The effects of supraphysiological oestrogen levels on ventricular repolarisation parameters

Omer Yiginer[1], Mehmet Dogan[2], Ismet Gun[3], Huseyin Tayfun Kutlu[4], Gokhan Degirmencioglu[5], Ikin Guliyev[2], Alptug Tokatli[6], Fethi Kilicaslan[7]

[1]Department of Cardiology, Bahcesehir University Hospital, Istanbul, Turkey
[2]Department of Cardiology, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey
[3]Department of Obstetrics and Gynaecology, Sultan Abdülhamid Han Training and Research Hospital, Istanbul, Turkey
[4]Department of Obstetrics and Gynaecology, Zeynep Kamil Training and Research Hospital, Istanbul, Turkey
[5]Department of Cardiology, Sultan Abdülhamid Han Training and Research Hospital, Istanbul, Turkey
[6]Department of Cardiology, Golcuk Necati Celik Hospital, Kocaeli, Turkey
[7]Department of Cardiology, Medipol University Hospital, İstanbul, Turkey
*Omer Yiginer and Mehmet Dogan contributed equally to this work.

Abstract

Background: The frequency of arrhythmic death developing without a structural cardiac disease is higher in women. Also, female sex is an independent risk factor regarding development of torsades de pointes. Several studies have been conducted on the physiological and therapeutic effects of sex hormones on the cardiac conduction system.

Aim: In this study we aim to examine the effect of hormonal changes, especially supraphysiological E2 level changes occurring during in vitro fertilisation treatment, on ventricular repolarisation parameters.

Methods: The study included female patients aged between 23 and 39 years, who were administered controlled ovarian hyperstimulation treatment. Patients' electrocardiograms and blood samples were obtained and analysed before and after the ovarian hyperstimulation treatment.

Results: Mean QTc intervals before ovarian hyperstimulation were 411.9 ± 23.7 ms. Measurements during oestradiol peak were calculated as 420.7 ± 23.3 ms, and the QTc interval increase was significant ($p = 0.007$). Corrected QT dispersion averages were not significant before or after hyperstimulation (53 ± 17 ms vs. 54.5 ± 18.2 ms, respectively, $p > 0.05$). Tp-e, J-T peak, and PR dispersion changes were not significant after the ovarian hyperstimulation therapy.

Conclusions: Supraphysiological oestradiol levels that occur during controlled ovarian hyperstimulation cause prolongation of QTc intervals, but not to a pathological level. Although this prolongation is not significant in healthy individuals, it might increase ventricular arrhythmia risk in patients with congenital long QT syndrome and in patients taking medication that prolongs QT.

Key words: oestrogen, QT interval, QT dispersion, ventricular repolarisation, ovulation induction, in vitro fertilisation

Kardiol Pol 2018; 76, 6: 974–979

INTRODUCTION

Sudden cardiac deaths (SCDs) make up 10% to 15% of natural deaths. The majority of SCDs develop in individuals who have structural cardiac diseases such as coronary artery disease and cardiac insufficiency. Even with a structural cardiac disease, the reason for SCD is fatal ventricular arrhythmia such as ventricular tachycardia and ventricular fibrillation. Although it is often seen in men, the frequency of arrhythmic death developing without a structural cardiac disease is higher in women [1]. It has been shown in numerous studies that female sex is an independent risk factor regarding development of torsades de pointes (TdPs), which is a fatal arrhythmia [2]. A lot of studies have been carried out recently to find out the reasons for this increased arrhythmic case risk in women.

Individuals with prolonged cardiac repolarisation carry the risk of developing fatal ventricular arrhythmia. Prolonged action potential usually occurs due to prolonged cardiac repolarisation. Prolongation in QT interval, which is the equivalent of action potential duration in an electrocardiogram (ECG), is a significant electrocardiographic predictive indicator of fatal ventricular arrhythmias. The effect of sex hormones on cardiac action potential and ECG has been shown in studies carried out in animals and humans. In these studies it was revealed that endogen testosterone and progesterone shorten QT interval, whereas oestrogen prolongs QT interval [3]. Also, it was shown that hormonal fluctuations occurring during menstrual cycle do not have a direct effect on QT interval duration [4]. However, women were shown to be more sensitive during menstruation and ovulation periods compared to men regarding QT prolongation induced with ibulitide [5]. This gives rise to the thought that progesterone, which peaks in the luteal phase, protects drug-induced QT prolongation related to oestrogen in women. In studies that examined the effects of hormone replacement treatments (HRT) applied to postmenopausal women, it was shown that HRT involving oestrogen only caused prolongation of QT interval. However, HRT that involves both oestrogen and progesterone does not have an effect on QT interval [6].

In vitro fertilisation (IVF) is administered to about 1.5 million infertile women who want to get pregnant all around the world every year. E2 increase to supraphysiological levels may also be due to the effect of exogenic gonadotropins administered to patients during IVF.

While E2 levels fluctuate between 27 and 123 pg/mL (in the follicular phase) and between 96 and 436 pg/mL (in the luteal phase) during a normal menstruation cycle, E2 levels rise to 4000 pg/mL due to gonadotropins administered in IVF treatment. These levels are much higher than both physiological limits and levels that can be reached with HRT administered in the postmenstrual period. In this study we aim to examine the effect of hormonal changes occurring during IVF treatment, and especially supraphysiological E2 levels, on ventricular repolarisation parameters. Thus, it will be revealed whether gonadotropins administered to patients during IVF treatment increase TdP risk via supraphysiological E2 levels, and whether oestrogen level has an effect on cardiac repolarisation parameters.

METHODS

This study was carried out in patients who applied to Zeynep Kamil Maternity and Children's Training and Research Hospital for infertility treatment between September and December 2014. The study included female patients aged between 23 and 39 years, who were administered controlled ovarian hyperstimulation treatment. Inclusion criteria were the absence of abnormalities in cardiac examination, bio-chemical laboratory investigations, and myocardial repolarisation parameters.

However, patients who were obese (body mass index > 30 kg/m^2), were taking medication other than infertility medication, had a sudden cardiac death history in the family, and were diagnosed with a known chronic disease (diabetes mellitus, hypertension, etc.) were excluded from the study.

The study was approved by the Ethics Committee of Zeynep Kamil Maternity and Children's Training and Research Hospital (Istanbul, Turkey), and all subjects gave written, informed consent to participate.

Study protocol

Patients' regular physical examinations and laboratory tests were done in Zeynep Kamil Maternity and Children's Training and Research Hospital. ECG and blood sampling were performed twice in each patient: before ovarian hyperstimulation treatment (while oestradiol was < 50 pg/mL) and when the follicle was developed and was available for human chorionic gonadotropin. Blood samples were taken between 8.30 and 9.30 a.m. in the same setting and under the same circumstances. In order to prevent diurnal changes in QT interval, ECG was done on the same day at about 10 a.m. following bloodletting. ECG was done in the same room with patients after taking a 20-min rest in the supine position. ECG was performed at a paper speed of 50 mm/s and with 20 mm/mV amplitude. All ECG results were codified and recorded. Cardiologists who were blind to the coding system examined the ECG results and performed manual measurements. ECG samples were scanned and computerised, and digital measurements were done. All measurements were recorded by calculating the average of three successive beats.

ECG measurements and repolarisation parameters

The QT interval is the distance between the beginning of the QRS complex and the return of the T wave to the isoelectric line. QT interval represents the periods of ventricular depolarisation and repolarisation phases. QT-interval measurements were done from lead II in three successive beats from the beginning of the RS wave to the end of the T wave. Cases where the end of the T wave could not be determined were excluded from the study. If there was a U wave in the lead, the bottom point of the segment between the T and U waves was assumed as the end of the T wave [7]. The average QT interval was calculated in milliseconds.

QT dispersion was calculated as the difference between the longest and shortest QT interval on a 12-lead ECG. QTc interval and QTd were calculated with heart rate correction of the QT interval and QTd using Bazett's formula ($QTc = QT\sqrt{RR}$) [8].

J-T peak interval, from the J point to the T-wave peak, was measured for early repolarisation assessment; it reflects the early repolarisation phase of action potential. Tpeak-Tend (Tp-e) is the distance between T-wave peak point and the returning point to the isoelectric line. Tp-e represents late

phase of action potential. PR dispersion was obtained by subtracting minimum PR distance from maximum PR distance in a 12-lead ECG, calculated in milliseconds.

Statistical analysis

Statistical analyses were done using SPSS 11 software (SPSS Inc., Armonk, NY, USA). Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as the mean ± standard deviation. Kolmogorov-Smirnov test was used to determine whether the data followed normal distribution. Comparisons between the groups were performed using paired t test or Wilcoxon signed-rank test, as appropriate. P values < 0.05 were accepted as significant.

RESULTS

Demographic features and laboratory findings

A total of 59 female patients who were administered IVF treatment and controlled ovarian hyperstimulation in Zeynep Kamil Maternity and Children's Training and Research Hospital were included in the study. Clinical characteristics and laboratory findings of the patients are presented in Table 1. Mean values of laboratory investigations were within the reference ranges.

Oestradiol levels

Oestrogen levels of the patients before administering ovarian hyperstimulation were 47 ± 30 pg/mL, whereas after ovarian hyperstimulation they were 1656 ± 878 pg/mL (p < 0.001; Fig. 1).

Electrocardiographic repolarisation parameters

Regarding corrected QT, QTc measurements were done in DII, V2, and V5 derivations, which yield the clearest measurements on 12-lead ECG. Mean QTc intervals before ovarian hyperstimulation were 411.9 ± 23.7 ms, 418.6 ± 23.2 ms, and 411.1 ± 20.1 ms, respectively. Measurements at the same derivations during oestradiol peak were calculated as 420.7 ± 23.3 ms, 426.3 ± 27 ms, and. 418.7 ± 24.1 ms, respectively, and the prolongation of QTc intervals was significant for each derivation (p = 0.007, p = 0.02, and p = 0.01, respectively, Fig. 2). However, QTc values obtained after this prolongation were still within the normal range.

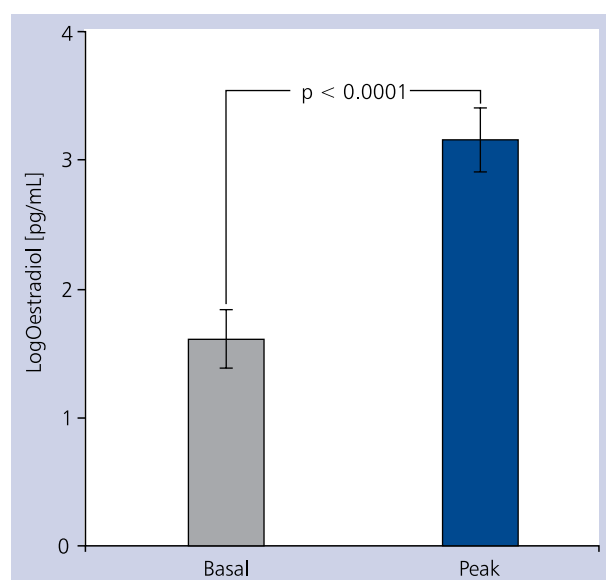QT dispersions before hyperstimulation were 46 ± 14 ms, whereas these were measured as 45.8 ± 15 ms during E2 peak (p > 0.05). Similarly, corrected QT dispersion averages were not significant before or after hyperstimulation (53 ± 17 ms vs. 54.5 ± 18.2 ms, respectively, p > 0.05).

Regarding Tp-e and J-T peak, although there was no significant difference, Tp-Te values were prolonged after the hyperstimulation (75.4 ± 10.4 ms vs. 78.2 ± 9.3 ms, respectively, p > 0.05). J-T peak values, which indicate early repolarisation, were found to be significantly shortened (203.9 ± 25.3 ms vs. 196.4 ± 29.1 ms, p = 0.002; Fig. 2).

Table 1. Clinical characteristics and laboratory findings of the study population

Number	59
Age [years]	31.8 ± 4.4
WBC [$\times 10^3\,\mu L$]	7.7 ± 1.8
Haemoglobin [g/dL]	12.8 ± 1.0
Platelet [$\times 10^3\,\mu L$]	264 ± 52
Serum urea [mg/dL]	10.1 ± 2.8
Mg [mg/dL]	1.96 ± 0.1
K [mEq/L]	4.2 ± 0.3
Ca [mg/dL]	9.5 ± 0.5
Basal FSH [mlU/mL]	6.6 ± 3.1
Basal TSH [mlU/mL]	2.1 ± 1.2

Data are given as mean ± standard deviation. WBC — white blood cell; Mg — magnesium; K — potassium; Ca — calcium; FSH — follicle stimulating hormone; TSH — thyroid stimulating hormone

Figure 1. Oestradiol levels after logarythmic transformation before and after controlled ovarian hyperstimulation

Regarding PR dispersion, while average PR dispersion before hyperstimulation was 33.3 ± 11.3 ms, it was found to be 30.8 ± 10.5 ms after hyperstimulation, and this was not a significant difference (p > 0.05).

DISCUSSION

This study shows that QTc interval was prolonged with supraphysiological oestradiol levels after controlled ovarian hyperstimulation. This prolongation was consistent in all three ECG derivations. Therefore, it was concluded that oestradiol peak in IVF treatment increased QTc interval prolongation and
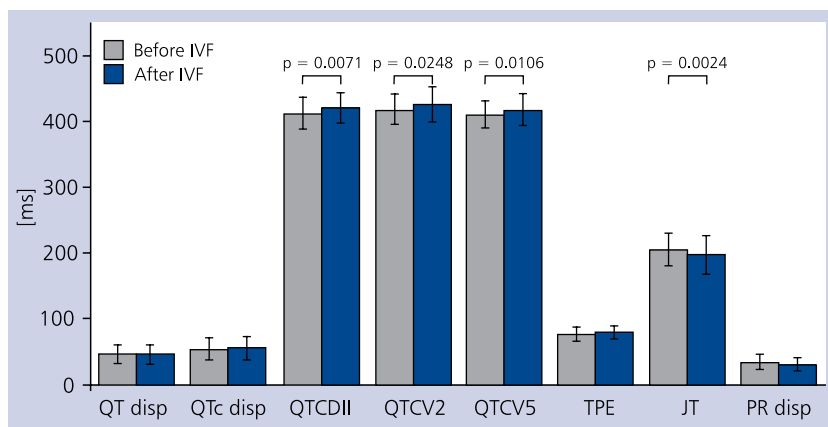
Figure 2. Electrocardiography measurements before and after in vitro fertilisation (IVF) therapy

therefore risk of arrhythmia. To the best of our knowledge, this is the first study that describes the effect of ovarian hyperstimulation on QTc interval prolongation. We found one English study in which ECG changes were examined after ovulation induction. Uckuyu et al. [9] found that QTc interval did not change with ovulation induction. Therefore, our results are different from those reported by Uckuyu et al. [9]. The reason for this inconformity may originate from either the fact that oestradiol levels in the mentioned study were lower (684.1 ± 219.8 pg/mL vs. 1656 pg/mL ± 878 pg/mL, respectively) or that ECG measurements were done manually.

The QT interval is longer in premenopausal women compared to men [8]. Also, the QT interval is longer in women, despite the higher heart rates that shorten QT interval. Moreover, women tend to develop TdP when exposed to medication that prolongs the QT interval [10]. Also, female sex is an independent risk factor for syncope and sudden death in patients with congenital long QT syndrome [11]. Differences in QT interval between the sexes begin in puberty and end in the postmenopausal period. QT shortens in men in puberty, and similarly men after orchiectomy have longer QT compared to other men [12]. In addition, QT intervals in women with virilisation were found to be shorter compared to other women.

Study results regarding QT interval changes during menstrual cycle are inconsistent. In general, although it is possible to say that the QT interval does not change during the menstrual cycle [13], some studies showed that the QT interval shortened while progesterone levels were high in the luteal phase [14]. Also, it was shown that in the case of exposure to medication that prolonged QT, greater QT prolongation occurred in women in the ovulatory phase compared to women in the luteal phase [4]. The fact that progesterone level and progesterone/oestradiol rate is inversely proportional to drug-related QT prolongation might show that progesterone has a protective role [4, 15]. These studies also support the

theory that oestrogen prolongs QT interval whereas progesterone shortens it.

Studies on the effects of oestrogen replacement treatment on QT in postmenopausal women are contradictory. Although there are many studies pointing out that oestrogen replacement treatment does not have an effect on QT [16, 17], Gökçe et al. [6] reported that in long-term replacement treatment the QT interval was prolonged, and they revealed that when combined with progestin, this effect was not observed. Similarly, Haseroth et al. [18] showed that the QT interval was prolonged in oestrogen treatment.

We found in our study that QTc interval prolongation varied between 7.6 and 8.8 ms. These values were within the reference range; therefore, it is hard to assess their effect on the risk of arrhythmia. It would be important to examine these parameters in future in patients requiring IVT treatment who have long QT syndrome or whose QT intervals are dose to abnormal values.

In our study there was no significant change regarding supraphysiological oestradiol levels in terms of QT dispersion and corrected QT dispersion. Also, in the study in which we compared hormonal changes during physiological menstrual cycle and ECG and 24-h Holter ECG findings, there was no correlation between ovulation and QT dispersion [19]. There are also other studies showing that there is no significant relation between menstrual cycle and QT dispersion [4]. The data regarding QT dispersion were not consistent with the study carried out by Uckuyu et al. [9]. In their study QT dispersion was shown to have decreased with ovulation. This difference might result from about a threefold difference in oestradiol levels or different measurement methods.

In this study the Tp-e interval, an indicator of electrical heterogeneity and late repolarisation, was found to be slightly prolonged, but the increase did not reach statistical significance. Myocardium is composed of three different

myocyte types: endocardial, epicardial, and midmyocardial M cells [20]. Although these layers are morphologically similar, they exhibit different electrophysiological characteristics. For instance, midmyocardial M cells have the longest action potential duration. Some studies point out a relationship between Tp-e and ventricular arrhythmia, cardiac insufficiency, and sudden cardiac death [21]. Tp-e prolongation represents a potential liability to reentrant arrhythmia. Also, previous studies have shown that transmural repolarisation dispersion might predict arrhythmic cases in Brugada, short QT, and long QT syndromes [20]. Again, some studies have revealed that in clinical cases such as obstructive sleep apnoea, chronic arsenic exposure [22] and ST-elevated myocardial infarction [20] transmural dispersion of repolarisation increase, and in patients with stable coronary artery disease, they decrease with the increase in the collateral circulation [23].

J-T peak interval is an early repolarisation parameter that was found to be shortened during the oestradiol peak. These data are concordant with our previous study on the physiological cycle [19]. This finding suggests that calcium ion influx currents (responsible for early repolarisation) may be affected by hormonal changes. Calcium channel inhibitory effects of oestrogen have been shown in some studies [24]. The shortening of J-T peak supports the theory that oestradiol may have a protective effect against early repolarisation-related arrhythmia and may increase the risk of late repolarisation abnormalities.

PR dispersion was shown to be prolonged in atrial fibrillation, hypertension, diabetes mellitus, and cardiovascular disease [25]. In our study, we found out that there was no relationship between supraphysiological oestradiol levels and PR interval. Hence, it might be assumed that a supraphysiological oestradiol level is not associated with elevated risk of arrhythmia, including atrial fibrillation. To the best of our knowledge, this is the first study that shows the effect of female sex hormones on PR dispersion. However, more comprehensive studies are necessary in this topic.

In conclusion, supraphysiological oestradiol levels that occur during controlled ovarian hyperstimulation cause prolongation of QTc interval, though not to a pathological level. Although this prolongation is not significant in healthy individuals, it might increase the risk of ventricular arrhythmia in patients with congenital long QT syndrome and in patients taking medication that prolongs QT. For this reason, it is appropriate to investigate family history and medication history of patients who will be administered controlled ovarian hyperstimulation, in terms of developing arrhythmia.

Conflict of interest: *none declared*

References

1. Vaitkus PT, Kindwall KE, Miller JM, et al. Influence of gender on inducibility of ventricular arrhythmias in survivors of cardiac arrest with coronary artery disease. Am J Cardiol. 1991; 67(6): 537–539, doi: 10.1016/0002-9149(91)90020-l, indexed in Pubmed: 1998288.
2. Gowd BM, Thompson PD. Effect of female sex on cardiac arrhythmias. Cardiol Rev. 2012; 20(6): 297–303, doi: 10.1097/CRD.0b013e318259294b, indexed in Pubmed: 22531673.
3. Drici MD, Burklow TR, Haridasse V, et al. Sex hormones prolong the QT interval and downregulate potassium channel expression in the rabbit heart. Circulation. 1996; 94(6): 1471–1474, doi: 10.1161/01.cir.94.6.1471, indexed in Pubmed: 8823008.
4. Rodriguez I, Kilborn MJ, Liu XK, et al. Drug-induced QT prolongation in women during the menstrual cycle. JAMA. 2001; 285(10): 1322–1326, doi: 10.1001/jama.285.10.1322, indexed in Pubmed: 11255387.
5. Gowda RM, Khan IA, Punukollu G, et al. Female preponderance in ibutilide-induced torsade de pointes. Int J Cardiol. 2004; 95(2-3): 219–222, doi: 10.1016/j.ijcard.2003.04.034, indexed in Pubmed: 15193823.
6. Gökçe M, Karahan B, Yilmaz R, et al. Long term effects of hormone replacement therapy on heart rate variability, QT interval, QT dispersion and frequencies of arrhythmia. Int J Cardiol. 2005; 99(3): 373–379, doi: 10.1016/j.ijcard.2003.03.030, indexed in Pubmed: 15771916.
7. LEPESCHKIN E, SURAWICZ B. The measurement of the Q-T interval of the electrocardiogram. Circulation. 1952; 6(3): 378–388, doi: 10.1161/01.cir.6.3.378, indexed in Pubmed: 14954534.
8. Bazett HC. The time relations of the blood-pressure changes after excision of the adrenal glands, with some observations on blood volume changes. J Physiol. 1920; 53(5): 320–339, doi: 10.1113/jphysiol.1920.sp001881, indexed in Pubmed: 16993419.
9. Uckuyu A, Ciftci FC, Ciftci O, et al. Effect of ovulation induction on QT dispersion in electrocardiography. Turk J Med Sci. 2012; 42(3): 491–496, doi: 10.3906/sag-1010-1249.
10. Makkar RR, Fromm BS, Steinman RT, et al. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA. 1993; 270(21): 2590–2597, doi: 10.1001/jama.1993.03510210076031, indexed in Pubmed: 8230644.
11. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome: a prospective international study. Circulation. 1985; 71(1): 17–21, doi: 10.1161/01.cir.71.1.17, indexed in Pubmed: 2856865.
12. Bidoggia H, Maciel JP, Capalozza N, et al. Sex differences on the electrocardiographic pattern of cardiac repolarization: possible role of testosterone. Am Heart J. 2000; 140(4): 678––683, doi: 10.1067/mhj.2000.109918, indexed in Pubmed: 11011345.
13. Hulot JS, Démolis JL, Rivière R, et al. Influence of endogenous oestrogens on QT interval duration. Eur Heart J. 2003; 24(18): 1663–1667, doi: 10.1016/s0195-668x(03)00436-6, indexed in Pubmed: 14499229.
14. Nakagawa M, Ooie T, Takahashi N, et al. Influence of menstrual cycle on QT interval dynamics. Pacing Clin Electrophysiol. 2006; 29(6): 607–613, doi: 10.1111/j.1540-8159.2006.00407.x, indexed in Pubmed: 16784426.
15. Cheng J. Evidences of the gender-related differences in cardiac repolarization and the underlying mechanisms in different animal species and human. Fundam Clin Pharmacol. 2006; 20(1): 1–8, doi: 10.1111/j.1472-8206.2005.00384.x, indexed in Pubmed: 16448390.
16. Sbarouni E, Zarvalis E, Kyriakides ZS, et al. Absence of effects of short-term estrogen replacement therapy on resting and exertional QT and QTc dispersion in postmenopausal women with coronary artery disease. Pacing Clin Electrophysiol. 1998; 21(11 Pt 2): 2392–2395, doi: 10.1111/j.1540-8159.1998.tb01188.x, indexed in Pubmed: 9825354.

17. Larsen JA, Tung RH, Sadananda R, et al. Effects of hormone replacement therapy on QT interval. Am J Cardiol. 1998; 82(8): 993–995, doi: 10.1016/s0002-9149(98)00523-2, indexed in Pubmed: 9794362.

18. Haseroth K, Seyffart K, Wehling M, et al. Effects of progestin–estrogen replacement therapy on QT-dispersion in postmenopausal women. Int J Cardiol. 2000; 75(2-3): 161–165, doi: 10.1016/s0167-5273(00)00317-x, indexed in Pubmed: 11077128.

19. Dogan M, Yiginer O, Uz O, et al. The Effects of Female Sex Hormones on Ventricular Premature Beats and Repolarization Parameters in Physiological Menstrual Cycle. Pacing Clin Electrophysiol. 2016; 39(5): 418–426, doi: 10.1111/pace.12821, indexed in Pubmed: 26842421.

20. Gupta P, Patel C, Patel H, et al. T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol. 2008; 41(6): 567–574, doi: 10.1016/j.jelectrocard.2008.07.016, indexed in Pubmed: 18790499.

21. Gellert KS, Rautaharju P, Snyder ML, et al. Short-term repeatability of electrocardiographic Tpeak-Tend and QT intervals. J Electrocardiol. 2014; 47(3): 356–361, doi: 10.1016/j.jelectrocard.2014.03.002, indexed in Pubmed: 24792986.

22. Kilicaslan F, Tokatli A, Ozdag F, et al. Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio are prolonged in patients with moderate and severe obstructive sleep apnea. Pacing Clin Electrophysiol. 2012; 35(8): 966–972, doi: 10.1111/j.1540-8159.2012.03439.x, indexed in Pubmed: 22671991.

23. Taşolar H, Ballı M, Çetin M, et al. Effects of the coronary collateral circulation on the Tp-e interval and Tp-e/QT ratio in patients with stable coronary artery disease. Ann Noninvasive Electrocardiol. 2015; 20(1): 53–61, doi: 10.1111/anec.12173, indexed in Pubmed: 24934391.

24. Bett GCL. Hormones and sex differences: changes in cardiac electrophysiology with pregnancy. Clin Sci (Lond). 2016; 130(10): 747—759, doi: 10.1042/CS20150710, indexed in Pubmed: 27128800.

25. Yazici M, Ozdemir K, Altunkeser BB, et al. The effect of diabetes mellitus on the P-wave dispersion. Circ J. 2007; 71(6): 880–883, doi: 10.1253/circj.71.880, indexed in Pubmed: 17526984.