Relationship of QT dispersion with sex hormones and insulin in young women with polycystic ovary syndrome: an observational study

Polikistik over sendromu olan genç kadınlarda QT dispersiyonu ile gonadal hormonlar ve insülin arasındaki ilişki: Gözlemsel bir çalışma

Emine Gazi, Meryem Gencer, Volkan Hancı**, Ahmet Temiz, Burak Altun, Ayşe Nur Çakır Güngör*, Ufuk Öztürk, Bahadır Kırılmaz*

From Departments of Cardiology, *Gynecology and Obstetrics and **Anesthesiology and Reanimation, Faculty of Medicine, Çanakkale Onsekiz Mart University, Çanakkale-*Turkey*

ABSTRACT

Objective: Polycystic ovary syndrome (PCOS) is a common endocrinopathy in reproductive women. Cardiovascular disease risk factors are more frequent in this population. We aimed in this study to investigate presence of QT dispersion and effects of sex hormones and insulin on QT duration in young PCOS patients.

Methods: This present study was cross-sectional observational study. A total of 47 women, 25 patients with PCOS and 22 healthy, were included. Serum testosterone, estradiol and insulin levels were studied and electrocardiography was performed at 2nd or 3th days of menstrual cycle. The study population was divided into groups according to serum testosterone and estradiol levels. Sub-groups and pairwise groups were compared by Mann-Whitney U or student t-test. The associations of QTc durations with hormone levels were calculated using Spearman rank correlation analysis. The results were evaluated at the $p<0.05$ significance level.

Results: No differences found between groups regarding to demographic parameters. Estradiol and testosterone levels were higher in patients with PCOS (41.12±13.59 vs. 35.57±19.29 pg/mL, p=0.09 and 105±58.5 vs. 17.6±10.9 ng/dL, p=0.01, respectively). QT dispersion was significantly longer in PCOS patients (47.1 vs. 32.7 ms, p=0.01). A positive correlation was found between the serum insulin level and QTc min, QTc max, and QTc mean (r=0.402, p=0.011; r=0.341, p=0.033; r=0.337, p=0.036; respectively). QT dispersion with serum testosterone and estradiol levels were positively correlated (r=0.525, p=0.001and r=0.326, p=0.046; respectively).

Conclusion: Our results suggest that QT dispersion is prolonged and testosterone, estradiol and insulin are associated with QT duration in young PCOS patients. *(Anadolu Kardiyol Derg 2013; 13: 772-7)*

Key words: Electrocardiography, QT dispersion, polycystic ovary syndrome, insulin resistance, insulin

ÖZET

Amaç: Polikistik over sendromu (PKOS) reprodüktif dönemdeki kadınlarda sık karşılaşılan bir endokrinopatidir. PCOS hastalarında kardiyovasküler hastalık risk faktörleri sık görülür. Bu çalışmada PCOS tanısı alan genç kadınlarda QT dispersiyonu varlığını ve gonadal hormonlar ve insülinin QT süresi üzerine etkilerini araştırmayı amaçladık.

Yöntemler: Gözlemsel ve enine kesitli bu çalışmaya PKOS tanısı alan 25 hasta ve kontrol grubu olarak 22 sağlıklı olmak üzere toplam 47 kadın dahil edildi. Serum testosteron, östrojen ve insülin düzeyleri, elektrokardiyografik ölçümler menstrürasyon döngüsünün 2. veya 3. gününde yapıldı. HOMA-IR hesaplandı. Çalışma olguları östrojen ve testosteron düzeylerine göre gruplara ayrıldı. İkili grupların karşılaştırılmasında student-t veya Mann-Whitney U testi kullanıldı. Testosterone, östrojen, insülin ve HOMA-IR düzeyleri ile QT süreleri arasındaki ilişkinin değerlendirilmesinde Spearman rank korelasyon analizi kullanıldı. P değeri <0,05 anlamlı kabul edildi.

Bulgular: Gruplar arasında demografik özellikler bakımından fark yoktu. Östrojen düzeyi ve testosteron düzeyleri PKOS olan hastalarda daha yüksek bulundu (41,12±13,59 ve 35,57±19,29 pg/mL, p=0,09, 105±58,5 ve 17,6±10,9 ng/dL, p=0,01, sırasıyla). PKOS olan hastalarda maksimum QTc süresi daha uzun (436,3±30,2 ve 420,9±21,9 ms, p=0,05), QT dispersiyonu anlamlı olarak daha fazla bulundu (47,1 ve 32,7 ms, p=0,01). Serum insülin düzeyi ile

Address for Correspondence/Yazışma Adresi: Dr. Emine Gazi, Çanakkale Onsekiz Mart Üniversitesi, Eğitim ve Araştırma Hastanesi, Kardiyoloji Bölümü, Sahil Yolu Cad., No: 5, 17110, Kepez, Çanakkale-*Türkiye*
Phone: +90 286 263 59 50 E-mail: eordulu@hotmail.com

Accepted Date/Kabul Tarihi: 07.03.2013 **Available Online Date/Çevrimiçi Yayın Tarihi:** 25.10.2013

doi:10.5152/akd.2013.264

maksimum (r=0,341, p=0,033), minimum (r=0,402, p=0,011) ve ortalama (r=0,337, p=0,036) QTc süreleri arasında pozitif korelasyon bulundu. Serum östrojen ve testosteron düzeyleri ile QT dispersiyonunun korele olduğu saptandı (sırasıyla r=0,326, p=0,046 ve r=0,525, p=0,001).
Sonuç: Bu çalışmamız PKOS olan genç kadınlarda QT dispersiyonunun arttığını ve östrojen, testosteron ve insülin düzeylerinin QT süresi üzerine etkileri olduğunu göstermiştir. *(Anadolu Kardiyol Derg 2013; 13: 772-7)*
Anahtar kelimeler: Elektrokardiyografi, QT dispersiyonu, polikistik over sendromu, insülin direnci, insülin

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinopathy that affects 4.6 to 11.2% of women (1). The incidence of metabolic syndrome is increased due to high incidence of obesity, insulin resistance and hyperlipidemia. Hyperandrogenism and anovulation are the most important characteristics of PCOS. Hence, the prevalence of non-insulin dependent diabetes mellitus and cardiovascular disease are also found to be higher in patients with PCOS (2).

In healthy population, QT and corrected QT (QTc) durations are prolonged in women compared to men, which may lead to increased risk of syncope, life threating ventricular arrhythmias and sudden cardiac death (3-5). It is also believed that increased QT dispersion is a risk factor for ventricular arrhythmias and sudden cardiac death (6). Despite the presence of several studies relevant to early atherosclerosis and cardiovascular disease, in only few investigations, electrocardiographic findings and risk of arrhythmia were evaluated in these patients. It has been reported that a negative correlation between serum testosterone level and QT duration, and shorter minimum QT durations in patients with PCOS (7). Accordingly, a study suggested that QT dispersion did not differ in patients and control subjects, however, relationship between sex hormone levels and QT durations was not reported in this study (8). It was known that change in hormonal values is related to menstrual cycle. Hence, QT dispersion might be dependent to hormonal status in patients with PCOS.

There was no information about the relationship between serum insulin level and QT durations.

In the present study, we aimed to investigate whether QT dispersion is different in patients with and without PCOS, and effects of sex hormones related to menstrual cycle, insulin and insulin resistance on the QT durations and QT dispersion in young women with PCOS.

Methods

Study design

The present study was an observational cross-sectional controlled study.

Study population

Twenty-five patients with PCOS and 22 healthy women as controls who applied the gynecology clinic of Çanakkale Onsekiz Mart University between February and April 2012 participated in this study. Women who under the 40 years old and not on medication for any indication at last month were included the study. Patients with hypertension, diabetes mellitus, electrolyte imbalance, chronic renal failure, chronic inflammatory disease, chronic lung disease, heart failure, valvular, structural or congenital heart disease, smoking history were excluded. Two patients were excluded because of incidental patent foramen ovale diagnosis. The study population were divided to patient or control groups whether PCOS or not. The study protocol was approved by the Local Ethics Committee and written informed consent was obtained from each patient and control subject.

Study protocol

According to whether PCOS presence the women divided into two groups as patient and control. PCOS was diagnosed if there were enlarged ovaries (2 to 8 mm in diameter) with 8 and more cysts detected by an ultrasonographer with same ultrasonography device, oligoamenorrhea, hirsutism (Ferriman-Gallwey scoring is ≥7) and elevated serum level of total testosterone (80 ng/dL or more) (9). After the diagnosed PCOS or normal control subjects, the visit was repeated at 2nd or 3th days of next menstrual cycle for study. Blood samples were collected from the patients after a 12-hr overnight fasting and electrocardiography was performed at 2nd or 3th days of menstrual cycle.

Study variables

In all cases baseline variables that age, weight, height, waist and hip circumferences were recorded. Serum fasting blood glucose, lipid parameters, thyroid stimulating hormone, gonadotrophin hormones, testosterone, estradiol and insulin levels were studied. Insulin resistance was assessed using the homeostasis model assessment (HOMA-IR) calculation: "fasting serum insulin (micro units per milliliter) x fasting plasma glucose (mg/dL)/405" (10). QT intervals and dispersion on electrocardiography were examined. Maximum and minimum QT durations were recorded. Mean QT duration (QT) was calculated from all measured QT intervals. All QT intervals were corrected for heart rate by using Bazett's (11) formula (QTc interval=QT interval/square root of the RR interval). QT dispersion was defined as difference between QTc max and QTc min. The duration of QT dispersion was recorded as outcome variable and correlation between QT duration with testosterone, estradiol, insulin and HOMA-IR was recorded as predictor variables.

Laboratory analysis

Laboratory measurement for all patients by the same devices was evaluated at 2nd or 3th days of menstrual cycle. Fasting blood glucose and lipid profile were studied with the Cobas e-601 (Roche Diagnostics, Indianapolis, USA) auto-analyzer device by chemiluminescence method. Insulin and hormones

were studied with the same device by electrochemiluminescence immunoassay "ECLIA" method (insulin Kit Lot No: 0016983902, Reference range: 2.6-24.9 µU/mL; estradiol Kit Lot no: Kit Lot No: 0017033802, reference range: 12.5-166 pg/mL for follicular phase; testosterone kit no: Kit Lot No: 001685005, reference range: 5.9-75.6 ng/dL for 20-40 years women) at biochemistry laboratory of the university hospital.

Electrocardiography

A 12-lead surface electrocardiogram (Nihon-Kohden Cardiofax ECG1350K, Tokyo, Japan) was used to evaluate QT duration for all participants. The paper speed and amplitude were 50 mm/second and 20 mm/mV, respectively. QT duration was calculated the time from the beginning of the Q wave up to isoelectric TP segment at least 3 cardiac cycles at each derivation.

Statistical analysis

Statistical analyses were performed using SPPS software program (version 15.0, SPSS, Chicago, İllinois, USA). An assessment of the normality with Kolmogorov-Smirnov was done initially. All numerical data was expressed as mean±standard deviation or median (interquartile range). Sub-groups and pairwise groups were compared by Mann-Whitney U or student *t* test.

The study population was divided into tertiles based on estradiol levels. A high estradiol group (n=18) was defined as a value in the third tertile (>45 pg/mL), and a low estradiol group (n=29) was defined as a value in the lower two tertiles (≤45 pg/mL). In addition the study population was divided two groups based on serum total testosterone levels. A high testosterone group (n=16) was defined as a value of >80 ng/dL, and a low testosterone group (n=31) was defined as a value of ≤80 ng/dL.

The associations of QTc durations and the testosterone, estradiol, insulin and HOMA-IR were calculated using Spearman rank correlation analysis in patients with PCOS and in both groups. The results were evaluated at the $p<0.05$ significance level.

Table 1. Demographic and laboratory findings of the patients and the controls

Variables	PCOS (n=25)	Controls (n=22)	*p
Age, years	26±8	29±5	0.296
BMI, kg/m^2	23.3 (18.7-40.4)	22.5 (17.5-28.6)	0.296
Waist/Hip ratio	0.80 (0.71-0.95)	0.78 (0.65-0.95)	0.550
BSA, m^2	1.71±0.19	1.67±0.11	0.417
Glucose, mg/dL	87±13	88±7	0.908
Cholesterol, mg/dL	181±38	174±33	0.556
LDL, mg/dL	95 (57-193)	92 (18-150)	0.606
HDL, mg/dL	53±16	55±16	0.767
TG, mg/dL	79 (32-422)	73 (21-236)	0.321
Insulin, µIU/mL	11.1 (1.9-82.7)	7.6 (3.1-77)	0.726
Testosterone, ng/dL	105±58.5	17.6±10.9	0.0001
Estradiol, pg/mL	41.1±13.5	35.6±19.3	0.096
FSH, mIU/mL	5.3 (2.9-7.8)	7.3 (2-19.1)	0.004
LH, mIU/mL	7.4 (2.3-39.2)	5.8 (2.1-14.5)	0.328
TSH, µIU/mL	2.03 (0.88-5.41)	1.75 (0.42-4.25)	0.410

Data are presented as mean±SD or median (interquartile range).
*Student t-test and Mann-Whitney U test.
BMI - body mass index, BSA - body surface area, FSH - follicular stimulant hormone, HDL - high density lipoprotein, LDL - low density lipoprotein, LH - luteinizing hormone, N - number of subjects, PCOS - polycystic ovary syndrome, TG - triglyceride, TSH - thyroid stimulating hormone

Results

Clinical characteristics of the study population

Table 1 summarizes the baseline characteristics. No significant differences were found between groups regarding to demographic parameters and resting heart rates. Median body mass index was 23.3 kg/m^2 (18.7-40.4) in patients with PCOS and 22.5 kg/m^2 (17.5-28.6) in control subjects (p=0.29). Body surface areas were similar in both groups (p=0.41). Serum follicular stimulating hormone (FSH) levels were lower in PCOS patients than normal subjects (p<0.01). However, estradiol levels were higher in patients with PCOS than control subjects (p=0.09). Accordingly serum total testosterone levels were significantly higher in PCOS patients than control subjects (p<0.01).

Electrocardiographic measurements

Table 2 summarizes the electrocardiographic findings. Resting heart rate was 80±13 bpm in PCOS group and 77±11 bpm in healthy subjects (p=0.31). In PCOS patients QTc max duration was longer (p=0.05). QTc min (p=0.77) and QTc mean (p=0.781) were similar in patients with PCOS and controls. QT dispersion was significantly longer in PCOS patients (p<0.01).

QT dispersion was significantly longer in subjects with high testosterone and high estradiol levels (p=0.007) and (p=0.007). QTc max, QTc min, and QTc mean were not different between patients with high and low testosterone as well as high and low estradiol levels (Table 3).

Table 2. Electrocardiographic findings of the patients and control subjects

Variables	PCOS (n=25)	Controls (n=22)	*p
Heart rate, bpm	80±13	77±11	0.31
QT max	376.6±23.5	377.0±23.2	0.29
QTc max	436.3±30.2	420.9±21.9	0.05
QT min	334.0±24.9	348.8±22.3	0.03
QTc min	386.9±30.9	389.3±21.6	0.77
QTc mean	407.1±28.3	409.1±19	0.78
QT dispersion	47.1 (21-82)	32.7 (22-46)	<0.01

Data are presented as mean±SD or median (interquartile range). QT values are given in msec.
*Student t test and Mann-Whitney U test
N - number of subjects, PCOS - polycystic ovary syndrome, QTc - QT corrected, QT max - maximum QT, QT mean- mean QT, QT min - minimum QT

Table 3. QT duration based on testosterone and estradiol levels

Variables	QTc max	QTc min	QTc mean	QTd
Testosterone >80 (n=16)	428.1±26.8	377±26	399.3±26.3	48.5 (21-82)*
Testosterone ≤80 (n=31)	428±25.8	390±24.5	410.9±21.3	33.4 (22-75)*
Estradiol >45 (n=19)	429.8±23.5	389.2±23.9	407.6 (373.1-465)	47.1 (22-55)*
Estradiol ≤45 (n=28)	424.7±28.1	385.8±27.3	406 (360.3-459.6)	36.3 (21-79)*

Data are presented as mean±SD or median (interquartile range). QT values are given in msec. Testosterone is given ng/dL and estradiol is given pg/mL
*p<0.001, Mann-Whitney U test
QTc max - corrected maximum QT, QTc mean - corrected mean QT, QTc min - corrected minimum QT, QTd - QT dispersion

Table 4. Correlation coefficients between hormone levels and QT duration*

Variables	r	p
Testosterone		
QTc max	0.175	0.287
QTc min	-0.160	0.331
QTc mean	-0.302	0.062
QTd	0.525	0.001
Estradiol		
QTc max	0.079	0.635
QTc min	-0.017	0.917
QTc mean	-0.020	0.903
QTd	0.326	0.046
Insulin		
QTc max	0.341	0.033
QTc min	0.402	0.011
QTc mean	0.337	0.036
QTd	-0.132	0.422
HOMA-IR		
QTc max	0.368	0.023
QTc min	0.431	0.007
QTc mean	0.373	0.021
QTd	-0.160	0.338
Waist circumference		
QTc max	0.308	0.057
QTc min	0.342	0.033
QTc mean	0.323	0.045
QTd	0.012	0.943

*Spearman rank correlation analysis
QTc max - corrected maximum QT, QTc mean - corrected mean QT,
QTc min - corrected minimum QT, QTd -QT dispersion, HOMA-IR - homeostasis model assessment- insulin resistance

Table 5. Correlation coefficients between hormone levels and QT duration in patients with PCOS*

Variables	r	p
Testosterone		
QTc max	-0.395	0.07
QTc min	-0.485	0.02
QTc mean	-0.474	0.03
QTd	0.105	0.60
Estradiol		
QTc max	0.099	0.67
QTc min	-0.005	0.98
QTc mean	0.103	0.66
QTd	0.410	0.07
Insulin		
QTc max	0.376	0.08
QTc min	0.471	0.02
QTc mean	0.341	0.12
QTd	-0.212	0.34
HOMA-IR		
QTc max	0.451	0.03
QTc min	0.583	0.01
QTc mean	0.437	0.04
QTd	-0.290	0.19

*Spearman rank correlation analysis
PCOS - polycystic ovary syndrome, QTc max - corrected maximum QT, QTc mean - corrected mean QT, QTc min - corrected minimum QT, QTd - QT dispersion, HOMA-IR - homeostasis model assessment- insulin resistance

Relationship between hormone levels and QT durations

A positive correlation between serum testosterone and QT dispersion (r=0.525, p=0.001) and a negative correlation between serum testosterone and QTc mean (r=-0.302, p=0.062) was found. Serum estradiol level was correlated significantly with the QT dispersion (r=0.326, p=0.046). HOMA-IR was significantly correlated with the QTc min, QTc max and QTc mean (r=0.431, p=0.007 and r=0.368, p=0.023 and r=0.373, p=0.021, respectively). In addition a positive correlation was found between the serum insulin level and QTc min, QTc max, and QTc mean (r=0.402, p=0.011; r=0.341, p=0.033; and r=0.337, p=0.036; respectively). Waist circumference was found to have a positive correlation with QTc min and QTc mean (r=0.342, p=0.033 and r=0.328, p=0.045; respectively) (Table 4).

Table 5 summarizes correlations between the serum hormone levels and QT durations in patients with PCOS. In patients with PCOS serum testosterone level was significantly negatively correlated with the QTc mean (r=-0.474, p=0.03), QTc min (r=-0.485, p=0.026) but was not correlated with QTc max. A correlation was not found between the serum estradiol and QT dispersion (r=0.41, p=0.073). However, HOMA-IR was correlated with the QTcmin (r=0.583, p=0.013) and QTc (r=0.437, p=0.042). Serum insulin level was correlated with the QTc min (r=0.471, p=0.027).

Discussion

The present study showed that QTc dispersion is longer in patients with PCOS whereas QTc max and QTc min durations

were not different between groups. Secondly, serum estradiol and testosterone were correlated to QT dispersion. Finally, insulin and HOMA-IR were correlated to QTc prolongation and this is first finding related to insulin levels and QT durations to our knowledge.

QT dispersion is a noninvasive method that measures in homogeneity in ventricular electrical activity (12) and prolonged QT dispersion is correlated with increased incidence of ventricular arrhythmias (5, 6, 13). It may occur as a result of myocardial ischemia, ventricular hypertrophy or dilatation, autonomic neuropathy, and electrolyte imbalance. QT and QTc intervals are longer in healthy women than in men. Furthermore, possibility of torsade's de pointes is more likely in women than in men (14). However, there has been no evidence of increased incidence of ventricular arrhythmias and sudden death in women. It is well known that atherosclerosis and related cardiovascular diseases are prevalent among women with PCOS (15, 16).

Alparslan et al. (8) reported that QT dispersion did not differ between women with PCOS and controls. There was no information about the levels of estradiol in their study. Orio et al. (17) evaluated electrocardiographic properties and there was no difference in QT dispersion. However, serum estradiol levels were elevated without statistical significance. In our study, estradiol levels were measured at 2nd or 3rd days of menstrual period and were found to be elevated in patients with PCOS, which may be linked to anovulatory cycles and persisting high estradiol levels (18). Nakagawa et al. (19) reported that QTc duration and serum estradiol levels were higher in follicular phase than in luteal phase in healthy women. Our study was performed in follicular phase of the menstrual cycle and this may explain how our results differed than that of other studies.

Clinical data suggest that both of endogenous and exogenous estrogen can cause prolongation in QT duration and QT dispersion (20, 21). Fulop et al. (21) reported that QTc duration is prolonged after surgical castration (orchiectomy) and estrogen replacement in male canines. QTc did not change after ovarectomy in female canines whereas shortened after testosterone replacement. This may determine that estrogen and testosterone have an effect on ventricular conduction (21). Experimental studies in animals showed that estrogen prolongs QT duration and repolarization phase of action potential by depressing the potassium current expression (22, 23). Hormone replacement therapy (HRT) with estrogen in postmenopausal women prolongs QTc (24-26). Gökçe et al. (27) found that QTc was prolonged and QT dispersion increased after the HRT with estrogen but not progestin plus estrogen in postmenopausal women. Vrtovec et al. (7) reported that QTc is shorter and serum testosterone level is negatively correlated with QTc duration in patients with PCOS. Both experimental and clinical findings support that estrogen and testosterone have some effects on QTc. In our study, serum estrogen and testosterone levels were elevated in patients with PCOS that may explicate the prominent QT dispersion. Serum testosterone and estradiol levels were correlated with QT dispersion and a negative correlation was found between serum testosterone and QTc mean. Moreover, in patients with PCOS, serum testosterone levels were negatively correlated with QTc min and QTc mean. QT dispersion is longer in patients with high testosterone and high estradiol which supports the effects of testosterone and estradiol on cardiac repolarization.

Number of studies showed that relation between insulin levels and QT duration (28, 29). QTc max, QTc min, and QT dispersion were found to be longer in patients with metabolic syndrome. A correlation between BMI, waist circumference and QT duration exists (30). The relationship between insulin level and QT prolongation has also been discovered (31, 32). Nigro et al. (33) reported that serum insulin levels and HOMA-IR were associated with QT dispersion in obese children. In our study, although serum insulin levels and HOMA-IR were not different between two groups, QTc duration correlated with HOMA-IR and insulin levels. Waist circumference was correlated with QTc min and QTc duration as well. In patients with PCOS, HOMA-IR and insulin were associated with QTc prolongation despite the patients were non-obese.

Our results suggest that increase in serum testosterone, estradiol, and insulin levels may have effect on cardiac repolarization in patients with PCOS. Increase in insulin and estradiol levels can cause QTc prolongation whereas high testosterone levels QTc shortening.

Study limitations

Our study is based on limited number patients. Determining the sex hormone binding globulin level may provide a better knowledge of serum active testosterone level and its effect on QT duration. The findings have to be supported by large prospective studies to assess the increase in QT dispersion which may induce ventricular arrhythmias and/or sudden death in patients with PCOS.

Conclusion

The present study suggests that QT dispersion is increased in young patients with PCOS. QT dispersion is correlated with serum estradiol and testosterone levels. Insulin levels and HOMA-IR are associated with QTc prolongation. QT dispersion is a risk factor for ventricular arrhythmias and sudden cardiac death. Electrocardiographic evaluation could be a practical way to assess the patients in the absence of well-established risk factors of cardiovascular diseases.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - E.G., M.G., V.H.; Design - E.G., M.G.; Supervision - M.G., A.T.; Resource- A.T., A.N.Ç.G., B.A.; Data collection&/or Processing - U.Ö., B.A., B.K.; Analysis &/or interpretation - E.G., M.G., V.H.; Literature search - E.G., U.Ö., V.H.; Writing - E.G.; Critical review - M.G., A.N.Ç.G., B.K.

References

1. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 1998; 83: 3078-82. [CrossRef]
2. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999; 84: 165-9. [CrossRef]
3. Hii JT, Wyse DG, Gillis AM, Duff HJ, Solylo MA, Mitchell LB. Precordial QT interval dispersion as a marker of torsades de pointes. Disparate effects of class Ia antiarrhythmic drugs and amiodarone. Circulation 1992; 86: 1376-82. [CrossRef]
4. Lehman MH, Hardy S, Archibald D, Quart B, Macneil DJ. Sex difference in risk of torsades de pointes with d,l-sotalol. Circulation 1996; 94: 2535-41. [CrossRef]
5. Kuo CS, Reddy CP, Munakata K, Surawicz B. Mechanism of ventricular arrhythmias caused by increased dispersion of repolarization. Eur Heart J 1985; 6: 63-70. [CrossRef]
6. Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. Am J Cardiol 1993; 72: 23-5. [CrossRef]
7. Vrtovec B, Meden-Vrtovec H, Jensterle M, Radovancevic B. Testosterone-related shortening of QTc interval in women with polycystic ovary syndrome. J Endocrinol Invest 2008; 31: 653-5.
8. Alparslan M, Onrat E, Yılmazer M, Fenkci V. QT dispersion in patients with polycystic ovary syndrome. Jpn Heart J 2002; 43: 487-93. [CrossRef]
9. Tapanainen JS, Koivunen R, Fauser BC, Taylor AE, Clayton RN, Rajkowa M, et al. A new contributing factor to polycystic ovary syndrome: the genetic variant of luteinizing hormone. J Clin Endocrinol Metab 1999; 84: 1711-5. [CrossRef]
10. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-9. [CrossRef]
11. Bazzet H. An analysis of the time-relations of electrocardiograms. Heart 1920; 7: 353.
12. Higham PD, Campbell RWF. QT dispersion. Br Heart J 1994; 71: 508-10. [CrossRef]
13. Yunus A, Gillis AM, Duff HJ, Wyse DG, Mitchell LB. Increased precordial QTc dispersion predicts ventricular fibrillation during acute myocardial infarction. Am J Cardiol 1996; 78: 706-8. [CrossRef]
14. Gowda RM, Khan IA, Punukollu G, Vasavada BC, Sacchi TJ, Wilbur SL, et al. Female preponderance in ibutilide-induced torsade de pointes. Int J Cardiol 2004; 95: 219-22. [CrossRef]
15. Cibula D, Cifkova R, Fanta M, Poledne R, Zivny J, Skibova J. Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a, ovary syndrome. Hum Reprod 2000; 15: 785-9. [CrossRef]
16. Dahlgren E, Janson PO, Johansson S, Lapidus L, Oden A. Polycystic ovary syndrome and risk for myocardial infarction. Evaluated from a risk factor model based on a prospective population study of women. Acta Obstet Gynecol Scand 1992; 71: 599-604. [CrossRef]
17. Orio F, Palomba S, Cascella T, Manguso F, Vuolu L, Tafuri D, et al. Lack of electrocardiographic changes in women with polycystic ovary syndrome. Clin Endcrinol 2007; 67: 46-50. [CrossRef]
18. Matalliotakis I, Kourtis A, Koukoura O, Panidis D. Polycystic Ovary Syndrome: etiology and pathogenesis. Arch Gynecol Obstet 2006; 274: 187-97. [CrossRef]
19. Nakagawa M, Ooie T, Takahashi N, Taniguchi Y, Anan F, Yonebochi H, et al. Influence of menstrual cycle on QT interval dynamics. Pacing Clin Electrophysiol 2006; 29: 603-17. [CrossRef]
20. Yang PC, Clancy CE. Effects of sex hormones on cardiac repolarization. J Cardiovasc Pharmacol 2010; 56: 123-9. [CrossRef]
21. Fulop L, Banyasz G, Szabo G, Toth IB, Biro T, Lorincz I, et al. Effects of sex hormones on ECG parameters and expression of cardiac ion channels in dogs. Acta Physiol 2006; 188: 163-71. [CrossRef]
22. Drici MD, Burklow TR, Haridasse V, Glazer RI, Woosley RL. Sex hormones prolong the QT interval and down regulate potassium channel expression in the rabbit heart. Circulation 1996; 94: 1471-4. [CrossRef]
23. Ebert SN, Liu XK, Woosley RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. J Womens Health 1998; 7: 547-57. [CrossRef]
24. Haseroth K, Seyffart K, Wehling M, Christ M. Effects of progestin-estrogen replacement therapy on QT dispersion in postmenopausal women. Int J Cardiol 2000; 75: 161-6. [CrossRef]
25. Carnethon MR, Anthony MS, Cascio WE, Folsom AR, Rautaharju PM, Liao D, et al. A prospective evaluation of the risk of QT prolongation with hormone replacement therapy: the atherosclerosis risk in communities study. Ann Epidemiol 2003; 13: 530-6. [CrossRef]
26. Yıldırır A, Aybar F, Kabakçı G, Yaralı H, Akgül E, Bükülmez O, et al. Hormone replacement therapy shortens QT dispersion in healthy postmenopausal women. Ann Noninvasive Electrocardiol 2001; 6: 193-7. [CrossRef]
27. Gökçe M, Karahan M, Yılmaz R, Örem C, Erdöl C, Özdemir S. Long term effects of hormone replacement theraphy on heart rate variability, QT interval, QT dispersion and frequencies of arrhytmia. Int J Cardiol 2005; 99: 373-9. [CrossRef]
28. Van de Borne P, Hausberg M, Hoffman RP, Mark AL, Anderson EA. Hyperinsulinemia produces cardiac vagal withdrawal and nonuniform sympathetic activation in normal subjects. Am J Phisiol 1999; 276: 178-83.
29. Watanabe T, Ashikaga T, Nishizaki M, Yamawake E, Arite M. Association of insulin with QTc dispersion. Lancet 1997; 350: 1821-2. [CrossRef]
30. Soydinç S, Davutoğlu V, Akçay M. Uncomplicated metabolic syndrome is associated with prolonged electrocardiographic QTc interval and QTc dispersion. Ann Noninvasive Electrocardiol 2006; 11: 313-7. [CrossRef]
31. Van Noord C, Sturkenboom MC, Straus SM, Hofman A, Kors JA, Witteman JC, et al. Serum glucose and insulin are associated with QTc and RR intervals in nondiabetic elderly. Eur J Endocrinol 2010; 162: 241-8. [CrossRef]
32. Lefrandt JD, Diercks GF, Van Boven AJ, Crijns HJ, Van Gilst WH, Gans RO. High fasting glucose and QTc duration in a large healty cohort. Diabetologia 2000; 43: 1332-3.
33. Nigro G, Russo V, Disalvo G, De Crescenzo I, Rago A, Perrone L, et al. Increased heterogeneity of ventricular repolarization in obese nonhypertensive children. Pacing Clin Electrophysiol 2010; 33: 1533-9. [CrossRef]