Annals of Medical Research
DOI: 10.5455/annalsmedres.2019.07.385 2019;26(10):2233-9

Original Article

Evaluation of Tpe-interval and Tpe/QT, Tpe/QTc ratios in patients with premature ovarian failure

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Abstract

Aim: Ventricular repolarization were evaluated in patients who had POF by using novel electrocardiographic parameters including Tpe-interval and Tpe/QT and Tpe/QTc ratios. A few studies have investigated the association between premature ovarian failure (POF) and cardiovascular diseases. However, none have examined ventricular repolarization in this respect.
Materials and Methods: This cross-sectional study included 60 female patients with POF (mean 32.6±4.7 years) and 54 control healthy female subjects (mean 30.9±4.6 years).All electrocardiogram (ECG) measurements were performed by a cardiologist using a computer, and the Tpe-interval, Tpe/QT, and Tpe/QTc were compared between groups.
Results: There were no significant differences between groups in terms of baseline characteristics and laboratory parameters. The Tpe-interval, Tpe/QT, and Tpe/QTc were significantly prolonged in POF group than control subjects (p<0.001 for all). There was a strong and positive correlation between the serum follicle-stimulating hormone (FSH) level and Tpe-interval (r=0.681; p<0.001) and Tpe/QTc (r= 0.636; p<0.001). Furthermore, high and negative correlation was found between serum estradiol and Tpe-interval (r=-0.531; p<0.001) and Tpe/QTc (r=-0.510). Multivariate linear regression analysis showed that that the FSH and estradiol level were independent predictors of both the Tpe-interval (B=0.541 and p<0.001, B=-0.202 and p<0.001, respectively) and Tpe/QTc (B=0.442 and p<0.001, B= -0.239 and p<0.001, respectively).
Conclusion: It was concluded in the study that ECG parameters of ventricular repolarization, namely, Tpe-interval, Tpe/QT, and Tpe/QTc were significantly prolonged in patients that had POF.

Keywords: Premature ovarian failure; ventricular repolarization; Tpe interval; Tpe/QT ratio.

INTRODUCTION

Premature Ovarian Failure (POF) is described as the disruption of normal ovarian function. In a woman in this condition, ovulation does not occur each month. The disruption of the ovulation function and the ovarian count lower than normal are the results of disrupted ovulation functions, and are characterized with amenorrhea, hypergonadotropinaemia and estrogen deficiency presence before the age of 40 in diagnostic terms (1). Previous epidemiologic studies have shown that women who are at the Early Ovarian Failure are at risk in terms of Cardiovascular Diseases (CVDs) (2). In most of the studies conducted on animals and humans, it was shown that sex-hormones and gender differences are associated with formations (3-7). However, so far, the mechanisms of sex-hormone (estrogen, progesterone and testosterone) changes in Cardiac Arrhythmia formation has not been elucidated yet (7,8).

Various ventricular repolarization dispersions including QT,QTc,QT dispersion, QTc dispersion and Tpeak -Tend (Tpe-interval) among surface electrocardiogram (ECG) markers are shown as the markers of risk formation. Tpe/QTc (QT interval corrected for heart rate) ratio of Tpe-interval is the well-known marker of the ventricular transmural dispersion of repolarization (9,10). An extended Tpe-interval reflects the abnormal distribution

Received: 13.07.2019 **Accepted:** 04.09.2019 **Available online:** 21.10.2019
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of the ventricular repolarization and is closely related with increased formation risk (11-13). However, it was determined in studies conducted recently that Tpe/QTc ratio is a stronger ventricular repolarization measurement that is independent from the changes in the heart rates (11, 13). In none of the previous studies that have been conducted so far Tpe-interval, Tpe/QT and Tpe/QTc ratios have been evaluated as the markers of ventricular arrhythmogenesis in POF patients. For this reason, for the first time in this study, it was aimed that Tpe-interval, Tpe/QT and Tpe/QTc ratios were compared and evaluated in POF patients and in age-gender-matched healthy individuals.

MATERIAL and METHODS

Patient Population

All of the patients who had clinical and biochemical evidence for POF (n=60), who applied to the Clinic of Obstetrics and Gynecology Clinics between March 2018 and September 2018, were included in the present study as the Study Group; and the Control Group consisted of healthy age-sex-matched individuals (n=54). Written informed consent forms were obtained from all the patients who agreed to participate in the present study. The study was conducted in line with Helsinki Principles; and the Ethics Committee of Gaziantep University approved the study (2018/137).

Age-sex matched healthy individuals were defined as the ones who were determined in physical examinations to be normotensive, non-smoking, and who did not have any clinical evidence for organic diseases in their medical histories, resting 12-lead ECG findings, in routine biochemical panels and full blood counts. In addition, all individuals who were healthy were defined as those with regular menstrual cycles (25-32 days) in past 3 months, who did not have pregnancy, and who did not use any hormonal contraceptives in the past 3 months.

Besides, (1) the individuals who had acute or chronic infections; (2) the individuals who had diseases that affected the autonomic nervous system; (3) the individuals who had CVD histories of hypertension, ischemic heart disease, congestive heart failure, heart valve disease, cardiomyopathy and cardiac arrhythmias; (4) the individuals who had a history of sudden death in their family history; (5) the individuals who used concomitant-permitted medication for any reasons (including beta-blockers or psychotropic drugs) or those who used medications without permission; (6) the individuals who had any history of syncope; or (7) those who had neurological disorders ; (8) who receive hormone replacement therapy for any reason; (9) had endometriosis, having ovarian follicles bigger than 10 mm and other cystic ovary masses, ovarian surgery history, malignancy, previous radiation or chemotherapy, (10) had autoimmune diseases, genetic diseases, metabolic and endocrine diseases were not included in the present study.

The anthropometric measurements and demographic data including weights, heights and Body Mass Indices (BMIs) were determined for all participants; and detailed cardiovascular and systemic tests were carried out at the beginning of the study. A biochemistry panel that contained fasting blood glucose, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and triglyceride values of all individuals who participated in the present study. In addition, the daily serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2) levels were measured in all participants.

Transthoracic Echocardiography

Echocardiography examinations were performed by the same echocardiography specialist with a X5-1 xMATRIX array transducer with an ultrasound system (EPIQ; Philips Medical Systems, Bothell, WA, the USA) to exclude organic heart disease. Standard imaging was carried out in line with the guidelines of the American Society of Echocardiography, and the European Echocardiology Association (14).

Electrocardiography

At the initial stage of the study, the ECGs of all patients were taken. The ECGs were carried out when the patient was in the supine position by using the resting-12-Lead ECG 10 mm/mV amplitude and at 25 mm/h rate (Nihon Kohden Corp., Tokyo, Japan). All ECGs were transferred to the PC through a scanner and were then enlarged to 400x by using Adobe Photoshop Software. The computer measurements were carried out by two cardiologists who were blind to the condition of the patients and the control group.

The patients who had U waves on ECGs and those who had bundle branch block or any other intraventricular conduction defects, and the ones that had proof for left ventricular dysfunction, left ventricular hypertrophy and evidence of atrial fibrillation were excluded from the study.

QT was defined as the time spent between the onset of QRS and the point where the T wave returned to the isoelectric line, and was calculated as the average of two readings per lead. QTc was calculated by employing the Bazett Formula, i.e. the QTc = QT/√R – R range. The RR range was measured as the average of the three complexes. The Tpe interval was defined as the range between the peak of the T wave and the end of the T wave where the wave reached the isoelectric line. The Tpe interval measurements were made in the lead V5; and then if the lead V5 was not suitable, the measurements were made with lead V4 and lead V6 (12,13,15). If the amplitude of a given lead was <1.5 mm of a certain amplitude, this lead was removed from the analysis. The Tpe/QTc ratio was calculated based on these measurements. The inter- and intra-observer variation coefficients were determined to be 2.9% and 3.1%, respectively.

Blood Samplings and Laboratory Assays:

Five-ml venous blood sample was drawn from each patient to a tube that contained 1.8 mg/ml ethylene diaminetetraacetic acid, and was maintained at 4°C. The blood samples that were collected in this way were centrifuged at 15000 g for 10 min at 4°C in 24 hours of collection. Then, the plasma that was collected

was stored at -80°C. The 17b-E2 serum levels were measured with a Chemiluminescent Immunoassay (DPC). The Plasma LH and FSH levels were measured by using a Radio-Immunoassay [Architest FSH, Architest LH, Chemiluminescent Microparticle Immunoassay (Abbott Laboratories)]. The High-Sensitive C-Reactive Protein (hsCRP) was determined by using Enzyme-Linked Immunosorbent-Assay (ELISA) kits (RelAssayDiagnostics). The lipid profiles and glucose levels were measured with Hitachi P800. The inter- and intra-variation variables were <10.0% for all tests.

Statistical Analyses

The continuous data are given as averages and standard deviations. The Kolmogorov-Smirnov test was employed to evaluate whether continuous variables showed normal distribution or not. The differences between the continuous variables in the POF and control groups were determined by using the Student's t-test or the Mann-Whitney U-test. In addition, the categorical variables were summarized as percentages, and were then compared by using the Chi-square Test or the Fisher's Exact Test. It was accepted that $p<0.05$ was statistically significant. The Statistical Analyses were made with Statistical Package 115 (SPSS 20.0) Windows (SPSS Inc., Chicago, Illinois, USA) for Social Sciences.

RESULTS

A total of 60 consecutive POF (mean 32.6±4.7 years) and 54 healthy controls (mean 30.9±4.6 years) were included in the present study. The basic characteristics of the study population summarized in Table-1.

There were no significant differences between groups in terms of age, BMI, and laboratory Parameters. All the patients and control groups were sinus rhythm. Mean QT and QTc interval were similar between groups. However, Tpe-range, Tpe/QT and Tpe/QTc ratio were significantly prolonged in POF group than control group. ($p<0.001$ for all) (Table-2). There was a strong and positive correlation between the serum FSH levels and Tpe-interval ($r=0.681$; $p<0.001$) and Tpe/QTc ratio ($r= 0.636$; $p <0.001$) (Figure-1). In addition, there was also a strong and negative relation between the serum estradiol and Tpe- interval ($r=-0.531$; $p<0.001$) and Tpe/QTc ($r=-0.510$) (Figure-2).

The multivariate liner Regression analysis which include; age, BMI, Left Ventricular Ejection Fraction (LVEF), heart rate, serum Estradiol and FSH were establisment. This analysis showed that the FSH and Estradiol levels are independent predictors of Tpe-interval (B=0.541 and $p<0.001$, B=-0.202 and $p<0.001$, respectively) and Tpe/QTc ratio (B=0.442 and $p<0.001$, B=-0.239 and $p<0.001$, respectively) (Table-3).

Table 1. Baseline demographic characteristics and laboratory parameters of the POF and control groups

Parameters	Patients (n=60)	Control (n=54)	P
Age (years)	32.6 ± 4.7	30.9 ± 4.6	0.152
BMI (kg/m2)	23 ± 2.1	22.9 ± 2.2	0.831
LVEF (%)	69.3 ± 5.3	68 ± 4.7	0.712
Diastolic blood pressure (mmHg)	74 ± 4	77 ± 5	0.324
Systolic blood pressure (mmHg)	116 ± 9	119 ± 11	0.513
Total cholesterol (mg/dL)	184 ± 21	178 ± 23	0.153
LDL-C (mg/dL)	97 ± 13	87 ± 15	0.071
HDL-C (mg/dL)	55 ± 15	54 ± 12	0.714
Triglyceride (mg/dL)	122 ± 50	108 ± 43	0.109
Serum creatine (mg/dL)	0.7 ± 0,1	0.7 ± 0.1	0.541
Hemoglobin (g/dL)	13.6 ± 1	12.8 ± 1.4	0.089
Fasting blood glucose (mg/dL)	91 ± 5.7	86 ± 7.3	0.231
Sodium (mmol/L)	139 ± 4.4	137 ±6.1	0.247
Potassium (meq/L)	4.2 ± 0.3	4.1 ± 0.2	0.441
HsCRP (mg/dL)	1.65 ± 1.04	1.26 ± 0.96	0.276
FSH (mean) Median (25th-75th percentile)	75.1 ± 34.9 76.4 (46.6-108)	5.1 ± 2.7 4.8 (3.0-6.8)	<0.001
LH (mean) Median (25th-75th percentile)	39.5 ± 24.5 36.9 (19.4-51)	7.1 ± 4.4 7.1 (3.1-9.4)	<0.001
Estradiol Median (25th-75th percentile)	18.4 ± 24 8.5 (6.2-11.8)	81 ± 56 68 (27-128)	<0.001

Table 2. Comparison of electrocardiography parameters between patients with POF and control subjects

ECG variables	Patients (n=60)	Control (n=54)	P
Heart rate (bpm)	63 ± 6.2	64 ± 4.9	0.191
PR interval (msn)	151.4 ± 22.5	150.8 ± 24.5	0.92
QRS duration (msn)	98.4 ± 15.4	101.6 ± 16.7	0.43
QT (msn)	393 ± 12.8	395 ±10.8	0.676
Tpe- interval (msn)	95 ± 7.4	72.5 ± 6.7	<0.001
QTc (msn)	382 ± 21.2	385 ± 21.9	0.345
Tpe/QT	0.241 ± 0.205	0.183 ± 0.017	<0.001
Tpe/QTc	0.249 ± 0.025	0.188 ± 0.021	<0.001

Table 3. Results of multivariate linear regression analysis for the independent predictors of Tpe-interval and Tpe/QTc

Parameters	Tpe-interval		Tpe/QTc	
	ßeta	p	ßeta	p
Age (years)	-0.032	0.643	-0.022	0.762
BMI (kg/m^2)	-0.074	0.269	-0.083	0.251
Heart rate	-0.056	0.399	-0.221	0.211
LVEF	0.199	0.132	0.155	0.241
Estradiol	-0.204	0.001	-0.239	0.006
FSH	0.541	<0.001	0.442	<0.001

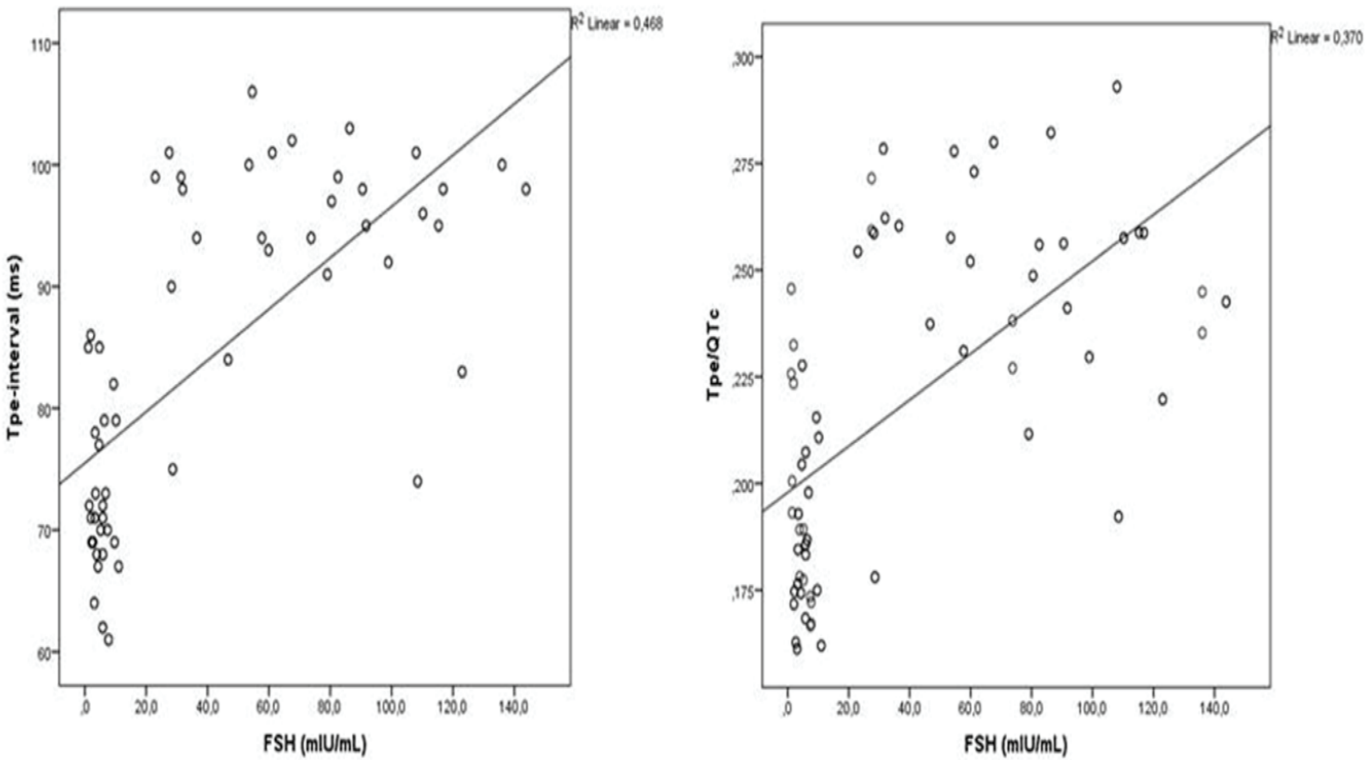

Figure 1. The correlation between the Follicle-stimulating hormone (FSH) and Tpe-interval and Tpe/QTc

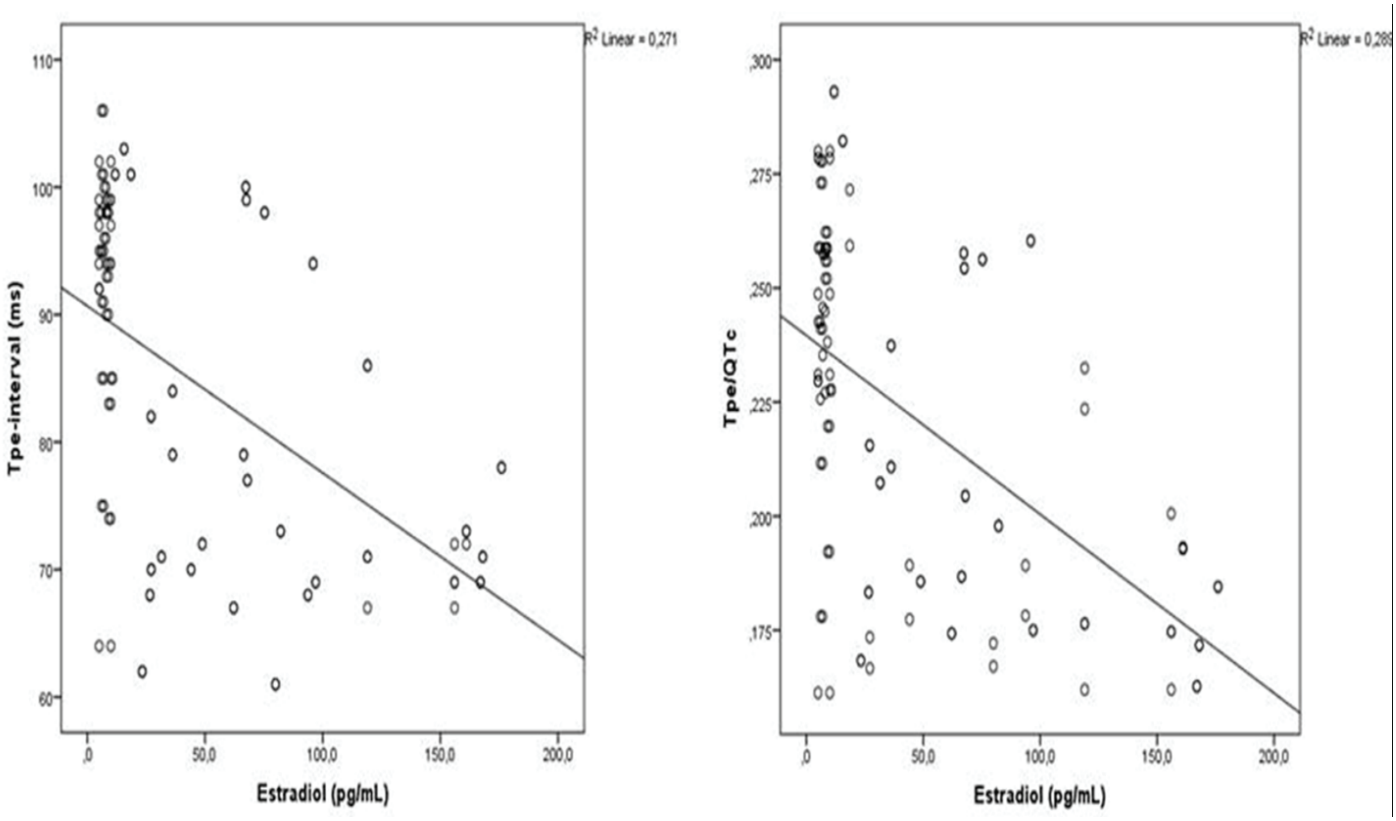

Figure 2. The correlation between estradiol and Tpe-interval and Tpe/QTc

DISCUSSION

In present study, we showed that the Tpe-interval, Tpe/QT and Tpe/QTc rates were prolonged in patients with POF compared with the control subjects.

The ventricular myocardium is a heterogeneous structure in electrical terms including three distinct cell types; Endocardial Layer, M cells and Epicardial Layers that have different electrophysiological features (16). The amplification of the ventricular repolarization dispersion showing the heterogeneity of the repolarization is considered as a substrate for Ventricular Arrhythmia.

The T-wave is an electrocardiographic outcome, which shows the ventricular repolarization. The Tpe- interval is used as an index for the total dispersion of ventricular repolarization. An increasing Tpe- interval is associated with Malign and cardiovascular events (17, 18). Since Tpe-range is affected by the changes in the body weight and heart rate, it is argued that the Tpe/QTc ratio is a more accurate measure of ventricular repolarization dispersion (19, 20).

POF might have important clinical effects because it is associated with early cardiovascular diseases like the early weakening of sex steroids, myocardial infarction and stroke (21, 22). However, although in many previous studies the effects of menopause on cardiovascular diseases and ventricular repolarization, were evaluated, little is known today on the cardiovascular and electrophysiological effects of POF in young women.

Animal and human studies were conducted on the effect of sex steroids on Cardiac Arrhythmias have shown that cardiac arrhythmias like drug-induced torsade de pointes are more common in women than in men (23).

In addition, female gender is an independent risk factor (24) for syncope and sudden deaths (24) in congenital long QT syndrome; and the high tendency to arrhythmias in normal women is associated with major differences in repolarization like the QTc interval being longer in women than in men (25). Philp et al. (26) found that estradiol could have an anti-arrhythmic effect by inhibiting the Ca2+ channel, which is larger in female rats than in male rats. This finding supports the result that reducing estradiol levels might have a pro-arrhythmic effect, and might lead to the activation of the Ca2+ channel.

In recent years, Hu et al. (27) reported that serum Estradiol levels were lower in patients who had ventricular arrhythmias compared to those in the postmenopausal control group; and that estrogen replacement therapy could significantly inhibit the number of Ventricular arrhythmias in these patients.

The present study is the first one that compares the ECG parameters in POF patients and control patients. It has been shown in this study that the well-known markers, which are associated with risk, in other words, Tpe-

interval, and Tpe/QTc, and which reflect the ventricular repolarization distribution, are prolonged in POF patients compared to those of the control subjects. In addition, a negative correlation was detected between the Serum Estradiol and Tpe- interval, and Tpe/QTc. The results of the study support the hypothesis that the reduction in estradiol levels might reveal the ventricular repolarization dispersion and pro-arrhythmic effects, which were reported in previous studies. Although previous studies showed that there was a relation between inflammation parameters and prolonged QT and QTc, no significant differences were detected between POF and control subjects in the present study. However, although it was argued in the results of this study and in previous studies that E2 deficiency might be associated with abnormal ventricular repolarization dispersion, conflicting findings were reported in several studies evaluating the effects of hormone replacement therapy on postmenopausal women (28, 29). Larsen et al. (28) reported that E2 replacement did not have a significant effect on the heart rate, QT interval or QTc interval in postmenopausal women, Yıldırım et al. showed that hormone replacement treatment decreased the QT ve QTc values at a significant level in healthy postmenopausal women (30).

Although the effects of sex-steroids on ventricular repolarization has been recognized widely, the underlying mechanisms have not been elucidated completely. In addition, these mechanisms may vary according to groups of different ages (normal or early menopause) and different conditions (physiological/pathological conditions).

Limitations

Some limitations in this study must be considered. The present study was a case-control study that was conducted with few patients. Although it is difficult to conduct a wider-scope study on rare patient groups is difficult, more accurate data might be obtained with a study that will have a wider sampling size. In addition, the hormonal status of the women was not interfered in the present study. Studies that will be conducted with POF patients by applying hormonal replacement might explain these mechanisms more.

CONCLUSION

The Tpe-interval and Tpe/QT rate measurement might reflect the POF-associated increased unwanted cardiovascular event risk. According to the findings of the present study, the risk of development may increase in POF patients due to repolarization heterogeneity. With this study, it has been shown for the first time that the new ventricular repolarization indices, Tpe- interval, Tpe/QT and Tpe/QTc ratios increase in POF patients compared to the control group.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports

Ethical approval: The study was conducted in line with Helsinki Principles; and the Ethics Committee of Gaziantep University approved the study (2018/137).

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