaration of Helsinki, ensuring the ethical treatment of human subjects in medical research.

Following a fasting period of 8–10 hours, serum glucose, ALT, aspartate aminotransferase (AST), and lipid profile were evaluated with routine standard enzymatic methods using the Roche Cobas 8000 c 702 device. An ALT level >25 IU/ml in boys and an ALT level >22 IU/ml in girls was considered abnormal.[13] Insulin resistance was determined by applying the Homeostasis Model Assessment (HOMA-IR) formula, which involves the product of fasting insulin concentration (U/mL) and fasting glucose concentration (mg/dL), divided by 405.[14]

Serum total cholesterol (TC) levels over 200 mg/dL and triglyceride levels over 100 mg/dL in subjects aged between 6 and 9 years, triglyceride levels over 130 mg/dL in subjects aged between 10 and 19 years, low-density lipoprotein-cholesterol (LDL-C) levels over 130 mg/dL, or high-density lipoprotein-cholesterol (HDL-C) levels under 40 mg/dL were accepted as dyslipidemia.[6] Liver US was performed using Toshiba Alpio 500 by the same radiologist in all patients. The group with NAFLD was classified as grade 1 (mild), grade 2 (moderate), and grade 3 (marked) hepatic steatosis according to liver echo pattern.[8]

Statistic Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences, version 21.0 (IBM Inc., Chicago, Ill, USA). Normal data distribution was tested with the Kolmogorov-Smirnov test. Descriptive statistics for categorical variables were presented as frequencies and percentages. The continuous variables were displayed as mean±standard deviation or median [interquartile range (IQR)] according to their distribution. The Student T-test (for two groups) or one-way variance analysis (for three or more groups) was used for comparison of the normally distributed continuous variables. The continuous variables without normal distribution were compared using the Mann-Whitney U test or the Kruskal-Wallis test. The categorical variables were compared with the Chi-square test. Spearman correlation analyses were used for correlations between the grade of NAFLD and other parameters. For multivariate analysis, binomial logistic regression analysis was used to evaluate the independent predictive factors of NAFLD. A p-value of <0.05 was considered significant.

Table 1: Demographic, physical and biochemical parameters of the NAFLD and non-NAFLD patients

	Non-NAFLD (n=66)	NAFLD (n=89)	p
Age (years)	13.2 (5.30)	13.2 (4.35)	0.171
Gender (male/female) n, (%)	10/56 (15.2/84.8)	33/56 (37.1/62.9)	**0.003**
Pubertal status (prepubertal/pubertal) n, (%)	9/57 (13.6/86.4)	15/74 (16.9/83.1)	0.584
Weight SDS	3.00±0.99	3.31±1.17	0.075
Height SDS	0.22±1.17	0.42±1.18	0.296
BMI SDS	2.76±0.67	2.95±0.65	0.084
ALT (IU/L)	17.0 (10.0)	28.0 (20.5)	**<0.001**
AST (IU/L)	19.0 (7.5)	25.5 (16.0)	**<0.001**
Cases with increased ALT levels n, (%)	17 (25.8)	53 (59.6)	**<0.001**
FBG (mg/dl)	92 (9)	92 (12)	0.280
HbA1c (%)	5.4 (0.4)	5.5 (0.3)	**0.006**
Fasting insulin (IU/mL)	23.4 (16.7)	31.0 (20.2)	0.027
HOMA-IR	5.21 (3.90)	7.02 (4.83)	**0.015**
Total cholesterol (mg/dL)	160.5±29.4	162.6±28.2	0.660
LDL-C (mg/dL)	90.7±30.1	92.9±23.7	0.615
HDL-C (mg/dL)	49.0±10.6	43.7±9.2	**0.001**
Triglyceride (mg/dL)	112.5±38.1	130.8±58.2	**0.021**
Dyslipidemia n, (%)	37 (56)	55 (61.8)	0.472

NAFLD: Nonalcoholic fatty liver disease; SDS: Standard deviation score; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostatic model assessment of insulin resistance; LDL-C: Low-density lipoprotein-cholesterol; HDL-C: High-density lipoprotein-cholesterol.

RESULTS

One hundred fifty-five obese children and adolescents (43 boys, 131 pubertal) with a median age of 13.8 (4.93) years were included in the study. Hepatosteatosis was found in 89 patients (57.4%) on US examination. Sixty-three patients (70.8%) had grade 1 hepatosteatosis, 19 (21.3%) patients had grade 2 hepatosteatosis, and 7 patients (7.9%) had grade 3 hepatosteatosis. Alanine aminotransferase was found to be increased in 66 patients (42.8%) who were obese. At least one abnormal lipid concentration was found in 59.4% (n=92) of the obese subjects; 40% (n=60) of the patients had hypertriglyceridemia, 12.3% (n=19) had hypercholesterolemia, 25.2% (n=38) had increased LDL-C, and 10.6% (n=16) had decreased HDL-C.

When NAFLD and non-NAFLD were compared, age and pubertal status were not found to be different (p=0.171; p=0.584, respectively). NAFLD was more common in boys compared to girls (76.7% vs. 50%, p=0.003). Weight SDS, height SDS, and BMI SDS were indifferent between the NAFLD group and non-NAFLD group. In the NAFLD group, serum ALT, AST, and triglyceride levels, as well as HOMA-IR, were significantly higher (p<0.001, p<0.001, p=0.015, p=0.021, respectively), and serum HDL-C level was significantly lower (p=0.001) compared to the non-NAFLD group. In the non-NAFLD group, 25.8% (n=17) had increased ALT levels. In contrast, the NAFLD group exhibited a higher prevalence, with 59.6% (n=53) having increased ALT levels (p=0.001).

A comparison of the data between the NAFLD and non-NAFLD groups is shown in Table 1.

When the patients with NAFLD were compared according to the grade of hepatosteatosis, serum ALT level was found to be significantly higher in grade 2 and grade 3 compared to grade 1 (p=0.006 and p=0.013, respectively), and serum AST level was found to be significantly higher in grade 3 compared to grade 1 (p=0.019). Serum fasting insulin level was found to be significantly higher in grade 3 compared to grade 1 and grade 2 (p=0.008 and p=0.037, respectively), and HOMA-IR was found to be significantly higher in grade 3 compared to grade 1 (p=0.007). A comparison of the data between the three patient groups with grade 1, grade 2, and grade 3 hepatosteatosis is shown in Table 2.

In the binomial logistic regression analysis, it was observed that the model was statistically significant (Pseudo R^2=0.25, p<0.001). In the binomial logistic regression analysis, age (β=0.213, OR=1.23, p=0.040) and ALT value (β=0.047, OR=1.04, p=0.011) were found to be statistically significant determining factors in detecting NAFLD (Table 3).

A positive correlation was found between the degree of hepatosteatosis and weight SDS, BMI SDS, fasting insulin, HbA1c, HOMA-IR, ALT, and AST (p=0.009, r=0.309; p=0.024, r=0.182; p=0.003, r=0.241; p=0.003, r=0.235; p<0.001, r=0.268; p<0.001, r=0.454; p<0.001, r=0.372, respectively). A negative correlation was

Table 2: Comparison of data between three patient groups with grade 1, 2, and 3 NAFLD

	Grade 1 hepatosteatosis (n=63)	Grade 2 hepatosteatosis (n=19)	Grade 3 hepatosteatosis (n=7)	p
Age (years)	13.2 (4.73)	13.9 (3.57)	14.4 (2.61)	0.309
Gerder (male/female) n, (%)	25/38	5/14	3/4	0.545
Pubertal status (prepubertal/pubertal) n, (%)	12/51	3/16	0/7	0.442
Weight SDS	3.23±1.05	3.50±1.04	3.45±1.67	0.321
Height SDS	0.59±1.20	0.12±1.01	-0.26±1.16	0.138
BMI SDS	2.87±0.62	3.16±0.65	3.20±0.75	0.133
ALT (IU/L)	22.2 (17.5)	42.0 (45.2)	36.0 (42.5)	<0.001
				G1 vs.G2 0.006
				G1 vs.G3 0.013
				G2 vs.G3 0.889
AST (IU/L)	23.0 (12.5)	30.0 (26.5)	43.0 (28.5)	0.007
				G1 vs.G2 0.109
				G1 vs.G3 0.019
				G2 vs.G3 0.427
FBG (mg/dl)	92 (11)	96 (11.5)	90 (15.58)	0.462
HbA1c (%)	5.5 (0.3)	5.5 (0.4)	5.7 (0.6)	0.340
Fasting insulin (IU/mL)	27.1 (17.2)	32.1 (16.8)	40.0 (24.6)	0.009
				G1 vs.G2 0.671
				G1 vs.G3 0.008
				G2 vs.G3 0.037
HOMA IR	6.35 (4.03)	7.15 (4.05)	9.48 (16.8)	0.006
				G1 vs.G2 0.388
				G1 vs.G3 0.007
				G2 vs.G3 0.077
Total Cholesterol (mg/dL)	160.9±28.3	166.5±27.3	163.7±32.2	0.543
LDL-C (mg/dL)	92.7±24.4	93.0±24.7	94.4±17.5	0.949
HDL-C (mg/dL)	44.1±8.1	44.7±12.1	37.9±8.2	0.165
Triglyceride (mg/dL)	125.0±48.2	141.7±63.2	155.4±105.5	0.817
Dyslipidemia n, (%)	36 (57.1)	14 (73.7)	5 (71.4)	0.374

NAFLD: Nonalcoholic fatty liver disease; SDS: Standard deviation score; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostatic model assessment of insulin resistance; LDL-C: Low-density lipoprotein-cholesterol; HDL-C: High-density lipoprotein-cholesterol; G1: Grade 1 hepatosteatosis; G2: Grade 2 hepatosteatosis; G3: Grade 3 hepatosteatosis.

found between the degree of hepatosteatosis and HDL (p<0.001, r=-0.265). The correlations between the degree of NAFLD and other parameters are shown in Table 4.

Based on the ROC curve, the cut-off value for ALT to predict hepatosteatosis was found to be 26 IU/L, with a sensitivity of 56.8% and a specificity of 79.4% (AUC=0.723, p<0.001). The ROC curve for serum ALT level to predict NAFLD is shown in Figure 1.

Alanine aminotransferase was found to be increased in 51 patients (57.3%) who were found to have hepatosteatosis on liver US. The diagnostic accuracy of an increased ALT level in detecting hepatosteatosis was found to be 65.8% with a sensitivity of 77.3% and a specificity of 57.3% (positive likelihood ratio 1.81 and negative likelihood ratio 0.40). Increased ALT showed insufficient performance in detecting hepatosteatosis.

Table 3: Binomial logistic regression analysis of predictors for NAFLD in obese children

	β	Standard error	Odds ratio	p
Age	0.21358	0.10423	1.238	**0.040**
Gender (male)	0.91792	0.52310	2.504	0.079
Pubertal status (pubertal)	-0.99624	0.77119	0.369	0.196
Height SDS	0.30175	0.19399	1.352	0.120
BMI SDS	0.15613	0.39450	1.169	0.692
ALT	0.04771	0.01887	1.049	**0.011**
AST	-0.00790	0.01499	0.992	0.598
FBG	-0.01633	0.03050	0.984	0.592
HbA1c	1.74425	0.89435	5.722	0.051
HOMA-IR	0.06357	0.06722	1.066	0.344
LDL-C	0.00389	0.00862	1.004	0.652
HDL-C	-0.04739	0.02411	0.954	0.059
Triglyceride	0.00503	0.00495	1.005	0.310

SDS: Standard deviation score; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FBG: Fasting blood glucose; HbA1c: Haemoglobin A1c; HOMA-IR: Homeostatic model assessment of insulin resistance; LDL-C: Low-density lipoprotein-cholesterol; HDL-C: High-density lipoprotein-cholesterol.

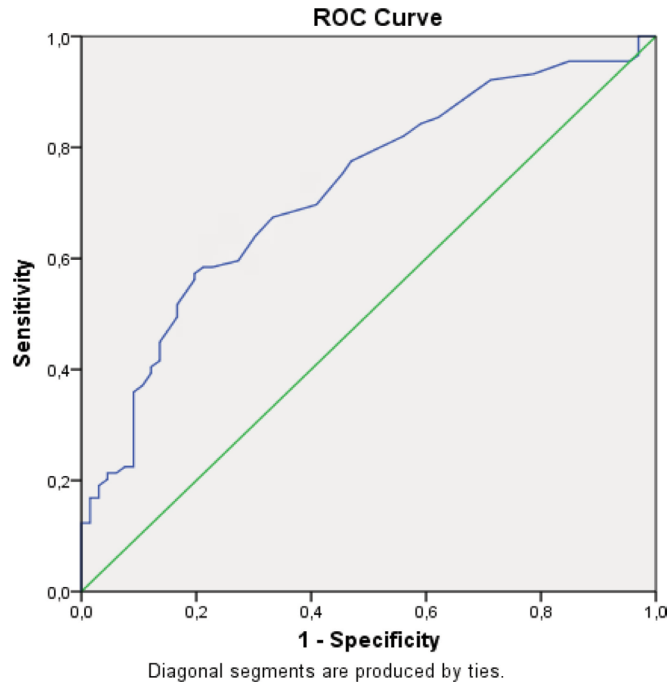

Figure 1: ROC curve for serum ALT level to predict NAFLD. The cut-off value for serum ALT level to predict NAFLD was 26 IU/L (sensitivity 56.8% and specificity 79.4%, respectivley).

Table 4: Correlation between NAFLD and other parameters

	r	p
Age	0.144	0.074
Weight SDS	0.309	**0.009**
BMI SDS	0.182	**0.024**
ALT	0.454	**<0.001**
AST	0.372	**<0.001**
FBG	0.107	0.183
Fasting insülin	0.241	**0.003**
HbA1c	0.235	**0.003**
HOMA-IR	0.268	**<0.001**
Total cholesterol	0.085	0.300
LDL-C	0.060	0.456
HDL-C	-0.265	**<0.001**
Triglyceride	0.140	0.088

SDS: Standard deviation score; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FBG: Fasting blood glucose; HbA1c: Haemoglobin A1c; HOMA-IR: Homeostatic model assessment of insulin resistance; LDL-C: Low-density lipoprotein-cholesterol; HDL-C: High-density lipoprotein-cholesterol.

DISCUSSION

In this study, the data obtained from 155 children and adolescents aged 6 to 18 years were used to determine the predictive factors of pediatric NAFLD. Using liver US, we found that 57.4% of obese children and adolescents had NAFLD. In the binomial logistic regression analysis, age and ALT level were found to be predictive factors for NAFLD. However, use of ALT level alone showed insufficient performance in detecting NAFLD.

Drawing upon earlier research findings, the prevalence of non-alcoholic fatty liver disease (NAFLD) in obese children and adolescents has been reported to range from 34.7% to 70.7%.[10,11,15–24] These prevalence rates are compatible with the NAFLD prevalence we found in our study. Considering the increase in the prevalence of obesity, it is inevitable that the prevalence of NAFLD will increase further in the future.[25]

In studies conducted up to now, age,[19] gender,[19] BMI,[10,16,19] ALT,[10,16] γGT,[3] uric acid,[3,10] glucose,[10] insülin,[10] HOMA-IR,[23] triglyceride,[16,20,26] LDL-C,[11] and HDL-C[16] have been reported to be predictive factors of NAFLD in the pediatric obese population. Discrepancies in study outcomes may be attributed to variations in the age composition of study populations, the inclusion of overweight children, and the utilization of different screening methods to assess NAFLD.

It is known that age, sex, and puberty have different effects on the development of NAFLD.[15,26,27] In our current study, no significant differences were observed in age and pubertal status when comparing subjects with and without NAFLD; however, boys exhibited a higher prevalence of NAFLD. This finding aligns with previous studies reporting a higher prevalence of NAFLD in male populations.[3,10,19,23,26,28] The most important cause of a higher prevalence of NAFLD in males is the fact that the possibility of obesity is higher in males compared to females.[25]

In our study, the lack of a significant difference in terms of pubertal status between individuals with and without NAFLD may be attributed to the predominant inclusion of participants in pubertal age groups. Increasing NAFLD prevalence with advancing age was associated with a longer disease period from the beginning of obesity. Another factor contributing to age difference is the role of puberty in NAFLD development.[26] Suzuki et al.[27] claimed that insulin resistance developing with pubertal maturation might be explained by the change in estrogen levels during puberty in both boys and girls. Akcam et al.[15] demonstrated that there was a strong relationship between NAFLD liver US scores and HOMA-IR. The relationship between insulin sensitivity and the degree of NAFLD may be evidence suggesting that insulin resistance may cause fat accumulation in hepatocytes in puberty.[15]

ESPGHAN recommends liver function tests and liver US for NAFLD screening in obese children,[8] whereas NASPGHAN recommends ALT as a screening test. Measuring serum ALT levels is considerably more cost-effective compared to imaging methods, and it is recommended as the primary screening test because it is minimally invasive. However, liver function tests used for screening NAFLD have significant limitations.[1] The cut-off value for serum ALT level to detect liver disease in children is controversial. In the Screening ALT for Elevation in Today's Youth (SAFETY) study, it was demonstrated that the upper threshold values of normal for ALT used in children were too high to detect chronic liver diseases.

According to data from the National Health and Nutrition Examination Survey (NHANES), the 95th percentile values for ALT in healthy pediatric participants were 25.8 U/L for males and 22.1 U/L for females. When current hospital ALT threshold values (53 U/L) were used, the sensitivity for detecting NAFLD was found to be 32% for the boys and 48% for the girls; the specificity was found to be 92% for the boys and 96% for the girls. When the threshold values derived from NHANES were used, the sensitivity was found to be 72% for the boys and 85% for the girls; the specificity was found to be 79% for the boys and 85% for the girls.[13]

In a study in which overweight and obese children, who were referred from primary care to pediatric gastroenterology, were evaluated, a diagnosis of NAFLD was made in 43% of the subjects who had an ALT level of 40–80 and in 81% of the subjects whose screening ALT level was ≥80. In this study, an ALT level of ≥80 had a sensitivity of 57% and a specificity of 71% for the diagnosis of NAFLD. In addition, it was shown that all overweight and obese children with a positive ALT screening result would not necessarily have liver disease, and might have liver disease other than NAFLD or advanced fibrosis.[29]

In other studies, significant histological abnormalities such as advanced fibrosis were shown in some of the children with NAFLD who had normal or slightly elevated ALT levels. Therefore, measurement of ALT alone may underestimate the degree of liver injury in NAFLD.[30] In addition, NAFLD screening based on ALT value alone may miss NAFLD.[7] In our study, ALT was found to be increased in 57.3% of the patients who were found to have NAFLD in liver US (ALT >25 in boys and ALT >22 in girls). The ALT cut-off value for NAFLD specified with ROC analysis (26 IU/L) was similar to the value recommended by Schwimmer et al.[13] to be used in detecting chronic liver diseases in children. However, the diagnostic accuracy of increased ALT alone was found to be 65.8%, which represented an insufficient performance in detecting NAFLD.

Ultrasonography, one of the routine imaging methods, is commonly used to identify the presence of hepatic steatosis. However, the positive predictive value of liver US for hepatosteatosis was found to be 47%–62% in a systematic review evaluating the imaging methods used for assessment of hepatosteatosis in children. Therefore, the use of US for diagnosing or grading NAFLD is not recommended in children.[31] Liver US is a noninvasive, safe, and inexpensive tool for the diagnosis of NAFLD, though it has limitations. In many studies, it was shown that liver US had benefits in the diagnosis of NAFLD.[7,26,32] Since US is not able to differentiate simple steatosis from non-alcoholic steatohepatitis accurately, it is only reliable when hepatic steatosis is moderate or severe, and it cannot assess the severity of fibrosis reliably.[26]

The fact that a correlation could not be shown between increased ALT and US findings in children demonstrated that measurement of liver enzymes alone for NAFLD screening was not sufficient. Therefore, screening with liver US is recommended to detect NAFLD in the early phase.[15] A screening strategy that used the combination of increased ALT and fatty infiltration on US was shown to increase the sensitivity for the detection of NAFLD.[7] Therefore, pediatric NAFLD screening panels that combine ALT with waist circumference and other metabolic data have been developed to increase screening sensitivity.[33]

It is known that the prevalence of dyslipidemia is high in obese children.[22,23] Due to the association between visceral adiposity and NAFLD, there is an excessive release of free fatty acids into

the bloodstream resulting from lipolysis, along with increased hepatic glucose production, leading to an increase in peripheral insulin resistance. Akcam et al.[15] reported that insulin resistance may adversely impact fat accumulation in the hepatocytes in puberty owing to a strong relationship between hepatosteatosis scores on liver US and HOMA-IR.

Free fatty acids released excessively because of lipolysis in obesity lead to hypertriglyceridemia by increasing the production of very low-density lipoprotein (VLDL) and TG in the liver and inhibiting lipoprotein lipase in fat and muscle tissues.[22] Therefore, the most commonly reported dyslipidemia in obesity is hypertriglyceridemia.[3,18,22,23,26] In a study conducted by Elmaoğulları et al.,[22] the prevalence of dyslipidemia was reported to be 42.9% in obese children and adolescents aged 2 to 18 years. In the same study, the association of dyslipidemia and hepatosteatosis was found to be correlated with higher HOMA-IR levels and abnormal liver function test results.[22]

In the current study, the prevalence of dyslipidemia was found to be 57.4% in children aged between 6 and 18 years, and 40% of the dyslipidemic subjects had hypertriglyceridemia. The higher prevalence of dyslipidemia in our cohort, possibly arising from the older age of obese children and differences in reference lipid levels, is noteworthy.

The limitations of our study included the fact that it was a single-center retrospective study, that NAFLD was diagnosed subjectively by way of liver US, and that methods evaluating body composition were not used to define obesity. Prospective studies are needed to make comparisons with a control group consisting of children with normal weight in order to determine the predictors of NAFLD in obese children and adolescents.

CONCLUSION

In conclusion, the prevalence of NAFLD is considerably high in obese children and adolescents. Age and ALT level are predictive factors for NAFLD. However, the use of ALT level alone showed insufficient performance in detecting NAFLD. Liver US is an eligible screening method for NAFLD, though it has some limitations.

Statement

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ORIGINAL ARTICLE

Clinical features in children and adolescents with Hashimoto's thyroiditis

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ABSTRACT

Objective: Hashimoto's thyroiditis (chronic autoimmune thyroiditis) is the most common cause of goiter and acquired hypothyroidism among children and adolescents. It is an autoimmune disease intrinsic to thyroid tissue. In our study, we aim to review the files of children and adolescents with Hashimoto's thyroiditis, being followed up in the Department of Pediatric Endocrinology, and to compare these results with findings in the literature.

Material and Methods: In the study, the files of 114 children and adolescents with Hashimoto's thyroiditis, being followed up in Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center, Pediatric Endocrinology Department, were reviewed retrospectively. Patients were grouped by age at diagnosis and the clinical parameters were compared between the groups.

Results: There were 102 females (89.5%) and 12 males (10.5%), with a female/male ratio of 8.5/1. The average age of the patients at diagnosis was 11.91±3.26 years. 77 (67.5%) patients have a positive family history. 14 (12.28%) patients have a concomitant autoimmune disease. On the first admission to the hospital, 47 (41.2%) patients were euthyroid, 46 (40.4%) patients were subclinical hypothyroid, 10 (8.8%) patients were overt hypothyroid, 3 (2.6%) patients were subclinical hyperthyroid, and 8 (7.0%) patients were overt hyperthyroid. Antithyroid peroxidase antibodies were positive in 109 (95.6%) and antithyroglobulin antibodies were positive in 105 (92.1%) of the patients. In the group under 12 years old, there were 7 (13.2%) patients with radiation exposure, whereas in the group over 12 years old, there was only 1 (1.9%) patient with radiation exposure, and thus the difference between the two groups was statistically meaningful.

Conclusion: Patients who have clinical and laboratory evidence of thyroid disease should be examined for autoimmune thyroiditis. Especially, it is very important that patients who have clinical evidence of other autoimmune diseases, have a family history of autoimmune thyroiditis, and/or a history of radiation exposure should be examined periodically and followed up closely.

Keywords: Autoimmune, children and adolescents, Hashimoto's thyroiditis.

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INTRODUCTION

Hashimoto's thyroiditis (chronic autoimmune thyroiditis) is the most common cause of goiter and acquired hypothyroidism among children and adolescents. It is characterized as an organ-specific autoimmune disorder in which both humoral and cellular immune responses play a role to varying degrees.[1–3] In childhood, Hashimoto's thyroiditis most commonly occurs in the early and intermediate periods of puberty.[4] The prevalence is four-seven times greater in females than in males.[5–7] Children and adolescents with Hashimoto's thyroiditis may be asymptomatic at the time of initial diagnosis, yet they may also present with symptoms associated with goiter and hypothyroidism.[8]

In a school-age child residing in an area not recognized for iodine deficiency, the presence of goiter, elevated TSH levels alongside normal T3 and T4 levels, and positive autoantibodies collectively indicate a likely diagnosis of Hashimoto's thyroiditis. Diagnosis is confirmed by the detection of high-titer autoantibodies in the blood.[1] In patients with Hashimoto's thyroiditis, the incidence of thyroid cancer is significantly higher than in the normal population.[9]

The present study investigates the demographic characteristics, clinical presentation features, and risk factors of patients diagnosed with Hashimoto's thyroiditis, along with any concurrent autoimmune disorders, and assesses the prevalence of thyroid nodules and their characteristics.

MATERIAL AND METHODS

The present study is based on a retrospective review of the medical charts of children and adolescents being followed up with a diagnosis of Hashimoto's thyroiditis in the Pediatric Endocrinology Outpatient Clinic of the Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center. Included in the study were 114 patients whose age, sex, presenting complaints, family history, radiation exposure history, presence of accompanying autoimmune or non-autoimmune conditions, presence of goiter on palpation, serum-free T4 (fT4) and thyroid-stimulating hormone (TSH) levels, anti-thyroid peroxidase antibody (anti-TPO), antithyroglobulin antibody (anti-Tg) levels, and thyroid ultrasound findings were reviewed retrospectively.

A positive family history was established when Hashimoto's thyroiditis was detected in the first- and second-degree relatives of the patient, and a history of severe systemic illness, trauma, and emotional stress were regarded as potential triggering factors. The study was approved by the ethics committee of Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center (17.10.2014; 168). The study was performed in compliance with the ethical standards of the 1964 Declaration of Helsinki.

Statistical Analysis

Descriptive statistics were analyzed using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.). A Chi-square test was used to compare categorical variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Of the study patients, 102 (89.5%) were female and 12 (10.5%) were male, with a female-to-male ratio of 8.5:1. Of the total, 59 (51.8%) had been diagnosed during puberty and 55 (48.2%) before reaching puberty, with a mean age at the time of initial diagnosis of 11.91±3.26 years (3.5–17.5 years). While there were 54 patients (47.4%) before puberty (<12 years), there were 60 patients (52.6%) after puberty (>12 years).

Thyroid testing was prompted by various factors among the patients, including a neck lump in 23 individuals (20.7%), excessive weight concerns in 19 (17.1%), routine investigation subsequent to a diagnosis of type 1 diabetes mellitus in eight (7%), positive family history in six (5.3%), and short stature and growth retardation in five (4.5%) patients. The patients had most frequently sought medical attention at the outpatient clinic due to a neck lump complaint (20.7%), while the condition was incidentally discovered during investigations conducted for various other reasons in 10 patients (8.8%). A positive family history was identified in 77 (67.5%) patients, and eight patients (7%) had a history of radiation exposure for imaging purposes.

14 of 114 patients (12.28%) had an accompanying autoimmune disease. The most common accompanying autoimmune disease was type 1 DM (9 patients, 7.89%). One patient had Autoimmune Polyglandular Syndrome Type 2. Among the minor findings, vitiligo was present in 4 (3.5%) patients.

An evaluation of the thyroid examination findings from the time of the initial presentation revealed that 55 patients (48.2%) had a detectable goiter on palpation, including 51 (50%) of the male patients and four (33.3%) of the female patients. When the patients were assessed based on the results of thyroid function tests, 47 (41.2%) were identified as euthyroid at presentation, 46 (40.4%) had subclinical hypothyroidism, 10 (8.8%) had overt hypothyroidism, three (2.6%) had subclinical hyperthyroidism, and eight (7%) had overt hyperthyroidism.

Among the study patients, 105 (92.1%) showed positivity for antithyroglobulin (anti-Tg) antibodies, and 109 (95.6%) tested positive for anti-thyroid peroxidase (anti-TPO) antibodies, while 100 patients (87.7%) tested positive for both antibodies. Thyroid ultrasound (USG) findings at the time of initial diagnosis were available for 106 patients and revealed thyroid nodules in 22 patients (20.7%), in sizes ranging from 2.8 mm to 20 mm. During the follow-up of these patients, the thyroid nodules increased in size in four patients (18.1%), decreased in size in seven patients (31.8%), and completely disappeared in eight patients (36.3%). Over the course of follow-up, thyroid nodules showed no change in 91 patients (79.8%). Patients with thyroid nodules larger than 1 cm in size underwent fine needle aspiration biopsy, and the analysis of the specimens indicated benign lesions.

An analysis of the patients by age revealed no significant differences in variables such as family history, iodized salt consumption, presence of goiter, anti-TPO and anti-Tg positivity, presence of a nodule, TSH and fT4 levels, and nodule size between prepubertal and pubertal patients. Of the patients under the age of 12 years, seven (13.2%) had a history of radiation exposure, while only one patient (1.9%) above the age of 12 had such a history, and this difference was statistically significant (p<0.05). The distribution of risk factors across the age groups is presented in Table 1.

Table 1: Distribution of risk factors across age groups

Risk factor	≤12		>12		p
	n	%	n	%	
Positive family history	35	30.7	41	36	0.206
Radiation exposure	7	6.1	1	0.8	**0.027***
Iodized salt consumption	49	43	51	44.7	0.401
Triggering factor	12	10.5	13	11.4	0.861

Chi-square Test *: <0.05.

DISCUSSION

Hashimoto's thyroiditis (chronic lymphocytic thyroiditis) is the most common thyroid disorder observed in children and adolescents and is the leading cause of acquired hypothyroidism and goiter in areas not known to be endemic for iodine deficiency. While there are documented cases within the first three years of life, the condition most commonly occurs after the age of six years, and especially during early and mid-puberty.[1,4] The mean age at initial presentation in the present study was 11.9±3.2 years, concurring with the findings of similar studies conducted in Türkiye.[7,10–12] In our patient group, the female-to-male ratio was 8.5, which is higher than the ratios of 3.6 reported by Özsu et al.[10] and 5.7 reported by Özen et al.[13] in Türkiye.

The majority of patients with Hashimoto's thyroiditis present with an asymptomatically enlarged thyroid gland.[14] In the present study, 20.2% of the patients presented with a neck lump, while 17.6% presented with excessive weight. In the study by Demirbilek et al.,[7] a goiter was reported in 55% of the patients, 18.6% of whom exhibited clinical findings suggestive of hypothyroidism. Aside from goiter and neck discomfort, the most common symptoms that can be expected in patients with autoimmune thyroid disorders include fatigue, increased or decreased weight, sleep and attention disturbances, emotional changes, menstrual irregularities in females, and changes in bowel habits. These symptoms can vary based on whether the patient presents with hypothyroidism, euthyroidism, or hyperthyroidism at the time of diagnosis. In our study group, 64 of the patients (56.1%) presented with complaints that could be linked to thyroid disorders, while the remaining patients (43.9%) were identified incidentally during screening for other purposes or while undergoing testing for nonspecific findings.

It is advisable to conduct a more thorough search for clinical findings in patients with a family history of autoimmune thyroid disorders. First-degree relatives of patients with Hashimoto's thyroiditis often test positive for thyroid autoantibodies,[14] and supporting this finding from the literature, 67.5% of the patients in the present study had first- and second-degree relatives with a history of thyroid disorders.

Hashimoto's thyroiditis can occur alongside various other autoimmune disorders. Marinovic et al.[15] reported the presence of an additional autoimmune disorder in 17% of their patients with chronic autoimmune thyroiditis. Clinicians should remain vigilant for the presence of other autoimmune disorders in patients with an autoimmune condition. Clinical findings that are inconsistent with the current condition should raise suspicion of another autoimmune disorder, and the possibility of polyglandular syndrome should be considered. Antithyroid antibody positivity has been reported in 16–25% of children with type 1 diabetes mellitus.

In the present study, 12.2% of patients had an additional autoimmune disorder, while 7.89% of them had type 1 diabetes mellitus, and of these, 3.5% had vitiligo. Furthermore, one patient was diagnosed with autoimmune polyglandular syndrome type 2, determined based on the presence of adrenal insufficiency, autoimmune thyroiditis, celiac disease, diabetes, and autoantibody positivity.

The most significant difference between the two age groups in our study related to a history of radiation exposure, being more common among those diagnosed before the age of 12 than in the older age group. The thyroid gland is among the tissues most vulnerable to damage from radiation exposure. While there have been numerous studies to date commenting on the association between medical or environmental radiation exposure and thyroid malignancies, there is a lack of comprehensive knowledge of the other pathological processes that may occur in the thyroid gland.

Among the many studies exploring the long-term effects of environmental radiation exposure in the proximity of nuclear accident sites is a study of 1,441 children born during the Chernobyl accident, conducted when they were between the ages of 13 and 17 years. The study reported increased thyroid autoantibody positivity, but no increase in the prevalence of overt thyroid disorder.[16] A large-scale study of 100,000 trauma patients suggested that radiation exposure associated with computerized tomography scans could be justified considering the benefits provided by such imaging studies.[17] It has been well-established that most autoimmune disorders occurring in childhood are triggered by puberty.

The significant history of radiation exposure in the younger age group in our study suggests that it may accelerate the development of autoimmune disorders. The complex pathogenesis of thyroid autoimmunity may be triggered in susceptible cases, although such triggering is not necessarily dose-dependent.[18] Further research is required into the impact of radiation exposure on everyday life and during medical examinations of the thyroid gland.

Thyroid function tests conducted at the time of presentation reveal euthyroidism or hypothyroidism (overt or subclinical) in a significant proportion of patients with Hashimoto's thyroiditis, with hyperthyroidism being a rare occurrence in some cases.[19] In a study carried out by Özsu et al.,[10] euthyroidism was identified in 42.5% of the patients, subclinical hypothyroidism in 24.5%, overt hypothyroidism in 29.2%, and subclinical hyperthyroidism in 2.8%. In the present study, 41.2% of the patients had euthyroidism, 40.4% had subclinical hypothyroidism, 8.8% had overt hypothyroidism, 7% had hyperthyroidism, and 2.6% had subclinical hyperthyroidism, which is in concurrence with the findings of other studies conducted in Türkiye.

The greater prevalence of euthyroidism compared to overt hypothyroidism may be due to several factors, including early patient presentation, increased awareness in those with a family history of thyroid disorders, the regular inclusion of thyroid function tests in routine check-ups at many healthcare centers, and the increased accessibility to screening tests.

The incidence of thyroid cancers is higher in patients with lymphocytic thyroiditis than in the general population. The form of thyroid cancer that most commonly occurs in association with lymphocytic thyroiditis is papillary thyroid carcinoma.[20] In a study conducted in Türkiye, one case of papillary thyroid carcinoma was reported among 162 children and adolescents with Hashimoto's thyroiditis.[7] As our study sample comprised young patients with a relatively short disease duration, there was only one patient who necessitated further investigation for thyroid carcinoma, and no other patients required such examination.

CONCLUSION

The large number of patients diagnosed before the age of 12 in the present study suggests that autoimmune disorders should not be overlooked in young children. The greater incidence of radiation exposure in the younger age group may indicate that environmental influences can shift the onset of the disease to earlier ages in those who are susceptible to autoimmunity. Since the present study involves a two-year follow-up of patients after diagnosis, the results do not reflect the long-term consequences. Lifelong follow-up is essential for patients diagnosed at a young age and for those in high-risk groups.

The findings of the present study also emphasize the need to keep other factors in mind, such as the presence of concurrent autoimmune conditions, a family history of autoimmune thyroid disease, and the incidental detection of elevated TSH levels.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center Clinical Research Ethics Committee granted approval for this study (date: 17.10.2014, number: 168).

Author Contributions: Concept – FMY; Design – FMY, DA; Supervision – HK, FMY; Resource – HK; Materials – HK, DA; Data Collection and/or Processing – HK, DA; Analysis and/or Interpretation – HK, DA; Literature Search – DA; Writing – DA, HK; Critical Reviews – FMY.

Conflict of Interest: The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Vaginal progesterone versus oral dydrogesterone for luteal phase support in intrauterine insemination cycles: A prospective cohort study

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ABSTRACT

Objective: To compare vaginal progesterone and oral dydrogesterone for luteal phase support in intrauterine insemination (IUI) cycles.

Material and Methods: This study was conducted with patients who applied to the Infertility Clinic of the Department of Obstetrics and Gynecology at İstanbul Medeniyet University Prof. Dr. Süleyman Yalçın City Hospital between June 2021 and December 2021. In this prospective cohort study, 109 IUI cycles of 49 patients were examined. Vaginal progesterone (Progestan® 200 mg Soft Capsule, Koçak Farma) 1×200 mg was given to 54 cycles in the control group, and oral dydrogesterone (Duphaston® 10 mg Film Tablet, Abbott) 2×10 mg was given to 55 cycles in the study group.

Results: Eleven (20.4%) pregnancy test results in the vaginal progesterone group and six (11.1%) pregnancy test results in the dydrogesterone group were found to be positive. There was no significant difference between vaginal progesterone and dydrogesterone groups in terms of end-of-cycle pregnancy positivity, including the subgroup analyses for treatment type and infertility etiology (p>0.05). As a result of univariate analyses, it was determined that follicle-stimulating hormone (FSH) was negatively correlated with end-of-cycle pregnancy positivity (OR: 0.547; 95%CI: 0.328–0.913; p=0.021). One unit increase in FSH level reduces pregnancy positivity by 54%. According to the results of multivariate analysis, one unit increase in FSH level reduces pregnancy positivity by 56%, but it is not statistically significant (OR: 0.565; 95%CI: 0.315–1.012; p=0.055).

Conclusion: Although there were higher pregnancy rates in patients who used vaginal micronized progesterone for luteal phase support in IUI cycles, compared to patients who used oral dydrogesterone, no statistically significant difference was found between the two groups.

Keywords: Intrauterine insemination, luteal phase support, oral dydrogesterone, vaginal progesterone.

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INTRODUCTION

Infertility is defined as the inability to get pregnant despite unprotected intercourse for one year and affects 10–15% of couples in the reproductive period.[1] Intrauterine insemination (IUI) is the process of releasing semen into the endometrial cavity with the help of a special catheter. IUI is performed with indications such as unexplained infertility, cervical factor-related infertility, ovulatory dysfunction, ejaculatory dysfunction, mild male factor, stage 1–2 endometriosis, donor sperm use, and vaginismus. There are many factors affecting the success of IUI, and one of these factors is the quality of the luteal phase. The presence of luteal function and continuous production of progesterone from the corpus luteum are important for implantation and pregnancy.[2–5]

Several theories have been proposed as the cause of luteal phase failure in *in vitro* fertilization (IVF) cycles. One of them is that steroid hormones secreted in supraphysiological doses in the early luteal phase by the multiple corpora lutea developing in stimulated cycles inhibit LH release from the hypothalamo-hypophyseal axis and thus shorten the luteal phase.[6,7] It is thought that this theory is also valid in IUI cycles with ovarian induction (OI-IUI). The study by Erdem et al.[8] showed that pregnancy rates of patients given progesterone for luteal phase support after gonadotropin-stimulated IUI were higher. However, the effectiveness of luteal phase support in OI-IUI is still controversial. Although progesterone support throughout the luteal phase in these cycles is a common approach, the optimal route, dose, duration, and type of administration are unknown.[9]

Available progesterone formulations vary as oral, vaginal, rectal, intramuscular (IM), subcutaneous. There are applications such as oral micronized capsule, vaginal micronized capsule, vaginal cream, IM injections, and dydrogesterone, which is an oral synthetic progesterone. Vaginal micronized progesterone is a natural form of progesterone ve has been used for luteal phase support orally or vaginally for many years. It is more preferred than oral progesterone in luteal phase support because of its higher bioavailability, not undergoing liver first-pass metabolism, rapid absorption ve a less side-effect profile. However, micronized capsule progesterone may have side effects such as discharge, temperature increase, ve irritation secondary to vaginal administration. Dydrogesterone is a selective synthetic progesterone with high oral bioavailability. Side effects of dydrogesterone are migraine, headache, nausea, breast tenderness, ve pain. Dydrogesterone is used in many indications such as dysmenorrhea, menometrorrhagia, menstrual irregularities, endometriosis, recurrent miscarriage treatment, premenstrual syndrome, luteal phase support, ve hormone replacement therapy.[10]

There are limited studies in the literature comparing vaginal progesterone with oral dydrogesterone for luteal phase support after IUI. For this reason, we aimed to compare the effects of vaginal natural progesterone ve oral dydrogesterone for luteal phase support after IUI on pregnancy outcomes.

MATERIAL AND METHODS

Our prospective cohort study was conducted with 49 patients in 109 IUI cycles who applied to the Infertility Clinic of the Department of Obstetrics and Gynecology at İstanbul Medeniyet University Prof. Dr. Süleyman Yalçın City Hospital between June 2021 and December 2021.

Patients who were older than 18 years old and younger than 40 years old, had at least 1 year of infertility, anti-Müllerian hormone (AMH) value >1 ng/ml, basal follicle-stimulating hormone (FSH) level <14 mIU/ml, normal cervical cytology result, and appropriate indications for IUI such as unexplained infertility, ovulatory dysfunction, mild male factor, and mild endometriosis were included in our study. Patients with an indication for IVF, bilateral tubal obstruction on hysterosalpingography (HSG), severe male factor, contraindications for progesterone therapy, and clinically significant systemic, endocrine, or metabolic diseases were excluded from the study. All patients were informed about the study and consent was obtained. This study was approved by the hospital ethics committee (2021/0317) and was conducted in accordance with the principles of the Declaration of Helsinki 2013.

Semen analysis was requested and taken from all male partners under appropriate conditions. The results were evaluated according to World Health Organization (WHO) standards. Those with normal or mildly impaired semen analyses were included in the study. Sperm samples prepared by removing the supernatants were prepared using soft catheters or using a cannula with a guided wire for cases where cervical passage could not be achieved. In all female partners, basal transvaginal ultrasonography was performed by a single physician in the first week of their cycle after a bimanual examination. After evaluating all the results, basal transvaginal ultrasonography was performed on the 2nd day of the patients' cycle, and IUI preparations were started. Patients who were started on clomiphene citrate (Klomen® 50 mg, oral, Koçak Farma) or r-FSH, Follitropin alfa (Gonal-f® 75 IU, 5.5 microgram, subcutaneous, Merck) were called for the follow-up of follicle development by transvaginal ultrasonography at regular intervals from the 6th day of their cycles. The antral follicle number and development were followed, and dose adjustments were made when necessary. The initial and total doses of clomiphene citrate and gonadotropin administered to all patients, the number of days of treatment, the days of human chorionic gonadotropin (hCG) administration, and the endometrial thickness on the days of hCG administration were recorded. In our patients for whom we planned monofollicular development, the cycles of those with 2 or more dominant follicles were canceled and excluded from the study. Subcutaneous administration of 250 mg/0.5 mL choriogonadotropin alfa-recombinant hCG (Ovitrelle®, Merck) was applied to all our patients with preovulatory follicles of approximately 18–20 mm.

IUI was performed 36 hours after hCG. IUI procedures were started with the preparation of the samples by a single embryologist in our andrology laboratory within 1 hour. Then, the cervix of the female partners who were placed in the lithotomy position was visualized with a speculum and washed with saline solution. After the uterocervical angle was optimized, sperm samples were slowly given to the uterine cavity within about 10–30 seconds. The procedures were completed after the patients were placed in the supine position for 10–15 minutes after the procedure.

Table 1: Demographic data of the patients

	Vaginal progesterone (n=54)	Oral dydrogesterone (n=55)	p
Age (years)[a]	30.5 (21–43)	28 (22–40)	0.254
BMI (kg/m2)[a]	24 (16.5–42)	25.90 (18.30–42.00)	**0.035**
Duration of infertility (months)[a]	30 (8–84)	24 (8–87)	0.409
Number of ovulation induction[a]	1 (1–3)	2 (1–5)	**0.020**
Etiology[b]			
Unexplained	18 (33.3%)	20 (36.4%)	0.896
Male factor	6 (11.1%)	11(20.0%)	0.310
Anovulation (PCOS)	34 (63.0%)	32 (58.2%)	0.610
Endometriosis	3 (5.6%)	2 (3.6%)	0.679
Type of infertility[b]			
Primary	50 (92.6%)	41 (74.5%)	**0.023**
Secondary	4 (7.4%)	14 (25.5%)	
Treatment[b]			
Clomiphene citrate	27 (50.0%)	29 (52.7%)	0.776
Gonadotropin	27 (50.0%)	26 (47.3%)	

a: Mann Whitney U test was performed and results were shown as median (minimum-maximum); b: Pearson Chi-square and Fisher Exact tests were performed, and the results were shown as number (n) and percentage (%); BMI: Body mass index; PCOS: Polycystic ovary syndrome.

As luteal phase support, on the day of intrauterine insemination, vaginal natural micronized progesterone (Progestan® 200 mg Soft Capsule, Koçak Farma) 1×200 mg was given to the control group patients, and oral dydrogesterone (Duphaston® 10 mg Film Tablet, Abbott) 2×10 mg was given to the study group patients and continued until the 10th week in those with a positive pregnancy test result. In the 4th–5th week after intrauterine insemination, the patients who had positive pregnancy results in blood tests were re-examined with transvaginal ultrasonography to define fetal cardiac activity. All the patients who had positive β-hCG results were found to be clinically pregnant. Therefore, all of them were included in the study.

Statistical analysis

Data were analyzed using SPSS Statistics 18 (IBM Corp., Armonk, NY, USA) software. Conformity of continuous variables to normal distribution was examined by Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables in the study were presented with frequency (n) and percentage (%), and continuous variables with mean±standard deviation (SD), median (minimum and maximum) values. Pearson Chi-square and Fisher Exact were used in the analysis of categorical variables. Student t-test was used when parametric test assumptions were met, and Mann-Whitney U test was used when parametric assumptions were not met in the comparison of two groups' mean. Univariate and multivariate logistic regression analysis was performed to determine the independent risk factors associated with dependent variables, and variables with p<0.02 in univariate analyzes were included in the multivariate model. Obtained results are presented with odds ratio (OR) and 95% confidence intervals (CI). The statistical significance level was accepted as 0.05 in the study.

RESULTS

In this study, 109 cycles of 49 patients were evaluated because some patients had more than one IUI cycle. Two groups were formed as the control group and the study group. Vaginal progesterone was given to 54 cycles in the control group, and oral dydrogesterone was given to 55 cycles in the study group.

Pregnancy was achieved in 17 (15.6%) of 109 cycles. Demographic data of the patients are summarized in Table 1. The BMIs of the patients given dydrogesterone were found to be statistically significantly higher than those given vaginal progesterone (25.90 [18.30–42.00] and 24 [16.5–42], respectively, p=0.035). The total number of ovulation induction cycles in the dydrogesterone group was higher than those in the vaginal progesterone group, and this difference was statistically significant (2 [1–5] and 1 [1–3], respectively, p=0.020). While primary infertility was detected in 92.6% and secondary infertility in 7.4% of the group given vaginal progesterone, primary infertility was detected in 74.5% and secondary infertility in 25.5% of the dydrogesterone group. The rate of secondary infertility was found to be significantly higher in the dydrogesterone group (p=0.023).

Patient and cycle characteristics are shown in Table 2. The median TSH value of the female partner was 1.68 (0.40–4.69) mIU/ml in the vaginal progesterone group and 1.99 (0.73–4.14) mIU/ml in the dydrogesterone group. This difference was statistically significant (p=0.049). The median prolactin value of the female partner was 14.20 (2.24–64.03) ng/ml in the vaginal progesterone group and 17.90 (4.70–64.03) ng/ml in the dydrogesterone group. This difference was statistically significant (p=0.015). There was no significant

Table 2: Characteristics of partners and cycles

	Vaginal progesterone (n=54)	Oral dydrogesterone (n=55)	p
Hormone profile of female partner[a]			
FSH (mIU/ml)	6.00 (2.80–12.30)	6.00 (2.80–8.70)	0.667
LH (mIU/ml)	5.00 (1.70–52.00)	4.80 (0.00–17.00)	0.308
TSH (mIU/ml)	1.68 (0.40–4.69)	1.99 (0.73–4.14)	**0.049**
Prolactin (ng/ml)	14.20 (2.24–64.03)	17.90 (4.70–64.03)	**0.015**
AMH (ng/ml)	3.10 (1.04–16.00)	2.86 (1.21–16.30)	0.868
Estradiol (pg/ml)	35.00 (5.00–63.00)	35.00 (4.99–58.70)	0.484
Sperm parameters of male partner[a]			
Sperm count (10 million/ml)	44.00 (8.70–263.00)	49.00 (11.50–590.00)	0.316
Normal morphology (%)	7.00 (2.00–70.00)	7.00 (4.00–85.00)	0.768
Total sperm motility (%)	49.00 (34–88)	57.00 (25–94)	0.361
Progressive motility (%)	35.00 (0–77)	44.00 (0–77)	0.243
Cycle characteristics[a]			
Gonadotropin dose (IU) (n=27/26)	600 (150–1650)	562.5 (225–1350)	0.695
Clomiphene citrate dose (mg) (n=27/29)	250 (12.5–1250)	250 (30–750)	0.846
***hCG-Ovitrelle (days) (n=52/54)	10 (6–23)	10 (5–24)	>0.99
Endometrial thickness (mm) (n=54/55)	9 (5.10–16.00)	9.20 (4.00–14.70)	0.587
Patient satisfaction[b]			
Easy to use	14 (25.9%)	55 (100%)	**<0.001**
Difficult to use	40 (74.1%)	0 (0%)	

a: Mann Whitney U test was performed and results were shown as median (minimum–maximum); b: Pearson Chi-square and Fisher Exact tests were performed, and the results were shown as number (n) and percentage (%); FSH: Follicle stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid stimulating hormone; AMH: Anti Mullerian hormone; hCG: Human chorionic gonadotropin.

Table 3: Pregnancy outcomes

	Vaginal progesterone	Oral dydrogesterone	p
Positive pregnancy test	11/54 (20.4%)	6/55 (10.9%)	0.273
Treatment type			
Clomiphene citrate	6/27 (22.2%)	3/29 (10.3%)	0.288
Gonadotropin	5/27 (18.5%)	3/26 (11.5%)	0.704
Etiology			
PCOS	8/34 (23.5%)	3/32 (9.4%)	0.226
Unexplained	3/18 (16.7%)	3/20 (15.0%)	0.999

Pearson Chi-square and Fisher Exact tests were performed, and the results were shown as number (n) and percentage (%); PCOS: Polycystic ovary syndrome.

difference in sperm parameters and cycle characteristics (p>0.05). When patient satisfaction was evaluated, it was observed that all patients in the dydrogesterone group expressed easy use, while the majority (74.1%) of the patients in the vaginal progesterone group expressed difficult use, and this difference was found to be statistically significant (p<0.001).

In terms of end-of-cycle pregnancy test results, 11 (20.4%) results in the vaginal progesterone group and 6 (10.9%) results in the dydrogesterone group were found to be positive (Table 3). There was no significant difference between vaginal progesterone and dydrogesterone groups in terms of end-of-cycle pregnancy test positivity, including the subgroup analyzes for treatment type and infertility etiology (p>0.05).

Table 4: Results of univariate and multivariate logistic regression analysis of factors affecting end-of-cycle pregnancy test positivity

Variables	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age (years)	1.019 (0.918–1.131)	0.727		
BMI (kg/m^2)	1.100 (0.998–1.211)	0.054	1.115 (0.994–1.251)	0.064
Infertility duration (months)	0.996 (0.965–1.027)	0.785		
Number of ovulation induction	0.585 (0.304–1.123)	0.107	0.764 (0.369–1.582)	0.468
Unexplained infertility	1.023 (0.346–3.022)	0.968		
Secondary infertility	1.100 (0.281–4.304)	0.891		
Anovulatory infertility (PCOS)	1.233 (0.419–3.626)	0.703		
Gonadotropin dose (IU)	1.002 (0.999–1.004)	0.160		
Clomiphene citrate dose (mg)	1.001 (0.999–1.004)	0.410		
hCG-Ovitrelle (days)	1.100 (0.987–1.225)	0.085	1.058 (0.930–1.203)	0.393
Endometrial thickness (mm)	0.881 (0.712–1.090)	0.244		
FSH (mIU/ml)	0.547 (0.328–0.913)	0.021	0.565 (0.315–1.012)	0.055
LH (mIU/ml)	1.044 (0.974–1.120)	0.223		
TSH (mIU/ml)	0.848 (0.450–1.598)	0.610		
Prolactin (ng/ml)	0.986 (0.945–1.030)	0.525		
AMH (ng/ml)	1.058 (0.910–1,229)	0.464		
Estradiol (pg/ml)	0.979 (0.942–1.018)	0.285		
Sperm concentration (10 million/ml)	1.003 (0.997–1.008)	0.400		
Normal morphology (%)	1.017 (0.986–1.048)	0.285		
Total sperm motility (%)	1.012 (0.981–1.044)	0.449		
Progressive motility (%)	1.022 (0.994–1.051)	0.121	1.029 (0.995–1.064)	0.097
Difficult to use	2.214 (0.778–6.300)	0.136	1.725 (0.226–13.149)	0.599
Vaginal progesterone	2.089 (0.712–6.126)	0.179	1.668 (0.221–12.596)	0.620

Variables with p<0.02 in univariate analysis were included in multivariate analysis (Nagelkerke R Square: 0.234). BMI: Body mass index; PCOS: Polycystic ovary syndrome; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid stimulating hormone; AMH: Anti-Mullerian hormone; hCG: Human chorionic gonadotropin; OR: Odd ratios; CI: Confidence interval.

In Table 4, univariate and multivariate logistic regression analysis results of factors affecting end-of-cycle pregnancy test positivity are presented. As a result of univariate analyzes, it was determined that FSH was negatively correlated with end-of-cycle pregnancy test positivity (OR: 0.547; 95% CI: 0.328–0.913; p=0.021). One unit increase in FSH value reduces pregnancy positivity by 54%. According to the results of multivariate analysis, one unit increase in FSH value reduces pregnancy positivity by 56%, but it is not statistically significant (OR: 0.565; 95% CI: 0.315–1.012; p=0.055).

DISCUSSION

Our study shows that the clinical pregnancy rate was 20.4% with the use of vaginal micronized progesterone for luteal phase support in IUI cycles, while this rate was found to be 10.9% with oral dydrogesterone. However, no statistically significant difference was found between the two groups (p=0.273). In our demographic data, the BMI of the group using oral dydrogesterone was found to be significantly higher than the BMI of the vaginal progesterone group (p=0.035). This may have caused a difference between the pregnancy rates of the two groups. In the regression analysis, in which we examined the factors affecting end-of-cycle pregnancy test positivity, it was seen that FSH was negatively correlated with end-of-cycle pregnancy test positivity, and a one-unit increase in FSH level decreased pregnancy positivity by 54%. Again, in the regression analysis, the rate of pregnancy test positivity was 2.08 times higher in patients in the group given vaginal progesterone than in patients given dydrogesterone; however, both regression analyses results were not statistically significant (p>0.05).

Although the role of luteal phase support in IUI cycles is still debated, the general opinion is in favor of applying luteal phase support in IUI cycles. In a meta-analysis published by Green et al.,[11] which included 11 randomized controlled studies, 2,842 patients, and 4,065 cycles, it was observed that luteal phase support with progesterone

increased clinical pregnancy and live birth rates in the group that underwent ovulation induction with gonadotropins and IUI. For this reason, it seems reasonable to give luteal phase support in OI-IUI cycles.

Many different forms of progesterone can be used for luteal phase support, such as oral/vaginal micronized capsules, vaginal cream, IM injections, vaginal gel, tablet, pessary, and oral dydrogesterone. There are studies in the literature comparing vaginal micronized progesterone and oral dydrogesterone in IVF cycles. In the multicenter randomized controlled Lotus 1 study published in 2017, 30 mg dydrogesterone and 600 mg vaginal micronized progesterone were compared for luteal phase support in IVF cycles.[12] As a result of the study, it was reported that pregnancy and live birth rates were similar and oral dydrogesterone was as effective as vaginal progesterone. It was also reported that patients tolerated dydrogesterone better and that the side-effect profiles of the two drugs were similar. In a meta-analysis that investigated the use of oral dydrogesterone and vaginal progesterone for luteal phase support in IVF cycles, oral dydrogesterone was reported to be at least as effective as vaginal progesterone.[13] In this study, clinical pregnancy rates and live birth rates were similar in both treatment regimens.

Although there are many studies in the literature reporting that oral dydrogesterone is at least as effective as vaginal micronized progesterone for luteal phase support in IVF cycles, there are limited studies that make this comparison in IUI cycles. In a randomized controlled trial published by Khosravi et al.,[14] vaginal progesterone and oral dydrogesterone were compared for luteal phase support after IUI. A total of 180 people were included in this study, and the groups were divided into 90 people using vaginal progesterone and 90 using dydrogesterone. As a result of this study, the clinical pregnancy rates of both groups were similar (vaginal progesterone 25.7% vs. oral dydrogesterone 29.7%, p=0.582).

The strengths of this study are that it is prospective, the distribution of study groups is similar, and patient satisfaction is measured. If we compare this study with our study, both studies were prospective, but our study was a cohort study, while the study by Khosravi et al.[14] is a randomized controlled study. Since our study could be conducted for 6 months, only 109 cycles were evaluated. However, Khosravi et al.'s[14] study was conducted with a larger sample. In our study, the clinical pregnancy results of the use of dydrogesterone and vaginal progesterone were statistically similar, but the total number of pregnancies in the vaginal progesterone group was approximately two times higher than in the dydrogesterone group, despite the low-dose vaginal progesterone application.

In our study, luteal phase support was also applied to patients diagnosed with PCOS, and although the number of patients treated with vaginal progesterone and dydrogesterone was almost equal, it was observed that pregnancy rates were much higher in the vaginal progesterone group than in the dydrogesterone group. However, there was no statistically significant difference (p>0.05). An important difference of our study from this study is that while we aimed to develop a monofollicle in our ovulation inductions, multifollicular development was aimed for, and at least 2–3 dominant follicles were formed in each cycle in Khosravi et al.'s[14] study because all of the patients were in an unexplained infertile group. The multifollicular dominant follicles they obtained may be the reason for the higher pregnancy rate. However, it is not clear whether the reason for this pregnancy rate in this study is the high number of developing follicles or the form, dose, and duration of the luteal phase support.

In a retrospective single-center study published by Taş et al.,[15] oral dydrogesterone and vaginal micronized progesterone were compared for luteal phase support in IUI cycles. A total of 620 cycles of 432 patients with unexplained infertility were included in the study. Dydrogesterone was administered to 233 patients (337 cycles), while vaginal progesterone was administered to 199 patients (233 cycles). Dydrogesterone was administered at a dose of 3×10 mg/day, and vaginal micronized progesterone was administered at a dose of 3×200 mg/day. As a result of that study, a total of 58 pregnancies were obtained in 620 cycles, 41 of which resulted in live births. Although clinical pregnancy and live birth rates were higher in the vaginal progesterone group, no statistically significant difference was found between the groups in terms of total, chemical and clinical pregnancy, abortion, and live birth rates (p>0.05). However, both the dydrogesterone and progesterone doses used in this study were higher than in our study, and there were patients with multifollicular development. While the pregnancy rate was 15.6% in our study, it was 9% in this study. The advantage of this study is that the sample size is large and live birth and miscarriage analyzes are performed, while the advantage of our study is that it is prospective and has patient satisfaction analysis.

There are strengths and limitations to our study. The strengths are the prospective design, similar demographic characteristics between the groups, homogeneous distribution of treatment regimens, luteal phase support applied to patients diagnosed with PCOS, and similar pregnancy rates despite monofollicular development with a lower progesterone dose compared to other studies in the literature. However, the small sample size and the inability to report the live birth, miscarriage, and multiple pregnancy rates are important limitations.

CONCLUSION

Although there were higher pregnancy rates in patients who used vaginal micronized progesterone for luteal phase support in IUI cycles, compared to patients who used oral dydrogesterone, no statistically significant difference was found between the two groups. With further studies, the role of dydrogesterone in luteal phase support in IUI will become clearer.

Statement

Ethics Committee Approval: The İstanbul Medeniyet University Clinical Research Ethics Committee granted approval for this study (date: 16.06.2021, number: 2021/0317).

Author Contributions: Concept – NHD, ED; Design – NHD, AT; Supervision – ED, AT; Resource – NHD; Materials – ED; Data Collection and/or Processing – NHD, ED; Analysis and/or Interpretation – AT, ED; Literature Search – NHD; Writing – NHD; Critical Reviews – ED.

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ORIGINAL ARTICLE

The effect of serum biomarkers on the requirement for surgical intervention in tuboovarian abscess

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ABSTRACT

Objective: Tubo-ovarian abscess (TOA) is a complex infectious mass of the adnexa, which is treated by antibiotherapy or surgery. Antibiotherapy failure may occur during TOA treatment. The aim of this study is to assess the effect of TOA size and serum biomarkers on the requirement for surgical intervention.

Material and Methods: Eighty-four patients over five years in our clinic were evaluated. TOA size and laboratory values such as hemoglobin, white blood cell count, lymphocyte, monocyte, platelet, albumin, neutrophil, C-reactive protein (CRP) levels, and if antibiotics were switched to another treatment protocol or changed to a surgical approach, were also reported. Prognostic Nutritional Index (PNI), the platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and monocyte-lymphocyte ratio (MLR) were also used to evaluate medical therapy failure and the requirement for surgery.

Results: Eighty-four patients hospitalized with the diagnosis of TOA, 13 of them required surgery due to antibiotherapy failure and the surgical intervention rate was calculated as 15.47%. Platelet count and TOA size were found to be statistically significantly higher and hospital stay was found to be statistically significantly longer in the surgery group. CRP and other laboratory values did not have a statistically significant difference between groups. Among the indexes, only PLR had a statistically significant prediction value (p=0.020).

Conclusion: TOA volume and PLR were found to be effective predictors in antibiotherapy failure and surgical intervention.

Keywords: Antibiotic failure, surgical intervention, tubo ovarian abscess.

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INTRODUCTION

Tubo-ovarian abscess (TOA) is a complex infectious mass of the adnexa, which is classically characterized by symptoms of fever, pelvic pain, and vaginal discharge, and an increase in vaginal temperature.[1] It is mostly a polymicrobial infection and frequently seen as a complication of untreated pelvic inflammatory disease (PID). The prevalence of PID is 3.6–10%, and 2.3–20% of PID patients may develop TOA.[2] Usually, Chlamydia spp. and Neisseria spp. are isolated in PID, whereas Bacteroides spp., Peptostreptococcus spp., and Peptococcus spp. are isolated from TOA samples.[3] First-line therapy for TOA is antibiotherapy; however, if abscess rupture occurs, the disease can be mortal.[4] While there are varied antibiotic regimens, a combination of clindamycin and gentamicin is used in our clinic as a first-line therapy for TOA.[5]

Antibiotherapy failure may occur during TOA treatment. Resistance to antibiotherapy is also a problem in the treatment of TOA, as well as other diseases. The most common resistance mechanisms are modifying the production of hydrolase enzymes, ribosomal protection, and target site mutation.[2] Antibiotherapy failure, rupture of the abscess, and sepsis are the main indications for surgery. Approximately 25% of patients with unruptured TOA require surgery.[6] The goal of surgery for TOA treatment is the drainage of the abscess and to lessen the infectious burden through peritoneal lavage.[7] It is recommended to place a drain in the abdomen to help continue the drainage. There is not enough data for a definite way to determine which patients will have success with antibiotherapy and which will require surgery according to guidelines; the aim of this study is to show the parameters that can help predict the requirements for surgery in patients.

MATERIAL AND METHODS

This protocol has been reviewed and approved by the Clinical Researches Ethics Committee of the Hospital (approval number: 2022/0214). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this retrospective study, we reviewed 84 patients who underwent treatment with gentamicin plus clindamycin for TOA between 01.01.2017 and 25.03.2022 in our Obstetrics and Gynecology clinic. Files of these patients were examined, and age, gravida, parity, abortus, methods of delivery, comorbidities, hospital stay length, TOA size, and laboratory values such as hemoglobin (Hmg), white blood cell count (WBC), lymphocyte (Lym), monocyte (Mon), platelet (Plt), albumin (Alb), neutrophil (Neut), and C-reactive protein (CRP), change of antibiotherapy, and if surgery had been necessitated for treatment of TOA are reported. The day of hospitalization of the patient is accepted as 'day 1'. Laboratory examinations were recorded on 'day 1' and 'day 7'.

In this study, inclusion criteria include symptomatic TOA patients who apply to our clinic. Exclusion criteria are patients whose data were incomplete, pathology results being incompatible with TOA or the presence of another malignant disease, and the requirement for blood transfusion. Patients with ruptured TOA were also excluded since it is a known indication for surgical intervention.

Abscess size was calculated using the ellipsoid formula, where two dimensions are taken of the abscess: the widest single line in the abscess (W) and the perpendicular measurement to that measurement (L) by twisting the ultrasound probe, which is how abscess sizes are calculated in our hospital. The final formula was found to be Volume (mm^3)=$0.5 \times L \times W^2$.[8,9]

The Prognostic Nutritional Index (PNI), which is calculated as serum albumin (g/dL)+5× total lymphocyte count (10^9/L), is used in patients undergoing surgery to predict the prognosis of patients. This parameter was also used in gastric and mammary cancer patients.[10,11]

The platelet-lymphocyte ratio (PLR) was used to evaluate the inflammatory state of the body and predict cardiovascular events. This value is calculated in a complete blood count and does not have an extra cost. We used this test to evaluate the inflammatory response in our patients.[12]

The neutrophil-lymphocyte ratio (NLR) and lymphocyte-monocyte ratio (LMR) were also used to discern the inflammatory status of the body, as different types of leukocytes have different roles. These ratios were included in this study to understand if they are linked with antibiotherapy failure or were higher in the surgery group.[13,14] We used day 1 results to calculate abscess size, PNI, PLR, NLR, LMR.

Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 statistical package. In the descriptive findings section, categorical variables were presented with numbers and percentages, and continuous variables with mean±standard deviation and median value (smallest, largest value). Pearson's Chi-square test was used to compare categorical variables; the Kolmogorov-Smirnov test was used to examine the suitability of the data for normal distribution in the comparison of variables specified by the measurement. The Paired t-test was used to compare two repetitive measurements suitable for normal distribution. The statistical significance level was set at $p<0.05$ in the analysis.

RESULTS

A total of 84 patients were hospitalized with the diagnosis of TOA. The group that did not require surgery (No-Surgery Group, NSG) consisted of 71 patients, and the surgery group (SG) consisted of 13 patients. The surgical intervention rate was calculated as 15.47%. Our results are presented in the tables below. In Table 1, general demographic values and clinical data were examined, along with the average TOA size of the patients.

In Table 2, the laboratory results were compared between SG and NSG. While the Hemoglobin (Hmg) value was found to be statistically significantly lower, the platelet (Plt) count and TOA size were found to be statistically significantly higher, and hospital stay was found to be statistically significantly longer in SG. White blood cell (WBC), C-reactive protein (CRP), and other laboratory values did not show a statistically significant difference between groups.

In Table 3, we examined the Prognostic Nutritional Index (PNI), Platelet-Lymphocyte Ratio (PLR), Neutrophil-Lymphocyte Ratio (NLR), and Lymphocyte-Monocyte Ratio (LMR). Among these indices, only PLR showed a statistically significant difference between SG and NSG.

Table 1: General demographic values and clinical data

	Average±SD (min; max)
Age (n=84)	39.1±7.2 (19; 58)
Gravida (n=84)	2.6±1.6 (0; 8)
Parity (n=84)	1.6±1.1 (0; 5)
Abortus (n=84)	0.8±1.1 (0; 6)
Method of delivery (n=70)	
NSVB	38 (54.3)
C/S	21 (30.0)
C/S-NSVB	11 (15.7)
Day 1 Hmg (n=84)	11.0±1.7 (6.6; 14.5)
Day 7 Hmg (n=84)	10.7±1.6 (7.3; 14.8)
Day 1 WBC (n=84)	13.7±5.2 (4.2; 31.9)
Day 7 WBC (n=84)	9.1±3.2 (4.4; 24.1)
Day 1 CRP (n=84)	114.9±87.1 (1; 314)
Day 7 CRP (n=84)	41.3±49.8 (0.3; 195)
Toa Size (mm^3) (n=84)	110.0±124.1 (4; 682)
Average hospital stay (day) (n=84)	6.0±3.0 (1; 17)

Min: Minimum; Max: Maximum; NSVB: Normal spontaneus vaginal birth; C/S: Cesarean section; WBC: Blood cell count; CRP: C-reactive protein.

Table 2: Laboratory result comparison between groups

	Surgery group (n=13)	No-surgery group (n=71)	p
Hemoglobin day 1*	9.7±1.7	11.2±1.6	0.003
Neutrophil day 1*	14.7±3.8	13.5±5.4	0.490
CRP day 1**	137.9±74.3	110.7±89.1	0.255
Hemoglogin day 7*	10.4±1.1	10.8±1.7	0.253
Neutrophil day 7*	9.4±3.1	9.1±3.2	0.787
CRP day 7**	49.1±56.2	39.9±48.9	0.290
Alb gr/dl*	3.6±0.6	3.7±0.5	0.443
Lymphocyte**	1.9±0.5	2.2±0.9	0.301
Monocyte**	0.5±0.1	0.6±0.3	0.335
Platelet**	381.9±128.9	300.4±102.7	**0.039**
Antibiotic change			0.372
No	9 (69.2)	57 (80.3)	
Yes	4 (30.8)	14 (19.7)	
Gravida**	2.4±1.5	2.6±1.7	0.471
Parity**	1.6±0.6	1.7±1.1	0.776
Abort**	0.8±1.3	0.8±1.1	0.592
Method of delivery***			0.078
NSVB	8 (61.5)	30 (52.6)	
C/S	1 (7.7)	20 (35.1)	
C/S+NSVB	4 (30.8)	7 (12.3)	
TOA size (mm^3)**	137.1±89.3	105.0±129.4	**0.049**
Hospital stay (days)**	7.7±2.6	5.7±2.9	**0.015**

*: Student t test; **: Mann Whitney U test; ***: Chi Square Test; CRP: C-reactive protein; NSVB: Normal spontaneus vaginal birth; C/S: Cesarean section; TOA: Tubo-ovarian abscess.

DISCUSSION

In this study, we examined multiple parameters to predict the requirement for surgery in TOA patients. Among those diagnosed with TOA, 15.5% of patients required surgery, and no demographic values were associated with the need for surgical treatment. The average hospital stay was found to be 2.1±0.3 days longer, hemoglobin (Hmg) values were lower, and platelet (Plt) counts were higher in SG patients on day 1. TOA volume was found to be larger in patients who required surgery. Additionally, the Platelet-Lymphocyte Ratio (PLR) was higher in SG patients. For the other parameters, there were no statistical differences.

TOA is the most common cause of intraabdominal abscess in premenopausal women.[15] TOA mostly develops from PID, since women have peritoneal perforations in their internal genitalia, which differ from men.[16] Modern treatment for TOA involves hospitalization and IV antibiotics, and treatment failure within 48–72 hours can necessitate surgical intervention. In a study similar to ours involving 350 patients over 8 years, the surgery rate was estimated at 49.8%.[17] In another study with 135 TOA patients, the surgery rate was found to be 35%.[18] Another study reported a surgery rate of 25%.[6] In a further study with ceftriaxone, metronidazole, and doxycycline, 44 out of 174 patients required surgery, and the medical treatment success rate was calculated as 77%.[19] In our population, the requirement for surgery was found to be 15.5%. The reason for the lower surgical rate in our study compared to others may be that patients in our country have easy access to health services and can be treated earlier.

Treatment failure was defined as fever, exacerbation of clinical findings, enlargement of the abscess, increased leukocytosis, and sepsis. Patient age >35, white blood cell count >16000/mm^3, and TOA greater than 70 mm in greatest diameter were identified as risk factors for surgery. Additionally, inadequate antibiotic therapy and bilateral abscess were evaluated as risk-increasing factors for antibiotic failure, leading to the development of a risk scoring system.[17] CRP and TOA size were observed to be risk factors for drainage requirement and longer hospital stay.[19] While the mean diameter of the medically successfully treated TOA was 6.3 cm, a diameter of 7.7 cm was associated with the need for surgery, and each 1 cm increase in diameter increased the hospitalization time by 0.4 days.[18] TOA volume was statistically significantly different between groups, and in the SG group, it was found to be larger. We couldn't draw a specific margin for TOA volume, as we did have to operate on some patients with smaller TOA volumes. However, we can safely conclude that as TOA volume increases, the risk of treatment failure also increases. In the study done by Mizushima et al.,[20] a TOA size larger than 5 cm was associated with an increased risk of antibiotherapy failure.

Table 3: Values compared between surgery group and no surgery group

	Surgery group	No-surgery group	p
Prognostic Nutritional Index	13.4±2.9	15.0±4.7	0.279
Neutrophil/lymphocyte ratio	7.8±2.7	7.2±4.6	0.157
Platelet/lymphocyte ratio	207.7±95.6	157.4±91.8	**0.020**
Lymphocyte/monocyte ratio	3.8±1.5	4.0±2.3	0.887

Mann Whitney U test.

In the indices we examined, PNI, LMR, and NLR did not show a statistically significant difference between groups. Among these indices, only the PLR ratio had a statistically significant difference between the surgery group (SG) and the no-surgery group (NSG). Although more randomized controlled trials are needed, we can conclude that as the ratio increases, the risk of antibiotherapy failure also increases.

PNI is especially used in oncologic and rheumatologic patient populations to assess prognosis. We did not find this index being used in TOA patients, nor did we find a statistically significant difference with PNI being lower in the surgery group. We believe this is due to the fact that the main parameter of PNI, albumin, is affected more in chronic processes. A larger population should be analyzed to assess the effectiveness of PNI.

In the study, NLR levels higher than 4.15 were predictive for TOA with 95.2% sensitivity and 99.4% specificity. The PLR cutoff value was 164.37 with 86.7% sensitivity and 92% specificity for TOA.[21] In another study, NLR and PLR levels were used for assessing the success of medical treatment, and 55% of the patients required surgical intervention. In the surgery group, abscess volume, platelet count, and PLR were found to be higher, similar to our results. WBC count was also higher in the surgery group. The cutoff for NLR was 6, and the cutoff for PLR was 165.[22] In a study that included 285 TOA cases, WBC, CRP, NLR, LMR, and PLR were significantly higher in the surgery group. It has been stated that NLR may be an independent marker for antibiotherapy failure.[23] Another study identified risk factors for antibiotherapy failure as age 41.5, BMI 26.72 kg/m², CRP 143.6 mg/L, and abscess diameter of 62.5 mm.[24] In our study, NLR levels were above the cutoff value in both of our groups, however, PLR was statistically significantly higher in the surgery group.

The average hospital stay was longer by 2.1±0.3 days, hemoglobin values were lower, and platelet counts were lower in SG patients on day one. These changes may be related to the severity of the TOA and systemic infection. Day-seven values were no longer statistically significantly different, indicating treatment success. The length of hospital stay can also be associated with the surgical intervention itself, as we routinely observe patients for 48 hours after laparotomy or for 24 hours after a laparoscopy procedure.

There are two important populations when surgery is considered for TOA patients. The first group consists of young adults who wish to preserve fertility, and the second group includes older patients with completed fertility but with advanced age and multiple comorbidities. In the first group of patients, we aim to avoid surgery if possible to minimize interventions to the ovaries. In older patients, we seek to avoid infectious complications as they usually have multiple comorbidities, and delaying surgery might negatively affect their prognosis. In this aspect, we have two special groups: the first group where we try to avoid operation, and the second group where we want to operate as soon as possible if surgery is required.

Our study has multiple limitations; we did not have the course of vitals during the patients' stay in our hospital, which could be useful to determine if surgery is needed for a TOA patient. This study also did not include whether the patients had an intrauterine device present, although the study done by Ginsburg et al.[25] did not reach a definitive conclusion related to antibiotherapy failure.

To conclude, we believe that TOA volume is the most important predictor of antibiotherapy failure, with PLR also playing a significant role in prognosis. Hemoglobin and platelet levels are also important in patients; however, it is challenging to draw a conclusive line for these laboratory levels as they are affected by multiple factors. More prospective trials are needed on this subject.

Statement

Ethics Committee Approval: The Göztepe Training and Research Clinical Research Ethics Committee granted approval for this study (date: 13.04.2022, number: 2022/0214).

Author Contributions: Concept – CSÖ, ED; Design – AK, CSÖ; Supervision – ODY; Materials – AK; Data Collection and/or Processing – AK; Analysis and/or Interpretation – MÇ; Literature Search – CSÖ; Writing – CSÖ, AK; Critical Reviews – AT.

Conflict of Interest: The authors have no conflict of interest to declare.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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ORIGINAL ARTICLE

Relationship between first trimester maternal PAPP-A (pregnancy associated plasma protein-A) and free β-hCG (human chorionic gonadotropin) levels with fetal birth weight

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ABSTRACT

Objective: The aim of this study was to evaluate the relationship between maternal serum PAPP-A (pregnancy-associated plasma protein A) and free β-hCG (human chorionic gonadotropin) values with fetal birth weight.

Material and Methods: 554 patients who applied to Yıldırım Beyazit University Atatürk Training and Research Hospital Obstetrics Clinic between January 2009 and December 2016 for first trimester combined screening tests were included in the study. Antenatal follow-up and pregnancy outcomes were examined. The relationship between adjusted multiples of median (MoM) values of maternal serum PAPP-A and free β-hCG levels and fetal birth weight (FBW); small for gestational age (SGA—fetal birth weight <10th percentile) and large for gestational age (LGA—fetal birth weight > 90th percentile) were analyzed.

Results: Maternal serum PAPP-A level was found to have a relationship with SGA development (p=0.03). Every decrease per unit in the adjusted MoM value of maternal serum PAPP-A level increases the risk of SGA development three times (RR, 1/0.333; 95% CI, 0.1–0.8, p=0.030).

Conclusion: Correlation between PAPP-A value and SGA was found to be statistically significant. However, a similar prediction was not eligible between maternal serum PAPP-A level and LGA fetuses. On the other hand, maternal serum free β-hCG level did not have a statistical significance as a predictor for both SGA and LGA fetuses.

Keywords: β-hCG, fetal birth weight, first trimester screening, LGA, PAPP-A, SGA.

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INTRODUCTION

One of the main purposes of antenatal screening tests has been accepted as to detect pregnant women at risk for developing pregnancy complications and to reduce the morbidity and mortality rates with the use of preventive policies. For this reason, the majority of studies have focused on early pregnancy. In the first trimester, maternal serum free beta human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein A (PAPP-A) levels have been proved to predict the risk of aneuploidies. Also, the association between first trimester maternal serum free β-hCG and PAPP-A levels and adverse pregnancy outcomes has been investigated by different studies.

Placental insufficiency has been suggested as the underlying mechanism for adverse pregnancy outcomes such as spontaneous preterm birth, pre-eclampsia, preterm prelabor rupture of membranes, and intrauterine growth restriction.[1] The relationship between first trimester biomarkers of placental function and adverse pregnancy outcomes is controversial.[2–4]

The aim of this study is to evaluate maternal serum free β-hCG and PAPP-A levels as components of combined screening tests at 11–14 weeks of gestation and to determine that these markers are predictors for fetal development abnormalities; small for gestational age (SGA) and large for gestational age (LGA).

MATERIAL AND METHODS

The entire study group consisted of 1378 patients who applied to Yıldırım Beyazıt University Atatürk Training and Research Hospital Gynecology and Obstetrics Clinic for first trimester combined screening tests between January 2009 and December 2016. Six hundred seventy-three patients were lost to follow-up. Twin pregnancies (n=46), post-term pregnancies, patients with diabetes mellitus and chronic hypertension, fetal chromosomal anomalies, and major fetal anomalies were excluded from the study group. Also, patients who developed intrauterine growth restriction (IUGR) due to placental insufficiency were excluded. Finally, the study included 554 singleton pregnancies. Data related to patients were obtained from retrospective research in the Gynecology and Obstetrics Clinic's electronic database system and patients' files. Ethical approval was obtained by the local Ethics Committee of Yıldırım Beyazıt University Faculty of Medicine (26379996/312/268 date: 19.12.2018) in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. Thus, the requirement to obtain informed consent was waived. The study was conducted in concordance with the Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects.

Maternal serum PAPP-A and free β-hCG levels were measured using the chemiluminescence method in the hospital's biochemistry laboratory Immulite 2000 analyzer. Adjusted multiples of median (MoM) values were calculated by the PRISCA package software program with patients' information gathered from outpatient clinical forms. Adjusted MoM values of maternal serum PAPP-A and free β-hCG levels were classified according to the 5th, 10th, 90th, and 95th percentiles. The relationship between these groups and fetal birth weight percentile groups (SGA, LGA) was evaluated. SGA was defined as fetal birth weight (FBW) under the 10th percentile and LGA was defined as FBW over the 90th percentile. For the evaluation of SGA vs. non-SGA; FBW under the 10th percentile and FBW over the 10th percentile (FBW<10p and FBW=10-90p) groups were compared. For the evaluation of LGA vs. non-LGA; FBW over the 90th percentile and FBW under the 90th percentile (FBW>90p and FBW=10-90p) groups were compared.

Table 1: Patients' demographical, clinical features and pregnancy outcomes

Study group (n=554)	Mean±SD (min–max)
Age (years)	26±4.9 (16–43)
Gravida	1.9±1.1 (1–8)
Parity	0.6±0.7 (0–4)
Abortion	0.19±0.4 (0–3)
BMI (kg/m^2)	24±2.3 (19–34)
Delivery mode, n (%)	
Vaginal	377 (68%)
Caesarean	177 (32%)
Gestation week at delivery, n (%)	
Preterm	68 (13.9%)
Term	486 (86.1%)
Gender, n (%)	
Male	285 (51.4%)
Female	269 (48.6%)
Fetal birth weight (gr)	3324±491 gr
(630–5265)	
Percentile (n;%)	
<10%	50 (9%)
10–90%	474 (85.6%)
>90%	30 (5.4%)

BMI: Body mass index.

Statistical Analysis

SPSS 21.0 (SPSS Inc., Chicago, IL) software package was used for data management and statistical analysis. Analysis of nominal variables was performed using the χ^2 test, Student-T test, Mann-Whitney U test, or the Fisher-exact test where appropriate. The Kolmogorov-Smirnov test was used to crosscheck the distribution of variables. Descriptive statistics were expressed as mean±standard deviation or median (min–max) for continuous variables and number/percentage for categorical variables. All variables with a p-value <0.05 in the univariate analysis were included in the multivariate analysis. Multivariate analysis was performed using the stepwise logistic regression model, and relative rates of variables were calculated. Odds ratios with 95% confidence intervals were calculated. P-values less than 0.05 were considered significant.

Table 2: Association of PAPP-A percentile groups and SGA (fetal birth weight <10p)

PAPP-A percentile (n, %)	FBW <10p	FBW >10p	RR (95% CI)	p
<5p	3 (10%)	21 (4%)	1.4 (0.2–8)	0.063
<10p	5 (16.6%)	47 (9%)	1.1 (0.3–4.3)	0.060
>90p	4 (13%)	58 (11%)	0.7 (0.1–1.1)	0.737
>95p	2 (6.6%)	26 (5%)	0.5 (0–0.8)	0.801
PAPP-A (MoM) (mean±SD)	0.96±0.61	1.08±0.59	0.3 (0.1–0.8)	0.030

SD: Standard deviation; PAPP-A: Pregnancy associated plasma protein - A; SGA: Small for gestational age; FBW: Fetal birth weight; RR: Relative ratio; CI: Confidence interval; MoM: Multiples of median.

Table 3: Association of free β-hCG percentile groups and SGA (fetal birth weight <10p)

β-hCG percentile (n, %)	FBW <10p	FBW >10p	RR (95% CI)	p
<5p	2 (6%)	26 (5%)	0.9 (0.3–3.3)	0.938
<10p	3 (10%)	52 (10%)	1 (0.2–4.4)	0.778
>90p	5 (17%)	53 (10%)	0.8 (0.2–2.5)	0.596
>95p	2 (7%)	28 (5%)	0.7 (0.1–2.5)	0.666
PAPP-A (MoM) (mean±SD)	0.99±0.47	1.27±0.86	0.9 (0.8–1)	0.542

SD: Standard deviation; β-hCG: Human chorionic gonadotropin; SGA: Small for gestational age; FBW: Fetal birth weight; RR: Relative ratio; CI: Confidence interval; MoM: Multiples of median.

RESULTS

The mean age of the study group was 26±4.9 (range 16–43) years. The mean number of gestations was 1.9±1.1 (ranged between 1 and 8 gestations) and the mean number of parities was 0.6±0.7 (ranged between 0 and 4 parities). The median time for first trimester screening was 85.9±5.2 days. The median fetal birth weight was 3324±491 g and ranged between 630 and 5265 g. Demographical, clinical features, and pregnancy outcomes of the study population are shown in Table 1.

Three hundred seventy-seven (68%) pregnancies resulted in vaginal birth and 177 (32%) with cesarean section (CS). Seventy-seven (14%) patients underwent surgery for previous CS, 40 (7%) patients for fetal distress, 22 (4%) patients for cephalopelvic disproportion, and 40 (7%) patients for other reasons (placenta previa, abruptio placenta, maternal morbidity, etc.). There was no statistical significance between FBW and mode of delivery (p>0.05). There were 285 (51.4%) male newborns and 269 (48.6%) female newborns. Tobacco use was positive in 86 (6.2%) pregnancies. The duration of pregnancy was under 37 weeks in 68 (13.9%) patients and equal to or more than 37 weeks in 486 (86.1%) patients.

Mean adjusted MoM values of maternal serum PAPP-A level was 0.96 and ranged between 0.1 and 5.8 in entire study group. Patients with FBW <10th percentile and FBW ≥10th percentile were compared and mean maternal serum PAPP-A level was found to have a relationship with SGA development by using backward regression analysis (p=0.03). It was calculated that every decrease per unit in adjusted MoM value of maternal serum PAPP-A level increases the risk of SGA development 3 times (RR, 1/0.333; 95% CI, 0.1–0.8, p=0.030). Adjusted maternal serum PAPP-A levels were investigated for <5p, <10p, >90p and >95p groups with regression analysis however the association of PAPP-A levels and SGA risk did not reach a statistical significance (Table 2).

Mean maternal serum PAPP-A levels between FBW >90th percentile and FBW ≤90th percentile (LGA vs non-LGA) fetuses were not statistically significant (p>0.05).

Mean maternal serum free β-hCG adjusted MoM level was 1.26±0.8 and ranged between 0.2 and 7.4. FBW <10th percentile and ≥10th percentile (SGA vs. non-SGA) fetuses were compared and mean maternal serum free β-hCG levels were not statistically significant between these groups (p>0.05) (Table 3). Additionally, FBW >90th percentile and FBW ≤ 90th percentile (LGA vs non-LGA) fetuses did not have a statistical significance for mean maternal serum free β-hCG levels (p>0.05).

DISCUSSION

In the first trimester of pregnancy, maternal serum free β-hCG and PAPP-A levels, combined with nuchal translucency (NT) measurement, were proved to diagnose fetuses with Down syndrome (Trisomy 21) with 89% positivity and 5% false positivity. Also, these biochemical markers were evaluated as predictors for adverse

pregnancy outcomes.[5] PAPP-A is a protease for insulin-like growth factor-binding protein-4 (IGFBP-4).[6] Therefore, low serum PAPP-A levels cause high IGFBP-4 levels resulting in low levels of maternal serum free insulin-like growth factor (IGF). IGF plays a major role in fetal growth regulation by controlling glucose and amino acid intake to trophoblasts.[7,8] For this reason, conditions with trophoblast invasion anomalies such as spontaneous fetal loss, SGA, IUGR, and preeclampsia could have low maternal serum PAPP-A levels in the first trimester. Westergaard et al.[9] were the first authors to suggest that low maternal serum PAPP-A levels predict adverse pregnancy outcomes 25 years ago. In their study, pregnancies with low PAPP-A levels had a tendency to develop miscarriages within days or weeks. These results were confirmed by other investigators with different reports.[9,10]

Patients with low maternal serum PAPP-A levels have a risk for developing spontaneous preterm delivery, pregnancy-induced hypertension, spontaneous abortion, SGA, and gestational diabetes mellitus.[11,12] Also, different investigators reported that pregnancies with SGA fetuses have low maternal serum PAPP-A levels and pregnancies with LGA fetuses have high maternal serum PAPP-A levels in early pregnancy.[13,14] A maternal serum PAPP-A level <5th percentile increases the risk for SGA, preeclampsia, spontaneous abortion, and intrauterine fetal death.[15,16] However, there are some authors suggesting that low first trimester maternal serum PAPP-A levels are not related to IUGR. These authors reported that insufficient placentation induces a maternal systemic inflammatory response syndrome and releases different mediators, which enhances PAPP-A production from other non-placental tissues.[17,18]

We found that a decrease per unit in adjusted maternal serum PAPP-A levels increases SGA risk three times in 10–14th weeks of gestation (RR, 1/0.333; 95% CI, 0.1–0.8, p=0.030). Our findings correlate with the literature review. First trimester free β-hCG levels did not affect fetal growth in our study. On the other hand, different studies assessed the relationship between low free β-hCG levels and pregnancy complications. The FASTER (First and Second Trimester Evaluation of Risk Trial) study was expanded by Dugoff et al.,[15] and a total of 34,271 pregnant women were enrolled in a larger study cohort. In their study, first trimester maternal serum free β-hCG level <1st percentile (0.24 MoM) increased the risk of fetal loss before the 24th week of pregnancy. They concluded that first trimester maternal serum free β-hCG level <5th percentile (0.42 MoM) indicates a low FBW with <10th percentile. As a result, insufficient placentation and low placental volume were considered responsible for decreased maternal serum free β-hCG levels in 10–14th weeks of gestation. In the second trimester of pregnancy, hypoperfusion-induced hormone production was admitted as the cause of high maternal serum free β-hCG levels.[12,19] Different investigators established their findings that support the role of first trimester maternal serum free β-hCG levels as predictors for pregnancy complications.[11,12,15,20,21] However, several studies, including our study, suggest that first trimester maternal serum free β-hCG levels have no impact on fetal development and fetal birth weight.[12,15,22]

A Cochrane Library review between the years 1966 and 2007 was carried out by the Society of Obstetricians and Gynaecologists of Canada Genetics Committee in 2008.[23] According to this algorithm, maternal serum markers are not recommended for predicting pregnancy complications due to low sensitivity and high false positivity. During ordinary antenatal screening procedures such as screening for chromosomal anomalies, abnormal results in maternal serum markers could be investigated for pregnancy complications. Unexplained low maternal serum PAPP-A (<0.4 MoM) and/or low free β-hCG (<0.5 MoM) levels in the first trimester are associated with adverse pregnancy outcomes. However, a specific follow-up protocol could not be defined. Uterine artery Doppler Ultrasonography (USG) estimates might be suitable for the evaluation of abnormal and unexplained maternal serum markers. An abnormality in uterine artery Doppler USG along with low first trimester maternal serum PAPP-A levels and high second trimester alpha-feto protein (AFP), β-hCG, inhibin-A levels carry an elevated risk for IUGR and preeclampsia. Thus, obstetricians can rearrange antenatal visits according to the patient's symptoms, follow-up signs (fetal growth, amniotic fluid volume, fetal biophysical profile, uterine artery Doppler USG, cervical measurement), or the patient's education status.

CONCLUSION

Our study suggested that low levels of first trimester maternal serum PAPP-A and free β-hCG values could predict adverse pregnancy outcomes. A decrease per unit in adjusted maternal serum PAPP-A level tripled the risk of SGA in our study (RR, 1/0.333; 95% CI, 0.1–0.8, p=0.030). However, a similar prediction was not viable between maternal serum PAPP-A level and LGA fetuses. On the other hand, maternal serum free β-hCG level did not have statistical significance as a predictor for both SGA and LGA fetuses.

The results of routine first trimester screening tests might be extended to get an anticipation for pregnancy complications. Thus, the cost-effective power of these tests would be enhanced, and the morbidity of pregnancy complications could be reduced. The most important limitation of this study is its retrospective design. On the other hand, a high number of patients is an advantage. Besides, inclusion and exclusion criteria strengthen study homogenization. However, precise conclusions could not be made for using antenatal routine screening tests as predictors of pregnancy outcomes. For more accurate results, more randomized controlled trials should be conducted in this patient group.

Statement

Ethics Committee Approval: The Yıldırım Beyazıt University Clinical Research Ethics Committee granted approval for this study (date: 19.12.2018, number: 26379996/312/268).

Author Contributions: Concept – GK, HLK, AFY; Design – GK, AFY; Supervision – HLK, AFY; Data Collection and/or Processing – GK, GFY, EİS; Analysis and/or Interpretation – GK, EİS; Literature Search – GK, GFY, EİS; Writing – GK, GFY, HLK; Critical Reviews – HLK, AFY.

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ORIGINAL ARTICLE

Non-reassuring fetal heart rate patterns in association with umbilical artery acidosis

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ABSTRACT

Objective: The main purpose of the study was to evaluate the clinical outcomes of fetuses who had intrapartum non-reassuring fetal heart rate tracings.

Material and Methods: Patients who underwent cesarean section as an emergency operation due to non-reassuring fetal heart rate patterns were included in the study. All FHR paper traces were reevaluated by an expert obstetrician, blinded to the neonatal outcomes, based on the guidelines of the NICHD workshop. Patients were placed into five groups considering the variability and accompanying deceleration type. Clinical outcomes, Apgar scores, and umbilical artery blood parameters were evaluated.

Results: The study consisted of 84 patients; Group 1, normal variability with late decelerations (n=32); Group 2, normal variability with variable decelerations (n=16); Group 3, decreased variability (n=10); Group 4, decreased variability with late decelerations (n=14); Group 5, decreased variability with variable decelerations (n=12). Groups with decreased variability and decelerations (groups 4 and 5) had higher rates of NICU admission than the groups with normal variability with decelerations (groups 1 and 2) ($p<0.05$). In the decreased variability with late decelerations group (Group 4), umbilical artery blood pH and ABE were significantly lower while lactate levels were higher than in groups 1, 2, and 3 ($p<0.001$). Among all patients, inverse correlations were shown between umbilical artery blood lactate and pH ($r=-0.734$, $p<0.001$), and also between lactate and ABE ($r=-0.581$, $p<0.001$). For the prediction of umbilical artery blood pH<7.1 and/or ABE<-12, the optimal umbilical artery blood lactate cut-off level is 7 mmol/L with a sensitivity of 88.9% and specificity of 89.3%.

Conclusion: Decreased variability in non-reassuring intrapartum fetal heart rate patterns should be considered as important as decelerations. In the evaluation of intrapartum fetal asphyxia, lactate appears to be as good a marker as pH and ABE.

Keywords: Fetal heart rate, fetal hypoxia, nonreassuring fetal status, lactate, umbilical cord blood.

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INTRODUCTION

During labor, transient but recurrent interruptions in fetal oxygenation may occur due to regular uterine contractions. It is well tolerated by many fetuses, but in some, metabolic changes due to decreased oxygenation are reflected in fetal heart rate (FHR) tracings. Detection of fetal heart rate changes that may be associated with decreased fetal oxygenation is aimed with continuous intrapartum fetal heart rate monitoring.[1] Although its effects on fetal death or long-term neurological outcomes are controversial, continuous intrapartum FHR monitoring is recommended in patients with high-risk conditions (e.g., growth-restricted fetuses, hypertensive disorders, type 1 diabetes mellitus).[2] Algorithms have been developed to identify FHR patterns that are normal, that require more attention, and that are abnormal which requires immediate delivery of the fetus.[3,4] Although normal results seem reliable in determining fetal well-being, intrapartum FHR monitoring is associated with increased cesarean rates due to high false positive rates.[5] One of the most common indications for primary cesarean delivery is non-reassuring FHR patterns.

The Apgar score provides a universally accepted, easily applicable method for revealing the status of the newborn just after birth. Although lower Apgar scores are associated with higher neonatal mortality and morbidity, it is not recommended as a prognostic tool.[6,7] Umbilical artery blood sampling provides more objective information in demonstrating fetal status at birth. An umbilical artery pH below 7.0 is defined as fetal metabolic acidemia.[8] It is also suggested that the umbilical artery pH <7.10 and ABE <-12 mmol/L threshold to identify fetuses with non-reassuring heart rate patterns that may benefit from intervention before pathological fetal acidosis and fetal damage develop.[8–10] Lactate concentration is also useful in demonstrating tissue hypoxia as a result of anaerobic metabolism.[11]

The main purpose of our study was to assess the relationship between intrapartum nonreassuring fetal heart rate tracings and early neonatal clinical findings. Secondly, to investigate the importance of umbilical artery blood lactate in the evaluation of fetal status.

MATERIAL AND METHODS

This prospective observational study was carried out at İstanbul Medeniyet University Göztepe Training and Research Hospital, Türkiye, from February 2015 through January 2016. Ethical approval was obtained from the local ethics committee, and the study was conducted in accordance with the Declaration of Helsinki. Patients who were admitted to the delivery room due to the onset of labor gave informed written consent. All patients in the delivery room were monitored with external cardiotocography (CTG) continuously, and FHR paper traces were obtained for later evaluation. Eighty-four patients who underwent cesarean section as an emergency operation due to non-reassuring FHR patterns were included in the study. The selection criteria were beyond the 34th gestational weeks of pregnancy with singleton, cephalic presentation fetuses. Patients with medical disorders that might affect the fetal acid-base status, such as cardiopulmonary disease, chronic renal failure, or poorly controlled diabetes mellitus, were excluded. Pregnancies with known fetal anomalies, growth-retarded fetuses, and multiple gestations were also not included in the study. All operations were performed under general anesthesia, and premedication protocols were identical in all patients.

Comen Fetal Monitor Star 500F or Sunray SRF 618B was used as external cardiotocography to record electronic fetal heart rate tracings. The time between the last recorded non-reassuring FHR tracing and the time of cesarean section was no more than 30 minutes. All FHR paper traces were reevaluated by an expert obstetrician, blinded to the neonatal outcomes, based on the guidelines of the NICHD workshop.[3,4] We combined tracings with absent and minimal variability and labeled them as decreased variability. Variable and late deceleration definitions of the NICHD workshop were also complied with. All FHR tracings were grouped into five according to the variability and deceleration parameters: group 1, normal variability with recurrent late decelerations; group 2, normal variability with recurrent variable decelerations; group 3, decreased variability with no decelerations; group 4, decreased variability with recurrent late decelerations; and group 5, decreased variability with recurrent variable decelerations.

Immediately after delivery, the umbilical cord was double clamped and arterial blood samples were collected in a plastic syringe washed with heparin solution. Blood samples were analyzed for pH, actual base excess (ABE), and lactate within 15 minutes of delivery using a Radiometer Copenhagen ABL 510 Blood Gas System.

The study data were analyzed using IBM SPSS Statistics version 21.0 (IBM Corporation, Armonk, New York, United States). Data were presented as mean±SD and categorical parameters were presented as frequencies with group proportions. Fisher's exact test was used for pairwise group comparisons of categorical variables. For numerical variables with a normal distribution, the One-Way ANOVA test was used, and the Kruskal-Wallis test was used for variables without a normal distribution to compare more than two independent FHR pattern-based groups. Tukey and Tamhane's T2 tests were used for post-hoc analysis for variables with normal and non-normal distributions respectively. A receiver operating characteristic (ROC) analysis was performed to assess the best cut-off level of umbilical artery blood lactate which predicts the fetuses who may benefit from intervention. To evaluate the relationship between quantitative variables, Spearman's rank correlation was used. Differences were interpreted as statistically significant at $p<0.05$.

RESULTS

The study consisted of 84 participants; Group 1, Normal Variability with Late Decelerations (n=32); Group 2, Normal Variability with Variable Decelerations (n=16); Group 3, Decreased Variability (n=10); Group 4, Decreased Variability with Late Decelerations (n=14); Group 5, Decreased Variability with Variable Decelerations (n=12).

Table 1 shows the clinical characteristics of the five FHR pattern groups. The groups were similar in terms of age, gravida, parity, gestational age at delivery, and birth weights ($p>0.05$). When we compared groups according to the APGAR scores; in the Decreased Variability with Late Decelerations group (group 4), both 1- and 5-minute APGAR scores were lower than in groups 1 and 2 ($p<0.05$). First and fifth minute APGAR scores were similar in decreased variability groups (groups 3, 4, and 5) irrespective of accompanying decelerations ($p>0.05$). The Decreased Variability with Late Decelerations group (group 4) had the highest rates of meconium-stained amniotic

Table 1: Clinical characteristics of the groups of fetal heart rate pattern groups

	Group 1 Normal variability with late decelerations (n=32)	Group 2 Normal variability with variable decelerations (n=16)	Group 3 Decreased variability (n=10)	Group 4 Decreased variability with late decelerations (n=14)	Group 5 Decreased variability with variable decelerations (n=12)	p
Maternal age (years)	28.31±6.75	28.50±6.09	28.50±6.87	28.36±6.37	27.17±3.76	NS*
Gravidae (n)	1 [1–6]	1 [1–5]	1 [1–8]	2 [1–5]	1 [1–3]	NS**
Parity (n)	0 [0–2]	0 [0–3]	0 [0–3]	0 [0–3]	0 [0–1]	NS**
GA at birth (weeks)	38.5±2.0	38.6±2.0	37.9±2.6	38.5±1.7	38.5±1.9	NS*
Birth weight (gr)	3015±530	3043±560	2946±371	3928±685	2901±727	NS*
APGAR 1	8 [4–10]	8 [6–9]	6 [5–10]	4 [1–8)$^{\alpha}$	6 [3–9]	**<0.001****
APGAR 5	9 [6–10]	10 [8–10]	9 [7–10]	8 [6–9]$^{\alpha}$	8 [6–10]	**0.001****
MSA	10 (31.2%)	1 (6.2%)	3 (30.0%)	13 (92.9%)$^{\beta}$	3 (25.0%)	**<0.001*****
NICU admission	4 (12.5%)	0 (0.0%)	2 (20.0%)	12 (85.7%)§	6 (50.0%)$^{¥}$	**<0.001*****

Data presented as mean±standart deviation, median [min–max], n (%). *: One-Way ANOVA; **: Kruskal-Wallis Test; ***: Fisher Exact Test; NS: Not significant; GA: Gestational age; MSA: Meconium stained amniotic fluid; NICU: Neonatal intensive care unit; α: Thamannes posthoc test showed significant difference when compared with group 1 and 2; ß: Fisher exact test showed significant difference when compared with other groups; §: Fisher exact test showed significant difference when compared with group 1–2 and 3; ¥: Fisher exact test showed significant difference when compared with group 1–2.

Table 2: Umbilical artery blood pH, lactate and actual base excess in fetal heart rate pattern groups

	Group 1 Normal variability with late decelerations (n=32)	Group 2 Normal variability with variable decelerations (n=16)	Group 3 Decreased variability (n=10)	Group 4 Decreased variability with late decelerations (n=14)	Group 5 Decreased variability with variable decelerations (n=12)	p
pH	7.30±0.08	7.31±0.05	7.26±0.11	7.15±0.13$^{\alpha}$	7.24±0.04	**<0.001***
Actual base excess (mmol/L)	1.37±2.89	-1.19±2.75	0.29±4.73	-7.62±5.23$^{\alpha}$	-5.25±3.60$^{\beta}$	**<0.001***
Lactate (mmol/L)	3.19±1.84	2.61±1.53	4.48±3.21	7.76±4.20$^{\alpha}$	6.39±3.04§	**<0.001***

Data presented as mean±standart deviation; *: One-Way ANOVA; a, ß: Tukey post test showed significant difference when compared with groups 1, 2 and 3; §: Tukey post test showed significant difference when compared with groups 1 and 2.

fluid among the groups (p<0.001). Groups which showed decreased variability with decelerations (groups 4 and 5) had higher rates of NICU admission than the groups that had normal variability with decelerations (groups 1 and 2) (p<0.05).

Group comparisons of the umbilical artery acid-base parameters are shown in Table 2. In group 4 (decreased variability with late decelerations), significantly lower umbilical artery blood pH and ABE levels and higher lactate concentration were observed than in groups 1, 2, and 3 (p<0.001). Significantly lower actual base excess was observed in group 5 (decreased variability with variable decelerations) than in groups 1, 2, and 3 (p<0.001). Group 5 also had higher levels of umbilical artery blood lactate concentrations compared to the groups with normal variability (groups 1 and 2) (p<0.001).

The relationship between Apgar scores and umbilical artery acid-base parameters is given in Table 3. pH and ABE were positively correlated with 1- and 5-minute Apgar scores (p<0.05), while lactate levels had a stronger negative correlation with 1- and 5-minute Apgar scores (p<0.05). The relationship between umbilical artery blood lac-

Table 3: Correlations between 1st and 5th minute Apgar scores and umbilical artery blood pH, actual base excess and lactate (n=84)

	1-minute Apgar score		5-minute Apgar score	
	r_s	p	r_s	p
pH	0.495	<0.001	0.354	0.001
Actual base excess (mmol/L)	0.352	0.001	0.262	0.016
Lactate (mmol/L)	-0.625	<0.001	-0.498	<0.001

r_s: Spearman's correlation coefficient.

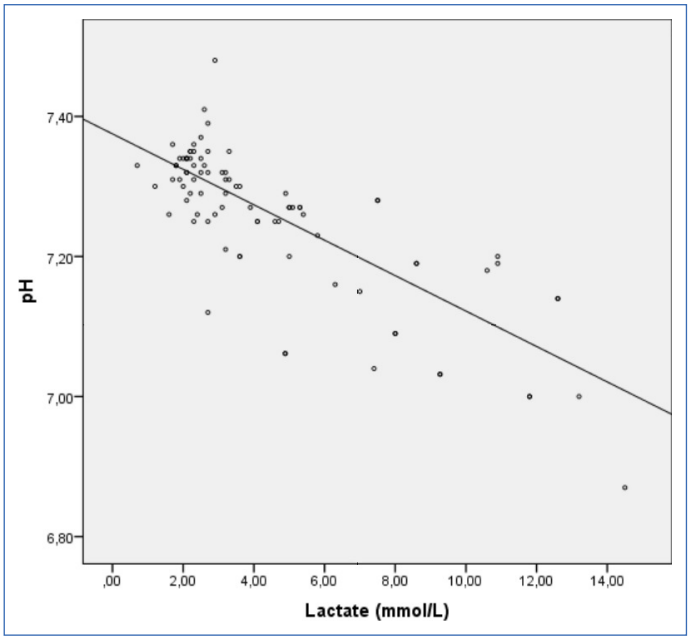

Figure 1: Scatter-dot diagram showing the relationship between umbilical arterial cord blood lactate concentrations and pH in all patients (n=84, r=-0.734, p<0.001).

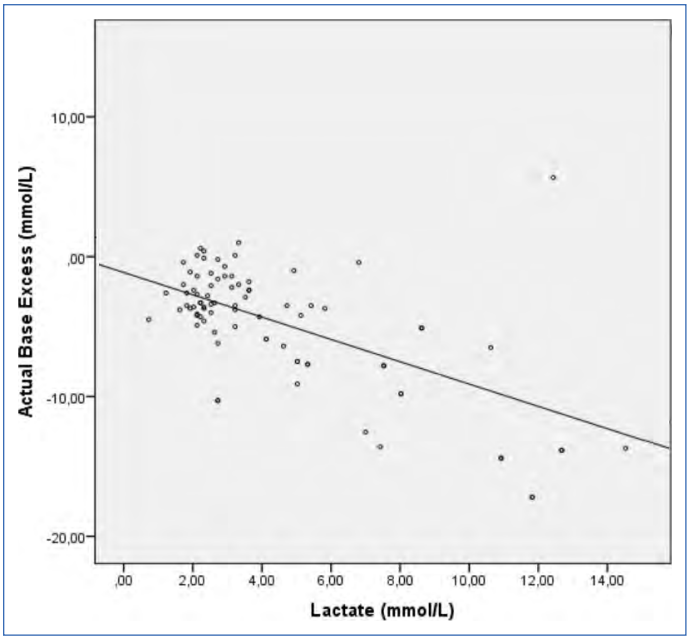

Figure 2: Scatter-dot diagram showing the relationship between umbilical arterial cord blood lactate concentrations and actual base excess in all patients (n=84, r=-0.581, p<0.001).

tate and pH - ABE is shown in Figures 1 and 2. Spearman's correlation showed a significant inverse correlation between lactate and pH (r=-0.734, p<0.001). There was also a moderate inverse correlation between lactate and ABE (r=-0.581, p<0.001).

Among 84 patients, there was only 1 newborn whose umbilical artery blood pH <7.0. Nine patients had umbilical artery blood pH <7.1 and/or ABE <-12. The ROC curve analysis was also performed to determine the best cut-off value of the umbilical artery blood lactate concentration to predict these nine fetuses (Fig. 3). The optimal umbilical artery blood lactate cut-off level of 7 mmol/L, above which the sensitivity and specificity were 88.9% and 89.3%, respectively. The area under the curve (AUC) was 0.915±0.056 (95% CI 0.805–1.00).

DISCUSSION

Intrapartum fetal heart rate monitoring aims to identify fetuses with intrapartum acidosis and prevent fetal death through timely intervention. The secondary purpose is to prevent fetal neurological damage. Although there is evidence that intrapartum fetal monitoring reduces intrapartum deaths, its contribution to long-term neurological outcomes is unknown. Intrapartum continuous electronic fetal monitoring results in increased operative vaginal delivery and cesarean rates due to high false-positive rates of intrapartum fetal monitoring.[5] Although fetal scalp blood sampling and fetal oxygen saturation have been suggested to reduce this false-positive rate, these methods are invasive.[12,13]

There are many reports in the literature showing that late decelerations are associated with fetal acidemia. In addition, decreased variability was suggested as an indicator of fetal acidemia.[14,15] Williams et al.[16] also showed that decreased variability accompanied by late decelerations is associated with lower pH, ABE values, and increased incidence of acidemia. In addition, they reported that the incidence of acidemia increased in cases of decreased variability in which decelerations were not observed. Inconsistent with this data, it has also been suggested that late, variable, and prolonged decelerations are associated with acidemia, but variability in the last 30 minutes is not.[9] In the

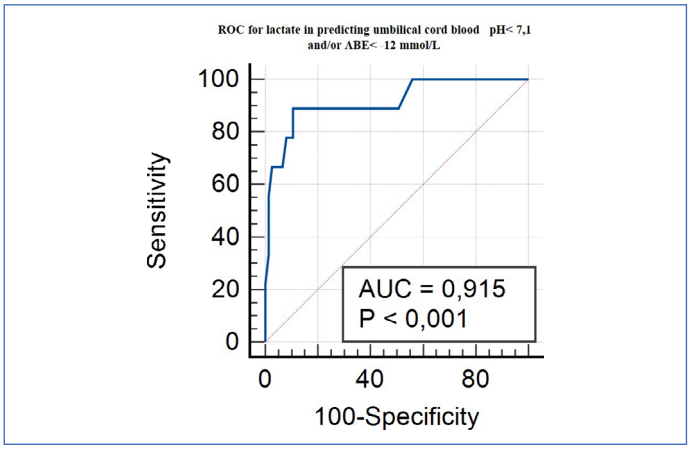

Figure 3: Receiver operating characteristic (ROC) curve for umbilical arterial cord blood lactate concentration to determine umbilical artery pH <7.1 and/or ABE <-12 mmol/L. Optimal cut-off=7 mmol/L. Area under the curve, 0.915; 95% CI: 0.805–1.00; sensitivity, 88.9%; specificity, 89.3%.

current study, late decelerations accompanied by decreased variability were associated with worse neonatal clinical outcomes compared to groups with only late or variable decelerations (with normal variability). Umbilical artery blood acid-base evaluation was also consistent with clinical findings. Decreased variability accompanied by decelerations, especially late decelerations, was associated with lower pH and ABE and higher lactate levels. It was reported in the NIHCD workshop that minimal variability or loss of variability may be the result of hypoxemia and acidosis. It occurs due to insufficient compensatory mechanisms in cases of insufficient oxygenation of the fetal brain. In this situation, decreased variability may be accompanied by recurrent decelerations.[4] Therefore, variability should be considered along with decelerations when evaluating FHR traces.

Regarding the early neonatal clinical findings, there was a positive correlation between 1- and 5-minute Apgar scores and pH and actual base excess. Additionally, there was a stronger inverse correlation with lactate concentration. In contrast to our results, pH and lactate were not significantly correlated with Apgar scores in the study reported by Hamed. They reported that the reason for this situation is that the Apgar score does not provide information about causes such as obstruction of the respiratory tract by secretions, anesthetic drugs, or cardiovascular malformations.[17] Despite the accepted criteria of pH <7.0 and ABE <-16 mmol/L in the diagnosis of fetal asphyxia, there are reports that lactate is a better marker for determining fetal status.[18]

Since the number of fetuses whose umbilical artery blood parameters meet the threshold values for fetal acidemia is only one, we could not determine an optimal cut-off level of lactate concentration for fetal acidosis. Instead, in our study, a lactate cut-off level of >7 mmol/L was shown to be a very good marker in predicting umbilical artery blood pH <7.1 and/or ABE <-12 mmol/L to identify the fetuses with non-reassuring heart rate patterns that may benefit from intervention before fetal acidosis develops. Umbilical artery blood lactate concentration was inversely related to pH and ABE. Consistent with these findings, a lactate cut-off level of 8 mmol/L was suggested to indicate intrapartum fetal asphyxia, given the inverse correlation with pH and ABE.[19]

Despite all these definitions, the positive predictive value (PPV) of intrapartum electronic fetal monitoring for acidosis is quite low. According to the current literature, neonatal acidemia was reported between 12–30% in patients with non-reassuring intrapartum fetal heart rate tracings.[20,21] In our study, the PPV of intrapartum FHR monitoring for fetal acidosis was lower than the values reported in the literature (11% for pH <7.1). This was interpreted as "obstetricians in Türkiye are not guaranteed by the laws, and there may be increased malpractice concerns, so they may act hastily in the cesarean section decision."

In addition, the presence of inter- and intraobserver variations in the evaluation of the traces is a situation that limits the reliability of the method. Nevertheless, its negative predictivity of 99% serves as a guide for the clinician for fetal well-being.[22]

Relatively small sample size and not evaluating interobserver and intraobserver variability in the assessment of fetal heart rate tracings were the main limitations of the study. Nonetheless, it provides useful information for the assessment of fetal well-being with continuous intrapartum electronic monitoring. Further large-scale studies are recommended, especially for the routine use of umbilical artery lactate concentration to identify intrapartum fetal acidosis.

CONCLUSION

Due to the high false-positive rates of intrapartum fetal heart rate monitoring for adverse neonatal outcomes, we recommend careful interpretation. Decreased variability in non-reassuring intrapartum fetal heart rate patterns should be considered as important as decelerations. In the evaluation of intrapartum fetal asphyxia, umbilical artery blood lactate appears to be as good a marker as pH and ABE.

Statement

Ethics Committee Approval: The İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 24.02.2015, number: 2015/0015).

Author Contributions: Concept – ÖGE; Design – ÖGE; Supervision – AG; Resource – ÖGE; Materials – ÖGE; Data Collection and/or Processing – ÖGE; Analysis and/or Interpretation – AG; Literature Search – ÖGE; Writing – ÖGE; Critical Reviews – AG.

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ORIGINAL ARTICLE

The effect of gestational diabetes mellitus on sexual function, anxiety, depression and quality of life in pregnant women

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ABSTRACT

Objective: Gestational diabetes during pregnancy causes many adverse effects in mothers and affects them in various aspects. The aim is to investigate the impact of gestational diabetes during the course of pregnancy on patients' quality of life, depression and anxiety levels, and sexual functions.

Material and Methods: The study was conducted on 131 third-trimester pregnant women (healthy pregnant women: 79, patients with GDM: 52) by using the WHO Quality of Life-BREF (WHOQOL-BREF), Female Sexual Function Index (FSFI), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) between September 2020 and August 2021. The patients with GDM were then divided according to their treatment strategies (Lifestyle Modification: 43 and Insulin Therapy: 9) for further evaluations.

Results: Healthy pregnant women have a higher score (69.30±14.68) on the general health domain of WHOQOL-BREF than patients with GDM (63.22±18.25) with statistical significance (p=0.037). The Insulin Therapy Group has a significantly (p=0.008) lower psychological health score (60.18±18.05) on the psychological health domain of WHOQOL-BREF than the Lifestyle Modification Group (76.06±15.05). There was no significant difference in FSFI, BAI, BDI, and other domains of WHOQOL-BREF scores between the two groups and treatment strategies.

Conclusion: Suffering from GDM or using different treatment options has no impact on patients' quality of life, levels of depression or anxiety, or sexual function.

Keywords: Anxiety, depression, gestational diabetes, quality of life, sexual dysfunction.

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INTRODUCTION

Diabetes Mellitus (DM) is a disease of glucose metabolism and occurs in pregnant women in three groups such as pre-gestational diabetes (diagnosed before the onset of pregnancy, e.g. Type 1 and Type 2 DM), gestational diabetes (diagnosed at any time during the antenatal period but not expected to persist postpartum), and diabetes in pregnancy (firstly diagnosed in pregnant women with hyperglycemia and meeting WHO criteria for diabetes in the non-pregnant state).[1]

According to the most recent (2021) International Diabetes Federation records, gestational diabetes mellitus (GDM) affects approximately 16% of pregnancies worldwide.[2] Struggling with a health condition such as gestational diabetes during a delicate process of pregnancy affects the patient's quality of life, anxiety, depression status, and sexual function.[3–5]

Studies have shown that quality of life may be affected in patients with gestational diabetes due to concerns about their health and that of the newborn, requiring close follow-up for taking control of the disease and using regular insülin.[6] In addition, pregnant women with GDM are aware of the fact that uncontrolled disease could be the cause of pregnancy complications and adverse neonatal outcomes, which increases their anxiety and depression levels.[7] A few recent studies declared that patients with gestational diabetes also experience sexual function problems.[4]

The literature is limited for such a complex disease that affects the individual's life in various aspects. In our study, we aimed to investigate the impact of gestational diabetes on patients' lives in different dimensions such as quality of life, anxiety and depression levels, and sexual function by comparing patients with gestational diabetes and the control group during their pregnancy period with validated, unbiased, accepted questionnaires.

MATERIAL AND METHODS

Study Design and Setting

This study was performed on 131 participants at the education and research hospital between 1st of September 2020 to 30th of August 2021. The protocol has been reviewed and approved by the Clinical Research Ethics Committee of the Hospital (approval number: 2020/0500). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who attended the obstetrics outpatient clinic for regular checkups were selected voluntarily for the study. After written informed consent was obtained from all participants, patients were asked to complete validated Turkish forms of the World Health Organization Quality of Life—BREF (WHOQOL-BREF), Female Sexual Function Index (FSFI), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI). The questionnaires were completed by participants after being interviewed and given clear instructions by two of the authors (Satır Ozel, Loclar Karaalp), reducing the problems that can arise in a self-completion approach to such a long questionnaire.

Study Population

The inclusion criteria were women who were older than 20 years of age, had third-trimester pregnancy, had been sexually active with the same partner for at least 6 months, and had a 75 g oral glucose tolerance test (OGTT) at least 4 weeks ago at 24–28 weeks.

The exclusion criteria were women currently diagnosed with type 1 and type 2 DM, situations where sexual intercourse is not recommended such as placenta previa, premature rupture of membranes, threatened premature birth, those who use drugs that may affect sexual functions (antihypertensive, antidepressant, anxiolytic drugs, etc.), those with diagnosed psychological diseases (depression, schizophrenia, neurosis, etc.), alcohol and substance addiction, pregnancies after rape, hospitalization in the last 30 days, and patients who could not be together with their partner in the last month.

Sampling Method

Pregnant women were divided into two different groups as the control group and patients with GDM according to the results of the 75 g OGTT performed at 24–28 weeks of gestation. After fasting for approximately 8 hours, patients were given 75 g glucose and blood glucose levels were measured at zero (fasting), first, and second hours. According to the results, the diagnosis of gestational diabetes was excluded in values lower than 92 mg/dl at the zero hour, 180 mg/dl at the first hour, and 153 mg/dl at the second hour, and the pregnant women were considered healthy in this respect.[8] If one value is higher than the cut-off levels, patients have been diagnosed with GDM. Hemoglobin A1c (HbA1c), also known as glycosylated hemoglobin, levels of patients with GDM were also recorded.

Both groups were compared in terms of the difference in sexual function score, anxiety score, depression score, and quality of life score, and the effect of the presence of gestational diabetes on the scores was investigated. In addition, the group with GDM was divided into 2 subgroups according to the type of treatment, such as the lifestyle modification group and the insulin therapy group (in addition to lifestyle modification), and compared in terms of the effect of the treatment method on the scores.

Instruments

In our study, the Turkish validation and reliability of the World Health Organization Quality of Life—BREF (WHOQOL-BREF), Female Sexual Function Index (FSFI), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) were used.[9–12]

The WHOQOL-BREF test is an unbiased test providing clinicians with an evaluation of the quality of life (QoL) in both healthy and ill patients. It consists of 26 questions in 4 domains: physical (somatic), psychological, social relationships, and environmental. Responses are scored from 1 to 5, and a cumulative score is obtained for each domain. The total score is not calculated. A higher score represents better QoL as specified by the respondent.[13] In the validated WHOQOL-BREF, the 27th question is a national question and has not been included in the scoring, and the 1st and 2nd questions were calculated as the general health score, unlike the original.

FSFI is a questionnaire used for clinical research by evaluating many aspects of female sexual function, with 19 questions consisting of 6 domains such as desire, arousal, lubrication, orgasm, satisfac-

Table 1: Demographic data

	Control group (n=79)	Patient with GDM group (n=52)	p
Age	29.4±5.3	31.7±5.1	0.013
Spouse age	33.4±6.6	34.4±5.8	0.388
Duration of marriage (year)	6.2±5.6	6.9±5.3	0.465
Gravida			0.120
1	35 (44.3%)	17(32.7%)	
2	18 (22.8%)	15 (28.8%)	
3	18 (22.8%)	8 (15.4%)	
4	2 (2.5%)	7 (13.5%)	
5	5 (6.3%)	4 (7.7%)	
6	1 (1.3%)	0 (0%)	
7	0 (0%)	1 (1.9%)	
Parity			0.252
0	37 (46.8%)	20 (38.5%)	
1	23 (29.1%)	16 (30.8%)	
2	16 (20.3%)	12 (23.1%)	
3	1 (1.3%)	4 (7.7%)	
4	2 (2.5%)	0 (0%)	
Abortion			0.576
0	65 (82.3%)	40 (76.9%)	
1	11 (13.9%)	10 (19.2%)	
2	2 (2.5%)	1 (1.9%)	
3	1 (1.3%)	0 (0%)	
4	0 (0%)	1 (1.9%)	
Number of vaginal birth			0.521
0	47 (59.5%)	36 (69.2%)	
1	18 (22.8%)	9 (17.3%)	
2	11 (13.9%)	4 (7.7%)	
3	6 (3.8%)	3 (5.8%)	0.026
Number of cesarean birth			
0	65 (82.3%)	34 (65.4%)	
1	11 (13.9%)	8 (15.4%)	
2	3 (3.8%)	8 (15.4%)	
3	0 (0%)	2 (3.8%)	
Current body mass index (BMI)	29.9±5.08	31.3±5.6	0.165
Pregestational BMI	25.4±5.05	27.1±5.32	0.081
Planned pregnancy	61 (77.2%)	33 (63.5%)	0.087
Education			0.588
Illiterate	1 (1.3%)	2 (3.8%)	
Primary and secondary school	30 (38%)	20 (38.5%)	
High school	17 (21.5%)	14 (26.9%)	
University and postgraduate	31 (39.2%)	16 (30.8%)	
Spouse education			0.709
Illiterate	1 (1.3%)	1 (1.9%)	

Table 1 (cont): Demographic data

	Control group (n=79)	Patient with GDM group (n=52)	p
Primary and secondary school	29 (36.7%)	24 (46.2%)	
High school	24 (30.4%)	14 (26.9%)	
University and postgraduate	25 (31.6%)	13 (25%)	
Employment			0.840
Employed	21 (26.6%)	13 (25%)	
Unemployed	58 (73.4%)	39 (75%)	
Spouse employment			0.654
Employed	77 (97.5%)	51 (98.1%)	
Unemployed	2 (2.5%)	1 (1.9%)	
Monthly income of house			0.271
Income below minimum wage	14 (17.7%)	12 (23.1%)	
Income between minimum wage and triple	56 (70.9%)	30 (57.7%)	
Income beyond three fold minimum wage	9 (11.4%)	10 (19.2%)	
Gestational week of when questionnaire filled in	35.4±3.35	35.4±3.21	0.980
Gestational week of at 75 gr OGTT	26.1±1.52	25.9±1.21	0.320
0^{th} hour blood glucose level (mg/dl)	80.7±6.44	97.2±21.66	0.000
1^{st} hour blood glucose level (mg/dl)	120.5±28.62	189.41±32.94	0.000
2^{nd} hour blood glucose level (mg/dl)	106.5±22.98	148.6±38.06	0.000

GDM: Gestational diabetes mellitus; OGTT: Oral glucose tolerance test.

tion, and pain. Each domain is scored according to respondents' answers, with a minimum to maximum range of 1–5, 0–5, 0–5, 0–5, 0–5, and 0–5 respectively, resulting in an additive score range of 2–36. If the total score is ≤26, it suggests a risk for sexual dysfunction.[14]

Beck Depression Inventory is a clinically used self-report screening inventory comprising 13 cognitive and 8 somatic multiple-choice questions to measure the seriousness of depression. Each question is scored on a scale of 0–3 according to the respondent's answer to the statements. The total score represents the severity of the depression. The cut-off points for severity scores are: 0–9 minimal; 10–16 mild; 17–29 moderate; and 30–63 severe.[15,16]

Beck Anxiety Inventory is a self-report questionnaire consisting of 21 questions used to document anxiety levels clinically. Each question is rated on a 4-point Likert scale ranging from 0–3, and the total obtained score range is 0–63. A total score of 0–21 is determined as low anxiety, 22–35 as moderate anxiety, and 36–63 as potentially concerning levels of anxiety (severe).[17] Validation and reliability were studied in the Turkish population.[9]

Statistical Analysis

One-sample Kolmogorov-Smirnov test was used to check whether the data showed normal distribution for numerical variables. Mean±standard deviation was found in data with normal distribution, and median (interquartile range (IQR)) values were recorded in data without normal distribution. Numerical variables were compared with Student's t-test when parametric test criteria were met. In the absence of these criteria, the Mann-Whitney U test was used. Pearson Chi-Square Test and Fisher's Exact Test were used to determine whether there was a difference between the percentages of categorical variables. For all tests, the probability of a first type error was α=0.05. Statistical analysis of the study was performed using IBM SPSS 22.0 package program.

RESULTS

According to the OGTT results, 79 healthy participants in the control group and 52 participants in the GDM patient group were included in the study. The demographic data of both groups participating in the study are documented in Table 1. Patient age and number of cesarean sections were statistically significantly higher in the GDM group than in the control group.

The questionnaire results are documented in separate sections in Table 2. The general health score of WHOQOL-BREF was significantly higher in the control group than in the GDM group. In contrast, no statistically significant difference was observed between both groups in terms of FSFI, BDI, and BAI scores.

The subgroup data analysis is documented in Table 3. In Group 2, 43 patients were treated with diet and exercise, while 9 patients used insulin in addition to diet and exercise. No patients were taking oral antidiabetic drugs. For GDM patients, a subgroup analysis was performed between those treated with lifestyle modification and those receiving insulin therapy. The psychological health score of WHOQOL-BREF was found to be significantly lower in the insulin therapy group, while no difference was found in all other domains.

Table 2: WHOQOL-BREF, BDI, BAI and FSFI scores between main groups

	Control group (n=79)	Patient with GDM group (n=52)	p
BAI total score	12.25±8.86	9.58±7.52	0.075
Low anxiety	66 (83.5%)	49 (94.2%)	
Moderate	12 (15.2%)	3 (5.8%)	0.174
Severe	1 (1.3%)	0 (0%)	
FSFI total score	15.91±10.54	13.45±10.68	0.197
Desire	2.71±1.16	2.35±1.01	0.099
Arousal	2.31±1.65	1.96±1.67	0.236
Orgasm	2.46±2.09	2.07±2.14	0.362
Lubrication	2.89±2.14	2.46±2.21	0.344
Satisfaction	3.07±2.50	2.53±2.52	0.249
Pain	2.45±2.03	2.06±2.07	0.338
BDI total score	9.65±7.23	10.75±7.72	0.407
Minimal	45 (57%)	28 (53.8%)	
Mild	20 (25.3%)	17 (32.7%)	0.736
Moderate	13 (16.5%)	6 (11.5%)	
Severe	1 (1.3%)	1 (1.9%)	
WHOQOL-BREF			
General health	69.30±14.68	63.22±18.25	0.037
Physical health	63.56±16.97	61.60±16.89	0.519
Psychological health	72.04±12.69	73.31±16.56	0.621
Social relationship	56.96±15.82	55.12±13.97	0.498
Social environment	69.38±13.58	64.72±16.01	0.076

GDM: Gestational diabetes mellitus; BAI: Beck anxiety inventory; FSFI: Female Sexual Function Index; BDI: Beck Depression Inventory; WHOQOL-BREF: World Health Organization Quality of Life—BREF.

DISCUSSION

There are many studies in the literature investigating the impact of gestational diabetes on QoL. However, these studies are mostly qualitative studies performed by interviews with GDM patients about their experience over the course of pregnancy.[18,19] Quantitative studies are rare but are tending to increase.

Pantzartzis et al.[20] showed that the WHOQOL-BREF social environment score of the control group (30.8±3.4) was significantly higher than that of patients with GDM (28.5±3.9). They claim that the diagnosis of GDM affects the QoL of pregnant patients in the third trimester negatively. Iwanowicz-Palus et al.[21] supported this argument with a study of 676 patients in Poland. The study showed that patients with GDM had worse quality in all domains of WHOQOL-BREF (general quality of life, general health, physical health, psychological, social relationships, and environment).

In our study, the general quality of life score was significantly higher in the control group compared to patients with GDM, while in the other domains no significant results were obtained. This result is also supported by a recent meta-analysis, which states that QoL would be significantly compromised as patients cope with GDM.[3] It is clear that having GDM during pregnancy affects a patient's quality of life. At this point, it can be suggested that the patients should be examined carefully and supported in each outpatient follow-up visit.

Our patients with GDM were divided into two groups according to their treatment options, such as lifestyle modification. In our study, WHOQOL-BREF scores were higher in patients with lifestyle modification compared to those on insulin. When WHOQOL-BREF was evaluated in detail, the psychological domain was significantly higher (p=0.008) in GDM patients controlled with diet. This outcome is supported by a study of 339 participants conducted in 2019, which demonstrates higher general quality of life and psychological scores in patients with GDM controlled by diet and exercise compared to those controlled by diet and insulin treatment.[22]

In another study with 114 patients with GDM, it was shown that the general health score and physical activity scores were significantly higher in the patients with GDM treated only with diet.[6] On the other hand, Pantzartzis et al.[20] stated that the type of treatment of GDM does not seem to have a further effect on the QoL of the subgroup of patients with GDM. In addition, Abolfathi et al.[23] showed in 2021 that low-income patients with GDM had worse psychological scores.

Although pregnancy is the most joyful time of expectation, coping with complications can cause significant psychological challenges for women. It is expected that psychological domain scores would be higher in patients knowing that complications could be controlled with easy and accessible treatment methods such as diet and exercise because insulin therapy is an expensive treatment option and requires commitment.

Many physicians have studied female sexual dysfunction (FSD) and diabetes in the literature. However, there are a limited number of studies that investigated FSD and GDM, and their results are controversial. Souza et al.[4] investigated the FSFI results of second-trimester patients with GDM and compared them with low-risk pregnancies. They stated that although all domains have a higher score of FSFI in the low-risk pregnancy group, only the total score and orgasm domain were statistically significant. On the other hand, in another study investigating FSD with a different questionnaire (Golombok-Rust Inventory of Sexual Satisfaction) in Türkiye, it was shown that sexual functions of third-trimester patients with GDM are better than those of healthy pregnant women.[24] In another study, Ribeiro et al.[25] claimed that the sexual function of 87 third-trimester pregnant women with and without gestational diabetes did not differ according to the FSFI survey. The same author also stated that overweight women with GDM in the third trimester have worse FSD than normal-weight women with GDM.[26]

In our study, we have not found a significant difference in sexual dysfunction between patients with and without GDM during their third trimester. In addition to that, the fact that FSFI scores are below 26 in both groups means that all participant women have poor sexual functions. This may be attributed to the stress of pregnancy itself and the difficulty of disclosing their thoughts as a cultural

Table 3: Subgroup analysis due to treatment method

	Lifestyle modification group (n=43)	Insulin therapy group (n=9)	p
HbA1c	5.79±0.52	5.74±0.62	0.809
Age	31.35±4.59	33.78±7.19	0.200
Spouse age	34.02±5.61	36.33±7.17	0.290
Duration of marriage (year)	6.83±5.22	7.50±6.32	0.740
Current BMI	31.28±5.85	31.51±5.06	0.913
Pregestational BMI	26.55±5.43	29.46±4.19	0.138
0th hour blood glucose level (mg/dl)	93.88±12.77	112.56±42.56	0.227
1st hour blood glucose level (mg/dl)	187.60±35.18	199.13±13.93	0.369
2nd hour blood glucose level (mg/dl)	145.71±39.72	163.88±24.50	0.220
BAI total score	8.81±7.18	13.22±8.51	0.111
Low-anxiety	41 (95.3%)	8 (94.2%)	
Moderate	2 (4.7%)	1 (5.8%)	0.450
Severe	0 (0%)	0 (0%)	
FSFI total score	13.14±11.11	14.97±8.67	0.592
Desire	2.31±1.06	2.53±0.78	0.491
Arousal	1.99±1.75	1.83±1.31	0.874
Orgasm	1.96±2.16	2.62±2.06	0.524
Lubrication	2.47±2.29	2.43±1.90	0.551
Satisfaction	2.42±2.63	3.02±2.01	0.694
Pain	1.96±2.10	2.53±1.94	0.777
BDI total score	10.02±6.20	14.22±12.73	0.360
Minimal	25 (58.1%)	3 (33.3%)	
Mild	14 (32.6%)	3 (33.3%)	0.082
Moderate	4 (9.3%)	2 (22.2%)	
Severe	0 (0%)	1 (11.1%)	
WHOQOL-BREF			
General health	63.66±19.05	61.11±14.58	0.707
Physical health	61.69±16.94	59.92±17.56	0.746
Psychological health	76.06±15.05	60.18±18.05	0.008
Social relationship	56.27±13.11	49.62±17.35	0.197
Social environment	65.84±16.28	59.37±14.23	0.275

BMI: Body Mass Index; BAI: Beck anxiety inventory; FSFI: Female Sexual Function Index; BDI: Beck Depression Inventory; WHOQOL-BREF: World Health Organization Quality of Life—BREF.

feature. Patients might not clearly express their complaints; they hide their sexual problems and do not share them easily. Finally, treatment variation of GDM has shown no significant differences in sexual function in our results.

The American College of Obstetricians and Gynecologists Committee Opinion recommends the use of a depression inventory at least once during pregnancy or the first year postpartum to document new-onset depression related to pregnancy.[27]

In 2018, Pace et al.[28] showed in their retrospective study with a high number of participants that GDM increased the incidence of depression by 2-fold in the second and third trimesters of pregnancy. The same study also revealed that GDM is a risk factor for depression in the first year postpartum and beyond. Another study in 2015 compared depression scores of diabetes type 1, diabetes type 2, and GDM. They claimed that although there is an association between diabetes and depression, the correlation is not significant, and approximately 13% of the GDM patients experienced severe depression.

This ratio is significantly lower than that of other type 1 and type 2 DM groups.[29] Gezginç et al.[30] investigated BDI scores between glucose tolerance abnormality and depression in 24–28-week pregnant women and found that BDI scores were significantly higher in the group with abnormal glucose results. However, the subgrouping of the patients was based on the results of the 50 g glucose intolerance test, but the confirmation of GDM was not performed following the 100 g glucose intolerance test.

In the literature, there is only one study investigating the BDI score of patients with or without GDM during the course of pregnancy. Keskin et al.[31] claimed that there are no statistically significant differences between the two groups. In our study, we also found that there is no significant difference between patients with GDM and the control group in their BDI scores. Furthermore, GDM treatment differences have no statistically significant effect on the depression scores of the subgroups. The cut-off score of BDI is determined as 17 in an analysis of the validity and reliability of its use in Turkish university students, which means above 17 demonstrates clinical depression.[32] In our study, all groups have BDI scores lower than this value. Further studies are needed to reveal the relationship between GDM and depression during pregnancy.

The relationship between anxiety and GDM is controversial, and it is not clear which one causes the other. Many studies support that anxiety causes many hormonal dysregulations, such as increased secretion of cortisol and insulin resistance, leading to GDM.[33,34] In a study of 1,426 singleton pregnancies, it was shown that GDM was higher in patients with anxiety than in those non-anxious ones.[35]] In contrast, some studies determined that GDM is also a reason for the development of anxiety. Lee et al.[36] showed that the prevalence of anxiety is higher among GDM patients in their cross-sectional study with 526 participants using the Depression, Anxiety, and Stress 21 questionnaire. In addition, they found that the risk of developing anxiety increases in GDM patients of younger ages.[36] The same study group also found a positive relationship between neonatal respiratory distress and the presence of depression symptoms in patients with GDM one year later.[37] A recent meta-analysis declared that patients with GDM have a significantly higher risk of developing postpartum depression.[38]

Our study is unique in that we used the BAI to determine the anxiety level of the patients. In our study, there is no significant difference between the control group and patients with GDM.

In the literature, Hui et al.[39] claimed that the patients whose diabetes was regulated with insulin during pregnancy have higher anxiety about diet management compared to those who received only diet treatment. As we evaluated subgroups of GDM treatment strategies, insulin users have higher BAI scores than the diet-regulated group, but this was not statistically significant. This result is supported by Langer and Langer,[40] who found that there is no significant impact of insulin usage on negative mood in GDM patients compared to diet treatment.

Our study is unique in that it is the first study to evaluate different aspects of specified diabetes patients who are pregnant using four different validated questionnaires (WHOQOL-BREF, FSFI, BDI, BAI). The most important limitation is that the investigation is specified solely to the third trimester of pregnancy, and no previous questionnaire scores have been provided pre-pregnancy. Another limitation is the relatively small sample size. The patients' group was divided into two treatment subgroups, so the reduced sample size may lead to insignificant statistical results. Finally, the study was conducted in a specific cultural community, so heterogeneous results may occur when compared to worldwide results.

Our recommendation for future studies is to explore the anxiety, depression, QoL, and sexual functions of this targeted group with a more multicultural, multicenter approach and more participants. In addition, they might investigate the comparison of anxiety, depression, QoL, and sexual functions in patients with pre-gestational diabetes, GDM, and healthy populations.

Statement

Ethics Committee Approval: The Istanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital Clinical Research Ethics Committee granted approval for this study (date: 12.08.2020, number: 2020/0500).

Author Contributions: Concept – CSÖ, ÖE; Design – CSÖ, ÖE; Supervision – AY, AT; Resource – CSÖ; Materials – İLK, CSÖ; Data Collection and/or Processing – İLK, CSÖ; Analysis and/or Interpretation – ÖE; Literature Search – ÖE, CSÖ; Writing – CSÖ, ÖE, İLK; Critical Reviews – AT, AY.

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ORIGINAL ARTICLE

Determining the anxiety levels, postpartum support needs, and the levels of received support in puerperae during the COVID-19 pandemic period

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ABSTRACT

Objective: This research was conducted to determine the anxiety levels, postpartum support needs, and the levels of received support in puerperae during the pandemic period.

Material and Methods: The cross-sectional study was carried out between April and August 2020 at the Postpartum Service of the Gynecology and Children's Diseases Training and Research Hospital on the Anatolian side of Istanbul. Three hundred postpartum mothers who met the sampling criteria and volunteered to participate were included in the study. Data were collected using a survey form containing the participants' demographic, individual, and obstetric characteristics, their opinions on the COVID-19 process, the Beck Anxiety Scale (BAS), and the Postpartum Support Scale (PSS).

Results: It was determined that the average Beck Anxiety Scale score of the participants was 13.71±11.21, and 55% of them experienced moderate postpartum anxiety. The total Postpartum Support Scale mean score regarding the importance of support for the puerperae was calculated as 149.65±47.50, and the support received related to this need was found to be 118.32±48.58.

Conclusion: It was determined that women experienced postpartum anxiety at a moderate level, needed considerable support during this period, but did not receive much support.

Keywords: Anxiety, COVID-19, postpartum, support.

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INTRODUCTION

The COVID-19 pandemic has affected individuals of all age ranges, but it has particularly had negative effects on the health of the mother and fetus/neonate during the pregnancy, birth, and postpartum periods, which are considered sensitive periods in life even before the pandemic.[1,2]

Although studies have been conducted on the effects of COVID-19 on pregnant women, fetuses, and neonates, the findings are still far from adequate. Moreover, taking measures to protect the mother, fetus, and neonate from infection and maintaining quality care during the delivery and postpartum periods are important for improving the health of both the mother and the neonate.[3–5]

The delivery and postpartum period is marked by complex psychological factors and significant physiological changes. During this time, the mother faces various challenges as she adapts to the baby, the new family order, postpartum physiological and psychological changes, and postpartum disorders.[6,7]

During the postpartum period, women encounter physical and psychological changes along with new roles and responsibilities, which can create stress in emotional, behavioral, and cognitive areas. If women cannot adapt to this period or find adequate support, they may face mental problems such as anxiety and depression. Literature states that 2–25% of women experience postpartum emotional problems.[8–10] Studies indicate that these problems negatively impact mother-infant interactions, family and marital relationships, and child development.[11,12] While one meta-analysis stated that depressed mothers were more irritable and exhibited less warm behavior towards their babies in the first three months,[13] another study found a significant negative relationship between postpartum emotional problems and marital relationships.[14]

With the addition of the global pandemic process and related restrictions to this special and important period, it is doubtless that the concerns and worries of mothers and their families will increase.[3] It has been noted that isolation and quarantine conditions, use of protective equipment, transportation difficulties, worries about access to food, travel restrictions, reduced support from family and friends, social and psychological loneliness, and financial limitations during the pandemic may cause mothers and their families to experience anxiety and posttraumatic stress disorders, as might all individuals of various age ranges.[3,5,15]

While midwives and nurses deliver services such as care, training, and consulting during the pre-delivery, delivery, and postpartum periods, they should be aware that the postpartum period also involves other family members and consider the woman's family as a whole.[16,17] Especially during the COVID-19 pandemic, it is important to determine mothers' social support needs and concerns related to the process in the postpartum period, during which significant health-related concerns are expected to increase daily and potentially affect society as much as health and clinical problems.[5,18]

In this study, which covers all needs, the aim was to determine the anxiety levels, postpartum support needs, and levels of received support in puerperae during the COVID-19 pandemic period. The study sought answers to the following questions:

1. In which area do women who gave birth during the COVID-19 pandemic period need the most support?
2. Regarding which COVID-19 related issues do women who gave birth experience anxiety?
3. From whom do women who gave birth during the COVID-19 pandemic period most want to receive support?
4. At what level is the anxiety severity of women who gave birth during the COVID-19 pandemic period?
5. Is there a difference between the sociodemographic and obstetric characteristics and the anxiety severity levels of women who gave birth during the COVID-19 pandemic period?
6. What is the status of support received in the postpartum period by women who gave birth during the COVID-19 pandemic period?
7. Is there a difference between the sociodemographic and obstetric characteristics and the support received in the postpartum period by women who gave birth during the COVID-19 pandemic period?
8. Is there a relationship between experiencing anxiety and receiving postpartum support among women who gave birth during the COVID-19 pandemic period?

MATERIAL AND METHODS

Location and Time of the Study

The study was conducted as a cross-sectional research at the Maternity and Children Training and Research Hospital Postpartum Care Service, located on the Anatolian side of Istanbul province. This facility serves a high population of pregnant women, has a high birth rate, and continued its services without interruption during the pandemic period, between April and August 2020.

Population and Sample

The population of the study comprised puerperae who gave birth at the hospital and volunteered to participate in the study. The sample consisted of 300 puerperae who gave birth at the hospital, were between the ages of 20–40 years, literate, had no barriers in terms of communication, and consented to fill in the questionnaire after being informed of the study's purpose. Puerperae who were suspected or diagnosed with COVID-19 and those previously diagnosed with a psychiatric disorder were excluded from the study.

The sample size was calculated using OpenEpi (version 3) software, based on an unpredictable anxiety rate predicted at 50%. A sample size of 287 was found sufficient to represent the number of puerperae who gave birth at the study hospital within a month with a 5% alpha error and 99% power rate.

Study data were collected through face-to-face interviews conducted by the researchers at the postpartum clinic of the relevant hospital and two hours before the women were discharged.

Data Collection Tools

Data were collected using the Puerperae Identifying Information Form, which contained sociodemographic and obstetric characteristics of the participants, their views on the COVID-19 and postpartum processes, the Beck Anxiety Inventory (BAI), and the Postpartum Support Scale (PSS).

Table 1: Participants' concerns about the COVID-19 Infection

Concerns about the COVID-19 infection	Yes		Undecided		No	
	n	%	n	%	n	%
I do not want to go to follow-up appointments for fear that I might contract the COVID-19 infection	154	51.3	89	29.7	57	19.0
I believe adequate measures have been taken in the hospital where I gave birth.	125	41.7	115	38.3	60	20.0
I think the COVID-19 infection might be transmitted from health professionals.	202	67.3	76	25.3	22	7.3
My husband is working, and I fear that he may bring the COVID-19 infection to our home.	179	59.7	575	19.0	64	21.3
I think my baby may be harmed if I contract the COVID-19 infection during the puerperal period.	201	67.0	85	28.3	14	4.7
It worries me to go out with a face mask on in the COVID-19 process.	153	51.0	45	15.0	102	34.0
I am worried that if I become COVID-19 positive, I may not breastfeed my baby.	105	35.0	106	35.3	89	29.7
I am worried about who would take care of my baby if I contracted the disease.	123	41.0	120	40.0	57	19.0
I will not be able to get support from my family elderly in the postpartum period, so I have concerns about breastfeeding and baby care.	84	28.0	47	15.7	169	56.3
I am worried about visiting a health care institution for vaccination and control of my baby.	142	47.3	75	25.0	83	27.7

Puerperae Identifying Information Form: This form, prepared by the researchers in line with the literature, includes 28 questions that inquire about the puerperae's sociodemographic and personal background (age, date of marriage, education, employment, economic status, family type, presence of a chronic disease) and obstetric background (number of pregnancy weeks, whether the pregnancy was planned/unplanned, experiences of difficulty in previous and current pregnancies, labor process), their worries related to the COVID-19 pandemic, their anxiety status regarding COVID-19 infection, and evaluation of their need for social support during the COVID-19 pandemic period.[5,6,18] Prior to the study, the questionnaire was piloted on some women, and the content was revised accordingly.

Beck Anxiety Scale (BAS): Developed by Beck et al.[19] (1988) and adapted to Turkish by Ulusoy et al.[20] (1998), the BAS evaluates the frequency of anxiety symptoms experienced by an individual. This 21-item scale is scored between 0 and 63, with higher scores indicating greater severity of anxiety. Ulusoy et al.[20] determined the scale's Cronbach's alpha internal consistency coefficient as 0.93. In the present study, the Cronbach's alpha internal consistency coefficient of the Beck Anxiety Scale was determined to be 0.92.

Postpartum Support Scale (PSS): Developed by Logsdon et al.[21] (1996) to determine postpartum social support and social needs of mothers, the validity and reliability studies of the scale were conducted by Ertürk[22] (2007). The scale comprises two subdimensions: "the importance of the need" and "received support" related to this need. The 34-item scale is an 8-point Likert-type scale. The Cronbach's alpha coefficient for the importance of the need subdimension of the scale is 0.88, while for the received support subdimension, it is 0.95. The lowest and highest scores that can be obtained from each subdimension of the scale range from 0 to 238. A total score below 130 on the importance of the need subdimension is evaluated as "Not Important," scores between 131 and 150 as "Important," and scores above 151 as "Very Important." In the present study, the total Cronbach's alpha coefficient for the "Importance of the Need" subdimension of the PSS scale was found to be 0.89, and for the "Received Support" subdimension, it was determined to be 0.92.

Ethical Considerations

Necessary permissions for the study were obtained from the institution where the study was conducted, and the Hospital Ethics Board evaluated and approved the study (decision dated 06.05.2020 and numbered 84). After the puerperae participating in the study were informed about the purpose of the study and were explained that the information collected would be used only in this study, their written consent was obtained. The study was conducted in accordance with the Declaration of Helsinki.

Table 2: Opinions of participants regarding the support process

	n	%
Subjects she wants to get postpartum support		
Mother's self care	108	15.9
Baby care and feeding	165	24.3
Chores	170	25.1
Adaptation to the emotional process	117	17.2
Adaptation to social and family life	104	15.4
Other	14	2.1
Persons who want to get postpartum support		
Husband	197	65.7
Experienced family members	64	21.3
Health personnel	36	12.0
Other	3	1.0
Total	300	100.0

Data Analysis

The data collected in the study were evaluated using the SPSS software package. Chi-square tests were used to test the relationships between categorical variables, and for data that showed a normal distribution, independent groups t-test and One-Way ANOVA were employed. As descriptive statistics, mean±SD (standard deviation) and min–max values were calculated for numerical variables, while number and percentage values were calculated for categorical variables. The relationships between the scales were analyzed through Pearson correlation analysis. The statistical significance level was accepted as $p<0.05$.

Limitations of the Study

The results obtained from this study are limited to the cases from which the data were collected.

RESULTS

When examining the sociodemographic and health characteristics of the puerperae participating in the study, it was observed that the mean age of the women was 29.4±5.9, they had been married for 6.4±5.1 years, and the majority (31.2%) were secondary school graduates. It was also determined that 77.3% of the women had a nuclear family structure, the majority (84%) were not working during the pandemic period, their incomes were almost equal to their expenses (58.3%), and 99.7% had social security. The majority of the participants (63.4%) had a planned pregnancy, 72% were multiparous, and 26% had a risky pregnancy. Additionally, it was found that 36.3% of the participants had received postpartum care training, 58% had a C-section in their current pregnancy, and the majority (88.7%) breastfed their babies.

Table 1 illustrates the participants' concerns about COVID-19 infection. The puerperae were most worried about the transmission of the COVID-19 infection from health professionals during the pandemic period (67.3%), followed by concerns about their babies being harmed if they contracted the COVID-19 infection (67%), and concerns about their husbands bringing home the COVID-19 disease (59.7%).

Among the issues for which the puerperae needed support in the postpartum period, assistance with household chores was the most significant (25.1%), followed closely by baby care and feeding the baby (24.3%). It was determined that women needed the most support from their husbands during this period (65.7%) (Table 2).

Table 3: Comparison of participants' BECK anxiety scale mean scores and some variables (n=300)

Individual and obstetric features	BECK anxiety score		p
	Mean	±SD	
Age group			0.678*
19–29	15.15	11.46	
30–40	13.36	11.22	
41- above	14.26	11.38	
Education status			0.656*
Primary school	12.12	11.30	
Middle school	13.36	11.32	
High school	14.15	11.48	
University	13.32	10.96	
Working status			0.776**
Not working	13.38	11.28	
Working	13.46	11.44	
Income rate			**0.042***
Income less than expenses	16.85	12.22	
Income equal to expenses	11.24	10.36	
Income more than expenses	10.25	9.17	
Type of birth			**0.036****
Vaginal birth	11.78	11.36	
Cesarean	15.30	12.97	
Voluntary pregnancy			**0.023****
Yes	12.125	11.20	
No	17.55	11.52	
Parity			**0.033****
Primipara	17.42	11.56	
Multipara	12.28	11.12	
Postpartum care training during pregnancy			**0.046*****
Yes	11.16	10.25	
No	16.82	12.41	

SD: Standard deviation; *: One-Way ANOVA Kruskal-Wallis; **: T-test; ***: Mann-Whitney U.

Table 4: Distribution of average scores of Postpartum Support Scale

Scale sub-dimensions	Postpartum Support Scale Total score average ±SD	
	Importance of need	Support received
Financial support	38.50±12.978	27.12±12.98
Emotional support	45.22±14.57	32.71±16.67
Information support	47.13±17.75	37.15±14.68
Comparison	19.75±9.26	17.46±9.32
Total	149.65±47.50	118.32±48.58

SD: Standard deviation.

It was found that the average score of the participants on the Beck Anxiety Scale was 13.71±11.21, indicating that 55% of participants experienced moderate levels of anxiety. When comparing the mean scores obtained from the Beck Anxiety Inventory with certain variables as presented in Table 3, it was determined that income level, type of delivery, whether the pregnancy was planned, and parity were influential, and the differences between them were statistically significant ($p<0.05$).

The PSS total mean score for the importance of the need subdimension was 149.65±47.50, while for the received support subdimension, it was 118.32±48.58 (Table 4). An evaluation according to the scale's cutoff points indicated that the women needed significant support, but the support they received was limited.

When comparing the PSS mean scores of the puerperae with certain characteristics as presented in Table 5, it was determined that in the importance of the support subdimension, age group, employment status, and having received postpartum care training significantly affected their perception of needing support, with significant differences between mean scores ($p<0.05$). Particularly, the mean scores of the puerperae who were in the 19–29 age group, were actively working, and had received postpartum care training were higher compared to other groups.

In the received support subdimension, significant differences were found between age group, employment status, type of delivery, and having received postpartum care training, with mean scores obtained from the received support subdimension ($p<0.05$). The mean scores of the puerperae who were in the 19–29 age group, were actively working, had a C-section, and had received postpartum care training were higher in comparison to other groups.

The relationship between the puerperae's mean scores obtained from the Beck Anxiety Inventory (Mean=1.40, SD=0.52), PSS importance of the need subdimension (Mean=4.50, SD=2.07), and PSS received support subdimension (Mean=2.24, SD=2.21) was measured with Pearson correlation analysis. While a positive and low-level relationship was found between these variables, the difference between them was found to be insignificant ($r(228)=0.067$, 0.089, $p>0.05$) (Table 6).

DISCUSSION

The postpartum period is a turning point for the mother and the family. It is particularly a significant period in which the mother and the family who newly experienced the event are in need of information and support the most.[7] In the study, it was aimed to determine the anxiety levels of the puerperae, their need for support, and the levels of support they received in the COVID-19 pandemic period.

It was found that 10% of the women participating in the study experienced anxiety at a severe level, that especially the anxiety levels of those who gave birth for the first time, had an unplanned pregnancy, and had not received training prior to birth were higher, that the puerperae who were in the 19–29 age group, were actively working, gave C-section birth, and had received postpartum care training needed to receive support.

The number of studies in which the challenges, worries and support needs that puerperae experienced in relation to COVID-19 are limited. The lack of social support received by the individuals leads to anxiety and stress disorders.[23]

In the study, when the concerns of the puerperae related to the pandemic period were evaluated, it was determined that they were worried about the transmission of the COVID-19 infection from health care professionals (67.3%), and about their babies' being harmed if they contracted the COVID-19 infection in the puerperal period (67%). In a study conducted, it was reported that 12% of the participants experienced difficulty in sleeping due to their worries about the pandemic. In various studies conducted, it was determined that women were worried about being infected and the risk of cross contamination during the coronavirus epidemic.[23–27] It is important that all health care professionals assume an integrated role and activate and restructure their support processes in order to alleviate the increased concerns in puerperae and their families stemming from uncertainties in the pandemic period.

In addition to being a physiological process in which significant biological changes are experienced, the puerperal period is also a complicated and sensitive process where suppressed and unsolved conflicts in the early developmental period surface again.[28] In the study, it was determined that 55% of the participants experienced a low-level anxiety, and that only 10% had severe anxiety levels. In the comparison made between the BAS mean scores and the variables, it was found that the BAS mean scores of the puerperae who had low-level income, gave C-section birth, had unplanned pregnancy, had their first pregnancy, and had not received postpartum care training were high ($p<0.05$).

In a study conducted in the Wuhan district of China with the participation of 1,210 individuals to investigate the psychological effects of the epidemic in its early period, it was determined that 53.8% of the participants displayed moderate or severe psychological effects of the epidemic, 16.5% exhibited moderate depression symptoms, and 28.8% showed moderate or severe anxiety symptoms.[27] When risk factors related to postpartum anxiety and stress were examined, it was reported that mother and father candidates who would have a baby for the first time experienced more anxiety before the birth and in the postpartum period compared to the couples who had had a baby before, although there are also studies which state that the anxiety experienced before the birth and in the postpartum period is not associated with the number of children the couples had.[17,29,30]

Table 5: Comparison of PSS scores mean according to some characteristics of the participants (n=300)

Individual and obstetric features	PSS importance of need average score		Testing and materiality	PSS average score of support received		Testing and materiality
	Mean	±SD		Mean	±SD	
Age group						
19–29	159.6	42.6	KW: **6.3**	105.4	40.4	KW: **8.2**
30–40	151.9	45.4	p<**0.05**	118.7	44.6	p<**0.05**
41- above	132.6	52.2		102.8	51.8	
Education status						
Primary school	139.4	49.3	KW: 7.3	109.5	46.4	KW: 6.7
Middle school	143.2	47.5	p>0.05	128.4	48.5	p>0.05
High school	148.7	46.3		131.6	47.6	
University	151.6	45.7		142.2	49.8	
Working status						
Not working	133.6	50.2	t: **2.8**	116.4	47.4	t: **2.7**
Working	156.4	46.1	p<**0.01**	139.4	50.6	p<**0.01**
Type of birth						
Vaginal birth	145.2	48.6	t: 0.6	123.2	46.5	t: **0.6**
Cesarean	152.4	42.1	p>0.05	132.1	44.5	p<**0.05**
Voluntary pregnancy						
Yes	151.6	43.6	t: 1.2	145.2	48.6	t: 1.4
No	137.3	48.3	p>0.05	152.4	42.1	p>0.05
Parity						
Primipara	154.6	46.2	t: 1.5	124.6	45.2	t: 1.6
Multipara	138.4	50.1	p>0.05	108.4	52.3	p>0.05
Postpartum care training during pregnancy						
Yes	158.2	38.4	t: **2.7**	141.2	46.2	t: **2.6**
No	136.7	46.6	p<**0.01**	118.6	50.1	p<**0.01**

SD: Standard deviation. Kruskal Wallis, T-test.

In some epidemiological studies conducted, it was revealed that in terms of the occurrence of serious mental diseases, the postpartum period is three to four times riskier than the pregnancy period.[20,28,31]

During the pandemic, the anxiety level of the puerperant increases due to being in a risk group, fear of transmitting the disease to the baby, and social isolation and quarantine practices. Especially in the postpartum period, these uncertainties and fears experienced by the woman regarding the health status of both herself and her baby could cause fluctuations in mood and increase the level of anxiety.[32,33]

Studies conducted during the pandemic period have determined that the levels of fear, panic, anxiety, and uncertainty that women may experience in the postpartum period due to the epidemic disease have increased significantly.[27,34] Another study showed that the anxiety and depression levels of women who had just given birth and had children increased significantly during the pandemic.[35]

According to the findings of the present study, among the issues that the puerperae wanted to receive support for the most, support in household chores was in the first place (25.1%), which was followed by baby care and feeding (24.3%). It was determined that women demanded support from their husbands the most during this process (65.7%). In the study they conducted, Gulsen and Merih[17] reported that mothers wanted support from their husbands the most in the postpartum period.

In the study, it was found that the puerperae needed support at a significant level, but that they could not get adequate support in this regard (p<0.05). Various studies demonstrated that puerperae who were supported by their families had a more comfortable pregnancy, birth, and postpartum period.[36–38] It was also determined in a variety of studies conducted that social support positively affected the woman's adaptation to the role of motherhood in the pregnancy and postpartum period, increased the mother's sensitivity towards her baby,

Table 6: Relationship between BECK anxiety scale mean scores and PSS scores mean

Scales	Mean±SD	r	p
BECK anxiety scale mean	1.40±0.52	0.067	>0.05*
PSS scores mean			
Importance of need for PSS	4.50±2.07	0.089	
PSS received support	2.24±2.21		

SD: Standard deviation; PSS: Postpartum Support Scale; *: Pearson correlation.

and facilitated her relations with her close ones, and that support levels varied according to the family structure.[16,17,38,39]

In the study they conducted, Gülsen and Merih[17] found the mean score for the importance of support subdimension as 144.40±77.56, and for the received support subdimension as 108.80±80.45, and they determined that mothers needed a significant amount of support, but that the support they received in this regard was not much. It is believed that the fact that the support levels of the mothers in the postpartum period varied in the present study may have stemmed from the changes brought about by the pandemic, and changes in preferences as a result of cultural and individual differences.

In the study conducted by Cheng et al.,[40] it was determined that as the educational levels of the pregnant women and their husbands increased, the social support that the pregnant women received from their husbands increased. In the study conducted by Oztürk et al.,[39] it has been found that the quality of life of mothers has been at a moderate level and they have needed a significant amount of support, but the support provided to them has not been enough. In other studies conducted, it was determined that there was a statistically significant relationship between mothers' educational levels and received social support.[41–43] Unlike the results of other studies, no significant relationship was found in the present study between educational level and postpartum need for support and the level of received support.

CONCLUSION

The puerperal period increases anxiety and depression levels, and social support is very important for navigating this period without issues. The need for such support significantly increases during times when uncertainties and obligatory changes brought about by epidemics such as COVID-19 are experienced. Puerperae need significant support in the postpartum period, but the support they receive is often insufficient. Providing social support is crucial for maintaining the health of the mother, the baby, and the family. Nurses/midwives should offer counseling to the woman, the husband, and the family about social support starting from the pregnancy period, and they should be able to identify inadequacies in terms of support provided. In line with the findings of the study, it can be recommended that training and counseling services should be provided to women and their families to help them adapt to the postpartum period, and necessary measures should be taken to improve support systems during this time.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center Clinical Research Ethics Committee granted approval for this study (date: 06.05.2020, number: 84).

Author Contributions: Concept – YDM, DCP; Design – YDM, DCP, SK; Supervision – YDM, DCP; Resource – YDM, DCP, SK, KDB; Materials – YDM, DCP, SK, KDB; Data Collection and/or Processing – YDM, DCP, SK, KDB; Analysis and/or Interpretation – YDM, DCP; Literature Search – YDM, DCP, KDB; Writing – YDM, DCP; Critical Reviews – YDM, DCP.

Conflict of Interest: The authors have no conflict of interest to declare.

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CASE REPORT

Budd-Chiari-like syndrome presenting with hydrothorax in a neonate with right diaphragmatic hernia

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ABSTRACT

The diagnosis of congenital diaphragmatic hernia (CDH) is usually straightforward. However, cases with right-sided CDH can be challenging. We report a case of a neonate with right-sided diaphragmatic hernia presenting with hydrothorax.

Keywords: Budd-Chiari syndrome, diaphragmatic hernia, hydrothorax, neonate.

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INTRODUCTION

Congenital diaphragmatic hernia (CDH) is an anomaly characterized by defective development of the diaphragm.[1] Ninety-two percent of CDHs are postero-lateral defects, and 80% of these seem to have a left-sided preponderance.[2] Symptoms of right-sided CDH are less severe and frequently inconspicuous at presentation. The association of right-sided CDH with hydrothorax is not an ordinary diagnosis, but it must be kept in mind. The mechanisms responsible for the cases presented with hydrothorax are obstruction of the superior vena cava and hepatic veins, respectively.

CASE REPORT

A 1610 g male infant was born at 34 weeks of gestational age due to placental abruption. Prenatal ultrasound had revealed right-sided pulmonary hypoplasia. He required respiratory support with high-frequency oscillatory ventilation. A subsequent chest X-ray demonstrated opacification of the right hemithorax (Fig. 1a). Hydrothorax and atelectatic pulmonary parenchyma were seen on the right side with thorax ultrasound, and the liver was situated in an upper than normal position. A tube thoracostomy was carried out with the anticipation that draining the hydrothorax would relieve atelectasis in the lung. Pleural fluid rich in protein was drained via tube thoracostomy. An echocardiogram demonstrated tetralogy of Fallot. The right lobe of the liver was seen in the right hemithorax in computed tomography of the thorax. Following this finding, surgery was performed on the third day after birth. The diaphragmatic hernia was repaired and during the operation, the liver was found to be herniated into the right hemithorax and the three lobes of the right lung were seen (Fig. 2). After the operation, a chest X-ray demonstrated that the lungs had expanded bilaterally and there was no fluid accumulation in the right hemithorax (Fig. 1b). However, on the second day post-operation, abdominal ultrasound revealed fluid accumulation at the perihepatic area. Hepatic venous flow of the right hepatic veins was demonstrated to be partially obstructed with Doppler ultrasonographic evaluation. Budd-Chiari syndrome secondary to the displacement of the liver and liver vessels was suspected. However, this fluid accumulation did not last long and regressed spontaneously two days later. There were no operative findings of Budd-Chiari syndrome other than fluid accumulation and radiological findings. We were unable to extubate the baby due to complications associated with chronic lung disease and congenital heart disease. A tracheostomy tube was placed when he was 5 months old. He underwent surgery twice for tetralogy of Fallot. He is still being ventilated with a home ventilator and is followed up by our clinic.

The parents of the patient were informed, and written informed consent was obtained.

DISCUSSION

Our case described here presented with two complications—hydrothorax and ascites—both due to the right diaphragmatic hernia. Fernandez-Gonzalez et al.[3] reported a Budd-Chiari-like syndrome in two adults associated with rupture of the right diaphragm after abdominal trauma. They observed that venous outflow returned to normal after the liver was placed back into the intraabdominal cavity. In our case, after the operation, there was no fluid accumulation in the right hemithorax anymore. Kaifi et al.[4] reported a 24-year-old woman who had a right-sided diaphragmatic hernia due to thoracoabdominal trauma. She developed irreversible Budd-Chiari syndrome as a result of right hepatic vein thrombosis and very late clinical presentation.[4] Gilsanz et al.[5] described five neonates with right-sided diaphragmatic hernia and hydrothorax in 1986 for the first time in the literature. Four of the infants with large right hydrothoraxes were found to have an incarcerated peritoneal sac with fluid. One of them had ascites. Distinctively, in our case, no peritoneal sac was seen during the operation, only the liver was found to be herniated into the right hemithorax. After the operation, fluid accumulation revealed by abdominal ultrasound lasted for a few days. The fluid was rich in protein content. These manifestations directed us to the diagnosis of a Budd-Chiari-like syndrome due to the right-sided CDH. Since Gilsanz's publication about this serious clinical entity, no case reports had been published regarding neonates.

In cases with hydrothorax without a clearly described etiology, the diagnosis of this entity should be kept in mind. Knowledge about the possibility of the co-occurrence of right-sided diaphragmatic hernia and hydrothorax is important for appropriate treatment.

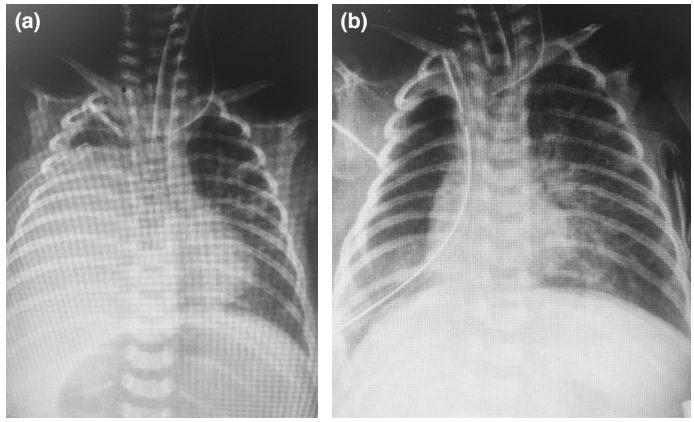

Figure 1: (a) Chest X-ray demonstrating opacification of the right hemithorax. **(b)** Chest X-ray demonstrating expanded lungs after the operation.

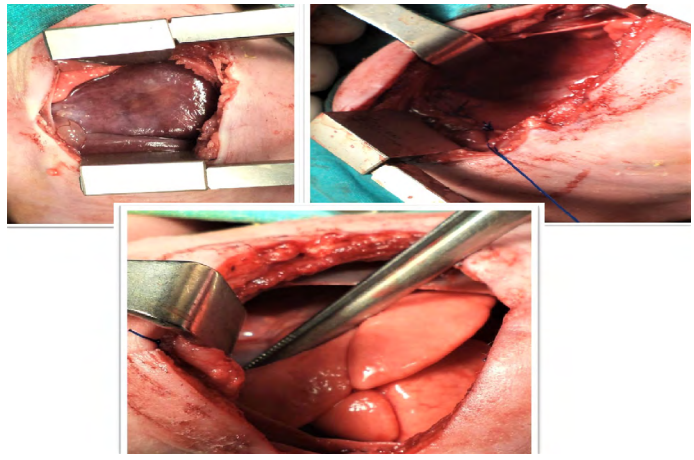

Figure 2: The liver in the right hemithorax and the three lobes of right lung was seen during operation.

Statement

Author Contributions: Concept – AC, DA; Design – DA, AC; Supervision – GK, HA; Resource – AC, HFO; Data Collection and/or Processing – TG, KP; Analysis and/or Interpretation – AT; Literature Search – ST; Writing – DA, ST; Critical Reviews – AC, GK.

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CASE REPORT

Case report of a trochanter minor fracture management of a young patient after a scooter incident

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ABSTRACT

Trochanter minor fractures are generally seen in individuals aged 12 to 16 years, commonly associated with sports such as martial arts or self-defense techniques, while the growth plate is still open. The management of trochanter minor fractures in adolescents typically involves conservative methods including early quadriceps and hip exercises; surgery is reserved for a small number of cases. This case report discusses the management of a young patient who sustained a trochanter minor fracture following a scooter accident. The fracture was successfully treated using conservative measures during follow-up.

Keywords: Avulsion fracture, ischiofemoral impingement syndrome, ludhoff sign, trochanter minor.

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INTRODUCTION

Trochanter minor fractures usually occur between the ages of 12 and 16 years. Elderly patients are not very common. Isolated fractures can be related to tumor metastasis and trauma in elderly patients.[1] In adolescents, the apophysis of the iliopsoas tendon attachment has not completely fused with the body of the femur. The avulsion fracture is then caused by traction of the iliopsoas tendon. In most cases, the fracture is displaced cranially. This type of injury typically occurs in patients engaged in self-defense sports when they attempt to kick their opponents. The fracture doesn't usually result from direct trauma in young patients.[2]

Trochanter minor fractures are generally treated conservatively. Surgery is performed rarely, especially in young patients. The main criteria for surgery are fractures with displacement between 2 to 3 cm and fractures involving more than 75% of the medial Wall.[3] Proximal femoral nailing, plate-screw fixation, or fixation with cannulated screws can be preferred. However, in younger patients, better functional results are shown with conservative treatment.[4]

In this case report, our aim is to demonstrate a patient's trochanter minor fracture managed with conservative treatment.

CASE REPORT

A 13-year-old male patient was admitted to our emergency department with hip pain and tenderness in the groin. The patient's family reported that he had fallen from a scooter the previous day. The patient had no comorbidities, was not using any medical drugs, and had not undergone any surgeries. Patient consent was obtained before any medical interventions were made. During the physical examination, the patient reported pain in his right hip, medially near the inguinal region. He also had difficulties flexing the hip and experienced tenderness in the groin region. A positive Ludhoff sign was observed—a special test in which the patient sits on a chair, extends his knees, and attempts to lift the leg (Fig. 1). The patient experienced pain while trying to lift the leg, indicating that the iliopsoas muscle's tendinous insertion on the trochanter minor was affected. There was no neurovascular injury, and the patient had no other complaints. The patient had a full range of motion in both hip joints; however, pain was reported on the right side. While lying down, the patient experienced difficulty fully elevating the lower extremity. The patient's Harris Hip Score was calculated upon admission as 81.

Radiological imaging detected an isolated trochanter minor fracture with a 2 cm displacement superiorly. There was no comminution of the fragment. Additionally, the patient's physial lines were open. The patient's fracture was classified as a Salter-Harris type 1 fracture (Fig. 2).

After the initial assessments, conservative treatment was initiated despite the patient's fracture being displaced more than 2 cm. The patient was advised not to bear weight for 2 weeks and to attend check-ups at 2-week intervals.

At the first follow-up, the patient was instructed to move with partial weight-bearing using a crutch. After an additional 2 weeks, he was asked to walk with full weight-bearing, still using a crutch. Subsequently, quadriceps exercises were initiated. Radiological evaluation in the first month confirmed that the displacement of the fractured fragment had not increased (Fig. 3).

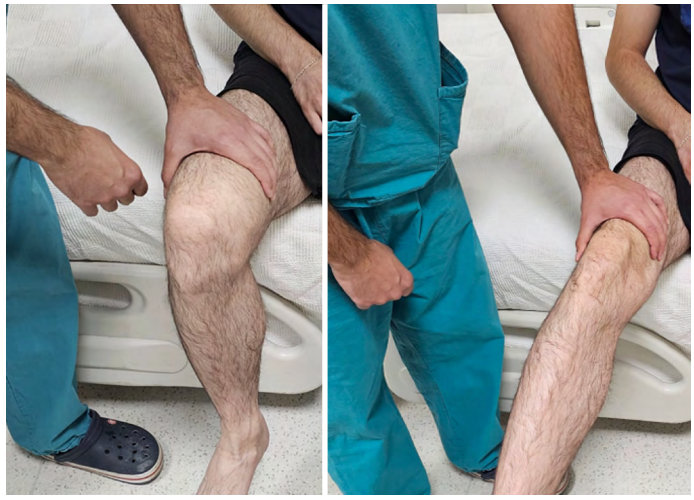

Figure 1: A positive Ludhoff sign can be observed at the patient.

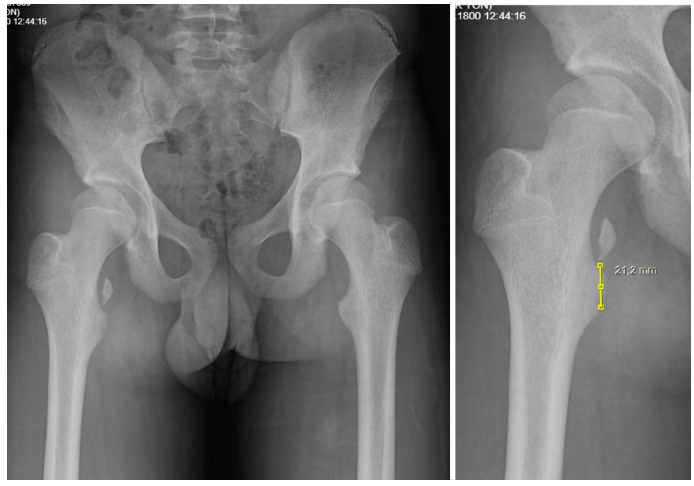

Figure 2: The patient's pelvic X-ray examination at admission.

The patient was scheduled for regular monthly follow-ups; however, he did not attend these regularly. His second visit to the hospital occurred 6 months after the incident. At this time, the patient reported no pain symptoms and mentioned that he had returned to his regular activities, including running sports and jumping, after 2 months.

Comparative analysis of the pelvis anteroposterior images taken at the patient's first admission, and at the 6th and 12th months, showed that the fracture had healed and the fragment had ossified within the trochanter minor (Fig. 4). The patient's Harris Hip Score was calculated as 89 at the one-year follow-up.

DISCUSSION

Trochanter minor fractures typically occur in adolescent patients who are involved in sports, with the mechanism of injury being traction of the iliopsoas muscle insertion on the trochanter minor. In most cases, the fracture fragment usually displaces superiorly. Our patient's fracture fragment was displaced 2.1 cm cranially in the initial examinations. Although some authors believe that over 2 cm displacement requires surgical fixation, others assert that displacements between 2–3 cm can be treated conservatively in younger patients.[4]

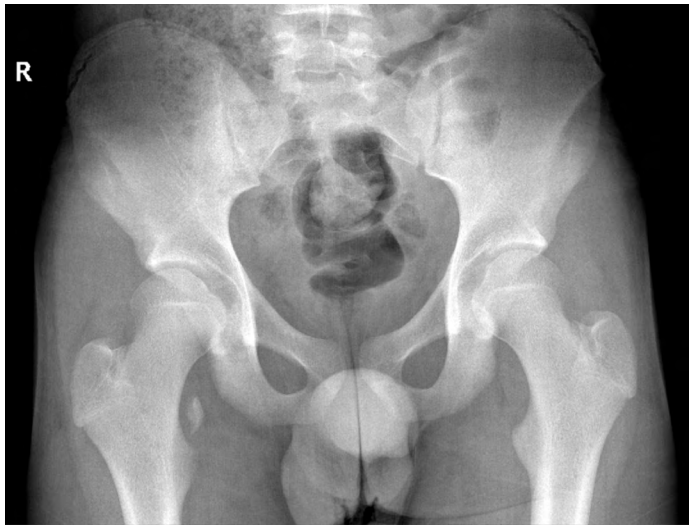

Figure 3: Pelvis anteroposterior radiogram of the patient 1 month after the incident.

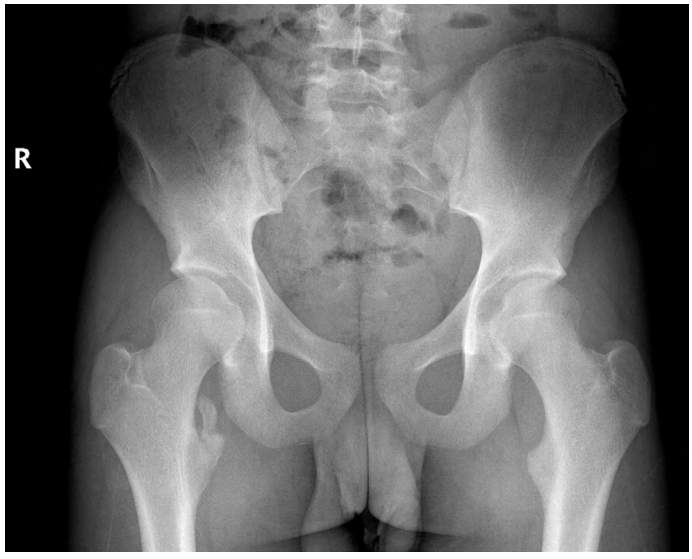

Figure 4: The pelvis anteroposterior radiological imaging of the patient after 1 year.

We opted to treat the patient conservatively. After 6 months of follow-up, the patient was fully able to participate in sports activities and could run at a competitive level.

Conservative treatment for trochanter minor fractures typically involves a series of steps: restricting active lifting of the leg, using crutches with partial weight bearing for 2–4 weeks, followed by progressive weight bearing for another 2–4 weeks. Complete weight bearing is typically allowed after 4 to 6 weeks. Patients generally regain a symptom-free state within 3–4 months.[4] In our case, the patient exhibited remarkable progress, being able to walk with complete weight bearing after just 1 month of conservative treatment. Although some clinics may advocate waiting for 6 weeks before allowing full weight bearing, we decided to initiate this at 4 weeks because the patient was comfortable with their current mobilization and had experienced no pain during the first 2 weeks.

Hip pain is also very common when fracture healing is complete, often due to ischiofemoral impingement syndrome. There are reported cases indicating that chronic avulsion injuries of the hamstrings and iliopsoas muscles can cause ischiofemoral impingement in long-term follow-ups. The most common time of presentation for this condition is after 1 year. In our case, the patient exhibited no hip pain or limitations at the one-year mark.

Ischiofemoral impingement syndrome usually occurs after conservative treatment of trochanter minor fractures; therefore, it is important to keep this potential complication in mind during long-term follow-ups.[5,6]

Recent studies have indicated that a considerable proportion of trochanter minor fractures in young patients exhibit complete healing within approximately one year, without any detectable deformities upon clinical examination. Jason Mascoe and his colleagues indicated in their study that patients with non-displaced trochanter minor fractures are treated non-surgically with successful results.[7] In our case, the patient was 13 years old, and the bone healing process was almost fully completed within this timeframe, leaving no discernible traces of deformity. The Harris Hip Score increased in our patient from 81 to 89 in 1 year with conservative treatment, similarly to the study by Jason Mascoe and his colleagues.

CONCLUSION

Fractures of the trochanter minor are frequently observed in younger patients and typically respond well to conservative treatment, unlike in older patients. Engaging in early mobilization and exercises during the healing process does not adversely affect bone recovery; however, it is essential to perform these activities with caution and under proper supervision.

Statement

Author Contributions: Concept – AC, AŞ; Design – AC; Supervision – AŞ; Resource – AC; Materials – AC, FK; Data Collection and/or Processing – AC, ED, CE; Analysis and/or Interpretation – AŞ, ED; Literature Search – AC; Writing – AC; Critical Reviews – AŞ.

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