ORIGINAL ARTICLE

Electrocardiographic P-Wave Duration, QT Interval, T Peak to End Interval and Tp-e/QT Ratio in Pregnancy with Respect to Trimesters

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Background: P-wave duration helps to determine the risk of atrial arrhythmia, especially atrial fibrillation. QT interval, T peak to end interval (Tp-e), and Tp-e/QT ratio are electrocardiographic indices related to ventricular repolarization which are used to determine the risk of ventricular arrhythmias. We search for any alterations in electrocardiographic indices of arrhythmia in the pregnancy period with respect to trimesters.

Methods: We enrolled 154 pregnant and 62 nonpregnant, healthy women into this cross-sectional study. Maximum and minimum P-wave durations (Pmax, Pmin), and QT intervals (QTmax, QTmin) were measured from 12 leads. QT measurements were corrected using Fridericia (QTc-Fr) and Bazett's (QTc-Bz) correction. Tp-e interval was obtained from the difference between QT interval, and QT peak interval (QTp) measured from the beginning of the QRS until the peak of the T wave. Tp-e/QT ratio was calculated using these measurements.

Results: Pmax were 93.0 ± 9.1 , 93.9 ± 8.9 , 97.9 ± 5.6 , 99.0 ± 6.1 in nonpregnant women, first, second, third trimesters of pregnancy, respectively ($P = 0.001$); whereas Pmin values were not significantly different. QTc-Fr max were 407.4 ± 14.2 , 408.5 ± 16.1 , 410.1 ± 13.1 , 415.1 ± 10.1 ($P = 0.007$); Tp-e were 72.7 ± 6.2 , 73.2 ± 6.5 , 77.2 ± 8.9 , 87.2 ± 9.6 ($P < 0.001$); and Tp-e/QT were 0.17 (0.14–0.20), 0.17 (0.14–0.20), 0.18 (0.15–0.23), 0.20 (0.16–0.25) in nonpregnant women, first, second, and third trimesters of pregnancy respectively ($P < 0.001$). None of the participants experienced any arrhythmic event.

Conclusions: P-wave duration is prolonged in the second trimester, and resumes a plateau thereafter. Maximum QTc interval, Tp-e interval and Tp-e/QT ratio are increased in the late pregnancy. Although these indices are altered during the course of pregnancy, they all remain in the normal ranges.

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P-wave duration; QT interval; T peak to end interval; Tp-e/QT ratio

Normal healthy pregnancy is prone to significant adaptations in the cardiovascular system. Plasma volume increases beginning from the sixth week of pregnancy, it reaches almost more than half of the original volume by the end of second trimester, and then a plateau is resumed.¹ There is approximately 10–20% increase in the heart rate, and 30–50% in-

crease in the cardiac output.¹ Fall in the peripheral resistance leads to a decrease in the blood pressure of pregnant women, which returns to the pregestational levels by the term.¹ Increases in plasma volume causing stretch in cardiac chambers, increased sympathetic tone, and sex hormones all contribute to the proarrhythmic milieu during pregnancy.²

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P-wave duration (PWD), an indicator of atrial conduction, is used to trace atrial electrophysiological changes and help to determine the risk for atrial arrhythmias, especially atrial fibrillation (AF).^{3,4} In the recently published Copenhagen ECG study, both short and long PWD compared to the reference group were associated with an increased risk of AF in a large primary care population.⁵ In addition, other studies have shown that PWD was a marker of AF recurrence after electrical cardioversion, and AF ablation procedures.^{6,7}

Measurement of electrocardiographic QT interval is used to assess ventricular electrical activity determined by depolarization and repolarization phases.⁸ Alterations in the QT interval due to inherited diseases, and acquired clinical conditions and/or drugs have been associated with malignant ventricular arrhythmias, syncope and sudden cardiac death.^{9,10}

In addition to QT interval, T peak to end interval (Tp-e) has been introduced to analyse ventricular repolarization. Electrocardiographic T wave represents the voltage gradient between subendocardial and subepicardial myocardium. Peak of the T wave coincides with the end of the epicardial repolarization, whereas the end of the T wave shows the end of the repolarization in the entire myocardium.^{11,12} In this manner, Tp-e has been described as a useful indicator to assess the transmural dispersion of repolarization.¹³

Recently Tp-e/QT, which is the ratio of the interval between the peak and the end of the T wave to the QT interval, was introduced as a novel index of arrhythmogenesis providing an estimate of dispersion of repolarization relative to total duration of repolarization.¹⁴ It eliminates the confounding effects of variability of heart rate and inter-individual variation of QT interval.¹⁴

We aimed to investigate if there are any alterations in the electrocardiographic indices which may indirectly indicate the risk of atrial or ventricular arrhythmias, and if they change with respect to trimesters in healthy, noncomplicated normal pregnancy.

METHOD

We enrolled 154 pregnant and 62 nonpregnant, healthy women into this cross-sectional study between November 2014 and February 2015 at Obstetrics and Gynecology Departments of two university hospitals. Exclusion criteria were

multiple pregnancies, hypertension, diabetes mellitus, gestational diabetes, preeclampsia, eclampsia, atherosclerotic coronary artery disease, valvular heart disease, any inflammatory immunologic, rheumatologic disease, abnormal renal, hepatic or thyroid function tests, rhythm other than sinus, U waves or negative T waves on ECG, and electrolyte imbalance.

Patients rested in the supine position for 10 min, and electrodes were placed in the standard anatomical locations. The 12-lead ECG was recorded (AT-102, Schiller AG, Baar, Switzerland) at a paper speed of 50 mm/s and amplification of 0.1 mV/mm at rest in the supine position.

Onset of the P wave was defined as the first atrial deflection from the isoelectric line, and offset was the return of the atrial signal to baseline. Maximum PWD and minimum PWD were measured.

QT interval was assessed as the time between the first deflection of the QRS complex and the end of the T wave. The slope intercept technique was used to determine the end of the T wave, which is identified as the intercept of the line tangential to the point of maximum T wave down-slope with the isoelectric line.¹⁵ QT interval was measured in as many 12 leads as possible. Corrected QT (QTc) values were calculated using Fridericia and Bazett's formulas: QTc (Fridericia): $QT/\sqrt[3]{RR}$; QTc (Bazett's): $QT/\sqrt{RR}$. We preferred to depend primarily on Fridericia correction in this study, because it is more reliable at low and high heart rates. Bazett's correction may overestimate the duration of repolarization at fast heart rates and underestimate at low heart rates.¹⁶ Tp-e interval was measured in each precordial lead and obtained from the difference between QT interval and QT peak interval; measured from the beginning of the QRS until the peak of the T wave.¹⁷ Tp-e/QT ratio was calculated using these measurements.

Office blood pressure measurements were made in the sitting position after 5 minutes of resting using the nondominant arm. Blood pressure was calculated as the average of two consecutive BP measurements taken at least 10 minutes apart by a physician using a mercury sphygmomanometer. Complete blood count (Cell-Dyn 3700, Abbott, Abbott Park, IL, USA) and biochemistry analysis (Unicel Dx C800 Synchron, Beckman Coulter, Fullerton, CA, USA) were performed after an overnight fasting.

This study was conducted according to the recommendations of the Declaration of Helsinki

on Biomedical research, and it was approved by the institutional Ethics committee. All participants gave written informed consent.

Statistical Analysis

The SPSS statistical software (SPSS 18.0 for windows, Inc., Chicago, IL, USA) was used for all statistical calculations. Shapiro-Wilk test was used to test for normal distribution. Continuous variables were given as mean $\pm$ standard deviation or medians (min-max), whichever is appropriate. Continuous variables were compared by Analysis of variance (ANOVA) and Kruskal-Wallis tests. For post hoc multiple comparisons, Tukey's test or Bonferroni's correction was applied where appropriate. All tests of significance were 2-tailed. Statistical significance was defined as $P < 0.05$. When Bonferroni's correction was applied, $P < 0.008$ is considered as significant.

RESULTS

Participants were similar with respect to age in the first, second, third trimester pregnancies and the control group (Table 1). Body mass index (BMI) increased towards the end of the pregnancy naturally. Hemoglobin levels were lower in the third trimester compared to the control group and hematocrit levels were lower in second term and third term compared to the nonpregnant women. Mean heart rates of pregnant women especially in the later terms of pregnancy were higher and median blood pressures were lower as expected (Table 1).

Table 2 shows PWD, QTc, Tp-e, and Tp-e/QT values in nonpregnant women and pregnant women with respect to the trimesters of pregnancy. Pmax were 93.0 ± 9.1 , 93.9 ± 8.9 , 97.9 ± 5.6 , 99.0 ± 6.1 in nonpregnant women, first, second, and third trimesters of pregnancy, respectively ($P = 0.001$); whereas Pmin values were not significantly different.

QTc max values using both Fridericia and Bazett's correction were found to be the highest in the late pregnancy compared to the nonpregnant state or the earlier pregnancy period, as well as Tp-e interval and Tp-e/QT ratio (Table 2). However, QTc peak intervals were not significantly different between nonpregnant women and pregnant women in different trimesters of pregnancy. QTc min values were also comparable in nonpregnant

and pregnant women (Table 2). None of the participants experienced any arrhythmic event.

DISCUSSION

This is a descriptive study which provides information on indirect electrocardiographic indices of arrhythmia risk determination in normal healthy pregnancy with respect to trimesters. None of the participants experienced any arrhythmic event during the course of pregnancy. We demonstrate that maximum P-wave durations in the second and third trimester are prolonged compared to nonpregnant state and first trimester pregnancy. In addition, maximum QTc and Tp-e are found to be longer, and Tp-e/QT ratio is higher in the third trimester of the pregnancy period. Although alterations are observed in these electrocardiographic measurements during the course of pregnancy, they remain in the ranges which are generally acknowledged as "normal" according to the current literature.

PWD is an electrocardiographic tool which shows propagation of sinus impulses and have attracted attention as a marker to predict atrial fibrillation.¹⁸ Elevated atrial pressure due to cardiac and noncardiac conditions, ischemia and metabolic stress cause atrial remodeling thus provide a substrate for atrial fibrillation.³ Hypertension, diastolic dysfunction, diabetes, advanced age, and increased BMI were found to be associated with prolongation of P-wave indices due to atrial remodeling.¹⁹⁻²²

There are few studies investigating P-wave indices in pregnant women. Two of them demonstrated that P-wave dispersion was increased in pregnant patients with preeclampsia or cholestasis.^{23,24} To the best of our knowledge, there is only one study conducted in pregnant women without any complications, at which participants were not subdivided according to trimesters.²⁵ In that study, maximum P-wave duration was not altered, but P-wave dispersion was increased due to a shortening in Pmin value.²⁵ In this study, we did not focus on P-wave dispersion which is defined as the difference between the maximum and minimum P-wave durations and used to reflect regional differences in P-wave durations²⁶; because dispersion parameters are highly unreliable with large intra- and interobserver variability. Instead, we report that a significant prolongation in the

Table 1. Baseline Characteristics, Hemodynamic Measurements and Laboratory Test Results

	Nonpregnant (n = 62)	First Trimester (n = 41)	Second Trimester (n = 45)	Third Trimester (n = 68)	P
Age (years)	29.0 (20–40)	27 (21–37)	29 (22–41)	29 (17–39)	0.29
BMI (kg/m ²)	25.8 ± 2.7	26.7 ± 3.6	28.3 ± 2.9	29.4 ± 3.3	<0.001*
Heart rate (bpm)	73.4 ± 9.7	75.9 ± 10.6	85.8 ± 10.2	85.0 ± 11.5	<0.001*
SBP (mmHg)	117.5 (90–140)	110 (80–120)	100 (80–140)	100 (90–145)	<0.001**
DBP (mmHg)	75.0 (60, 90)	70 (50, 80)	60 (50–90)	70 (50–95)	<0.001**
FPG (mg/dL)	86.7 (62–107)	84.1 (64–110)	88.4 ± 17.9	86.8 ± 13.5	0.39
BUN (mg/dL)	15.7 ± 4.2	17.7 ± 6.5	15.3 ± 6	14.8 ± 4.5	0.06
Cretinine (mg/dL)	0.7 (0.4–0.9)	0.54 (0.2–0.7)	0.50 (0.35–0.70)	0.50 (0.40–0.80)	0.11
ALT (U/L)	14 (12–35)	11.5 (8–51)	12 (6–42)	12 (5–48)	0.14
AST(U/L)	17 (10–32)	14.5 (10–30)	14.5 (10–30)	16 (10–54)	0.06
Hb (g/dL)	12.6 ± 1.4	12.5 ± 1.3	12.5 ± 1.1	11.9 ± 1.2	0.007†
Htc (%)	38.7 (28.4–45.8)	37.9 (29.9–48)	36.7 (28.2–42.6)	36.1 (27–47)	<0.001‡
TSH (μIU/mL)	2.04 (0.4–5.3)	1.77 (0.50–2.72)	1.57 (0.50–3.5)	1.75 (0.42–4.3)	0.38

P < 0.05 is considered as statistically significant. For the comparisons where Bonferroni's correction was applied, P < 0.008 is considered as statistically significant.

*Significant difference is between nonpregnant group-second trimester, nonpregnant group-third trimester, first trimester-second trimester, first trimester-third trimester.

**Significant difference is between nonpregnant group-first trimester, nonpregnant group-second trimester, nonpregnant group-third trimester.

†Significant difference is between nonpregnant group-third trimester.

‡Significant difference is between nonpregnant group-second trimester, nonpregnant group-third trimester.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DBP = diastolic blood pressure; FPG = fasting plasma glucose; Hb = hemoglobin; Htc = hematocrit; SBP = systolic blood pressure; TSH = thyroid stimulating hormone.

Table 2. Electrocardiographic Measurements in Nonpregnant Women and Pregnant Women in First, Second, and Third Trimesters of Pregnancy

	Nonpregnant (n = 62)	First Trimester (n = 41)	Second Trimester (n = 45)	Third Trimester (n = 68)	P
Pmax	93.0 ± 9.1	93.9 ± 8.9	97.9 ± 5.6	99.0 ± 6.1	<0.001*
Pmin	62.4 ± 8.2	62.9 ± 6.8	64.4 ± 5.1	64.1 ± 4.9	0.83
QTc max (Bazett's)	425.98 ± 14.7	425.9 ± 15.05	428.5 ± 12.9	435.9 ± 4.7	<0.001†
QTc min (Bazett's)	397.7 ± 14.1	397.2 ± 14.1	399.9 ± 12.6	402.5 ± 4.7	0.19
QTc peak (Bazett's)	331.4 ± 13.1	333.1 ± 12.8	332.7 ± 11.9	335.6 ± 15.3	0.31
QTc max (Fridericia)	407.4 ± 14.2	408.5 ± 16.1	410.1 ± 13.1	415.1 ± 10.1	0.007‡
QTc min (Fridericia)	380.5 ± 13.7	381.1 ± 15.2	381.7 ± 13.7	383.6 ± 9.7	0.55
QTc peak (Fridericia)	315.1 ± 16.3	317.5 ± 11.6	317.2 ± 16.4	320.7 ± 16.6	0.25
Tp-e	72.7 ± 6.2	73.2 ± 6.5	77.2 ± 8.9	87.2 ± 9.6	<0.001†
Tp-e/QT	0.17 (0.14–0.20)	0.17 (0.14–0.20)	0.18 (0.15–0.23)	0.20 (0.16–0.25)	<0.001‡

P < 0.05 is considered as statistically significant. For the comparisons where Bonferroni's correction was applied, P < 0.008 is considered as statistically significant.

*Significant difference is between nonpregnant group-second trimester, nonpregnant group-third trimester, first trimester-third trimester.

†Significant difference is between nonpregnant group-third trimester, first trimester-third trimester, second trimester-third trimester.

‡Significant difference is between nonpregnant group and third trimester; first trimester-third trimester.

PWD is recorded at the second trimester and it is not further prolonged at the third trimester. This prolongation is in accordance with the normal physiology of pregnancy, considering the volume expansion which peaks at the second trimester.

Maximum QTc, Tp-e, and Tp-e/QT which reflect ventricular arrhythmogenicity were increased at the third term of pregnancy. Lechmanova et al.

found that late pregnancy caused a prolongation in QTc and it remained prolonged in the short term after delivery.²⁷ Several factors take part in the altered electrophysiological properties of the myocardium in pregnancy. Hormonal status; especially highly estrogenic milieu is one probable explanation. It was shown that cardiac repolarization was prolonged in females in human and animal

studies²⁸; although this difference is not translated into increased incidence of arrhythmias in female gender. In healthy postmenopausal women, hormone replacement therapy with estradiol was shown to prolong QT interval.^{29,30} Odening et al. showed that in prepubertal ovariectomized transgenic long QT rats who were treated with estradiol, the incidence of polymorphic VT was increased.³¹ Mechanisms underlying promotion of sudden cardiac death by estradiol were proposed as steepening of the QT/RR slope, prolongation of cardiac refractoriness and change in dispersion of action potential duration.³¹

The second mechanism related to the change in electrocardiographic indices of ventricular repolarization is the alteration in the volume status in pregnancy which possibly causes stretch in cardiac chambers. In an animal study, it was shown that volume overload due to increased cardiac output caused eccentric hypertrophy in the heart resembling the eccentric hypertrophy observed in athletes who participate in high dynamic exercise like running.³² In the same study, it was also shown that in late pregnancy, outward transient potassium channels were reduced, and thus action potential and QT interval were prolonged.³²

This study is the first to report any alterations in Tp-e and Tp-e/QT in pregnancy. Differences in the time of repolarization of electrophysiologically distinct types of cells in the ventricular myocardium determine the shape of the T wave. For this reason, Tp-e is a measure of transmural dispersion of repolarization.¹⁷ Although we detected an increase in the maximum QTc interval toward late pregnancy, the slight increase observed in QTc peak interval was not statistically significant. So the increase in QT interval is rather related to the increase in the Tp-e interval. Transmural dispersion of repolarization has gained popularity over prolongation of QTc interval; it is thought to be the principal factor in induction of malignant arrhythmias.³³ Increase in Tp-e and Tp-e/QT were observed in the late pregnancy. We think that volume status and hormonal changes are responsible for this finding as well as the increase in the QTc interval.

There are several limitations of this study. This is a cross-sectional study which does not allow to infer causality. It would be more informative if we could obtain serial ECG recordings in each trimester from all women during the course of

pregnancy. In this study none of the patients had any atrial or ventricular arrhythmic event. If we had adequately large population size including women who experienced arrhythmic events during the course of pregnancy, we could have compared the participants who had and had not experienced arrhythmic events. Finally, we did not perform echocardiographic assessment.

In conclusion, P-wave duration which is an index of atrial arrhythmogenesis is increased at the second trimester and resumes a plateau thereafter, whereas maximum QTc interval, Tp-e interval, and Tp-e/QT ratio, which are indices of ventricular arrhythmogenesis, are increased at the late pregnancy. All of these alterations remain in the normal range.

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