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Table 1: Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	350 (Structured)	40	6	6
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Case Report	1500	200	15	No tables	5
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Book section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290–308.

Books with a single author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561–5.

Scientific or technical report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

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Final publication: The final corrected version will appear in an issue of the journal and added to the journal website. To ensure rapid publication, we ask authors to provide your publication approval during the proofreading process as quickly as possible, and return corrections within 48 hours of receiving the proof.

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ORIGINAL ARTICLE

Investigation of plasminogen activator inhibitor-1 4G/5G gen polymorphism in Turkish preeclamptic patients

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ABSTRACT

Objective: The plasminogen activator inhibitor type-1 (PAI-1) is a genetic risk factor that plays a role in the pathogenesis of pre-eclampsia and elevated levels of PAI-1 may lead to an increased risk of thrombosis. At preent, there is considerable controversy about the association between PAI-1 gene polymorphism and preeclampsia. The aim of this study is to investigate whether the pattern of PAI-1 gene polymorphism is a useful marker for preeclampsia or not.

Material and Methods: Our study included 83 hypertensive pregnant women (64 preeclamptic women, 12 pregnant women with HELLP syndrome, and 7 eclamptic women) genotyped for PAI-1 gene polymorphism (4G/4G, 4G/5G, and 5G/5G) and 20 healthy pregnant women. The Chi-square analysis was used to evaluate the differences in genotype and allele frequencies between hypertensive pregnant women and healthy controls.

Results: The highest PAI-1 gene polymorphism rate was found in the hypertensive group and healthy controls in the 4G/5G allele distribution. No significant difference was determined between the hypertensive group and healthy controls regarding the distribution of PAI-1 4G/4G, 4G/5G, and 5G/5G polymorphic alleles.

Conclusion: According to the results obtained from present study, we think that PAI-1 gene polymorphism does not contribute to individual differences for the sensitivity of preeclampsia development. However, prospective cohort studies with larger sample sizes are needed to clearly demonstrate the contribution of PAI-1 gene polymorphism to serious pregnancy complications such as preeclampsia.

Keywords: PAI-1 gene polymorphism, preeclampsia, eclampsia, HELLP syndrome.

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INTRODUCTION

Preeclampsia is one of the leading causes of maternal and fetal morbidity and mortality in developed countries. It is considered that there is a deficiency in the natural anticoagulant pathway of patients with preeclampsia.[1] The addition of acquired or hereditary coagulopathies to the hypercoagulopathy state already present in the pregnancy increases the predisposition to preeclampsia and complications of preeclampsia. Early diagnosis of preeclampsia and to be able to perform the appropriate treatment is quite important for reducing maternal and fetal morbidity and mortality. In recent studies, it is aimed to be able to make a diagnosis of the disease well before the presentation of clinical symptoms of preeclampsia.

The plasminogen activator inhibitor type 1 (PAI-1) is mainly synthesized by endothelial cells and considered as a marker of endothelial cell dysfunction in preeclampsia.[2,3] PAI-2 is mainly synthesized by placental tissue and considered as a marker of placental function in pregnancy.[3,4] PAI-1 is responsible for approximately 60% of the PAI activity in the plasma[5] and it is the key inhibitor of fibrinolysis in the pregnancy when it is compared with PAI-2 and PAI-3.[6] It has been shown in many studies that PAI-1 was associated with many diseases such as severe hypertension, myocardial disease, deep venous thrombosis, malignancy, obesity, type 2 diabetes mellitus, polycystic ovary syndrome, and acute infection.[7]

The 4G polymorphism includes the deletion of a single guanine residue which is placed in the promoter region of the PAI-1gene located on chromosome 7q, 675 base pairs upstream from the transcriptional start site. This regulatory polymorphism does not alter the structure or function of the gene. But instead of this, it alters the expression of the gene and so it leads to higher circulating levels of PAI-1, which may increase the risk of thrombosis.[8]

The plasma level of PAI-1 in individuals with 4G/4G genotype (homozygous mutant) is approximately 25% higher than the individuals with 5G/5G genotype (homozygous normal).[9]

In this study, we aimed to investigate the contribution of genetic polymorphisms increasing the production of PAI-1 to serious pregnancy complications such as preeclampsia, eclampsia, and HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet levels).

MATERIAL AND METHODS

Our study was performed with 83 preeclamptic, eclamptic pregnant women with HELLP syndrome more than 20 weeks of gestation, and 20 healthy pregnant women more than 20 weeks of gestation presenting to the Department of Obstetrics and Gynecology of Dicle University, Faculty of Medicine between January 2010 and January 2011. All participants gave signed informed consent. This study was conducted in accordance with the Declaration of Helsinki.

Patient selection and classification were performed according to the ACOG criteria.[10] Accordingly, the diagnosis of preeclampsia was made with measurement of systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg in two measurements performed at least 4 h apart after 20th week of pregnancy in previously normotensive women and determination of proteinuria of ≥300 mg in 24-h urine collection or +1 proteinuria with urine dipstick test. The diagnosis of eclampsia was made with the observation of grand-mal convulsions in preeclamptic patients. The diagnosis of HELLP syndrome was made with determination of hemolysis (abnormal peripheral blood smear, serum bilirubin of >1.2 mg/dL, and lactic dehydrogenase of >600 IU/L), elevated liver enzymes (alanine aminotransferase or aspartate aminotransferase is more than 2 times the upper limit of normal), and low platelets (<100.000/mm^3).[11] Women who had multiple pregnancy, systemic diseases such as diabetes mellitus, autoimmune diseases, renal disease, chronic hypertension, using anticoagulant agents, pregnant women with a history of known thrombosis, and pregnant women who smoke were excluded from the study.

Patients in both groups were compared regarding demographic and clinical characteristics, blood pressures, laboratory values, gestational weeks at presentation, mode of delivery, the 1st- and 5th-min Apgar scores of neonates, birth weights of neonates, and PAI-1 gene polymorphism. Preeclamptic patients were compared regarding PAI-1 gene polymorphism in two groups as early-onset hypertensive disorder (24–32 weeks of gestation) and late-onset hypertensive disorder (35–42 weeks of gestation). In addition, all cases in the study group were compared regarding PAI-1 gene polymorphism according to their diagnoses (preeclampsia, eclampsia, and HELLP syndrome).

Hemogram has been studied in Cell–dyn 3700 device using the LYSE kit. Biochemical tests were studied in the ARCHITECT C 1600 device using the enzymatic method and ABBOTT kit. Proteinuria was measured in spot urine samples at Roche Urisys1800 device using Combur 10 Test S strips. Two milliliter of venous blood sample were taken into the EDTA tube for the determination of genetic polymorphism. DNA isolation was performed in the blood sample taken into the EDTA tube at Roche-Magna Pure Compact automated DNA isolation device using a ready-to-use isolation kit. Fifteen microliter of the mixed solution were taken into a capillary tube and 5 µL of DNA solution obtained previously was added onto it. A centrifugation procedure was performed for precipitation of master mix solution and DNA mixture onto the bottom of the capillary tube. The samples were studied in the Light Cycler 2.0 device. The 4G and 5G polymorphisms were amplified using previously defined primers. Amplification products obtained were evaluated using TIB Molbiol Light-Mix Kit Human.

Interpretation of Data

The samples were named according to temperatures at they were peaked using the melting curve. The samples peaked at 54.5°C were named as 4G/4G; the samples peaked at between 54.5°C and 62.0°C were named as 4G/5G; and the samples peaked at 62.0°C were named as 5G/5G. One peak was observed in homozygous samples and two peaks were observed in heterozygous samples.

Statistical Methods

The Statistical Package for the Social Sciences (SPSS Inc., version 15; Chicago, IL, USA) was used for statistical analyses. Data were expressed as numeric (%) or mean±standard deviation (SD) values, as appropriate. Kolmogorov–Smirnov test was performed for the distribution of continious data. Statistical analyses were performed by Student's t-test for normal distribution data and Mann–Whitney U-test for abnormal distribution data Chi-square and Fish-

er exact test were used for comparison of categorical variables. Statistical significance was set p≤0.05.

RESULTS

Eighty-three patients with diagnoses of preeclampsia, eclampsia, and HELLP syndrome were included in our study. The distribution of the patients in the study group was as follows: 64 (77.1%) preeclampsia, 7 (8.4%) eclampsia, and 12 (14.5%) HELLP syndrome. Twenty healthy pregnant women were evaluated in the control group.

The demographic characteristics of the patients are shown in Table 1. While the mean gestational week of the patients in the study group was 33.06±4.7 weeks, it was 34.05±4.7 weeks in the cases of the control group. No statistical difference was determined in this regard. When the study group and the control group were compared regarding the mode of delivery, while the delivery rate with caesarean section was 65% (n: 54) in the study group, it was found to be 40% (n: 8) in the control group. The difference was statistically significant.

The patients were compared regarding the 1st- and 5th-min Apgar scores, and mean birth weights of neonates after delivery. The 1st and 5th min Apgar scores of neonates in the study group were observed to be statistically significantly lower compared to the 1st and 5th min Apgar scores of neonates in the control group. Again, the mean birth weight of neonate in the study group was found to be statistically significantly lower compared to the mean birth weight of neonate in the control group.

When the patients in the study group and the control group were compared regarding PAI-1 gene polymorphism, no statistically significant difference was determined between groups (Table 2). However, when the patients in the study group were compared regarding PAI-1 gene polymorphism according to their pre-diagnoses; a statistically significant difference was determined between groups (p=0.005). While 17 (26.6%) of 64 preeclamptic patients had a mutation in the 4G/4G gene, 32 (50%) of them had a mutation in the 4G/5G gene, and 15 (23.4%) of 64 preeclamptic patients had a 5G/5G genotype. 4G/4G PAI-1 gene polymorphism was not found in any of the 7 eclamptic patients, while 2 (28.6%) of eclamptic patients had a mutation in the 4G/5G gene. Five (71.4%) of eclamptic patients had a 5G/5G genotype. While 1 (8.3%) of 12 patients with HELLP syndrome had 4G/4G genotype, 8 (66.7%) of them had 4G/5G genotype, and 3 (25.0%) of them had 5G/5G genotype (Table 3). While 4 (20%) of 20 control patients had a mutation in the 4G-4G gene, 13 (65%) of them had a mutation in the 4G-5G gene. Three (15%) of 20 control patients had a 5G-5G genotype. The patients in the study group were compared in two separate groups as early-onset hypertensive disorders (24–32 weeks of gestation) and late-onset hypertensive disorders (35–42 weeks of gestation) regarding PAI-1 gene polymorphism and no statistically significant difference was determined between groups (Table 4). Since 4 patients from the study group were seen during the postpartum period and their gestational weeks were not known, they were not included in the table.

Table 1: Demographic characteristics of the patient groups

	Study group (n=83)	Control group (n=20)	p
Maternal age	31.20±6.802	30.80±6.37	0.81
Gravida	4.40±3.268	4.15±2.943	0.75
Parity	2.98±3.044	2.80±2.64	0.81
Gestational age (wk)	33.06±4.759	34.05±4.718	0.40
SBP* (mm/Hg)	152.57±14.21	118.07±13.43	<0.001
DBP* (mm/Hg)	92.21±11.71	70.22±10.79	<0.001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; *: Blood pressure at the time of diagnosis.

Table 2: Distribution of the patient and control groups regarding PAI-1 genotype

PAI-1 genotype	Study group		Control group		Total		p
	n	%	n	%	n	%	
4G/4G	18	21.7	4	20	22	21.4	0.43
4G/5G	42	50.6	13	65	55	53.4	
5G/5G	23	27.7	3	15	26	25.2	
Total	83	100	20	100	103	100	

Chi-Square=1.67.

DISCUSSION

It is considered that predisposition to endothelial cell dysfunction which triggers abnormal activation of hemostatic and/or inflammatory systems plays an important role in the pathogenesis of preeclampsia, eclampsia, and HELLP syndrome.[12,13] It remains uncertain whether increased PAI-1 levels are a primary mechanism leading to the development of preeclampsia or a consequence of the associated endothelial and placental damage.[8,14]

It is known that PAI-1 provides a contribution to the formation of thrombus and the development and the clinical course of acute and chronic cardiovascular diseases.[15] It has been suggested that PAI-1 gene polymorphism (4G or 5G) plays a role in the regulation of the synthesis of the inhibitor 4G allele which is associated with the enhanced gene expression and plasma PAI-1 levels.[15–17] Glueck et al.[18] investigated the effect of PAI-1 gene polymorphism and they reported that the frequency of PAI-1 4G/4G polymorphism was increased in the presence of severe preeclampsia and the other obstetric complications (stillbirth, fetal growth restriction, and detachment of the placenta). In the study performed by Yamada et al.[19] in 115 preeclamptic patients and 210 healthy pregnant women, it was determined that an increase occurred in the quantity of PAI-1 due to an increase of mRNA expression in the placenta and plasma of preeclamptic women. It has been reported that the presence of the

Table 3: Comparison of the patient group according to prediagnosis regarding PAI-1 genotype

Diseases	PAI-1						Total		p
	4G/4G		4G/5G		5G/5G				
	n	%	n	%	n	%	n	%	
Pre-eclampsia	17	26.6	32	50	15	23.4	64	100	0.04
HELLP syndrome	1	8.3	8	66.7	3	25	12	100	
Eclampsia	0	0	2	28.6	5	71.4	7	100	
Total	18	21.7	42	50.6	23	27.7	83	100	

Chi-Square=9.76.

Table 4: Comparison of the patient group regarding PAI-1 genotype according to be early-onset hypertensive disorder and late-onset hypertensive disorder

	Early-onset hypertensive disorder		Late-onset hypertensive disorder		Total		p
	n	%	n	%	n	%	
4G/4G	6	15.4	12	30	18	22.8	0.28
4G/5G	21	53.8	19	47.5	40	50.6	
5G/5G	12	30.8	9	22.5	21	26.6	
Total	39	100	40	100	79	100	

Chi-Square=2.52.

4G/4G genotype of the PAI-1 gene could be a risk factor for preeclampsia in Japan population.

Wu et al.[20] suggested that even if it was combined with the other genetic risk factors associated with thrombogenesis when it was compared with the established clinical factors such as previous or familial history of preeclampsia, cigarette smoking, or elevated body mass index, PAI-1 4G/4G gene polymorphism would be insufficient to predict individual disease.

Conflicting findings were reported in genetic epidemiological studies investigating the association between PAI-1 (–675 4G/5G) polymorphism and preeclampsia. The majority of meta-analyses investigating the genetic and non-genetic risk factors for preeclampsia have warning that threatens their validity. The systematic review and meta-analysis performed by Giannakou et al.[21] provided strong evidence for an association between PAI-1 4G/5G polymorphism (recessive model) and preeclampsia. In the meta-analysis performed by Wiwanitkit investigating the correlation between the pattern of PAI-1 4G/5G polymorphism and preeclampsia in 880 patients and 810 controls, case–control studies of six different countries (Finland, Japan, South Africa, Germany, Scotland, and Italy) were evaluated and the authors suggested that the pattern of PAI-1 4G/5G polymorphism might represent a useful marker of increased risk for preeclampsia.[17] Whereas, in the study performed by Hakli et al.[22] in an eastern Finland population including 133 preeclamptic and 115 healthy control pregnant women, the authors found no difference regarding the allelic distribution of 4G/5G polymorphism between preeclamptic women and healthy control pregnant women.

de Maat et al.[23] compared 157 preeclamptic and 157 healthy control pregnant women and they determined the frequencies of the 4G/4G allele, the 4G/5G allele, and the 5G/5G allele in preeclamptic and healthy control pregnant women to be 34%, 51%, 15%, and 28%; 55%, 17%; respectively. As a result of the study, the authors reported that there was no difference between the frequency distribution of the 4G/4G allele in women with severe preeclampsia and in healthy control pregnant women.

In the systematic review of Morgan et al.,[24] a total of 1511 women with preeclampsia, eclampsia, and HELLP syndrome and 3492 healthy controls participating in 12 genetic association studies meeting all criteria were evaluated and although several potential sources of bias could not be neglected, it was reported that the fibrinolytic pathway regulated by the PAI-1 (4G/5G) gene might contribute to the pathogenesis of preeclampsia and related conditions. However, the authors supported that this genetic association did not justify screening pregnant women for PAI-1 (4G/5G) polymorphism but this condition might help to prioritize therapeutic targets that merit evaluation in randomized clinical trials.

Furthermore, in our study, we determined the highest rate of PAI-1 gene polymorphism in either hypertensive group or healthy controls regarding the distribution of 4G/5G allele. There was no significant difference between the hypertensive group and healthy controls regarding the distribution of PAI-1 4G/4G, 4G/5G, and 5G/5G polymorphic alleles.

As it is known, there are significant differences between early- and late-onset preeclampsia. At present, it is suggested that the role of the placenta in the development of these forms of the disease is different and therefore it is recommended that early- and late-onset preeclampsia should be evaluated as separate conditions while investigating pathophysiological factors and biochemical markers of preeclampsia.

Normally, the PAI-1 level increases beginning from 20 weeks of gestation. This increase is earlier and higher in preeclampsia.[14,25] Wikström et al.[26] compared early-onset (24–32 weeks of gestation) and late-onset (35–42 weeks of gestation) preeclamptic patients with healthy pregnant women and determined that placental oxidative stress was increased in women with early-onset preeclampsia secondary to this an increase occurred in PAI-1/PAI-2 ratio. Furthermore, in the study of Udenze et al.,[27] it has been shown that plasma levels of PAI-1 were increased in preeclamptic women, however, since there was no correlation between this marker and the severity of preeclampsia, the opinion was reported that its clinical benefit would be limited.

In our study, we evaluated the frequency of PAI-1 gene polymorphism among early- and late-onset hypertensive disorders and no significant difference was determined between early- and late-onset groups. Preeclampsia and HELLP syndrome among its more severe forms is characterized by increased placental thrombosis based on a procoagulatory state in the mother. While most of the studies have investigated the role of the PAI-1 4G/5G polymorphism in preeclampsia, very few studies have focused especially on HELLP syndrome. In the study performed by Muetze et al.[28] on this subject comparing 102 pregnant women with HELLP syndrome and 102 healthy pregnant women, the 4G/4G gene polymorphism was found to be more frequent in women with HELLP syndrome than in healthy controls (35.3% vs. 22.5%, respectively), but this difference was not significantly different (p=0.129). As the result of the study, the authors reported that women carrying a 4G/4G genotype of the PAI-1 gene were not at increased risk for developing HELLP syndrome and this condition was consistent with the majority of the previous studies investigating the association between the PAI-1 4G/5G polymorphism and preeclampsia. In the systematic review performed by Morgan et al.,[24] the authors reported that the frequency of 4G/5G polymorphism was not different between groups in the subgroup analysis of six studies in which participants were women with severe preeclampsia, eclampsia, and HELLP syndrome.

In our study, we determined 4G/4G genotype, 4G/5G genotype, and 5G/5G genotype in 8.3%, 66.7%, and 25% of 12 patients with HELLP syndrome; respectively. In addition, while 4G/4G genotype was encountered in none of 7 eclamptic patients, we determined 4G/5G genotype and 5G/5G genotype in 28.6% and 71.4% of the patients. Most of the studies in the literature investigate the relationship between PAI-1 gene polymorphism and preeclampsia. We think that the fact that we investigated the relationship between PAI-1 gene polymorphism and other hypertensive diseases (eclampsia and HELLP syndrome) besides preeclampsia makes our study different and powerful.

CONCLUSION

In summary, according to the results obtained from present study, we think that PAI-1 gene polymorphism does not contribute to individual differences for the sensitivity of preeclampsia development. However, prospective cohort studies with larger sample sizes are needed to clearly demonstrate the contribution of PAI-1 gene polymorphism to serious pregnancy complications such as preeclampsia.

Statement

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ÖT, ME; Design – ÖT, ME; Supervision – ÖT, ME; Data Collection and/or Processing – ÖT, ME; Analysis and/or Interpretation – ÖT, ME; Literature Search – EÇ; Writing – EÇ; Critical Reviews – EÇ.

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ORIGINAL ARTICLE

Which vaginal cuff closure route produces better clinical results after laparoscopic hysterectomy? Laparoscopic or the vaginal route

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ABSTRACT

Objective: The aim of this study was to compare the complications and clinical outcomes of laparoscopic closure of the vaginal cuff and cuff closure through the vaginal route after total laparoscopic hysterectomy (TLH).

Material and Methods: This retrospective study conducted from February 2012 to December 2021 involved a total of 362 patients who underwent TLH. Of these patients, 148 received vaginal cuff closure using no. 0 Vicryl™ (polyglactin 910), which is endoscopically absorbable, and 214 received vaginal cuff closure through the vaginal route using the same suture material. The gynecological examination findings 1 and 6 months after the operation were obtained from the electronic medical records of the postoperative treatment interventions and from the patients' files. Together with the major complications that occurred, complications such as vaginal cuff dehiscence, hematoma, cuff cellulitis, granulation, spotting, vaginal discharge, and cuff prolapse were recorded.

Results: The operation duration was found to be significantly shorter for the patients whose vaginal cuffs were sutured through the vaginal route than for the patients whose vaginal cuffs were endoscopically sutured (107.75±7.19 and 83.55±8.44, respectively; $p<0.01$). It was also found that laparoscopic suturing is more advantageous than suturing through the vaginal route in terms of the formation of vaginal cuff granulation, abnormal vaginal discharge, and abnormal mucosal band-shaped adhesion in the vaginal cuff.

Conclusion: Laparoscopic suturing and knotting is a process that requires much experience and skill and that may lengthen the operation duration. However, the laparascopically closure of the vaginal cuff seems safer.

Keywords: Laparoscopic suturing, total laparoscopic hysterectomy, vaginal cuff, vaginal cuff suturing.

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INTRODUCTION

Hysterectomy is the most common abdominal gynecological surgical practice.[1] Total laparoscopic hysterectomy (TLH) was first performed Reich et al. in 1989.[2] This minimally invasive method has come to be preferred more than laparotomic hysterectomy for several reasons, such as the fact that it causes less intraoperative bleeding, involves a shorter post-operative hospital stay, allows a quicker resumption of daily life activities, and is relatively less costly.[3] Complications related to the vaginal cuff after TLH, however, such as dehiscence, infection, hematoma, and healing disorders, are quite frequent. After a laparotomic and vaginal hysterectomy, the vaginal cuff dehiscence is within the range of 0.1–0.2%. On the other hand, it is estimated that this rate is 5–10 times higher in minimally invasive procedures.[4] The risk of vaginal cuff complications increases with coit in the early post-operative period, with early excessive activity, with diabetes, and with corticosteroid use. Nevertheless, closure of the vaginal cuff with the correct technique and with a suitable suture material can decrease the cuff closure complications.[5]

The endoscopic suture and knotting application requires a high level of surgical skill and is among the significant factors determining the operation duration.[6] The tension originating from laparoscopically and robotically applied knots in animal models was detected to be less compared to that from the conventional suturing, which is associated with the increase in post-operative bleeding, hematoma, and vaginal cuff dehiscence risk in the laparoscopic approach.[7]

The aim of this study was to compare the complications resulting from and clinical results of laparoscopic vaginal cuff closure and vaginal cuff closure through the vaginal route in patients who underwent TLH.

MATERIAL AND METHODS

The study was approved by the local ethics committee (Approval date: March 31, 2021, and No: 7/VI). The written informed consent was obtained from all participants in accordance with Helsinki Declaration.

This retrospective study was conducted from February 2014 to December 2021 and included a total of 362 patients who underwent TLH due to benign indications in the uterus. Of these patients, 148 received vaginal cuff closure using no. 0 Vicryl™ (polyglactin 910), which is endoscopically absorbable, and 214 received vaginal cuff closure through the vaginal route using the same suture material. Inclusion criteria were as follows: Age >18 years, laparoscopic completion of entire procedure up to colpotomy, and benign indication for hysterectomy. Patients who underwent hysterectomy due to invasive malignant lesions in the uterine cervix, ovarian, and endometrium or due to pelvic abscess, previous radiation therapy, and those who underwent a subtotal hysterectomy, and inability to express adequate informed consent to participate in the study and patients dropped out from the follow-up were excluded from the study.

The pre-operative demographic data, operation data, early and late period complications, and gynecological examination findings 1 and 6 months after the surgery, and data regarding the post-operative treatment interventions were obtained from the patients' electronic medical records and files. Demographic data (e.g., age, gravida, body mass index, and previous abdominal surgical data), data related to the operation (e.g., surgical indications, length of stay in the hospital, and operation duration), and data regarding the major complications that occurred after the surgery (e.g., bladder/ureter/great vessel/bowel injury and blood transfusion) were recorded. In addition, complications such as vaginal cuff dehiscence, hematoma, cuff cellulitis, granulation, spotting, vaginal discharge, and cuff prolapse were recorded.

Surgical Procedure

In this study, all the operations were performed by the same experienced surgeon, under general anesthesia, the patients were prepared in the dorsolithotomy position. For uterus manipulation, a RUMI® II system (Cooper Surgical, Trumbull, CT, USA) was inserted in the uterine cavity. Using the cervical cup adapted to the RUMI® II manipulator as a guide, monopolar cautery and colpotomy were performed, and the uterus was removed from the vaginal route. The vaginal cuffs of one group of patients were sutured through the vaginal route through the continuous locking technique using the absorbable no. 0 Vicryl™ (polyglactin 910; Ethicon, Somerville, NJ, USA) suture material, whereas the vaginal cuffs of the patients in the other group were sutured through laparoscopic intracorporeal separate and knotting with the same material. In both methods, the uterosacral ligament, dense connective tissue layers, rectovaginal fascia, and paravaginal fascia were included in the sutured vaginal cuff.

Statistical Analysis

The data obtained from the study were analyzed using the Statistical Package for the Social Sciences (SPSS) 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA) program. Continuous data were expressed as the mean±standard deviation and percentage. Student's t-test was used for continuous variables. Mann–Whitney U-test was used for the intergroup comparisons of parameters without normal distribution. Chi-square test was used for comparison of qualitative data. The statistical significance level of the data obtained from the study was interpreted with "p" value and $p<0.05$ was considered to be statistically significant.

RESULTS

The data obtained from the 362 patients who had undergone TLH were evaluated. The demographic features and TLH indications of the 148 patients whose vaginal cuffs were closed laparoscopically and of the 214 patients whose vaginal cuffs were closed through the vaginal route are presented in Table 1. It was found that in both groups, myoma uterine and abnormal uterine bleeding were the most common hysterectomy indications.

The mean operative time was 83.55±8.44 min in patients whose vaginal cuffs were sutured vaginally and 107.75±7.19 min in patients whose vaginal cuffs were sutured by the intracorporeal endoscopic method. The mean operation time of the patients whose vaginal cuff was sutured vaginally was statistically significantly shorter than the vaginal cuff sutured endoscopically ($p<0.01$). Although the weight of the hysterectomy materials was higher in the patients in whom the cuff was sutured vaginally (229.77±16.35 gr) than the cuff sutured endoscopically (199.60±14.18 gr), no statistical difference was found.

Table 1: Patients' demographic features and their hysterectomy indications

	Vaginal cuff closure method		
	Endoscopic suturing (n=148)	Vaginal suturing (n=214)	p
Age (year)	48.33±4.15	49.90±3.34	>0.05
BMI (kg/m^2)	28.56±3.23	27.46±2.05	>0.05
Parity (n)	3.73±0.42	3.38±0.34	>0.05
Previous abdominal surgery n, %			
Caesarean	35 (23.6)	42 (19.6)	>0.05
Appendoctomy	5 (3.3)	3 (1.4)	>0.05
Myomectomy	9 (6)	5 (2)	>0.05
Ovarian surgery	2 (1.3)	4 (1.8)	n/s
TLH indications n, %			
Uterine myoma	85 (57.4)	135 (63)	>0.05
Abnormal uterine bleedings	21 (14.1)	44 (20.5)	=0.02*
Premalignant lesions of the cervix	14 (9.4)	23 (10.7)	>0.05
Premalignant lesions of the endometrium	19 (12.8)	16 (7.4)	>0.05
Chronic pelvic pain	6 (4)	4 (1.8)	>0.05
Operative time (min)	107.75±7.19	83.55±8.44	=0.01*
Weight of the uterus (gr)	199.60±14.18	229.77±16.35	>0.05

*: P value <0.05; BMI: Bodymass index; Values were given as mean±standard deviation (range) or number (%).

For the patients who had undergone TLH, the intraoperative and post-operative major and minor complications that occurred are shown in Table 2. In terms of the major complications, no differences were found between the groups. It was found that endoscopic suturing is more advantageous than suturing through the vaginal route in terms of granulation formation, abnormal vaginal discharge, and mucosal-adhesion formation in the vaginal cuff. Within 39 patients whose vaginal cuff was sutured vaginally with complaints of abnormal vaginal discharge, six patients had Escherichia coli, and one patient had abnormal colonization of the Klebsiella strain in the vaginal discharge culture. Eight of the patients whose vaginal cuff was sutured endoscopically had abnormal vaginal discharge complaints, however, none of them had abnormal microbial strains isolated in their vaginal culture.

Only one of the patients whose vaginal cuff was endoscopically sutured intracorporeally had vaginal cuff dehiscence. Vaginal vault prolapse (stage >2) rates were similar between vaginally sutured (n=9) and endoscopically sutured (n=7) groups.

DISCUSSION

In this study, we aimed to compare the complications and clinical results of laparoscopic vaginal cuff closure and vaginal cuff closure through the vaginal route in patients who underwent TLH. We found no differences between the laparoscopic closure of the vaginal cuff and the vaginal cuff closure through the vaginal route in terms of intraoperative or post-operative major complications such as great vessel/bowel/bladder-ureter, bleeding, and blood transfusion in the patients who had undergone TLH. Besides, the operation duration was found to be significantly shorter for the patients whose vaginal cuffs were sutured through the vaginal route and also it was found that laparoscopic suturing is more advantageous than suturing through the vaginal route in terms of the formation of vaginal cuff granulation, abnormal vaginal discharge, and abnormal mucosal band-shaped adhesion in the vaginal cuff.

It was previously reported that more complications could occur (e.g., dehiscence, vaginal bleeding, granulation formation, cuff infection, and vaginal cuff prolapse) in hysterectomy performed with the laparoscopic method. Vaginal cuff dehiscence accompanied by evisceration is one of the life-threatening complications that are feared to develop in patients undergoing TLH.[8] Vaginal cuff dehiscence is characterized by partial- or full-thickness separation of the vaginal cuff. It can lead to evisceration of peritoneal contents, bowel ischemia, and peritonitis.[9] It is emphasized that after hysterectomy, especially in premenopausal patients, the most significant risk factor that increases vaginal cuff complications is coit earlier than 1 month post-operative.[10] Speculate that women after menopause had a lower risk of vaginal cuff dehiscence due to decline in sexual frequency.[11] Contrary to the results of the many early prospective studies that have been conducted, in the recent studies involving more patients, no difference was detected in terms of vaginal cuff dehiscence whether hysterectomy was performed laparoscopically or through the abdominal or vaginal route.[12] In their meta-analysis, Uccella et al. found that the dehiscence rate in the intracorporeal closure of the

Table 2: Postoperativ complications

Complications	Vaginal cuff closure method				p
	Endoscopic suturing (n=148)		Vaginal suturing (n=214)		
	n	%	n	%	
Major complications					
Bladder injury	4	2.7	4	1.8	n/s
Ureter injury	2	1.35	1	0.4	n/s
Great vessel injury	0	0	1	0.4	n/s
Bowel injury	1	0.6	2	0.9	n/s
Blood transfusion	31	20.9	37	17.2	0.05
Cuff complications					
Dehiscence	1	0.6	0	0	n/s
Vaginal cuff prolapse	7	4.2	9	4.2	>0.05
Vaginal cuff bleeding	4	2.4	3	1.4	n/s
Cuff cellulite	2	1.35	3	1.4	n/s
Granulation	3	1.8	25	11.6	<0.001*
Abnormal vaginal discharge	8	4.8	39	18.2	<0.001*
Cuff hematoma	2	1.3	3	1.5	n/s
Mucosal band-formed adhesion	1	0.6	19	8.8	<0.001*

*: P value <0.05.

vaginal cuff is 1% and that in the closure through the vaginal route is 2.9%.[13] In our study, among all the patients who underwent TLH, there was only one patient who experienced cuff dehiscence, and it was not complicated by evisceration.

Hysterectomy is considered to be a potential risk factor for pelvic organ prolapse (POP) with an incidence of post-operative vault prolapse varying from 2% to 43%.[14,15] Uccella et al.[13] found that there are no significant differences among the laparoscopic or abdominal or vaginal route closure of the vaginal cuff in terms of the risk of vaginal cuff prolapse. The route of hysterectomy is not associated with a difference in recurrence, grade, or subsequent treatment of prolapse when the indication for hysterectomy is considered.[16] Although there were no patients with POP indication in our study, according to the POP quantification grading[17] system after TLH, the rate of stage >2 vaginal cuff prolapse in our study was 4.2% in both endoscopically sutured and vaginally sutured groups.

One of the processes that are thought to increase cuff complications in TLH is colpotomy with electrocauterization.[6] Especially, it can increase the possible bowel adhesions on the vaginal cuffs of patients who underwent hysterectomy due to malignancy, the bowel problems in patients who need brachytherapy, and the risk of ileus. It may be safer for such patients to undergo colpotomy with the sharp dissection method using laparoscopic scissors instead of electrocauterization.

Intensive vaginal discharge and spotting are among the frequent complaints of patients after TLH. The infection rate related to vaginal cuff after TLH has been reported to be 7.4%.[15] In our study, the total infection rate in the laparoscopically sutured cases was 6.7%, and that in the vaginal route sutured cases was 19.6%. In the culture samples from the post-operative vaginal discharge of the subjects in our study, the most frequent microbial agent colonization was E. coli. Infection findings were seen more frequently in the patients whose cuffs were closed through the vaginal route (p<0.001).

In our study, prolonged and recurrent vaginal spotting with granulation formation finding on the vaginal cuff was the most frequently seen symptom which decreases the post-operative satisfaction of the patients. Biopsy was performed on the lesions of the patients with granulation, and the biopsy area was cauterized. None of the patients' pathology results showed malignant findings. The granulation rate after TLH has been reported to be 1.4% with laparoscopic suturing and 1.1% with suturing through the vaginal route.[6] In this study, the granulation rate after TLH with laparoscopic suturing was 1.8%, and that with suturing through the vaginal route was 11.6%. The granulation formation on the vaginal cuffs of the patients whose cuffs were sutured through the vaginal route was significantly higher (p<0.001).

In this study, the vaginal cuff hematoma rates were 1.3% and 1.5%, respectively, for the patients whose vaginal cuffs were closed laparoscopically and for those whose vaginal cuffs were closed through the vaginal route. In the literature, similar rates (1% and 2.9%, respectively) are reported.[13]

Safer cuff suturing can be applied by observing the vaginal cuff and the Douglas pouch peritoneum boundaries. For obese women

and those with atrophic vaginas, the cuff boundaries to be sutured can be visualized better with the laparoscopic method than with suturing through the vaginal route.[6]

Increasing surgical experience has been associated with lower rates of major complications, highlighting the effect of a learning curve.[18] Surgical complexity has also been associated with complications, with more complex surgeries usually performed by higher volume surgeons, with inherently higher complication rates.[19,20] Laparoscopic suturing and knotting is a process that requires much skill and experience.[21] Individual differences between surgeons in terms of quickness of knotting and strength of the knot are frequently observed.[22] The surgeon's skill and experience were among the determining factors of the operation time.[23] In our study, the average operation duration for the patients whose vaginal cuffs were closed laparoscopically was 107.75±7.19 min and that for the patients whose vaginal cuffs were closed through the vaginal route was 83.55±8.44 min, and a significant difference was found between the groups in favor of suturing through the vaginal route (p=0.01). Hwang et al.[6] found that the operation time was significantly shorter in the laparoscopically sutured group [76.74(40–220) min] than in the vaginal route group [85.77(45–290) min]. In a meta-analysis, Uccella et al.[13] found that operation time was 90.6±44.7 min in laparoscopically sutured group and 92.6±43.7 min in vaginal route group and there were no significant differences among groups.

Several surgical suture materials have been launched in the market to decrease these differences.[24] Among those are the self-fixing barbed suture materials (e.g., V-Loc™).[25] Studies have shown that these products can be reliably used in laparoscopic cuff suture, shorten the operation duration, and are effective suture materials.[26] However, some studies have indicated that these products are expensive and increase the risk of intra-abdominal adhesion.[27] Another study demonstrated the non-superiority of barbed suture with respect to conventional suture regarding surgical time and incidence of complications.[28] In our study, the vaginal cuffs of all the study participants were sutured with no. 0 Vicryl™ (polyglactin 910; Ethicon, Somerville, NJ, USA).

It has been reported that the vaginal length is better preserved in patients with laparoscopically sutured vaginal cuffs after TLH than in those with cuffs closed through the vaginal route; consequently, laparoscopic suturing of the vaginal cuffs is more advantageous in terms of sexual function.[29] Moreover, in patients with the vaginal cuff sutured through the vaginal route, the need for reconstruction due to vaginal cuff healing problems was found to be more frequent.[13] In our study, in 8.8% of the patients who underwent TLH and whose vaginal cuffs were sutured through the vaginal route, mucosal thin band-shaped adhesion that caused dyspareunia symptoms was found (Fig. 1). After we dissected this band formed adhesion, the patients' dyspareunia complaints resolved.

The most obvious limitation of this study was its retrospective nature, Apart from the total operation duration, the lack of data about the cuff suturing time was another limitation of our study. The main strength of our study is esteemed number of TLH cases including the data on post-operative vaginal cuff healing outcomes.

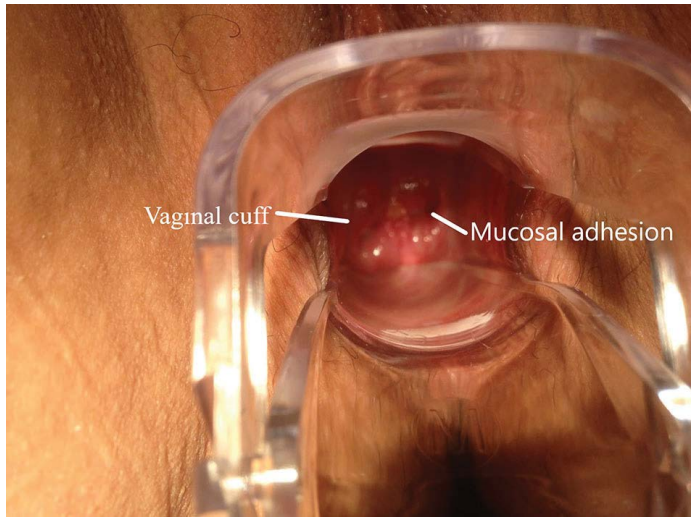

Figure 1: Vaginal mucosal adhesion.

CONCLUSION

Consequently, endoscopic suturing and knotting is a process that requires much skill and experience, but it seems that intracorporeal closure of the vaginal cuff after TLH is safer. Yet, although the closure of the cuff through the vaginal route requires greater caution in relation to the cuff complications, it is still an effective method. To determine whether laparoscopic vaginal cuff closure or vaginal cuff closure through the vaginal route is the superior technique, more prospective studies are needed.

Statement

Ethics Committee Approval: The Muğla Sıtkı Koçman University Clinical Research Ethics Committee granted approval for this study (date: 31.03.2021, number: 7/VI).

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

Peer-review: Externally peer-reviewed.

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ORIGINAL ARTICLE

PET/CT dilemma in para-aortic lymph node assessment in locally advanced cervical cancer?

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ABSTRACT

Objective: We aimed to discuss the relationship between the maximum standardized uptake value (SUVmax), which is the degree of involvement obtained in the radiopharmaceutical 18-Fluor-labeled glucose-utilized positron emission tomography-computed tomography (PET-CT), which is widely used in locally advanced cervical cancer, and para-aortic lymph node positivity as a result of histopathology in the light of the literature.

Material and Methods: The pre-operative PET-CT results of 66 patients who had been examined and treated for locally advanced (Stage IB3-IVA) cervical cancer between 2015 and 2020 were retrospectively examined and the relationship between the SUVmax values and para-aortic lymph node positivity in the histopathology results was evaluated. Patients with SUVmax 4≤ in PET-CT were accepted to have para-aortic lymph node involvement. In terms of para-aortic lymph involvement, a cross tabulation was created with PET-CT results and the final pathology, which is the gold standard, and the sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were calculated.

Results: The mean age of 66 patients included in our study was 48.2±13.2 years. The majority of our patients were at stage 1B3 (36.4%), while eight were at stage 3C2P. While para-aortic evaluation was performed through the laparoscopic method in 36 (54.5%) patients, it was performed by laparotomy in the remaining 30 (45.5%) patients. When the complaints of the patients were assessed, it was seen that the highest rate was that of post-coital bleeding in 32 patients (48.5%) and pelvic pain was observed in two patients (3%). The mean body mass index (BMI) was 22.69±4.14 and the squamous type was the most common in 44 patients (66.7%) in terms of histopathological typing. When we evaluated the results of 66 patients, the prevalence rate was around 12% and when we compared the SUVmax uptake rates found in PET-CT, which we used as a new diagnostic test with the pathology results, which is our gold standard test, the sensitivity and specificity rates were 50% and 48%, respectively. The PPV, the NPV, and accuracy were calculated as 11.7%, 87.5%, and 48.8%, respectively.

Conclusion: Considering the high risk of para-aortic lymph node metastasis in locally advanced cervical cancer through assessment of the high SUVmax values in PET-CT, it is necessary to confirm the status of the para-aortic lymph node with minimally invasive surgery in the foreground by experienced surgeons.

Keywords: Cervical cancer, para-aortic lymph node metastasis, PET-CT, SUVmax value.

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INTRODUCTION

Cervical cancer is the fourth most common female cancer among gynecological cancers in terms of morbidity and mortality.[1] Cervical cancer has lower incidence and mortality rates compared to uterine corpus and ovarian cancer as well as many other organ cancers. However, cervical cancer still remains an important cause of increased morbidity and mortality in female cancers in countries that do not have access to screening and prevention programs. Human papilloma virus is the main cause of cervical neoplasia and can be detected as the main factor in 99.7% of cervical cancers.[2] While the most common histological types of cervical cancer are the squamous cell types with a rate of approximately 70%, 25% are adenocarcinomas, and 5% are other rare types.[3]

Cervical cancer has traditionally been clinically staged, but surgical and radiological evaluation is part of staging after 2018 to detect pelvic and para-aortic lymph node involvement.[4–7] Surgery and post-operative histopathological evaluation and radiological staging provide important information that may affect the treatment.[8] It may be better and more practical to assess locally advanced disease (i.e., tumor size, vaginal, and parametrial involvement), especially since it is an easier and more accessible method in low-income areas where cervical cancer continues to be the most common malignancy among women. Thus, morbidity and mortality related to surgery are avoided in patients who are not candidates for surgical treatment.[9] The tumor stage is determined during the primary diagnosis of cervical cancer and does not change even when prognostic factors that increase the risk of recurrence after treatment are determined. This is also true for other gynecological cancers. Correct pre-treatment staging of cervical cancer is critical as it determines both surgical and medical treatment and the prognosis.

Cervical cancer increases the mortality and morbidity by causing more distant metastatic lesions as well as pelvic or para-aortic lymph node involvement. Historically, surgery with lymphadenectomy was required to evaluate lymph node metastases in cervical cancer. However, today, lymph node dissection, imaging methods, or both are used to evaluate lymph node metastases. The presence of lymph node involvement is the most important factor determining the prognosis in cervical cancer and is associated with a worse prognosis. Determining the stage by diagnosing lymphatic and distant metastases and planning the treatment of the cases accordingly are the most important factors in the prognosis, and in particular, detection of local advanced stage and metastatic cancer by pre-operative imaging methods affect the decisions regarding radiotherapy. Thus, be it laparotomy or laparoscopic surgery, the associated mortality and morbidity are decreased.[10]

We evaluated our cases diagnosed with local advanced stage cervical cancer, who had undergone pre-operative fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) and operated and histopathologically examined for staging, through histopathological comparisons, which is accepted as gold standard, with PET-CT. We aimed to discuss the dilemma of the use of FDG PET-CT to detect para-aortic lymph node involvement in the light of the literature.

MATERIAL AND METHODS

Approval was obtained from the ethics committee of our hospital for 66 cases who had been examined and treated for locally advanced (stage IB3-IVA) cervical cancer between 2015 and 2020. The study was evaluated by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee and was approved under the decision number KAEK-21 (date: 13.01.2021). Subsequently, the pre-operative FDG PET-CT maximum standardized uptake value (SUVmax) values and the histopathology results were evaluated retrospectively; the relationship between FDG PET-CT SUVmax reference value of 4 and above and below 4 with histopathological para-aortic lymph node positivity was evaluated. Sixty-six patients with a mass size of 4 cm and above, from Stage IB3 to IVA, where there is adjacent organ mucosa involvement according to The International Federation of Gynecology and Obstetrics (FIGO) 2018 staging, and who had undergone para-aortic lymph node dissection by either the laparoscopic technique or laparotomy, were included in our study. Two cases with early Stages IA and IB1, Stage IVB cases with distant metastasis and patients who did not continue their examination and treatment or who had not undergone histopathological sampling, were not included in the study.

The histopathological, demographic, and clinical characteristics of the cases were evaluated according to age, gravidity, parity, contraceptive use and methods, smoking status, first application complaints, BMI, and the cervical biopsy results.

While all patients were therapeutically given simultaneous cisplatin (40 mg/m^2), with extended-field radiotherapy to patients with positive para-aortic lymph node involvement, patients with lymph node negativity received pelvic radiotherapy.

After the treatment, in the first 2 years, the patients were followed-up every 3 months with cervical cytology and physical examination, pelvic examinations were carried out and the controls were continued every 6 months for the next 3 years. During the follow-up, pelvic examination, transvaginal or transabdominal ultrasonography, serum tumor markers evaluation, and radiological evaluations were performed in all cases.

For the descriptive statistics, the mean, standard deviation, median, min-max values, and frequencies were used considering whether there was a normal distribution or not. The categorical data were expressed in numbers and percentages (%). For the numerical data, Mann–Whitney U-test was used according to the normal distribution status. Patients with SUVmax ≤4 in PET-CT were accepted as having para-aortic lymph node involvement. The PET-CT results in terms of para-aortic lymph node involvement, and the final pathology results, which is the gold standard, were cross-tabulated and the sensitivity, specificity, PPV, and NPV were calculated. The Statistical Package for the Social Sciences 23 program was used to analyze the data. P values in all tests of lower than 0.05 were considered statistically significant.

RESULTS

The mean age of the 66 patients included in our study was 48.2±13.2 years. The gravity and parity evaluation of the patients showed that there was 1 case who had no pregnancy and no delivery, and all deliveries had been carried out through normal vaginal delivery. It was

determined that 36 patients (54.5%) did not use any contraceptive method and 54 patients were smokers and smoked at least 8 pack-years and 32 pack-years at most. When the presenting complaints of the patients were examined, it was seen that the highest rate was 32 patients (48.5%) with post-coital bleeding and two patients (3%) with pelvic pain. The mean BMI was 22.69±4.14 and the squamous type was the most common in 44 patients (66.7%) in terms of histopathological typing, followed by adeno-type in 18 patients (27.2%) (Table 1). Most of the patients were at Stage 1B3 (36.4%), and eight patients were at Stage 3C2P. While para-aortic evaluation was made using the laparoscopic method in 36 (54.5%) patients, it was made through laparotomy in the remaining 30 (45.5%) patients.

When we examined the number of para-aortic lymph nodes removed, the median for laparoscopy was found to be 7 (min: 0-max: 18) and 5 (min: 0-max: 13) for laparotomy. However, there was no statistically difference between the two groups (p:0.569).

When all of the SUVmax values in the FDG PET-CT of our 66 patients included in the study were evaluated, the mean value of 4 was accepted as reference, and in all calculations, a value of 4 and above was accepted as high risk for para-aortic lymph node positivity, while values below 4 were considered normal. When we evaluated the results of 66 patients, the prevalence rate was around 12.1% and when we compared the SUVmax uptake rates found in PET-CT, which we used as a new diagnostic test, with the pathology results, which is our gold standard test, the sensitivity and specificity rates were 50% and 48%, respectively. The PPVs and NPVs and the accuracy were calculated as 11.7%, 87.5%, and 48.8%, respectively. In addition, while our false positivity rate was 51%, our false negativity rate was calculated as 50% (Table 2).

Table 1: Clinical and demographic characteristic risk factors of the patients

	n	Mean/Median	SD/Min-Max/%
Age		48.2	±13.2
Gravidity		3	0–10
Parity		2	0–7
Contraception			
No	36		54.5
OC	20		30.3
IUD	10		15.2
Smoking			
Yes	54	16 (pack year)	8–32
No	12		
Complaint			
Post-coital bleeding	32		48.5
Vagial discharge	30		45.5
Menometroragy	2		3
Pelvic pain	2		3
BMI	33	22.69	±4.14
Histological type			
SCC	44		66.7
Adenocarcinom	18		27.2
Others	4		6.1
Stage			
1B3	24		36.4
2A2	8		12.1
2B	9		13.6
3A	1		1.5
3B	4		6.1
3C1P	10		15.2
3C2P	8		12.1
4A	2		3.0
Surgical type			
L/S	36		54.5
L/T	30		45.5
Number of para-aortic lymph nodes			
L/S		7 (0–18)	p=0.569
L/T		5 (0–13)	

SD: Standard deviation; OC: Oral contraseption; BMI: Body mass indeks; SCC: Skuamous cell cancer; IUD: Intra uterine device; L/S: Laparoscopy; L/T: Laparotomy.

DISCUSSION

In particular, patients with Stage IB3 and IVA disease are considered to be locally advanced stages, and it is necessary to clearly demonstrate lymph nodes and distant organ or system involvement to plan their treatment in detail with the least complication rates. In recent years, FDG PET-CT, which is a method based on the uptake and metabolic activity of the labeled glucose, FDG, by the lymph nodes, tumor cells, and metastatic foci, has emerged as a new method on the basis of CT scanning, which is one of the imaging methods to ensure less surgical complications.

The superiority of FDG PET over other imaging methods has been demonstrated in a meta-analysis of 72 studies including 5042 women, which reported the following sensitivities and specificities for detecting lymph node metastases: PET (sensitivity: 75% and specificity: 98%), magnetic resonance imaging (MRI) (sensitivity: 56% and specificity: 93%), and CT (sensitivity: 58% and specificity: 92%).[11] Compared to CT alone, PET-CT was found to be significantly sensitive in terms of diagnosis, treatment, and prognosis, especially in determining the width of radiotherapy areas and showing lymph node metastases, which is the most important risk factor affecting recurrence and disease-free survival.[12]

Although FDG PET-CT is the most accurate imaging examination for lymph node evaluation, it should be kept in mind that the rates of false-negative diagnosis are high.[12,13] As an example, in a study in 60 patients with Stage IB2 to IVA disease, 12% of those without positive para-aortic node findings on PET-CT were found

Table 2: Comparison of PET-CT and histopathological results

	Histopathological results		
PET-CT Results	**Positive**	**Negative**	**Total**
Positive (suvmax≥4)	4	30	34
Negative (suvmax<4)	4	28	32
Total	8	58	

Sensitivity: 50%; Specificity: 48%; Positive predictive value: 11.7%; Negative predictive value: 87.5%; Accuracy: 48.5%; False positive rate: 51%; False negative rate: 50%. PET-CT: Positron emission tomography-computed tomography.

to have histopathologically positive para-aortic nodes.[12] A higher rate of pathologically positive para-aortic disease was observed in a subgroup of patients with PET-CT findings with positive pelvic and negative para-aortic nodes (22%). In another PET-CT study and pathological analysis of para-aortic nodes, patients with PET-positive pelvic nodes were more likely to have surgically confirmed para-aortic lymph node metastases than patients with PET-negative pelvic nodes (24% vs. 3%).[14]

In 1950, after William Sweet and Gordon L. Brownell, Chief of Neurosurgery Service at Massachusetts General Hospital, had seen the need for some new imaging methods that were more sensitive for imaging brain tumors, the idea that annihilation radiation should be used for imaging, especially after positron emission, emerged.[11,15] Since biology and anatomy are combined with this technology, which required a long time to develop and use in the health field, the diagnostic accuracy rates have increased. Thus, especially with presurgical imaging methods, complications related to primary surgery have been reduced and adjuvant or neoadjuvant treatment methods and their effectiveness have been increased. Furthermore, it supports the need for additional treatment or surgery in cases with recurrence after treatment.[16]

All cases diagnosed with cervical cancer have been recommended lymph node evaluation by FIGO and the American Cancer Joint Committee, and lymph node condition was added to the latest FIGO 2018 cervical cancer staging, according to the radiological imaging or histopathological evaluation results.[17]

With the latest revision, lymph node involvement has been very important in the FIGO staging and the prognosis, and survival is lower in patients with lymph node metastasis. The 5-year survival at all stages in patients with pelvic and para-aortic lymph node metastases is between 19% and 60%.[18,19] Therefore, evaluation of lymph nodes, especially with imaging methods, is important in determining the prognosis of the disease and choosing the treatment in terms of the disease stage and related recurrence and disease-free survival.

In our study, we found that the sensitivity of FDG PET-CT to be 50% and this was compatible with the range of 30–93% reported in the literature, but the specificity, that is, the rate of finding para-aortic lymph node involvement negativity was 48%, and this rate was lower than the rates in the literature. The reason for this discrepancy can be considered as the retrospective design of our study and the non-targeted evaluation of the radiological findings of the patients, and these values were compared with histopathology results. We can say that if the SUVmax values of FDG PET-CTs had been obtained for the target of detecting para-aortic lymph node and the evaluation had been made accordingly, these values would be much higher and more compatible with the literature.

In the literature, PET-CT revealed lymph nodes larger than 10 mm better than both MRI and CT with a false negative rate of 4–15%. These conditions should be taken into consideration as false positivity is particularly present where there is a high incidence of tuberculosis, sarcoidosis, lymphoma, and HIV that cause lymphatic reactivity.[20]

Nowadays, with the advances in minimally invasive procedures, it may be more rational to surgically evaluate para-aortic lymph nodes. In addition, revealing the para-aortic lymph node status surgically by either laparoscopy or laparotomy has a better prognosis than radiological exclusion and has been accepted as the gold standard,[21] since it is clear that some patients will demonstrate a disruption in their actual staging and treatment due to the absence of radiological imaging and high false negativity. In the only randomized controlled UTERUS-11 study comparing surgical and radiological staging in advanced cervical cancer, 33% of the patients were shown to be at high stage as a result of laparoscopic staging. In the same study, both short-term and long-term survival was better in patients who had underwent laparoscopy, although it was not statistically significant. It was emphasized that performing laparoscopy on the patients in this study did not delay the chemoradiotherapy.[22]

Our study revealed that histopathological lymph node positivity was determined in 50% of the cases, who were found to be negative on FDG PET-CT. In other words, it turns out that our accuracy rate was around 50%, so that one out of two patients with positive para-aortic lymph nodes could not be detected and pre-operative evaluation should be performed precisely in the direction of imaging. However, we can confidently say that despite the low rate of detecting positive patients, our rate of detecting true negative patients was as high as 87.5%, and in this case, when we accept the SUVmax value of 4 and above in FDG PET-CT as a reference, our rates of finding true negatives are compatible with the literature and are high.

The limitations of our study comprise the fact that our study was conducted retrospectively and the targeted SUVmax values were not evaluated. Furthermore, the effect of SUVmax values on the treatment results, local control and survival was not investigated. However, histological confirmation of lymph node metastasis is the most important aspect of our study, and to avoid the complications of surgery and planning of extended-field radiotherapy, the evaluation of lymph node in locally advanced cervical cancer can be made according to its spread in imaging studies. In addition, in patients with lymph node involvement in FDG PET-CT, surgical lymph node dissection may have a decreasing effect on disease-free survival and overall survival, but this should be investigated.

CONCLUSION

In locally advanced cervical cancer, high SUVmax values and particularly, the high risk for para-aortic lymph node metastasis should be taken into consideration. However, the para-aortic lymph node status should be confirmed by experienced specialists in the foreground with minimally invasive surgery.

Statement

Ethics Committee Approval: The Akdeniz University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 13.01.2021, number: KAEK-21).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – MSB, ÖB; Design – MSB, ÖB; Supervision – HAT, SD, TŞ; Resource – CK, ÖB; Materials – CK, HAT, SD; Data Collection and/or Processing – MSB, ÖB, CK; Analysis and/or Interpretation – SD, MSB; Literature Search – MSB, ÖB, TŞ; Writing – MSB, ÖB, CK; Critical Reviews – TŞ, SD, HAT.

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ORIGINAL ARTICLE

Evaluation of the relationship between method of delivery and breastfeeding characteristics

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ABSTRACT

Objective: Many factors affect breastfeeding such as maternal method of delivery. The objective of this study was to evaluate the relationship between delivery method and breastfeeding characteristics.

Material and Methods: This study was conducted between January and May 2019. A total of 210 mothers were analyzed who were registered in the Child Health and Diseases Outpatient Clinic and were still breastfeeding at the time of enrollment. A 28-item questionnaire survey was administered to the participants regarding their family's socio-demographic characteristics, delivery method, and breastfeeding characteristics.

Results: Of the participants, 79 (37.6%) and 131 (62.4%) gave birth by vaginal delivery (VD) and by cesarean delivery (CD), respectively. A total of 55 (69.6%) mothers had VD breastfed their baby within the first ½ h of birth. The difference between the time of initial breastfeeding and the delivery method was statistically significant ($p<0.001$). A significantly higher proportion of babies born by VD (94.9%) received breast milk as their first food than babies born by CD ($p<0.001$). Moreover, significantly higher proportion of mothers who had VD exclusively breastfed their baby at 6 months than mothers who had CD ($p<0.001$).

Conclusion: This study found that the delivery method has a significant effect on breastfeeding characteristics, such as the time of initial breastfeeding and exclusive breastfeeding.

Keywords: Breastfeeding, breast milk, cesarean delivery, vaginal delivery.

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INTRODUCTION

Breast milk is the only suitable food for healthy babies up to 6 months after birth. Breastfeeding is beneficial in many ways for both the mother and the baby. Mothers are advised to start breastfeeding within 1 h of birth, to continue exclusive breastfeeding for the first 6 months, and to continue breastfeeding for at least 2 years.[1,2] However, many factors affect breastfeeding; one of these factors is the maternal method of delivery.[3]

Cesarean delivery (CD) is applied with high frequency in many parts of the world. Its morbidity and side effects are higher than those of vaginal delivery (VD) for both mothers and neonates.[4] Notably, medically unnecessary CDs are a global concern.[5] Although a clear consensus on the level of CD frequency is lacking, a consensus that its current frequency is too high to be explained by medical reasons does exist.[6–8] With the increase in the number of CD procedures being performed, research into the adverse health effects of CD is also increasing. A systematic review and meta-analysis study reported that early initiation of breastfeeding after an elective CD significantly reduced compared with that after VD, although it did not find any difference between emergency CD and VD on this parameter.[9] By contrast, another study determined that CD was associated with low risk of discontinuation of exclusive breastfeeding before 6 months postpartum.[10] In addition, a recent study in Turkey showed that the rate of exclusively breastfeeding babies born by CD was significantly higher than that of exclusively breastfeeding babies born by VD at 6 months.[11] These results show that the relationship between CD and breastfeeding characteristics remains contradictory. The objective of this study was to evaluate the relationship between delivery method and breastfeeding characteristics.

MATERIAL AND METHODS

This study was approved by the Clinical Research Ethics Committee (approval no. 18/347; approval date: 02/10/2019) and was conducted between January and May 2019. We analyzed 210 mothers who were registered at the Child Health and Diseases Outpatient Clinic and were still breastfeeding at the time of enrollment. Babies who did not have any health problems were included in the study.

We administered a 28-item questionnaire survey regarding the participants' family socio-demographic characteristics, delivery method, and breastfeeding characteristics. We recorded demographic data, including age, educational status, employment, and income status of the mothers and fathers. Moreover, we collected information about the delivery method, first food given to the babies, time of initial breastfeeding, duration of exclusive breastfeeding, and total breastfeeding time. Mothers who have not yet completed 2 years of breastfeeding were asked whether they intended to continue breastfeeding up to 2 years. The participants were informed about the research and asked to provide their verbal consent to participate in it, in accordance with the Declaration of Helsinki. They anonymously completed the questionnaire.

Statistical Analysis

Statistical analysis was performed with SPSS 20.0. The Kolmogorov-Smirnov test was used to evaluate normal distribution of the continuous variables. Descriptive data were expressed as number (percentage), mean±standard deviation, or median (range). The Pearson χ^2 test and Fisher exact test were used for categorical variables. P<0.05 was considered statistically significant.

Table 1: Baseline characteristics of parents

	Mothers	Fathers
Age, mean±SD	27.9±3.3	29.0±3.7
Education (years)		
≤8	61 (29.0%)	48 (22.9%)
≥9	149 (71.0%)	162 (77.1%)
Employment status		
Not working	155 (73.8%)	4 (1.9%)
Working	55 (26.2%)	206 (98.1%)
Income status		
<Minimum wage* TL	17 (8.1%)	
Between minimum wage and 5000 TL	102 (48.6%)	
>5000 TL	91 (43.3%)	

SD: Standard deviation; *: Minimum wage was accepted as 2.020,90 TL; TL: Turkish Liras.

RESULTS

The mean age of the 210 mothers was 27.9±3.3 years, while that of the fathers was 29.0±3.7 years. The difference between VD and CD in terms of mean maternal age was not significant (p=0.329). The mean age of the babies was 8.06±2.88 months, and 80 (38.1%) of them had at least one sibling. A total of 149 (71.0%) mothers and 162 (77.1%) fathers had high school or higher education. Moreover, 55 (26.2%) mothers were working, while four (1.9%) fathers were not working (Table 1).

Seventy-nine (37.6%) mothers gave birth by VD, and 131 (62.4%) mothers gave birth by CD. Of those who gave birth by CD, 90 (60.4%) had high school or higher education (≥9 years) and 42 (76.4%) were working. The difference between the educational status and income status of the parents and the delivery method was not significant (p<0.05).

Seventy-nine (37.6%) mothers had breastfeeding experience. Of all the mothers, 166 (79.0%) stated that the first food given to their baby after birth was breast milk; in contrast, 44 (21.0%) reported that the first food given to their baby was infant formula. A significantly higher proportion of babies born by VD (94.9%) received breast milk as their first food than babies born by CD (p<0.001). A higher proportion of mothers who had CD used infant formula than mothers who had VD (p<0.001).

Fifty-five (69.6%) mothers had VD breastfed their baby within the first ½ h of birth. In total, 75 (94.9%) mothers had VD and 49 (37.4%) who had CD breastfed their baby within the 1st h of life (p<0.001). The difference between the time of initial breastfeeding and the delivery

Table 2: Distribution of breastfeeding characteristics according to delivery type

	VD		CD		p
	n	%	n	%	
Breastfeeding initiation					<0.001
≤One hour	75	60.5	49	39.5	
>One hour	4	4.7	82	95.3	
Infant formula (as first food)					<0.001
No	75	45.2	91	54.8	
Yes	4	9.1	40	90.9	
Exclusive breastfeeding					0.001
<Six months	27	26.0	77	74.0	
≥Six months	52	49.1	54	50.9	
Two years breastfeeding					0.025
<Two years	29	29.6	69	70.4	
≥Two years	50	44.6	62	55.4	
Previous breastfeeding experiences					0.934
No	49	37.4	82	62.6	
Yes	30	38.0	49	62.0	
Feels competent about breastfeeding					0.017
No	27	28.7	67	71.3	
Yes	52	44.8	64	55.2	

VD: Vaginally delivery, CD: Cesarean delivery.

method was significant (p<0.001). One hundred and six (50.5%) infants were exclusively breastfed for the first 6 months of life. Fifty-two (65.8%) mothers who had VD fed their baby only breast milk during the first 6 months after birth, and this rate was significantly higher than that among the mothers who had CD (p<0.001). The difference between breastfeeding experience and delivery method was not statistically significant (p=0.934). Furthermore, 52 (44.8%) mothers who had VD felt competent in terms of breastfeeding (p=0.017) (Table 2).

DISCUSSION

This study investigated whether delivery type affects breastfeeding characteristics. The rates of exclusive breastfeeding at 6 months may differ between countries. According to the 2020 US Centers for Disease Control and Prevention Breastfeeding Report Card, only 25.6% of infants were exclusively breastfed up to 6 months.[12] Moreover, in 2018 and 2016, the rates of infants exclusively breastfed at 6 months were 25.5% and 22.3%, respectively.[13,14] Although the rate of breastfeeding at 6 months has shown a tendency to increase, it is still at a very low level. However, a recent study found that the exclusive breastfeeding rate up to 6 months in Turkey increased from 28.2% in 2013 to 46.0% in 2017.[15] In the present study, half the infants received breast milk exclusively for the first 6 months of life, which is contrary to the findings of the US Centers for Disease Control and Prevention, whereas it is similar to the findings reported in the above-cited study. Contrarily, it should be considered that the other half of the infants could not be exclusively breastfed up to 6 months. In light of this, issues that prevent breastfeeding for 6 months should be further discussed, and efforts should be made to resolve them. The previous studies have reported that CD has a negative effect on breast milk intake.[9,16–18] In accordance with the literature, we found that the rate of exclusive breastfeeding up to 6 months among mothers who had VD was higher than that among mothers who had CD.

CD is one of the major hurdles to early initiation of breastfeeding in hospital-born babies.[19] One study reported that VD was 2.78 times more highly associated with early initiation of breastfeeding than CD.[20] Delay in breastfeeding initiation causes some health problems in infants. A large cohort study showed that, compared with the risk of death among babies who started breastfeeding within the 1st h of birth, the risk of death among neonates who started breastfeeding between 2 h and 23 h after birth was 41%, whereas that among neonates who started breastfeeding between 24 h and 96 h after birth was 79%.[21] In a meta-analysis study of data collected from 33 countries, CD was reported to have negative effects on early initiation of breastfeeding.[22] In the present study, breastfeeding within the first ½ h of birth and that within the 1st h of birth were compared to the delivery method. The results of the present study showed that the frequency of breastfeeding in both the first ½ h and the 1st h of life was higher in the mothers who had VD than in the mothers who had CD.

Mothers' decision to start and continue breastfeeding can be influenced by many factors, and problems encountered in the initial stage of breastfeeding can influence their decision to either continue breastfeeding in the long term or stop breastfeeding completely.[23,24] Moreover, we evaluated the duration of total breastfeeding for at least 2 years relative to the delivery method. Most mothers who breastfed for <2 years gave birth by CD.

The present study had several limitations. First, maternal indications for CD and type of anesthesia used during CD were not reported. These parameters can affect postpartum breastfeeding characteristics. Second, the intention of mothers who have not yet completed 2 years of breastfeeding was recorded. This could have affected the overall results for the 2-year breastfeeding period that was analyzed.

CONCLUSION

This study found that the method of delivery significantly affects breastfeeding characteristics, such as the time of initial breastfeeding and exclusive breastfeeding. Pregnant women should be informed about all the possible side effects of CD, especially those involving breastfeeding. In addition, all expectant mothers should be encouraged to breastfeed within the 1st h of birth and to exclusively breastfeed for 6 months.

Statement

Ethics Committee Approval: The Bezmialem Vakıf University Clinical Research Ethics Committee granted approval for this study (date: 02.10.2019, number: 18/347).

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

Peer-review: Externally peer-reviewed.

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

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

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ORIGINAL ARTICLE

The role of functional platelet indices in dietary monitoring of children with celiac disease

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ABSTRACT

Objective: Determining the value of platelet count, mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW) on histologic disease stage and compliance to gluten-free diet (GFD) in children with celiac disease (CD).

Material and Methods: Children diagnosed as CD and healthy subjects were recruited. CD patients were classified into two groups: Newly diagnosed and on GFD for over 1 year. CD patients on GFD were further divided into two groups according to their dietary adherence determined by anti-tissue transglutaminase IgA levels. Samples for complete blood count were obtained from all participants.

Results: A total of 236 CD patients (60 newly diagnosed, 83 with good GFD adherence, and 93 with poor GFD adherence, mean age: 11±3.9 years, 59.3% female) and 92 healthy subjects (mean age: 10.7±3.8 years, 52.2% female) were studied. Platelets, MPV, PCT, and PDW values of newly diagnosed CD and poor GFD adherence cases were statistically similar ($p>0.05$) while they were statistically higher than the controls and good GFD adherents ($p<0.01$). In ROC analysis, MPV had the highest area under the curve (0.758). The sensitivity and the specificity of MPV were 70.3% and 71.7%, respectively, for the cutoff value of 8.65 fL. Only PCT was found correlated with modified Marsh stage in newly diagnosed CD patients (r^2: 0.302, $p<0.05$).

Conclusion: This is the first report about platelet functions in children with CD. Functional platelet indices, especially MPV and PCT, would be a promising tool for indirect determination of GFD adherence and villous atrophy stage, respectively, at a low cost compared to other modalities.

Keywords: Celiac disease, children, gluten-free diet, mean platelet volume, plateletcrit.

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INTRODUCTION

Celiac disease (CD) is an autoimmune condition triggered by gluten and other environmental factors in genetically susceptible individuals. Permanent gluten ingestion eventually results in progressive lymphocytosis, villous atrophy, and inflammation in the small intestine, which leads to small intestinal malabsorption. Dietary elimination of gluten is the only approved therapeutic approach at the moment. Reversal of malabsorptive signs and symptoms can be achieved by a strict gluten-free diet (GFD). However, a reliable marker quantifying dietary compliance does not exist.[1] The gold standard is repetitive duodenoscopies which are too invasive and impractical. Despite their high accuracy for individuating the subjects needing a diagnostic biopsy, serological tests lack reliability after diagnosis. The autoantibody titers do not correlate well with histological amelioration or CD patients' symptoms on a GFD.[2] Immunoglobulin (Ig)A- and IgG-class tests usually take up to 24 months to normalize after gluten elimination from the diet.[3] The autoantibodies' somewhat long half-life can explain whether these titers reflect the immune response to gluten rather than the direct intestinal injury. Moreover, small, infrequent, or intermittent exposures to gluten cannot be detected by such serological tests in the clinical setting.[4]

Cytokines such as interleukin (IL)-3 and IL-6 induce megakaryocytes to produce young platelets during inflammation.[5] Young platelets are more reactive and more prominent in size. An elevation in serum IL-6 levels was reported previously in CD, which was highly correlated with mucosal injury severity.[6] In this context, elevated IL-6 would trigger the young platelet synthesis. Consequently, as well as the platelet quantity, qualitative platelet indices such as mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution with (PDW) will be affected. These parameters are frequently provided in the complete blood count (CBC) examination reports; nevertheless, they are still overlooked by most clinicians. A recent study suggests MPV as a promising biomarker for monitoring dietary compliance in CD adults.[7] Pediatric data do not exist. Our purpose is to investigate the relationship between qualitative platelet indices and mucosal damage, and compliance to GFD in CD children.

MATERIAL AND METHODS

The current study evaluated the medical CD database of the Pediatric Gastroenterology outpatient clinic of the University of Health Sciences, Zeynep Kamil Women and Children's Training and Research Hospital, between January 2018 and 2021. The study protocol was approved by the hospital's Ethics Committee (17.03.2021, decision no:77). The CD diagnosis was established following the recommendations of the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition; therefore, "no biopsy" approach was not utilized.[8] Demographic, clinical, and laboratory data of CD children were extracted from the database. Newly diagnosed cases and subjects under GFD for a minimum period of 1 year were included in the study group. Subjects under GFD were further classified according to their GFD compliance. Serum tissue transglutaminase (TTG) IgA (Anti-TTG IgA ELISA kit, Euroimmun AG, Lübeck, Germany) level under 20 RU/mL was accepted as a marker of good GFD compliance. The control group was generated by otherwise healthy and non-CD siblings and/or cousins of the newly diagnosed CD subjects. Their laboratory data were obtained during family screening. Platelet count, MPV, PCT, and PDW data were extracted from CBC reports, analyzed by a Beckman Coulter analyzer.

The CD's severity was graded histologically by the modified Marsh classification (Marsh) in newly diagnosed individuals.[9] The study's exclusion criteria include inadequate patient data, potential CD, selective IgA deficiency, current fever or acute/chronic inflammatory/infectious state, diabetes mellitus, giardiasis, cerebral palsy, and the presence of any hepatic, metabolic, cardiac, or renal disease.

Data were analyzed using SPSS software (IBM SPSS version 20, IBM Corp., New York, USA). Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as numbers or percentages. The Shapiro–Wilk test tested the normality of the data. The one-way analysis of variance or Mann–Whitney U-test was used to compare groups where appropriate. For metric variables, Pearson's correlation coefficients were computed. Calculated $p<0.05$ indicated statistical significance.

RESULTS

Among 374 individuals, 328 cases (236 CD cases and 92 controls) fulfilling the inclusion criteria were studied. The excluded subjects were: Eight with inadequate data, three with potential CD, six with giardiasis, four with selective IgA deficiency, 14 with fever or acute/chronic inflammation, six with diabetes mellitus, and five cases with a chronic disease were excluded from the study. The mean age and the gender distribution were indifferent between the study group and the controls (11.0±3.9 years vs. 10.7±3.8 years, 59.3% vs. 52.2%, $p>0.05$, respectively). In the study group, 60 cases were newly diagnosed, and 176 were under GFD for more than 1 year. According to serum TTG IgA levels, the dietary compliance was classified as "good" in 83 and "poor" in 93 cases.

Mean thrombocyte, MPV, PCT, and PDW values of the groups are shown in Table 1. Thrombocytes, MPV, PCT, and PDW values of the newly diagnosed CD cases and individuals with poor GFD compliance were statistically similar ($p>0.05$). These values were also similar when the control group was compared with individuals with good GFD compliance ($p>0.05$). In contrast, a statistical difference was present when we compared newly diagnosed and poor GFD compliant cases with the control group and good GFD compliant cases, one by one ($p<0.01$). In ROC analysis, MPV had the highest area under the curve (0.758). The sensitivity and the specificity of MPV were 70.3% and 71.7%, respectively, for the cutoff value of 8.65 fL. Only PCT was found correlated with the modified Marsh stage of newly diagnosed CD patients (r^2: 0.302, $p< 0.05$).

DISCUSSION

According to our findings, platelet count, MPV, PCT, and PDW were significantly elevated in patients with newly diagnosed CD and poor GFD compliance compared to healthy controls and individuals with good GFD compliance. The main parameter was MPV, which had a sensitivity and specificity of 70.3% and 71.7%, respectively, for the cutoff value of 8.65 fL. Moreover, we found a correlation between the small intestinal mucosal injury and PCT. Since CD is a life-long chronic autoimmune disease, adequate adherence to GFD and rou-

Table 1: Mean thrombocyte, MPV, PCT, and PDW values of CD and control groups

Group	Thrombocytes (10^3/mL) (Mean±SD)	MPV (fL) (Mean±SD)	PCT (%) (Mean±SD)	PDW (fL) (Mean±SD)
Control	286.13±82.8	8.29±1.09	0.23±0.06	16.39±0.5
New diagnosed CD	380.12±98.7	9.23±1.34	0.26±0.05	15.2±1.6
CD good GFD compliance	288.14±66.3	8.48±1.03	0.24±0.04	16±0.9
CD poor GFD compliance	324.95±92.6	9.28±1.11	0.29±0.07	15.4±1.1

MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; CD: Celiac disease; GFD: Gluten-free diet; SD: Standard deviation.

tine outpatient follow-up are mandatory. Meanwhile, an established objective criterion to monitor dietary compliance is absent where the gold standard is the demonstration of histological improvement.[1–4] However, non-invasive methods such as serological tests are incapable of reflecting the actual histological injury status. One of the significant drawbacks of these antibody titers is the incapability of detecting small, infrequent, or intermittent exposures to gluten.[4] In some other autoimmune conditions, giardiasis, and other intestinal microbial disorders, the serology might be falsely positive and mimicking CD.[10] Quantifying gluten immunogenic peptides in CD patients' stool may help monitor adherence to a GFD.[10]

MPV, PCT, and PDW are straightforward indices that show the volume of platelets. These indices are obtained easily by a simple CBC order. Recently, many studies investigated a potential association between these platelet indices and inflammatory disorders such as systemic lupus erythematosus, Henoch-Schönlein purpura, hepatitis A, and acute bronchiolitis in children.[11–14] In these most recent pediatric studies, MPV was found elevated in systemic lupus erythematosus, Henoch-Schönlein purpura, and hepatitis A. In contrast, a reduction was present in cases with acute bronchiolitis. Despite these conflicting data, both high and low MPV levels might have a diagnostic and prognostic yield for disparate inflammatory disorders.

O'Grady et al.[15] compared the MPV levels between CD patients, splenectomized patients, and healthy controls. They discovered that CD patients with intact spleens had higher MPV values and platelet counts, similar to our results. However, the GFD adherence of the CD patients was not taken into account in that study. After three decades, Purnak et al.[7] studied MPV levels in newly diagnosed and under GFD CD subjects. They revealed that the elevated MPV values observed in newly diagnosed adult CD patients might reflect a continuing small intestinal mucosal injury. Moreover, they noticed a normalization in MPV levels with the introduction of GFD, which may specify a resolution in mucosal inflammation. Similar outcomes were achieved by extracting our data in children with CD. In addition, we found that PCT was elevated and correlated with mucosal damage in newly diagnosed CD children. This evidence should be further analyzed with prospective studies.

There are some limitations to this study that should be mentioned. Since this is a retrospective study, the results should be interpreted cautiously. Falsely elevated results induced by platelet-swelling should be avoided by studying the CBC samples within 2 h. However, we cannot guarantee this because of the retrospective nature of the study. Moreover, platelet indices might be affected by various factors which we excluded widely by our exclusion criteria. Therefore, we did not examine all patients for abnormal thyroid functions, hypercholesterolemia, and smoking which might affect the platelet size.

CONCLUSION

Our study suggests that measuring MPV levels exceptionally would be a practical, fast, and inexpensive choice to monitor children's dietary compliance with CD. Furthermore, a causal relationship between PCT and mucosal injury might exist, and oncoming prospective research is expected to clarify the exact mechanism's undisclosed pieces. We believe that together with serology, MPV and PCT might have a role in determining dietary adherence

Statement

Ethics Committee Approval: The Health Sciences University, Zeynep Kamil Women and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 17.03.2021, number: 77).

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

Peer-review: Externally peer-reviewed.

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

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ORIGINAL ARTICLE

Management of adnexal masses recognized incidentally during the cesarean: Our 5 years only central experience

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ABSTRACT

Objective: The objective of the study was to review our approach to adnexal masses detected incidentally during cesarean section and the data in the literature.

Material and Methods: This study was carried out by retrospectively scanning the files of patients who delivered by cesarean section between January 2015 and February 2020 in Süleyman Demirel University Faculty of Medicine Gynecology and Obstetrics Clinic. Patients with adnexal mass found in pre-operative examinations were excluded from the study. A total of 111 patients were included in the study.

Results: January 2015–February 2020 in our hospital between 3700 cesarean deliveries was realized one of them in their 111 (3% of cesarean births); adnexal mass was detected during cesarean section. Main patient age was 32.26±6.03 (18–43) and the mean pregnancy number was 1.95±1.07 (1–6). Cephalopelvic disproportion is the most common (32.4%) cesarean indication; previous cesarean (21.6%) was followed up in the second frequency. Mean week of gestation performed by cesarean was 37.09±2.39. The mean adnexal mass size was 2.77±1.73 (1–10 cm). Fifty (45.1%) of the adnexal masses were observed in the right adnexal area, 55 (49.5%) in the left adnexal area, and 6 (5.4%) were followed them bilaterally. While cyst excision was performed in 110 patients, oophorectomy was performed in one patient. Pathology of 1 (0.9%) patient was reported as malignant.

Conclusion: In pregnant women in the first trimester, obstetric ultrasonography performed routinely since both adnexal and should be examined in detail. Pelvic masses determined dimensions during cesarean section increases, whereas above 5 cm, especially torsion, hemorrhage or rupture must be removed because they have a risk of malignancy development.

Keywords: Cesarean section, incidental adnexal mass, ovarian cyst.

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INTRODUCTION

With the obstetric ultrasonography (USG) becoming a part of routine pregnancy follow-up, there has been an increase in the rates of adnexal mass detected during pregnancy. With this increase, the number of adnexal masses detected incidentally during cesarean section is too high to ignore due to the fact that the number of pregnant women without follow-up is still high. The incidence of adnexal masses detected during pregnancy varies between 1/100 and 1/8000.[1,2] The incidence of malignant adnexal masses detected during pregnancy is approximately 3%.[3] In this study, we aimed to reveal the characteristics of adnexal masses detected during cesarean section in our clinic in the past 5 years and their relationship with the pathology results and the literature.

MATERIAL AND METHODS

Data for adnexal masses detected during cesarean section in our clinic between January 2015 and February 2020 were retrospectively reviewed. The current clinical information of the patients was accessed using outpatient clinic notebooks, surgery notes, pathology records, and laboratory data. Demographic and clinical data such as maternal age, parity, laboratory findings, gestational week during cesarean section, cesarean indication, size and location of adnexal mass, intraoperative CA-125 value of patients with cyst, pathology result of the mass, pre-operative and post-operative hemoglobin values, and hospitalization time properties were recorded. Data analysis was done with SPSS for Windows 21.0 package program. Data of variables with normal distribution were presented as mean±SD.

RESULTS

Between January 2015 and February 2020, 3700 cesarean deliveries took place in our hospital, and in 111 of them (3% of cesarean deliveries), adnexal mass was detected during cesarean section.

The mean patient age was 32.26±6.03 (18–43), and the mean parity was 1.95±1.07 (1–6). Mean week of gestation performed by cesarean was 37.09±2.39. The mean post-operative hospital stay of the patients was 3.68±2.57 (1–19) days. The mean intraoperative CA-125 value requested from pregnant women with adnexal mass was 2.59±8.45 (0–50.2). The mean diameter of the incidentally detected adnexal mass was 2.77±1.73 (1–10 cm). The demographic characteristics and laboratory findings of the patients are presented in Table 1.

Cephalopelvic disorder is the most common (32.4%) cesarean indication; previous cesarean (21.6%) was the second and acute fetal distress was the third. The cesarean indications of the patients are presented in Table 2.

Thirty-nine (35.1%) of adnexal masses are in the left paratubal area, 30 (27%) of the mass are in the right paratubal area, 20 (18%) of them are in the right ovary, 16 (14.4%) of them are in the left ovary, and 6 (5.4%) of them are in the bilateral adnexal area mass watched. While cyst excision was performed in 110 patients, oophorectomy was performed in one patient. The pathology of 1 (0.9%) patient was malignant. No complications developed in any patient during post-operative follow-up. Considering the possibility of peritoneal spread of adnexal masses in all cases, the existing mass was removed without bursting. According to histopathological diagnoses, the most common cyst paramesonephric (paratubal) cyst was observed in 71 patients (64.5%). Afterward, mature cystic teratoma in 8 (7.3%) patients, serous cystadenoma in 8 (7.3%) patients, mucinous cystadenoma in 6 (5.5%) patients, corpus luteum cyst in 4 (3.6%) patients, hemorrhagic cyst in 3 (2.7%) patients, 3 inclusion cysts were observed in (2.7%) patients, endometrioma in 2 (1.8%) patients, fibroma in 2 (1.8%) patients, and mixed-type seromucinous cysts in 2 (1.8%) patients. Pathology result was reported as malignant mucinous borderline tumor in only 1 (0.9%) patient. The patients were followed up in the hospital for an average of 3 days. Post-operative antibiotic treatments were continued. The pathology results of the patients who were found to have an adnexal mass during cesarean section and were operated are shown in Table 3.

Table 1: Sociodemographic characteristics and laboratory findings of the patients

	Mean	Median	Min.	Max.	SD
Age	32.26	32.00	18.00	43.00	6.03
Day of lying	3.68	3.00	1.00	19.00	2.57
Parity	0.95	1.00	0.00	6.00	1.07
Pregnancy week	37.09	38.00	25.00	40.00	2.39
Ca125	2.59	0.00	0.00	50.20	8.45
Pre-operative hemoglobin	12.06	12.20	7.60	15.20	1.63
Post-operative hemoglobin	10.91	11.20	7.60	13.70	1.36
White blood cell	10.94	10.50	1.80	22.00	3.37
Cyst diameter (cm)	2.77	2.00	1.00	10.00	1.73

Min: Minimum; Max: Maximum; SD: Standard deviation.

Table 2: Cesarean indications

Indications	n	%
Repeated cesarean section	15	13.5
Old cesarean	24	21.6
CPD	36	32.4
NPL	10	9.0
IUGR	3	2.7
Placenta previa	2	1.8
AFD	18	16.2
Grand repeated cesarean	2	1.8
PUS	1	0.9

CPD: Cephalopelvic disorder; NPL: Non-progressive labor; IUGR: Intrauterine growth retardation; AFD: Acute fetal distress; PUS: Previous uterine surgery.

Table 3: Distribution of incidentally detected adnexal masses during cesarean section according to histopathological results

	n	%
Paramesonephric cyst	71	64.5
Luteal cyst	4	3.6
Mature cystic teratoma	8	7.3
Serous cystadenoma	8	7.3
Inclusion cyst	3	2.7
Mucinous cystadenoma	6	5.5
Mucinous borderline	1	0.9
Endometriotic cyst	2	1.8
Fibroma	2	1.8
Mixed serous+mucinous	2	1.8
Corpus hemorrhagicum	3	2.7

DISCUSSION

USG is a valuable diagnostic tool in detecting and evaluating adnexal masses during pregnancy. In contrast to early gestational weeks, the uterus in a pregnant woman in the third trimester may prevent accurate imaging and diagnosis. Adnexal pathologies can be missed because the assessment is focused on the fetus and placenta. While most of the adnexal masses are diagnosed in the first trimester during pregnancy, their frequency decreases as they approach the time of delivery.[4] It has been reported that adnexal masses occur at a rate of 1% during pregnancy.[1] Most of these masses are simple cysts or corpus luteum cysts, usually under 5 cm and disappear spontaneously until the 16th week of pregnancy.[5] However, some adnexal masses can persist and 1–3% of them can be malignant. Most of the adnexal masses seen during pregnancy are asymptomatic and the most common symptom is pain. With the advancement of gestational age, adnexal masses can also be pushed upward in parallel with the growth of the uterus or they may rarely cause dystocia at birth by squeezing in the pelvis.[6] In the study conducted by Baser et al.,[7] 61.6% of women with adnexal mass during pregnancy came to regular pregnancy follow-ups, and more than half were diagnosed with adnexal mass incidentally during cesarean section. In our study, patients who applied to our hospital in the term period close to birth, who were indicated for cesarean due to obstetric reasons, and who were found to have an adnexal mass incidentally during cesarean were included in our study. Therefore, there was no information in their files about prenatal antenatal follow-ups and pre-operative adnexal masses.

USG; it is the first-line imaging method used in the diagnosis and follow-up of adnexal masses in pregnancy. With transabdominal or transvaginal ultrasound, we can monitor the size of the mass, as well as vascularization, examination of other ovarian and peritoneal structures, and findings that support malignancy such as the presence of acid.[8] Color Doppler USG can help us differentiate between malignant and benign by evaluating the vascularization of adnexal mass. However, magnetic resonance imaging is helpful in understanding the mass originating from the uterus or ovary, evaluating its relationship with surrounding tissues, and evaluating the retroperitoneum or lymph nodes due to the difficulties created by the enlarged uterus in differential diagnosis, especially after the 20th week of gestation.[9]

Tumor markers are not very helpful in diagnosing adnexal mass in pregnancy. Because markers such as lactate dehydrogenase, alpha fetoprotein, β-human chorionic gonadotropin and cancer antigen 125 (CA-125) already increase physiologically during pregnancy and their diagnostic values decrease. Especially, CA-125 physiologically increases up to 1250 U/mL in the first trimester of pregnancy and regresses to 35 U/mL at term.[10]

In a retrospective study conducted by Ulker et al.[11] in 2010, adnexal mass was found incidentally during cesarean in 119 patients, and the incidence of these masses was reported as 1/329.In our study, the rate of adnexal mass detected and excised during cesarean section is 3/100 and is more common than in the literature. Because in our study, cysts were detected and removed in the paratubal area in 71 patients (64.5%).

Most of the adnexal masses detected during pregnancy regress spontaneously as they approach the term. However, growing and persistent masses have a rare risk of torsion, hemorrhage, rupture, and malignancy.[12] Cyst rupture and torsion are acute complications that require urgent surgery during pregnancy. Struyk and Treffers[13] performed emergency surgery in 9% of 90 pregnant women who were followed up with adnexal mass due to cyst rupture and 12% due to torsion. They reported that the rates of preterm birth and abortion in pregnant women who underwent emergency surgery were higher than those who underwent planned surgery. They emphasized that for adnexal masses that do not regress for 10 cm or more, surgery should be planned between 16 and 18 weeks of pregnancy and the cysts should be removed without waiting for the term period. In our study, the largest of the adnexal masses detected incidentally during cesarean section was 10 cm in size and none of the patients had complications such as torsion, rupture, or hemorrhage, and cesarean was planned for obstetric reasons. In addition, when the pre-operative and post-operative hemoglobin levels of the patients are compared; none of the patients had bleeding that was more than expected or at a level that would require blood transfusion. There are many approaches in the literature regarding the management of adnexal masses detected incidentally during cesarean section.

In the study of Thornton and Wells, it has been shown that all ovarian cysts 5 cm and below regress spontaneously.[14] They emphasized that the cystectomy performed simultaneously during the cesarean section did not cause any additional complications to the patient.[15]

In a comprehensive study by Bernhard et al.,[16] adnexal masses detected during pregnancy were followed up with serial ultrasound and examinations, and it was observed that only 6% of masses of 6 cm and below did not regress spontaneously and continued to exist until term. They found this rate around 40% for masses of 6 cm and above. They concluded that the size of the mass and its complex content are the most important factors in the persistence of adnexal mass until the end of pregnancy.

In the literature, functional benign cysts (follicle cyst, corpus luteum cyst, and theca lutein cyst) and mature cystic teratoma are the

most common histopathological types in adnexal masses detected during cesarean section.[17] In our study, in accordance with the literature, the most common histopathological type in adnexal masses removed during cesarean is mature cystic teratoma (7.3%). Serous cystadenoma (7.3%) is the second most common histopathological type, consistent with the literature. Since pregnant women are younger and most of the cysts seen during pregnancy are physiological cysts, the risk of malignancy is lower in pregnancy compared to normal women. The incidence of malignant adnexal mass during pregnancy varies between 0% and 9%.[18,19] In our study, mucinous borderline malignant tumor was detected in 1 patient (0.9%), and the patient underwent oophorectomy. In the study conducted by Ulker et al.,[11] 5% of the adnexal masses they detected during pregnancy were detected bilaterally. In our study, bilateral cysts were detected in 6 (5.4%) patients, and the pathology of four of them was mucinous cystadenoma.

The frequency of surgery for adnexal mass in non-pregnant women is approximately 10%. Laparoscopy is the most preferred method today.[20] Our study is about the management of incidentally detected masses in women who have undergone laparotomy for cesarean delivery. They should be removed due to clinical risk of developing torsion, hemorrhage, rupture, or malignancy or requiring additional surgical procedures in the future.

CONCLUSION

Simultaneous cystectomy did not cause additional complications, morbidity or mortality in any patient. In addition, in addition to evaluating the fetus in obstetric USG performed in pregnant women starting from the first trimester, both adnexa should be examined routinely and in detail.

Statement

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

Peer-review: Externally peer-reviewed.

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

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

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ORIGINAL ARTICLE

An evaluation of depression levels in asthmatic children and their mothers during the course of the disease

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ABSTRACT

Objective: Asthma, which has gradually increased in children in recent years, imposes limitations on their development from various perspectives. This study was planned to investigate whether asthma, a chronic illness, causes depression in children and their mothers, and to provide psychological support if necessary.

Material and Methods: Two hundred and fifty asthmatic children randomly selected from children diagnosed with asthma, aged between 6 and 14 years, and under follow-up for at least 6 months, together with their mothers, were included in the study. One hundred and twenty-five volunteer children from the same age group admitted to the general pediatric clinic, and their mothers, were included in the control group. The Children's Depression Inventory was applied to the children under the guidance of a specialist psychologist, and the Beck Depression Inventory was administered to the mothers, and the data were then collected.

Results: Statistically significant differences were found between the asthmatic children and control group in terms of mean depression scale test for children scores (p=0.01). When asthmatic children were evaluated among themselves, a significant relationship was found between severity of asthma and frequency of depression. A significant relationship was found between length of disease and frequency of depression in asthmatic patients (p=0.01). Depression scores were higher in patients diagnosed with asthma and under follow-up for 4 years or more than the 3–4 years follow-up group. The frequency of depression was higher in the mothers of patients than in the control group mothers (p=0.001).

Conclusion: Every clinician involved in the treatment of asthma should be aware of the important role that psychological and social factors can play in children and their mothers. Psychological support should be provided for children and their mothers during the treatment of the disease.

Keywords: Asthma, child, depression, mother.

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INTRODUCTION

Despite advances being made in the treatment of asthma, a chronic disease frequently encountered in childhood, its prevalence, morbidity, and mortality are rising. This is a result of growing air pollution resulting from increased urbanization in recent years in particular, the use of motor vehicles in daily life, energy plants, power plants, and factories, and rising atmospheric ozone and sulfur dioxide levels, in addition to congenital factors.[1,2] The importance of psychological and social factors in the onset and course of childhood asthma is becoming increasingly recognized. Studies in the field of child health and diseases show that 18% of all children have emotional and behavioral problems, while the prevalence of such emotional behavioral problems rises to over 20% in children with chronic diseases.[3–5]

Studies based on parental reports have demonstrated 3 times greater behavioral problems in children with asthma than children with no chronic disease. In addition, children with asthma, irrespective of severity, are reported to exhibit higher levels of anxiety than children with no chronic disease.[6–10]

Asthma not only creates various difficulties for the child but also for the family. Although psychiatric disorders are more frequent in the parents of asthmatic children, it is unclear whether this is a response to living with a sick child or a general genetic disposition.[11]

Asthma, which has gradually increased in children in recent years, places limitations on children's development from various perspectives. This study was planned to investigate whether asthma, a chronic illness, causes depression in children and their mothers, and to provide psychological support if necessary.

MATERIAL AND METHODS

Two hundred and fifty randomly selected children aged 6–14 years under follow-up due to mild-moderate-severe asthma for at least 6 months at our pediatric allergy clinic between October 2008 and February 2010 were included in the study, together with their mothers. Inclusion criteria were diagnosis of asthma by a specialist physician or being under follow-up due to previous diagnosis of asthma. Exclusion criteria were being in receipt of psychiatric treatment and use of medication, or the presence of any allergic disease other than asthma. Severity of asthma in the patient group was classified based on 2008 Global Initiative for Asthma criteria. One hundred and twenty-five children from the same age group, with no known chronic disease and with normal growth and development, presenting to the general pediatric clinic, and their mothers, were enrolled as the control group. Participants' age and gender and the family's sociodemographic characteristics were recorded. Family monthly income levels were classified as low (<600 Turkish lira [TL]), moderate (600–2000 TL), or high (>2000 TL) based on Turkish Statistical Institute data. Data were collected by applying the children's depression ınventory (CDI) to the children under the guidance of a specialist psychologist, and the Beck Depression Inventory (BDI) to the mothers. Approval for the study was granted by the hospital ethical committee (no. 52/F). Questionnaires were administered under clinical conditions. Data were recorded after receipt of written verbal consent following face-to-face interviews with all patients and parents meeting the inclusion criteria.

CDI

The CDI was developed by M. Kovacs[12] and measures levels of depression in children and adolescents aged 6–17. There is no time limit, and the inventory can be completed in approximately 30 min. The inventory consists of 37 items, each of which contains three sentences from which the participant is asked to select one on the basis of the previous 2 weeks. Each sentence set consists of statements concerning childhood depression symptoms (sleep, appetite problems, etc.). Responses are marked on the form. The scale was completed by being read to the children. The child was asked to consider the previous 2 weeks and to select the most appropriate sentence from the three options given. Responses were scored from 0 to 2. The total of these scores yielded the depression score. The highest possible score on the scale is 54. High scores indicate a high level of depression or high severity. The scale cutoff point is 19. The scale is based on the BDI. It was developed in 1980 by Kovacs with the addition of questions specific to depression in childhood concerning areas such as school and relationships with friends. The language was also simplified to be comprehensible to children aged 6–17.

The validity and reliability of the Turkish language version of the scale were confirmed by Öy,[13] and the coefficient of reliability determined in the scope of that study was 0.71.

BDI

The BDI was developed by Beck et al.[14] and is widely employed to measure depressive symptom levels. The reliability and validity of the Turkish language version were investigated by Hisli. A reliability coefficient of 0.71 was determined, together with a validity coefficient of 0.75 when the Hamilton Depression Rating Scale was used as a reference criterion. The aim of the inventory is to provide an objective measurement of the severity of depressive symptoms. The BDI consists of 21 depressive symptom categories. Each item is scored between 0 and 3, with a total possible maximum score of 63. The cutoff point for the BDI is 15.

Depression scores in children were analyzed in terms of associations with variables such as gender and age, parental consanguinity, number of siblings, birth number, the child's possessing its own room, family income level, maternal and paternal education levels, maternal and paternal ages, maternal employment status, paternal occupation, and severity and duration of disease using Statistical Package for the Social Sciences (SPSS) software. Depression scores in mothers were analyzed to determine relationships with variables such as number of children with asthma, severity of disease, age, education level, number of children, and income level using SPSS software.

Statistical Analysis

Statistical analyses were performed on SPSS software. In addition to descriptive statistical methods (mean, standard deviation, and frequency), the study data were compared using the Chi-square test and the ANOVA test. The results were evaluated at a 95% confidence interval and with $p<0.050$ being regarded as statistically significant.

RESULTS

The study involved 375 children, 164 (43.70%) girls and 211 (56.30%) boys. These were divided into two groups, with asthma (patient)

Table 1: Patient and control group sociodemographic characteristics

Characteristics	Patient group (n=250) n	%	Control group (n=125) n	%	p
Gender					0.120
Male	146	58	65	52	
Female	104	42	60	8	
Consanguinity					0.259
Present	51	20	22	18	
Absent	199	80	103	82	
Number of siblings					0.399
0	19	8	8	6	
1	162	64	85	68	
>1	69	28	32	26	
Birth number					0.257
1	113	46	63	51	
2	96	38	43	34	
3	30	12	14	11	
4 or more	11	4	5	4	
Own room					0.108
Yes	143	57	50	40	
No	107	43	75	60	
Income level					0.418
Low	73	29	31	25	
Average	159	64	92	73	
High	18	7	2	2	

Characteristics	Patient group (n=250) n	%	Control group (n=125) n	%	p
Maternal age					0.051
20–34 years	102	41	40	32	
35–49 years	148	59	85	68	
Paternal age					0.008
20–34 age	49	20	9	7	
35 or over	201	80	116	93	
Paternal education					0.318
Elementary school or lower	118	47	58	47	
Middle school	54	22	23	18	
High school	61	24	36	29	
University	17	7	8	6	
Maternal education					0.397
Elementary school or lower	171	69	82	65	
Middle school	32	13	20	16	
High school	40	16	22	18	
University	6	2	1	1	
Paternal education					0.172
Clerical	24	10	9	7	
Manual	136	54	66	53	
Self-employed	90	36	50	40	
Maternal employment status					0.449
Housewife	227	91	114	91	
Working	23	9	11	9	

(n=250) and without asthma (control) (n=125). The distribution of sociodemographic characteristics in the two groups is shown in Table 1.

Mean CDI scores were 27.81±3.01 among children with asthma and 24.87±2.87 among non-asthmatic children. The difference in mean CDI scores between the two groups was statistically significant (p=0.010).

The depression scores obtained were also compared with variables such as gender, parental consanguinity, number of siblings, the child's having its own room, family income level, parental education levels, maternal, employment status, and paternal occupation (Table 2).

Children's depression levels were analyzed according to health status and paternal occupation. Two-factor analysis of CDI scores and health status x father's occupation revealed significant variation in terms of paternal occupation [F(2.396)=6.97, p=0.03]. Post hoc analysis was applied to identify which occupation yielded a significant difference. Scheffe test analysis revealed a significant difference between the mean CDI scores of manual worker and self-employed fathers. The CDI scores of children with manual worker fathers were higher than those of children of self-employed fathers. However, the joint effect of disease status (with or without asthma) and paternal occupation on children's depression levels were not statistically significant [F(2.369)=1.708, p=0.183].

The patient group was also subjected to statistical comparison within itself based on variables such as severity of disease and duration of disease (Table 3).

Asthmatic children were classified in terms of disease severity based on respiratory function test results at the time of first presentation – mildly 31% (n=77), moderately 61% (n=154), or severely 8% (n=19) asthmatic. Severity of asthma was found to result in significant variation in children's depression levels. Post hoc analysis was applied to identify the severity of asthma responsible for significant variation. Scheffe test results showed a significant difference in mean CDI scores between children with mild asthma and those with moderate asthma. Mean CDI scores were higher in children with mild asthma than in those with moderate asthma.

Asthmatic children were also classified in terms of duration of disease, with 17% (n=43) having been asthmatic for 2 years, 15% (n=37) for 2–3 years, 16% (n=40) for 3–4 years, and 52% (n=130) for 4 years or more.

Table 2: CDI scores according to sociodemographic characteristics in the patient and control groups

Sociodemographic characteristics	Patient group CDI Mean±SD	Control group CDI Mean±SD	p
Gender			0.600
Male	27.92±2.76	24.83±2.75	
Female	27.66±3.33	24.91±3.3	
Consanguinity			0.060
Yes	28.88±3.87	24.68±2.99	
No	27.54±2.69	24.91±2.86	
Number of siblings			0.340
0	27.84±2.67	26.37±3.50	
1	27.74±2.89	24.87±2.56	
>1	27.98±3.40	24.50±3.43	
Own room			0.770
Yes	27.86±3.09	25.06±2.31	
No	27.74±2.92	24.74±3.20	
Income level			0.353
Low	27.95±2.84	25.64±3.49	
Average	27.77±3.14	24.66±2.57	
High	27.55±2.61	22.50±4.94	
Parental education			0.228
Literate	31.00±2.82	–	
Elementary school	28.22±3.25	24.67±3.19	
Middle school	27.42 ±2.93	25.65±2.82	
High school	27.54±2.54	24.86±2.29	
University	26.88±2.82	24.12±3.09	
Maternal education			0.178
Literate	27.66±0.57	–	
Elementary school	28.23±2.96	25.03±2.77	
Middle school	27.66±3.11	24.90±3.83	
High school	27.90±3.09	24.40±2.19	
University	28.66±0.51	21.00±0.10	
Paternal occupation			0.183
Clerical	27.25±2.78	24.33±1.93	
Manual worker	28.60±3.21	25.16±3.27	
Self-employed	26.77±2.37	24.58±2.42	
Maternal employment status			0.615
Housewife	27.78±2.89	25.36±2.54	
Working	27.81±3.03	24.82±2.91	

CDI: Children's Depression Inventory; SD: Standard deviation.

Table 3: CDI scores according to disease severity and duration in asthmatic

Disease severity and duration	CDI (Mean±SD)	p
Disease severity, n=250		0.030
Mild (77)	28.57±3.27	
Moderate (154)	27.48±2.87	
Severe (19)	27.40±2.56	
Disease duration		0.010
≤2 years (43)	28.1±2.89	
2–3 years (37)	28.2±2.93	
3–4 years (40)	26.3±2.24	
>4 years (130)	28.0±3.01	

CDI: Children's Depression Inventory; SD: Standard deviation.

Table 4: Maternal BDI scores according to possession of an asthmatic child and severity of asthma

The presence and severity of asthma	BDI (Mean±SD)	p
Asthma		0.001
Yes	14.26±8.1	
No	8.92±6.06	
Asthma severity		0.070
Mild	12.98±8.8	
Moderate	14.5±7.8	
Severe	17.5±6.4	

BDI: Beck Depression Inventory; SD: Standard deviation.

Increased duration of disease was found to lead to significant variation in children's depression levels (p=0.010). Post hoc analysis was applied to identify the duration of asthma responsible for significant variation. Scheffe test results showed a significant difference between mean CDI scores in patıents with disease durations of 3–4 years and those with durations of 4 years or longer.

No statistically significant difference was observed between other variables in children.

Depression scores in mothers were subjected to statistical comparison according to variable such as possession of an asthmatic child, age, education level, number of children, and income level (Table 4).

A statistically significant difference in depression scores was determined between patient and control group mothers (p=0.010).

However, no significant relationship was found between severity of disease, age, education level, number of children, or income level and maternal depression levels.

DISCUSSION

Asthma, a chronic disease frequently seen in childhood, is one of the main causes of restricted quality of life. Powerful emotions may sometimes exacerbate the disease and affect its course. Diagnosis and treatment reduced morbidity in asthmatic children and improves patients' quality of life. The principal aim in the treatment of asthma is to achieve control of the symptoms and improve patients' quality of life.[15,16]

The present study investigated the presence of depression in asthmatic children and their mothers. Mean CDI sores differed significantly between the patient and control groups. This shows that health status has a significant effect on childhood depression.

Bilfield et al.[17] reported greater psychosocial concerns in children with chronic disease compared to healthy children. Another study from Turkey reported that 20% of children with chronic health problems exhibited behavioral and emotional symptoms.[18]

Tousman reported that depression accompanied asthma in between 20% and 50% of children with the disease and that learned helplessness was observed in such individuals.[19]

Causes of depression include increased non-attendance at school due to asthma, children being raised with excessively protective attitudes on the part of their mothers and fathers, in turn leading to restriction of independence, weaknesses in physical development due to the disease and the idea that an attack may occur at any moment, frequent hospitalization or visits to hospital, and side effects of medications employed.

Whether or not an individual will be affected by the disease, and to what extent, depends on numerous factors. In addition to health status, this study investigated the effects on depression scores of a number of such variables, including sex, number of children, birth order, consanguineous marriage, number of rooms, family income status, parental education levels, parental ages, maternal employment status, and paternal occupation. Depression levels in children of manual worker fathers were significantly higher than those of children of self-employed fathers, although depression levels did not vary according to the variables of health status and paternal occupation. The fathers of both asthmatic and non-asthmatic children in this study were generally manual workers, and our findings show that asthma leads to depression in children. The high depression scores among children of manual worker fathers may be due to the difficult living conditions faced by such workers and perhaps to their also suffering from depression. Children of depressive parents are known to be at a greater risk of depression than children of non-depressive parents.[20,21]

This study also investigated whether depression levels of asthmatic children varied depending on the severity of the disease. Statistically significant differences were observed between the three groups' mean CDI scores. Post hoc analysis was applied to identify the degree of severity responsible for the difference and showed higher CDI scores in the mild asthma group. This was tentatively attributed to the difference in patient numbers among the groups. The lower number of patients in the severe asthma group compared to the other two groups also represents a limitation of this study.

One previous study reported that adolescents with moderate or severe asthma exhibited far greater hostility, anxiety, depression, and difficulty in controlling emotions than normal control individuals and adolescents with mild asthma.[18–22] Factors such as lack of hope for the future, fear of dying, a sense of being different, inadequacy, feeling abnormal, and a reduced quality of life have been implicated as causes of depression and anxiety in asthmatic adolescents.[23]

Janson et al.[24] reported that the severity of asthma had no effect on levels of depression in childhood.

In their adult study, Oğuztürk et al.[25] found no difference in depression scores between severe asthmatics treated in hospital and milder cases of asthma.

Some research has shown that depression scores vary in line with the severity of asthma, while other studies have reported no such variation. The results of studies on this subject are inconsistent. Further studies involving larger patient numbers, greater numbers of asthma groups with differing levels of severity, and with family groups with similar environmental factors affecting depression levels (such as maternal employment status and income level) might now be planned to resolve these inconsistencies.

Analysis of depression levels in terms of children's duration of disease revealed a statistically significant difference between the four groups established. Accordingly, patients with disease durations of 4 years or more had significantly higher CDI scores than those with durations of 3–4 years.

Ekşi[26] investigated the psychosocial aspect of asthma in a group of 60 patients aged 4–16 and reported no significant correlation between severity of disease and total Achenbach child behavior checklist scores, but observed negative correlation between severity of disease and the test's social competence scores. In other words, the greater the severity of the disease, the lower the child's social competence. Ekşi[26] concluded that the child's problems do not derive from the duration of the disease or its degree of severity, but deduced from interviews with others that children's problem scores were significantly correlated with the atmosphere in the home and particularly the attitudes of the mother.

Children with asthma and being treated for asthma, and their families, are at risk of secondary psychiatric problems. The sudden and unpredictable onset of asthma symptoms and complex therapeutic regimens impose various degrees of difficulty on families. Family problems flare up under this stress and lead to increasing difficulty in the child. Asthmatic children's inability to care for themselves adequately results in separation from normal socialization and athletic experiences, even if asthma is brought under control with modern treatments. Children with severe asthma can lose self-confidence due to the side effects of their medications. Parents experience severe stress due to financial anxieties, worries about their child's health, and increasing time requirements for treatment. These stresses can exacerbate psychiatric problems by compromising their relationship with the child. Increasing friction with the child increases the risk of emotional disorders in asthmatic children.[27]

The present study compared the depression scores of mothers with and without asthmatic children. The results showed a statistically significant difference in depressions cores between the two groups. Mothers are at risk for a number of reasons, including fear and helplessness during episodes, attempting to prevent the emergence of episodes due to physical exercise or psychological factors, the stress caused by medical care costs, loss of sleep, and continuous monitoring of the child's surroundings, anxiety, and guilt feelings.

Studies have also shown that chronic disease is a psychological risk factor for children and families.[27–29]

There are a number of limitations to this study. These include the fact that the participants were not equally grouped on the basis of sociodemographic characteristics, that the number of members of each asthma group was different, and the limited numbers of patients with severe asthma.

Factors affecting depression levels in this study included the presence of disease, duration of disease, and possession of a sick child. Asthma leads to psychiatric problems in patients and in their mothers. Due to this stress created in mothers by its chronic nature, asthma can further exacerbate children's psychiatric problems by impairing the relationship with an asthmatic child.

CONCLUSION

Asthma is a chronic disease that adversely affects the lives of almost all patients, both psychologically and socially. The severity of the disease must not, therefore, be underestimated, and its impact on human life must be reduced to a minimum. Further, more extensive studies investigating psychopathology in children with chronic disease, parental attitudes, and quality of life perceptions are, therefore, now needed.

Statement

Ethics Committee Approval: The Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 27.11.2008, number: 52/F).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.Ç., M.E.; Design – N.Ç., M.E., E.Y.K.; Supervision – N.Ç., M.E.; Resource – N.Ç., M.E., H.H.M.; Materials – N.Ç., M.E., E.Y.K.; Data Collection and/or Processing – N.Ç., E.Y.K., H.H.M.; Analysis and/or Interpretation – N.Ç., M.E.; Literature Search – N.Ç., E.Y.K, H.H.M.; Writing – N.Ç.; Critical Reviews – N.Ç., M.E.

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ORIGINAL ARTICLE

Evaluation of etiological, laboratory, and anthropometric characteristics of patients treated with the diagnosis of precocious puberty

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ABSTRACT

Objective: This study aimed to determine the etiological distribution of patients treated for precocious puberty and to compare the results of gonadotropin-releasing hormone (GnRH) analog treatment with clinical and laboratory data during the administration and follow-up period.

Material and Methods: The files of patients treated with a diagnosis of precocious puberty between October 2016 and July 2019 in the pediatric endocrinology outpatient clinic were retrospectively analyzed.

Results: While 39 (88.6%) of our patients with precocious puberty were female, five (11.4%) were male. True precocious puberty (TPP) was found in 42 patients (95.5%) and combined precocious puberty (CPP) in two patients (4.5%). While 37 (88.1%) of TPP patients were diagnosed with idiopathic precocious puberty, an organic cause was found in five patients. Both of the patients treated for CPP had late-onset congenital adrenal hyperplasia. The mean estimated adult height (EAH) before the treatment was 151.88±6.77 cm in our patients between the ages of 6 and 8 who were started on GnRH analog treatment with a diagnosis of TPP, while the mean EAH after treatment was 155.16±7.82 cm ($p<0.001$). An increase in body mass index-standard deviation score was found in patients who received triptorelin acetate treatment, but no statistically significant difference was found.

Conclusion: Precocious puberty is more common in girls, and idiopathic TPP constitutes the majority of cases. GnRH analog treatment may contribute positively to the EAHs of girls with TPP, especially those younger than 8 years old.

Keywords: Combined precocious puberty, estimated adult height, gonadotropin-releasing hormone analogs, true precocious puberty

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INTRODUCTION

Puberty includes physical, mental, and social changes in the transition from childhood to adulthood. Puberty is the developmental period in which secondary sex characteristics emerge with the onset of spermatogenesis in boys, ovulation in girls, and reproductive ability is acquired.[1] Precocious puberty is the onset of secondary sex characteristics before the age of eight in girls and nine in boys. The age of onset of puberty may vary according to environmental factors such as genetic and ethnic characteristics, socioeconomic factors, nutritional status, and geographical location.[2]

Precocious puberty is physiopathologically classified as true precocious puberty (TPP) (gonadotropin dependent/central) and peripheral precocious puberty (gonadotropin independent/pseudo). TPP is more common in girls than in boys, and it is always isosexual since pubertal findings always correspond to gender. The emergence of secondary sex characteristics with early activation of the hypothalamic-pituitary-gonad (HHG) axis is defined as TPP. While cases of TPP in girls are mostly idiopathic, organic causes of TPP are more common in boys. Pseudo-precocious puberty (PPP) is defined as precocious puberty in which secondary sex characteristics appear without normal HHG interaction, and isosexual or heterosexual development is observed. The addition of TPP as a result of the stimulation of long-term endogenous sex steroids to some diseases such as McCune-Albright Syndrome, which is a cause for PPP, congenital adrenal hyperplasia (CAH), which could not be treated sufficiently and in time, is defined as combined precocious puberty (CPP).[3]

Treatment in precocious puberty is aimed at the underlying cause. Early secretion of estradiol in cases diagnosed with TPP shortens the growth period and causes a shorter final height. A decrease in estradiol secretion is achieved by suppressing the pituitary-gonad axis with gonadotropin-releasing hormone (GnRH) analogs. Thus, bone age progression slows down, and the growth potential is maintained.[4]

This study aimed to determine the etiological distribution of patients treated for precocious puberty in the pediatric endocrinology clinic and to compare the results of GnRH analog treatment with clinical and laboratory data during the application and follow-up period.

MATERIAL AND METHODS

Forty-four patients treated with precocious puberty diagnosis between October 2016 and July 2019 in the pediatric endocrinology outpatient clinic were included in the study. Before the study, approval was obtained from the ethics committee of the relevant university with the decree dated May 21, 2019, and No 2019/4-22.

From the file information of the cases, gender, admission age, follow-up time, estimated adult height (EAH), treatment initiation age, duration of treatment, height, weight, body mass index (BMI), and standard deviation score (SDS) values at admission and follow-up, bone age (BA), pelvic USG, cranial-pituitary MRI results, and laboratory findings were recorded. In the pelvic USG, the anteroposterior diameter of the uterus and the ovarian dimensions, if viewable, were measured.

According to their BMI percentiles, the cases were evaluated and grouped as underweight if <5%, normal weight between 5–85%, overweight 85–95%, and obese if >95%. Data from Turkish children were used for weight and height SDS measurements.[5] BA was determined according to the Greulich Pyle method by taking radiographs of the left hand-wrist in all cases at the time of diagnosis. Puberty staging was done as per the Tanner Criteria. Testicular volume in men was determined by Prader Orchidometer. Baseline serum LH and FSH and estradiol (E_2)/total testosterone (TT) levels and, when necessary, luteinizing hormone-releasing hormone (GnRH) stimulation test was performed in the cases, and LH/FSH levels were examined at 0th, 20th, and 40th min.[6]

Serum hormone levels were studied in the Maternity and Children's Hospital Additional Service Building Laboratory. Immunochemiluminescent (ICMA) method was used to measure LH and FSH levels, while the radioimmunoassay (RIA) method was used to measure 17-hydroxyprogesterone (17OHP) and 1,4-delta androstenedione, and chemiluminescent microparticle enzyme method was used to measure serum E_2 and TT levels.

The onset of breast development before the age of 8 in girls and an increase in testicular volume above 4 ml before the age of 9 in boys was accepted as precocious puberty. Bone age at least 1 year older than the calendar age (CA), baseline LH of ≥0.3 or the highest LH examined by chemiluminescence immunoassay method reaches 5 mIU/mL after intravenous injection of exogenous GnRH, when examined by ultrasound, uterine long axis reaching ≥35 mm and/or ovarian volume of ≥2 mL were defined as findings supporting TPP.[6] High levels of TT or E_2 were defined as PPP, although baseline and stimulated gonadotropin levels were suppressed in children whose secondary sex characteristics started before the age of 8 in girls and 9 in boys.

The addition of TPP to PPP (late-onset CAH, McCune Albright syndrome, and familial testotoxicosis) was accepted as CPP. Patients admitted with premature adrenarche and a baseline 17OHP value of >10 ng/ml were diagnosed with late-onset CAH.[7] Genetic analysis was planned with the same diagnosis in cases with a baseline 17OHP value of between 2 and 10 ng/ml and if the stimulated 17OHP level was detected >10 ng/ml after the adrenocorticotropic hormone stimulation test. The cases were compared in terms of laboratory findings, and demographic and anthropometric characteristics according to their diagnoses.

Statistical Analysis

The data obtained in the study were evaluated with the SPSS 24.0 (SPSS Inc. Chicago, IL, USA) statistical program. The compliance of the variables to normal distribution was examined with the Kolmogorov–Smirnov Test. Intergroup differences were evaluated with Chi-square and Fisher's exact test. While variables showing normal distribution were evaluated between groups, they were analyzed with an independent-sample and paired-sample t-test. The cases where statistically $p<0.05$ was present were considered significant.

RESULTS

General Properties of the Cases

Thirty-nine (88.6%) of 44 patients who received GnRH analog treatment due to precocious puberty were female, while 5 (11.4%) were male. Precocious puberty rate was found to be 7.8 times higher in girls than boys. The mean age of diagnosis at the admission of the

Table 1: General characteristics of cases with true precocious puberty

	Female (n=44) Mean±SD	Male (n=5) Mean±SD
Calendar age (years)	7.17±0.80	8.12±0.50
Bone age (years)	9.18±1.78	11.00±1.50
BA-CA	1.65±0.88	2.50±0.90
BMI-SDS	0.63±0.89	0.13±1.19
Height-SDS	0.53±1.36	1.63±0.62
PAH (cm)	150.56±6.68	170.83±6.96
Duration of treatment (months)	20.37±16.82	12.00±7.57
Uterine longitudinal diameter (mm)	33.48±8.54	
Mean ovarian volume (cm^3)	1.71±1.03	
Basal FSH (mIU/mL)	3.95±2.50	2.65±1.50
Basal LH (mIU/mL)	1.13±1.14	0.21±0.20
Basal estradiol (pg/mL)	25.16±18.32	
Basal testosterone (ng/mL)		0.64±0.56
Peak FSH (mIU/mL)	17.89±7.93	7.23±2.27
Peak LH (mIU/mL)	17.62±17.84	12.03±6.65
Peak LH/FSH	0.25±0.18	0.93±0.09

BA-CA: Bone age-Calendar age; BMI: Body mass index; SDS: Standard deviation score; PAH: Predicted adult height.

cases was 7.2 years for girls and 8.1 years for boys. TPP was found in 42 (95.5%) of the cases, and CPP was found in 2 (4.5%). The number of patients diagnosed with TPP was 42 (38 girls, four boys), and 37 (88.1%) of these patients were idiopathic precocious puberty, while five patients had an organic cause.

In the TPP group, the BA in the admission was 9.1 years, 12 years in the CPP group on average, and the CA-BA difference in the TPP was 1.9 years and 3.3 years in the CPP group. General properties of our TPP cases are presented in Table 1.

When the cases were evaluated according to gender, 38 (97.4%) of the female cases had TPP and 1 (2.6%) had CPP, while 4 (80%) of the boys had TPP and 1 (20%) had CPP. Both patients with CPP were diagnosed with late-onset CAH.

While the result was normal in 22 (81.5%) of the patients who underwent cranial/pituitary MRI with a diagnosis of TPP, hydrocephalus was found in 2 (7.4%), macroadenoma in 2 (7.4%), and partially empty sella in 1 (3.7%). While TPP due to an organic cause was not detected in the male gender, all of our patients (5/5) were female, and the rate of TPP with an organic cause in girls was found to be 12.8%.

When our cases were evaluated in terms of BMI percentiles at admission, 26 female patients (66.7%) were thin and 13 patients (33.3%) were normal weight, while three male patients (60%) were thin and two patients (40%) were normal weight. There were more thin patients in both groups, but there was no statistically significant difference (p=0.563). No overweight or obese patients were found.

When the birth history of our patients diagnosed with precocious puberty was examined, it was found that 4 (9.1%) were born with intrauterine growth retardation (IUGR), and 3 (6.8%) were born with macrosomia.

When our patients were grouped in terms of age at initiation of treatment, four patients (9.1%) were under 6 years old, 26 patients (59.1%) were between 6 and 8 years old, and 14 patients (31.8%) were over 8 years old. While treatment was initiated in half of the patients (22/44) at the time of admission, treatment was initiated in the other half (22/44) during follow-up.

Complaint at Admission

In TPP cases, breast enlargement was present in 27 patients (64.2%), pubic hair growth in six patients (14.3%), vaginal bleeding in four patients (9.5%), penile enlargement in two (4.8%) patients, weight gain, and breast enlargement in two (4.8%) patients, and axillary hair growth in one patient (2.4%). The complaint at the admission of a patient with a CPP diagnosis was pubic hair growth, and the other was axillary hair growth.

Baseline Hormonal Evaluation

Mean baseline LH level in TPP cases was found as 1.12±1.14 mIU/ml, baseline FSH as 3.87±2.44 mIU/ml, and baseline E_2 as 25.14±18.57 pg/ml, and in the CPP group, the mean baseline LH level was found as 1.11±0.45 mIU/ml, baseline FSH as 6.94±6.51 mIU/ml, and baseline E_2 as 30.1±5.79 pg/ml, but no statistically significant difference was found between the two groups (p>0.05).

GnRH Stimulation Test Results

GnRH stimulation test was performed on application to 11 of our patients diagnosed with precocious puberty, and the mean peak FSH value was found as 13.62±8.18 mIU/ml, peak LH as 15.08±14.41 mIU/ml, and peak LH/FSH ratio as 1.24±0.90.

Hormonal Response to Treatment Given and GnRH Analog Treatment

Twenty-five of our patients diagnosed with real precocious puberty had received triptorelin acetate treatment, 17 of them leuprolide acetate treatment, one of our CPP patients had received triptorelin acetate and hydrocortisone, and the other had leuprolide acetate and hydrocortisone.

When the mean baseline LH, baseline FSH, and LH/FSH ratios were compared before and after treatment in our TPP cases, the mean baseline LH, FSH, and LH/FSH ratio after treatment was found to be significantly lower than before treatment (Table 2).

Comparison of TPP Cases Before and After Treatment in Terms of EAH

While the mean EAH of our cases before treatment was 151.91±7.35 cm, it was found to be 155.73±8.08 cm after treatment. Post-treatment EAH was higher and statistically significant compared to pre-treatment EAH (p<0.001). When the patients treated with triptorelin and leuprolide acetate were compared according to mean age of diagnosis and

Table 2: comparison of pre-treatment and post-treatment anthropometric and hormonal parameters of cases with true precocious puberty

	Pre-treatment	Post-treatment	%95 CI		p*
			Alt	Üst	
Height-SDS	0.49±1.22	0.62±1.25	-0.35	0.10	0.277
Weight-SDS	0.67±1.04	0.76±0.93	-0.27	0.08	0.305
BMI-SDS	0.57±0.93	0.61±0.83	-0.25	0.15	0.619
PAH-SDS	151.91±7.35	155.73±8.08	-5.05	-2.12	**<0.001**
LH (mIU/ml)	1.12±1.15	0.47±0.54	0.24	1.06	**0.003**
FSH (mIU/ml)	3.86±2.46	1.81±1.65	1.05	3.04	**<0.001**
LH/FSH	1.28±6.12	0.31±0.31	-1.06	2.99	0.342

Paired-Sample t-test; Parameters are shown as mean±standard deviation; CI: Confidence interval; * p<0.05; BMI: Body mass index; SDS: Standard deviation score; PAH: Predicted adult height.

treatment initiation, mean BA, and Tanner stages before treatment, no significant difference was found between the two groups (p>0.05).

The Effect of GnRH Analog Treatment Initiation Age on EAH

When the effect of treatment initiation age on EAH was compared, it was found that the mean EAH before treatment was 151.88±6.77 cm in our patients aged 6–8 years and 155.16±7.82 cm after treatment (p<0.001). In patients over 8 years of age, the mean EAH before treatment was 151.75±9.13 cm, and after treatment was 156.52±9.28 cm (p=0.009). When the patients were examined in terms of the age of treatment initiation, it was found that the contribution of starting treatment to EAH between the ages of 6 and 8 years was statistically higher than those who were started treatment above 8 years old (p<0.05).

The Effect of Treatment on Height SDS and BMI SDS Values

When the height SDS and BMI SDS values of the patients who received leuprolide acetate treatment before and after the treatment were compared, it was found that the mean height SDS increased and the BMI SDS decreased, but no statistically significant difference was found (p>0.05). In patients who received triptorelin acetate treatment, an increase in height SDS and BMI SDS was found after treatment, but no statistically significant difference was found (p>0.05).

DISCUSSION

Precocious puberty is seen in approximately one in every 5.000 children. Premature closure of the epiphyseal plates due to precocious puberty may adversely affect the height potential. Besides, precocious puberty can lead to negative psychological consequences.[6,8] It was reported in the literature that precocious puberty is observed approximately 10 times more frequently in girls than in boys.[8] In our study, 39 (88.6%) of the patients were girls, and 5 (11.4%) were boys, and precocious puberty was detected 7.8 times more frequently in girls.

In our study, the mean age of girls with precocious puberty was 7.2 years and 8.1 years for boys. Studies have reported that the age of precocious puberty diagnosis ranges from 6.6 to 7.6 years in girls and between 5.8 and 7.2 years in boys.[9–12] In our study, girls' mean age was generally consistent with the literature, while it was higher in boys. This finding was attributed to parents' late noticing of precocious puberty findings in boys.

In our study, 37 of 42 patients were diagnosed as TPP due to an idiopathic cause, and five due to an organic cause. When our cases were evaluated in terms of TPP etiology, the rate of organic causes in the female gender was 12.8%. In the literature, the rate of organic causes in girls with TPP has been reported as 10–20%,[13] and the findings of our study were evaluated per the literature. Cranial MRI detected partial empty sella in a female patient diagnosed with TPP, and literature review showed that precocious puberty might rarely accompany empty sella syndrome in patients with anterior pituitary hormone deficiencies.[14]

It is known that puberty shifts to early periods in cases with IUGR. In a meta-analysis study conducted by Deng et al.,[15] it was shown that IUGR is associated with precocious puberty and early menarche age, especially in girls. Consistent with the findings of this study, the rate of IUGR among girls with precocious puberty in our study constituted a substantial portion (8.7%) of the cases. Although the exact mechanism of the development of precocious puberty in cases with IUGR is unknown, it is thought that rapid postpartum growth and rapid increase in fat mass are effective in this process.[16]

Mogensen et al.[17] detected pathological MRI findings in 13 (6.3%) of 208 patients with TPP who underwent cranial imaging. MRI was performed in 27 patients, and pathological results were detected in five patients (18.5%) in our study. This result has been associated with a small number of patients. There are studies reporting that girls with high-fat mass and BMI have earlier and faster pubertal development.[18,19] Contrary to the literature, the absence of our overweight and obese patients in our study made us think that environmental factors should not be ignored in the etiology of precocious puberty and showed the need for studies to be carried out on the subject.

The fact that BA/CA ratio is more than 1.2 in cases followed up due to precocious puberty shows that TPP progresses rapidly.[20] In the study of Mogensen et al.,[7] the BA-CA difference was found to be 1.6. In our study, in cases with a diagnosis of TPP, the mean BA at admission was 9.1 years, 7.2 years for CA, and the difference between BA-CA was 1.9 years, and bone age was found to be advanced in accordance with the literature.

Gonadotropin level measurements are essential in determining whether the HHG axis is activated or not. The use of third-generation measurement methods such as immunofluorometric (IFMA) and ICMA increased the diagnostic value of baseline values in the diagnosis of precocious puberty. Kandemir et al.[6] showed that a baseline LH level of >0.3 has high sensitivity and specificity in indicating precocious puberty. In another study conducted, Vurallı et al.[21] reported that a baseline LH level of ≥0.65 IU/L could be used as a screening test to indicate TPP. However, at the onset of puberty, baseline LH levels may not always provide sufficient information about the HHG axis activation. Determining the peak LH level >5 mIU/ml and the LH/FSH ratio of >0.66 with the GnRH stimulation test performed in these cases is significant for TPP.[6,7] In our study, baseline LH, FSH, and E_2 were detected at prepubertal levels in 11 female patients admitted with early breast development, and a pubertal response was obtained to the GnRH stimulation test performed thereafter.

It was reported that when starting GnRH analog treatment before the age of 6, the treatment contributes to the height, the contribution is partial between the ages of 6 and 8, and starting treatment after the age of 8 does not contribute to the height.[22,23] Since we had a small number of patients under the age of six in our study, the treatment effect on height could not be evaluated in this age group. When we compared the patients between the ages of 6 and 8 and those older than 8, it was determined that the contribution of treatment to EAH in the 6–8 age group was more than those over 8 years old, and the treatment initiated at an early age contributed more to the patients per the literature.

The effect of GnRH analog treatment on BMI is still controversial. In addition to studies reporting that treatment increases BMI, there are also studies reporting that it does not cause a change in BMI or even causes a decrease.[24,25] In our study, a partial increase in BMI-SDS was detected after triptorelin acetate treatment. However, the increase in BMI-SDS was not found to be statistically significant.

CONCLUSION

Precocious puberty is more common in girls, and most of the cases are TPP cases. GnRH analog treatment may positively contribute to the EAH of girls with TPP, especially girls younger than 8 years old. More comprehensive studies are needed to evaluate the effects of treatment on body composition and adipose tissue.

Statement

Ethics Committee Approval: The Adıyaman University Clinical Research Ethics Committee granted approval for this study (date: 21.05.2019, number: 2019/4-22).

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

Peer-review: Externally peer-reviewed.

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

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

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CASE REPORT

Bilateral serous macular detachment as a complication of preeclampsia: A case report

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ABSTRACT

The objective of the study was to report a case of preeclamptic pregnant woman with bilateral serous macular detachment following cesarean section. This is a case report of a 29-year-old pregnant woman with bilateral serous macular detachment following cesarean section due to severe preeclampsia. The patient applied with a complaint of sudden vision blur in both eyes after an emergent cesarean delivery. Ophthalmologic examination revealed visual acuity of 1/10 on the right eye and 4/10 on the left eye. She had bilateral serous macular detachment. Within 10 days, visual acuity improved to 7/10 in both eyes. Optical coherence tomography revealed disappearance of the subretinal fluid with distribution of retinal photoreceptor layer in both eyes. Preeclampsia may lead to a transient serous macular detachment with visual sequelae.

Keywords: Eye, preeclampsia, pregnancy, serous macular detachment.

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INTRODUCTION

Preeclampsia is a pregnancy-specific vascular disorder, the pathogenesis of which is still not completely understood. According to the two new diagnostic criteria by the American College of Obstetricians and Gynecologists in 2013 and the International Society for the Study of Hypertension in Pregnancy, new-onset hypertension in the absence of proteinuria but combined with hematological complications, renal insufficiency, impaired liver function, neurological symptoms, or uteroplacental dysfunction also fulfill diagnostic criteria for preeclampsia.[1]

It occurs in 5% of first pregnancies and usually develops in the third trimester of pregnancy.[2] The primary ocular manifestations of preeclampsia are related to dysfunction of both retinal and choroidal circulations.[3,4] Cotton wool spots, hemorrhages, retinal edema, papilledema, and serous retinal detachment may develop in cases of preeclampsia.[5]

Herein, we describe a case of a 29-year-old pregnant woman with bilateral serous macular detachment following cesarean section due to severe preeclampsia. Patient consent was obtained and the Declaration of Helsinki was followed in this case report.

CASE REPORT

The patient was a 29-year-old pregnant woman who received cesarean delivery at week 38 due to severe preeclampsia. This was her first pregnancy. During delivery, her systemic blood pressure was 180/100 mmHg and urinary protein was 4+ (more than 2 g/day). She applied to our clinic the day after the cesarean delivery with a complaint of sudden vision blur in both eyes.

After her referral to the ophthalmology department, blood pressure was decreased to 140/90 mmHg. There was no preceding history of any ocular disease. Ophthalmologic examination revealed visual acuity of 1/10 on the right eye and 4/10 on the left eye.[6] There was no afferent pupillary defect. Intraocular pressure was 12 mmHg in the right eye and 14 mmHg in the left eye. She had normal anterior segment findings bilaterally. There were no inflammatory cells in the eye. Dilated fundus examination revealed bilateral serous macular detachment at the posterior pole in both eyes. Optical coherence tomography (OCT) (Spectralis®, Heidelberg Engineering Inc., Heidelberg, Germany) revealed a nearly bullous serous macular detachment and intraretinal cystoid spaces on both sides (Fig. 1a, b).[7]

Her systemic blood pressure gradually declined once she was started oral medications. At 10 days after the initial ophthalmological examination, systemic blood pressure was decreased to 110/70 mmHg. Visual acuity was 7/10 in both eyes (Snellen). There was no afferent pupillary defect. The eye was quiet. OCT revealed the disappearance of subretinal fluid in both eyes. There was distribution of photoreceptor cell layer and pigmentary changes in macular region in both eyes on OCT (Fig. 2a, b).

DISCUSSION

The most common ocular finding of preeclampsia is a severe arteriolar spasm.[4] Retinal hemorrhages, edema, and cotton wool spots secondary to arteriolar damage may also occur. Retinal vascular occlusive disease may also develop in these cases.[6]

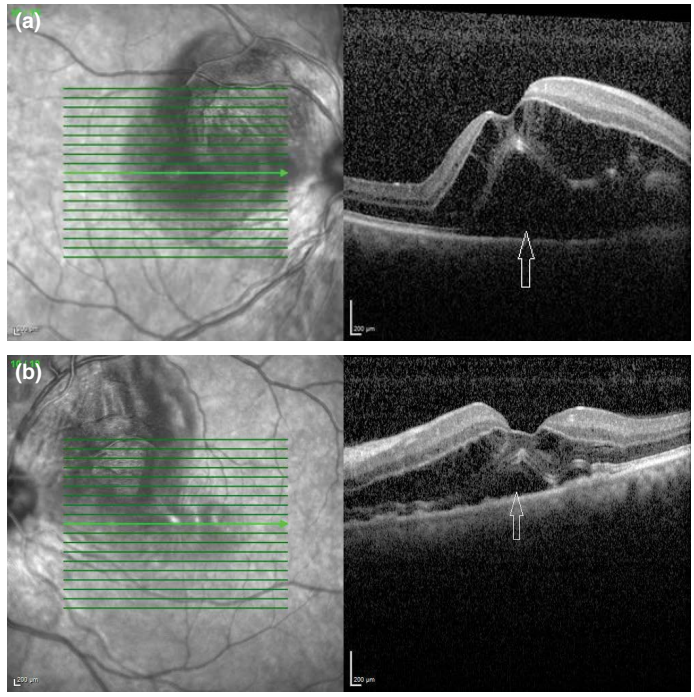

Figure 1: (a, b) Optical coherence tomography revealed large serous macular detachment (vertical arrow) with intraretinal cystoid spaces in both eyes.

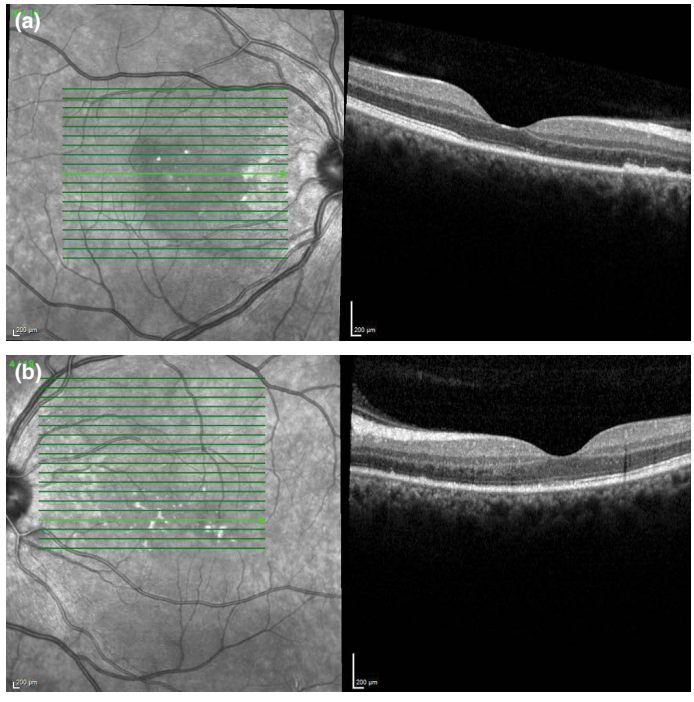

Figure 2: (a, b) The disappearance of the subretinal fluid with photoreceptor disruption in both eyes.

Serous macular detachment is a rare complication of preeclampsia. As known, the detachment usually develops in patients with severe preeclampsia (blood pressure >160/110 mmHg). The exact pathophysiology of serous neurosensory detachment in a case of preeclampsia is not well-known. Preeclampsia is supposed to cause

acute retinal pigment epitheliopathy due to choroidal ischemia. Some studies have also shown that non-perfusion of the choriocapillaris can cause necrosis of the overlying retinal pigment epithelium, which leads to the breakdown of the outer blood–retinal barrier and the development of serous retinal detachment.[8–11]

Postpartum bilateral serous macular detachment has been described in the literature.[12–14] Bilateral serous retinal detachment has developed a few hours after delivery in these reports. They emphasized that a few weeks after delivery, there was spontaneous resorption of the subretinal fluid and complete resolution bilateral serous retinal detachment, with residual pigmentary changes of the retinal pigment epithelium.[12–14]

In our case, bilateral serous retinal detachment developed on the 1st day after giving birth. The subretinal fluid gradually resolved without any treatment except for antihypertensive drugs. The patient's visual acuity significantly improved after 10 days. This case shows the importance of being cautious about the rare conditions that may occur in pregnant women with preeclampsia. Immediate evaluation can be needed. These patients require observation, and medical treatment with systemic antihypertensive agents may be helpful.

Serous macular detachment is a rare complication of preeclampsia. Mostly, it resolves spontaneously after the delivery and patients do not have much visual sequelae. Poor visual outcome can be associated with macular involvement as in this case. In a minority of patients with severe preeclampsia, there is a possibility of residual visual loss despite the resolution of the retinal detachment, due to the retinal photoreceptor layer disruption. Therefore, it should be noted that in cases of severe preeclampsia, serious ocular complications may occur.

CONCLUSION

The obstetricians should suspect possible retinal complications in the setting of preeclampsia associated visual loss and refer to the ophthalmologists for detailed evaluation to avoid further visual loss.

Statement

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – NA, ÖK, ET, KÖ; Design – NA, ÖK, ET, KÖ; Supervision – NA, ÖK, ET, KÖ; Resource – NA, ÖK, ET, KÖ; Materials – NA, ÖK, ET, KÖ; Data Collection and/or Processing – NA, ÖK, ET, KÖ; Analysis and/or Interpretation – NA, ÖK, ET, KÖ; Literature Search – NA, ÖK, ET, KÖ; Writing – NA, ÖK, ET, KÖ; Critical Reviews – NA, ÖK, ET, KÖ.

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CASE REPORT

Oncologic breast surgery of retroareolar breast cancer with racquet mammoplasty technique

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ABSTRACT

Oncoplastic breast surgery is increasingly preferred method of intervention today. Surgery allows for the removal of mass with clear borders while keeping the appearance within the acceptable standards. The success of breast conserving surgery is evident only after the radiotherapy received. Oncoplastic techniques that allow filling of the defect by shifting the breast tissue are the best option for the treatment. An invasive ductal carcinoma with dimensions of 23 mm × 21 mm, located in the retroareolar area on the upper outer quadrant of the right breast was detected in a 59-year-old postmenopausal female patient. Taking into the consideration of tumor-breast ratio, localization of tumor, the density of the breast and skin features, racquet mammoplasty technique was used. In today's world, breast cancer is considered to be a chronic disease by the World Health Organization. In a well-staged condition, the surgical intervention must be applied with an acceptable cosmetic appearance.

Keywords: Breast cancer, breast conserving surgery, mammoplasty, segmental mastectomy.

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INTRODUCTION

Breast cancer is a public health problem and the diagnosis and treatment of which require attention. If detected in the early stages of the condition, it can be treated almost up to 100% recovery. About 60–80% of the breast cancer cases detected in recent years can be treated with breast-conserving surgery.[1] Taking into consideration that the patients live a long time after the time of diagnosis, the effect of radical surgery costs a negative effect on patients' quality of life.

The aim of breast cancer treatment is to cure the condition, effective utilization of oncologic principles and having cosmetic appearance within the acceptable standards.[2] Clough et al.[3] classified the oncoplastic breast surgery techniques. After their study, the excision of tumors that required a great amount of tissue loss became possible. Rezai et al.[4] indicated the systemization of the applied oncoplastic techniques. Localization of tumor, tumor-breast ratio, requirement of radiotherapy, and surgical intervention are the factors that affect the appearance of the breast after the breast conserving surgery.[5] In some cases of breast conserving surgery, satisfaction with the esthetic appearance of the breast and the ratio of deformity can be up to 30%. This ratio, after the oncoplastic surgery, is 15–18%.

CASE REPORT

A 59-year-old postmenopausal patient applied to our hospital with the complaint of mass felt manually on her right breast. On ultrasonography, a well circumscribed solid mass with dimensions of 24 mm × 20 mm localized to the upper outer quadrant, posterior to nipple areola complex was detected. The mass was staged as BIRADS 4a. In mammography, no microcalcification was detected and on the right breast a mass was seen (Fig. 1). Before biopsy, magnetic resonance image was taken. The mass was found 23 mm × 21 mm in dimensions with heterogenous pattern appearance with contrast and had necrotic areas within with limited diffusion (Fig. 2). With Tru-cut biopsy, the mass was identified as invasive ductal carcinoma. The tumor was positive for estrogen and progesterone receptors, negative for Cerb2 and Ki 67 index was 20%. To screen for systemic disease, positron emulsion tomography was done. Localized to retro-areolar area in the upper outer quadrant of the right breast with SUV max of 6,2 a malignant mass was detected. There was no axillary lymph involvement or systemic involvement. After multidisciplinary discussion, surgery was planned. Taking into consideration the tumor size, its localization, the breast size, and the density of parenchyma, racquet mammoplasty technique was used. There was no complication of wound healing (Fig. 3). In pathological examination, the diameter of tumor was found to be 2.4 mm × 2.5 cm. The estrogen and progesterone receptors were 90% positive, Ki index was 10%, and Cerb2 negative invasive ductal cancer was identified. The surgical borders were well circumscribed and sentinel lymph node was negative. Lymph vascular invasion and necrosis were not detected.

DISCUSSION

Breast cancer is the most common type of cancer seen in women. One of every eight women suffers from breast cancer at one point of their lives. Due to early detection uprising rate and developed personalized approach, the overall survival is increasing.

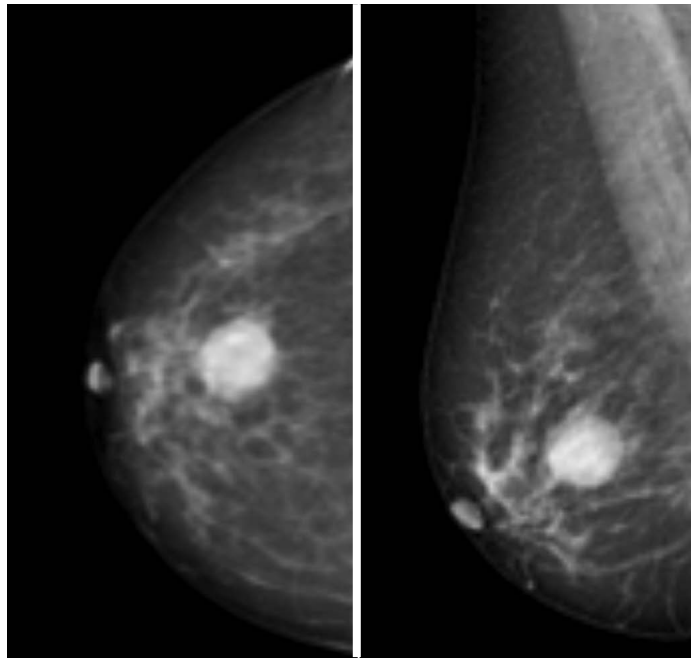

Figure 1: Appearance of a mass lesion in the right breast in CC and MLO mammography.

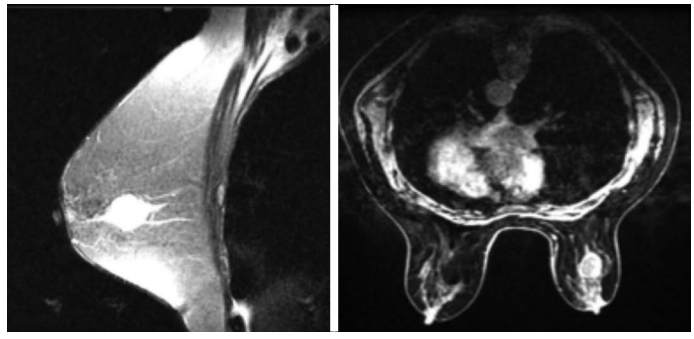

Figure 2: Magnetic resonance imaging of the tumor. The massive lesion is 23 mm × 21 mm in size. It has a heterogeneous enhancement pattern. It contains cystic necrotic areas. It shows pronounced diffusion restriction.

With the studies made in recent years, radical surgical treatment is replaced by breast conserving surgery. A study done by Deutsch et al.[6] was the turning point in this process. Radical and basic mastectomy was compared independent of radiotherapy. The results showed that there was no significant change in relapse, metastases, or general survival. It was evident that axillary dissection was enough for those patients with positive sentinel lymph node. In a study done by Christian et al.,[7] mastectomy, lumpectomy, and lumpectomy with radiotherapy were compared given that axillary dissection was performed to those with masses smaller than 4 cm. It was seen that, when lumpectomy is performed and followed by radiotherapy a better localized control was asserted than only lumpectomy operation. Thereby, in early staged breast cancer, breast conserving surgery was preferred instead of mastectomy, and the need of radiotherapy was emphasized. Breast conserving surgery is done in cases of ductal carcinoma in situ/Tis, T1, and T2 and with assurance of providing an acceptable cosmetic appearance. In studies, 5 cm was accepted as the threshold for the tumor size.

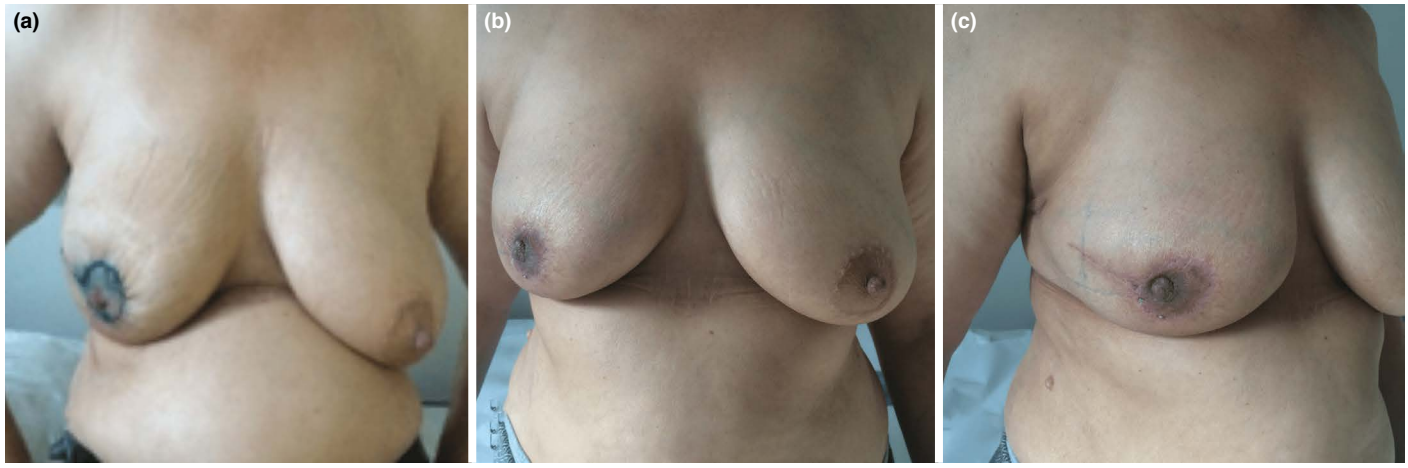

Figure 3: Appearance of the breast after surgical treatment. **(a)** Appearance 3 days after surgery **(b, c)** Appearance 1 week after the end of radiotherapy.

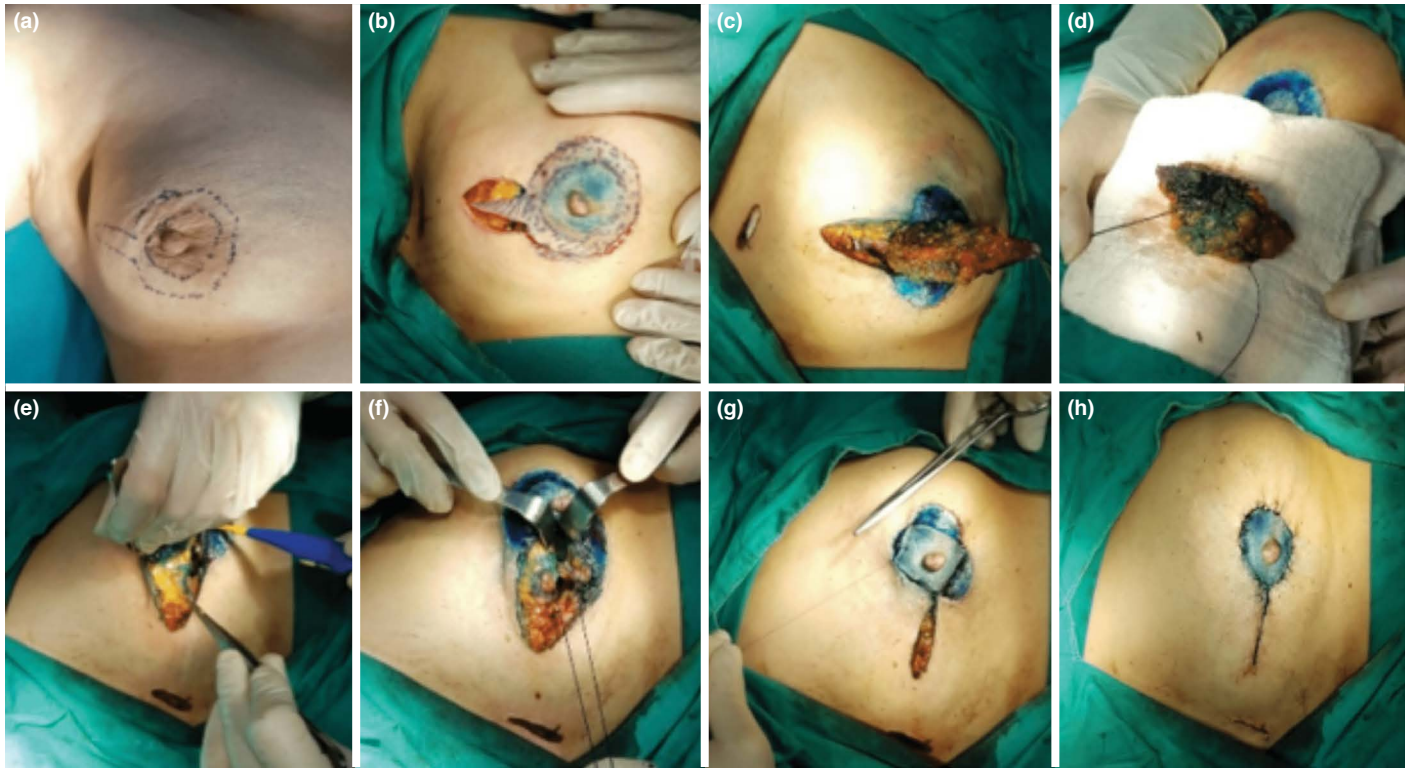

Figure 4: Racket mammoplasty technique. **(a, b)** The first incision is the circular incision made just around the areola complex with the nipple. A second incision is made around the nipple areola complex 1–2 cm beyond this incision. The third incision is in the form of a wedge extending from the areola to the axilla **(c, d)**. After the incisions, the tumor is removed with the surrounding breast tissue **(e, f)**. Skin flaps are separated from the breast tissue and the breast tissue is mobilized from the pectoral muscle laterally and medially **(g, h)**. The glandular tissue on both sides is approached one by one, with continuous absorbable sutures under the skin and under the skin.

The excision of lymph nodes is directed more toward staging and prognostic importance rather than being directed at treatment-wise. The main aim is to identify how to prevent excess treatment of axillary area and therefore decreases the likelihood of complications such as lymphedema. Krag et al.,[8] in their study, examined those patients with positive sentinel lymph node that have undergone axillary lymph node dissection. They discovered that women with only one positive sentinel lymph node contracted no other positive sentinel lymph nodes after axillary dissection. Study of Caudle et al.,[9] done in 2011 became a guide for the management of axillary area in cases of early detection of breast cancer. Those patients with tumor size smaller than 5 cm, or with clinically negative lymph nodes in axillary region or where after sentinel lymph node sampling, there were <3 positive sentinel lymph nodes and supported with the addition of adjuvant hormonal therapy or chemotherapy, there was no need for complementary axilla lymph node dissection.

In that sense, it is best to treat with current approach when there is no additional focus in breast and perform breast conserving sur-

gery with sentinel lymph nodes and radiotherapy to whole breast. Marrow[10] stated that no other surgery is more evidence based than breast conserving surgery. Breast conserving surgery is evaluated based on the survival, locale relapse, cosmetic appeal, and quality of life. Build on this, oncoplastic surgery surpasses some of the limitations. Especially in terms of decreasing the negative effect of radiotherapy on the incision site, this is very important. In addition, it allows for the reduction of large breasts, correction of ptosis, and the prevent the irregular shape of breast after lumpectomy. The success is dependent on the volume of excision, tumor localization, and glandular density. In all techniques, the main factors are the change in place of volume and replacement.

Breast tumors are mostly localized in the upper outer quadrant of the breast. Tumors in this quadrant can be excised without causing a deformity with standard breast conserving methods. Only in cases of small or middle-sized breasts, if more than 20% of the breast tissue is needed to be excised through lumpectomy, a deformity formation can be inevitable. Scar tissue after excision and radiotherapy may cause mispositioning of the nipple areolar complex. In such situations, the more preferred oncoplastic breast surgery technique is racquet mammoplasty. This can be applied with ease in cases of serious reduction of middle-sized breasts, planned large excisions, and for the correction of ptosis where outer quadrant mobilization is necessary.

In racquet mammoplasty technique, three subsequent incisions are used. The first incision is the circular incision around the nipple areolar complex. To the outer 1–2 cm of this circular incision a second circular incision is made. The third incision is wedge shaped incision stretching from areola to axilla. After the incisions, tumor is removed with the surrounding tissue. Excision is done to remove subcutaneous tissue and pectoralis facia. The area between the two circular incisions around the nipple areolar complex is de-epithelized. Skin flaps are separated from the breast, and breast tissue is separated from the pectoralis muscle on the medial and lateral surface (Fig. 4). The nipple-areolar complex may misposition toward lesion side and therefore needs to medially correct.

CONCLUSION

After oncoplastic surgical interventions, bleeding, infection, breast asymmetry, loss of sensation, seroma, prolonged wound healing, necrosis of nipple, and fat necrosis may be seen. When considered the cosmetic appeal and the success of the treatment in the long term, racquet technique may become a routine technique in breast tumor surgeries.

Statement

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

Peer-review: Externally peer-reviewed.

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

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

Financial Disclosure: The authors declared that this study has received no financial support.

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CASE REPORT

Acute dystonia after domperidone use: A rare and an unexpected side effect

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ABSTRACT

Domperidone is a dopamine receptor antagonist with gastrokinetic and anti-emetic effects. Domperidone is widely used worldwide as an anti-emetic and in the treatment of gastroparesis and gastroesophageal reflux. Because domperidone does not readily cross the blood-brain barrier, central nervous system side effects are not expected. Herein, we reported a 12-year-old girl who presented with dystonia after domperidone usage. We present a 12-year-old girl with a 40 kg body weight who was admitted to our pediatric emergency department with numbness, stiffness, and twisting in the neck, hands, arms, and tingling in the legs and back. We administered 3 mg biperiden, an anticholinergic, through slow intravenous infusion. The patient's dystonic reaction recovered 10 min after biperiden infusion. Based on our literature search, we presented one of the few acute dystonia cases after domperidone use in children. To the best of our knowledge, our case is the first case report in children who were successfully and rapidly treated with anticholinergic, biperiden.

Keywords: Biperiden, cholinergic antagonists, domperidone, dopamine antagonist, dystonia.

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INTRODUCTION

Domperidone is a dopamine receptor antagonist with gastrokinetic and anti-emetic effects.[1] Domperidone is widely used worldwide as an anti-emetic and in the treatment of gastroparesis and gastroesophageal reflux. Domperidone acts through both central and peripheral dopamine receptors. The prokinetic effect of this drug occurs through enteric dopamine receptors.[2] Domperidone works as an anti-emetic by the central dopaminergic receptor blockage around the area postrema and vomiting center.[3]

Another anti-emetic that has a similar mechanism of action to domperidone is metoclopramide. Metoclopramide, like domperidone, is both a peripheral and a central dopamine receptor antagonist.[1] Although metoclopramide crosses the blood-brain barrier well, domperidone does not readily cross the blood-brain barrier.[3] As a result, the expected central nervous system (CNS) side effects of metoclopramide are not commonly seen after domperidone use. Especially, dystonia developing after metoclopramide use is a well-defined side effect. Domperidone, which has serious side effects such as ventricular arrhythmias and sudden cardiac death, is a drug that is generally accepted as safe except for cardiac side effects. Herein, we reported a 12-year-old girl who presented with dystonia after domperidone usage.

CASE REPORT

A 12-year-old girl with 40 kg body weight was admitted to our pediatric emergency department with numbness, stiffness, and twisting in the neck, hands, arms, and tingling in the legs and back. The mother stated that her daughter received 10 mg domperidone suspension orally twice. She took the medication 3 and 5 h before the onset of her complaints. The drug was prescribed to her sister, who was admitted to the hospital due to nausea and vomiting. The patient had no history of illness or other medication use.

The patient was conscious, cooperative, and agitated on physical examination. Vital signs were within normal limits. We noticed involuntary muscle contractions in her hands, arms, and neck. Otherwise, the patient's neurological and systemic examinations were unremarkable. Blood chemistry, arterial blood gas, and complete blood count were also within the normal range.

We administered 3 mg biperiden, an anticholinergic, through slow intravenous infusion. The patient's dystonic reaction recovered 10 min after biperiden infusion. We observed her for the next 24 h for recurrence or complications, but she was completely normal after dystonia has resolved. One week later, she was admitted to the outpatient clinic for follow-up with no complaints. Her physical examination was normal.

Written informed consent was received from the patient's family to publish this case report.

DISCUSSION

Domperidone was considered a safe medication and used worldwide. Recent researches showed that domperidone is not as safe as we thought. Serious cardiovascular side effects of the intravenous form of domperidone were documented and withdrawn from the market in 1986.[4] New research stated that enteral forms could also cause cardiac arrhythmias and sudden cardiac death.[5] Therefore, the European Medicines Agency revealed a safety alert about domperidone in 2014, and restricted the use of domperidone to specific indications because of its cardiac side effects.[6] In 2019, domperidone was prohibited for using in patients younger than 12 years and weighing less than 35 kilograms in the UK.[7]

In one single-centered study for domperidone side effect profile, 44 (38.2%) out of 115 patients, who took domperidone for gastroparesis, had a side effect.[8] The most common side effects were headache (n:9), tachycardia (n:6), and palpitations (n:3). Syncope, prolonged QT interval, and death were reported in three patients separately. Neurological side effects such as anxiousness, disorientation and restlessness were also reported.

The CNS side effects are well documented for metoclopramide. Nearly 40% of patients who take metoclopramide experience some CNS side effects varying from somnolence to extrapyramidal symptoms such as tardive dyskinesia and parkinsonism.[9] Extrapyramidal side effects are not generally expected for domperidone because of its low blood-brain barrier penetration. Assumed CNS safety of domperidone is a major reason for preferring domperidone over metoclopramide, especially in children. In the literature, there are only a few adult case reports about dystonia after domperidone use.[10–13] Two recent case reports presenting children with dystonia after oral domperidone use were published from the USA and India.[14,15] Children recovered after discontinuation of domperidone, but recovery was in 1 and 7 days, respectively. No drug was given in either case. As we did in our case, anticholinergic drugs, like biperiden, can safely and rapidly reverse dystonic reactions.

Anticholinergic drugs are historically used for Parkinson's disease symptoms, movement disorders, and drug-induced extrapyramidal side effects.[16] Biperiden is one of the anticholinergic drugs and is commonly used for drug-induced dystonia.[17] Although drug-induced dystonia is usually reversible and self-limited, it is a cause of stress for patients and families. Therefore, rapid and safe recovery is crucial.

CONCLUSION

Oral forms of domperidone (suspension or blister) are widely prescribed worldwide and also in Turkey. Based on our literature search, we presented one of the few acute dystonia cases after domperidone use in children. To the best of our knowledge, our case is the first case report in children who was successfully and rapidly treated with anticholinergic, biperiden.

Physicians should be aware of possible rare, but severe extrapyramidal side effects as well as cardiac adverse effects, and assess the benefits and potential risks of domperidone before prescribing.

Statement

Informed Consent: Written, informed consent was obtained from the patient's family for the publication of thís case report.

Peer-review: Externally peer-reviewed.

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

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ERRATUM: CORRECTION OF THE AUTHORS' LIST

In the original investigation entitled "Benign Nedenlerle Yapılan Histerektomi Öncesi Probe Küretaj, Kolposkopi, Histeroskopi ve Endoservikal Küretajın Tanısal Değeri [Diagnostic value of preoperative probe curettage, hysteroscopy, endocervical curettage, and colposcopy in patients who were hysterectomized for benign diseases]" which was published in 2004, the 4th issue of the journal, one author name has been erroneously omitted from the final draft.

There is an error in the author list of this article, which should be corrected as follows:
Levent YAŞAR, Süha SÖNMEZ, Yakup ŞENSOY, Kadir SAVAN, Asiye TOKLAR,* Osman ÖZYURT, Ziya ÇEBİ, Fehmi YAZICIOGLU, Mehmet AYGÜN, Sefa KELEKCİ

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