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Evaluation of ventricular repolarization in pregnant women with intrahepatic cholestasis

Ozgur Kirbas [a], Ebru Hacer Biberoglu [b], Ayse Kirbas [b,*], Korkut Daglar [b], Ozge Kurmus [c], Nuri Danisman [b], Kutay Biberoglu [d]

[a] Department of Cardiology, Yuksek Ihtisas Education and Research Hospital, Ankara, Turkey
[b] Department of Perinatology, Zekai Tahir Burak Women Health Care, Education and Research Hospital, Ankara, Turkey
[c] Department of Cardiology, Ataturk Education and Research Hospital, Ankara, Turkey
[d] Gazi University Medical School, Department of Obstetrics and Gynecology, Ankara, Turkey

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ABSTRACT

Background: Bile acids can induce arrhythmia by altering cardiomyocyte contractility or electrical conduction. The aim of this study was to investigate, by means of QT dispersion parameter detected by simple standard electrocardiogram (ECG), ventricular repolarization changes in pregnant women with and without intrahepatic cholestasis of pregnancy (ICP).
Methods: In this case–control study including 75 pregnant women with cholestasis and 35 healthy, uncomplicated pregnancy cases, electrocardiographic QT interval durations and QT dispersion (QT-disp) parameters, corrected for the patients' heart rate using the Hodges formula, were investigated.
Results: Maximum corrected QT interval values were significantly higher in the severe ICP group than in the control group ($p < 0.001$) and significantly higher in the severe ICP group than in the mild ICP group ($p = 0.01$). The values of the mild ICP and control groups were similar. Corrected QT-disp values were also significantly higher in both ICP groups than in the control group and significantly higher in the severe ICP group than in the mild ICP group.
Conclusion: Cholestatic diseases predispose patients to cardiovascular complications. Our data clearly demonstrated that QT-disp values were significantly altered in pregnant women with cholestasis when compared to the normal ones. This simple ECG parameter can be used to screen high-risk women, in order to better target counseling regarding lifestyle modifications and to conduct closer follow up and management of women with a history of ICP.

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a transient form of cholestasis that is characterized by elevated serum bile acid (BA) levels and/or liver enzymes, as well as pruritus localized to the abdomen, legs, and palms. It typically occurs in the second half of pregnancy [1].

The main cause of ICP has not yet been identified; heterogeneous and multiple factors have been suggested in the pathophysiology [1–3]. Elevated total BA level (>10 μmol/L) is the most sensitive and specific diagnostic hallmark of ICP [1].

ICP is associated with increased risk of adverse fetal outcomes, including preterm labor, fetal distress, unexplained fetal death [4,5], and fetal dysrhythmia [6]. It has been suggested that elevated BA levels in ICP could alter cardiomyocyte contractility or electrical conduction, causing fetal arrhythmia or death [7,8].

The QT interval (QT) is defined as the interval from the onset of the QRS complex, the first sign of ventricular depolarization, to the end of the T wave, the final sign of ventricular repolarization. QT interval dispersion (QT-disp) is defined as the difference between the maximal and minimal QT durations recorded from multiple surfaces ECG leads. Abnormalities in the duration of the QT and QT-disp reflect abnormalities in ventricular repolarization [9,10]. Both prolonged QT duration and increased QT-disp have been identified as being related to electrical instability and increased risk of ventricular arrhythmias [10–12].

In contrast to the known arrhythmogenic effects of BAs on the fetal heart, little is known about their potential implications for the adult heart. Therefore, our aim was to investigate the ventricular repolarization

* Corresponding author at: Department of Perinatology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey.
E-mail addresses: ozgurkirbas@yahoo.com (O. Kirbas), ebru2513@gmail.com (E.H. Biberoglu), drayse1982@yahoo.com, ayseozdemirkirbas@hotmail.com (A. Kirbas), drhkd1@gmail.com (K. Daglar), ozge_kurmus@yahoo.com (O. Kurmus), nuridanisman@gmail.com (N. Danisman), kobiber@gmail.com (K. Biberoglu).

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changes, readily detectable by simple standard ECG criteria, via QT-disp in pregnant women with and without intrahepatic cholestasis.

2. Material and methods

This case–control study was conducted at the Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey. The local Institutional Review Board of the hospital approved the study, and the universal principles of the Helsinki Declaration were applied.

Seventy-five consecutive pregnant women with ICP (41 with mild and 34 with severe disease) and 35 healthy women with uncomplicated pregnancy (as the control group) all in the third trimester and matched for maternal and gestational ages, were recruited between December 2013 and November 2014.

ICP was diagnosed when a pregnant woman had pruritus and elevated total bile acid (TBA) ($\geq$10 μmol/L) and/or aminotransferase levels in the blood sample. The patients were classified with mild or severe ICP based on TBA concentrations of 10–40 or $\geq$40 μmol/L, respectively [1].

The presence of any pregestational liver or heart disease; multiple gestation or trophoblastic disease; history of systemic, inflammatory, endocrine, gastrointestinal, psychiatric, immunologic, or oncologic disease; smoking; alcohol consumption; or active labor were among the exclusion criteria.

The age, body mass index (BMI), resting heart rate, blood pressure, and TBA levels of each participant were recorded. The perinatal outcome parameters, including gestational age at delivery, preterm delivery, stillbirth, birth weight, 5-minute Apgar score, neonatal intensive care unit admission, and meconium-stained amniotic fluid, were also assessed.

All of the pregnant women were in sinus rhythm; there were no symptoms of arrhythmia, such as palpitation, chest pain, dizziness, or fainting. To exclude electrolyte abnormality, maternal serum sodium, potassium, calcium and magnesium levels were checked at admission. None of the patients were taking medications known to affect the cardiovascular system, such as anti-arrhythmics and antihypertensives. Patients on ursodeoxycholic acid treatment were also excluded from the study groups, due to the well-known anti-arrhythmogenic effects [13]. All of the cases and controls underwent standard ECG and 2D echocardiography.

The patients in both groups were asked not to consume caffeinated beverages within 3 h prior to the procedure. The 12-lead ECG was obtained at a paper speed of 50 mm/s and 1-mV/cm standardization. The ECGs were recorded when the patients first came to our unit, during the daytime, between 8:00 and 11:00 am, in a quiet room with the subjects in the resting position.

As it is well known that the heart rate modifies the QT interval, several formulas, such as Bazett's, which is still considered one of the most popular ones, have been used to correct the heart rate effect. However, these formulas are not accurate or sufficient enough to avoid the potential of false QT prolongations [14,15].

In view of all this, The American Heart Association (AHA), The American College of Cardiology Foundation (ACCF), and The Heart Rhythm Society (HRS) have recommended the application of linear regression functions rather than Bazett's formula. Therefore, the standardization and interpretation of the ECG, including the correction of QT intervals, were carried out according to the AHA, ACCF, and HRS recommendations [9].

A single experienced cardiologist without knowledge of the clinical characteristics of the patient and control groups analyzed all the ECGs. To improve the accuracy, the measurements were performed with calipers and a magnifying lens to define the ECG deflection. ECGs without clearly identifiable QT waves were excluded from the QT wave analysis. QT wave duration was evaluated in all 12 leads. Pregnant women with measurable QT waves in more than nine ECG leads were included in the study.

QT interval was measured from the start of the Q wave to the end of the T wave. QT intervals were corrected for the patients' heart rate using the Hodges formula ($QTc = QT + 1.75\ (\text{heart rate} - 60)$). When U-waves were present, the QT was measured to the lowest point of the curve between the T- and U-waves. Maximum (QT max) and minimum (QT min) QT-wave durations were defined as the longest and shortest measurable QT-wave durations, respectively, in any lead. Accordingly, corrected QT dispersion (QTc-dis) was calculated as the difference between maximal and minimal QTc intervals.

Blood samples were obtained from the antecubital vein early in the morning, following 10 h of fasting, as well as 2 h postprandial; TBA levels were determined by enzymatic assay. All of the other blood analyses were carried out within 2 h of blood sampling, using a hematology analyzer (GEN-S; Beckman-Coulter Inc., Brea, CA) at the central laboratories of Zekai Tahir Burak Women's Hospital.

3. Reproducibility

Thirty electrocardiograms were randomly selected for evaluation of the inter-observer variability of QT interval measurements by two independent observers. The same measurement was repeated twice, 3 days apart, to calculate the intra-observer variability. Mean percent error was

Table 1
The comparison of patient characteristics in the control (group 1) and intrahepatic cholestasis (group 2 mild & group 3 severe disease) pregnant groups.

	Group 1 (n = 35)	Group 2 (n = 41)	Group 3 (n = 34)	P value (groups)		
				1 vs 2	1 vs 3	2 vs 3
Maternal age, year	27.1 ± 2.4	28.7 ± 5.0	29.3 ± 4.1	0.98	0.23	0.33
Gravidity (range)	1 (1–3)	1 (1–2)	1 (1–3)	0.83	0.85	1
Gestational week at assessment	35.2 ± 1.5	35.6 ± 1.5	34.7 ± 2.14	0.56	0.47	0.95
BMI at assessment, kg/m^2	26.4 ± 2.16	26.6 ± 3.1	27.03 ± 1.5	0.60	0.63	0.97
Fasting BA (μmol/L)	2.25 ± 1.2	21.5 ± 5,8	59.9 ± 15.4	<0.001[a]	<0.001[a]	<0.001[a]
Postprandial BA (μmol/L)	2.88 ± 1.06 –	27.6 ± 7.7	65.2 ± 30.6	<0.001[a]	<0.001[a]	<0.001[a]
Heart rate, bpm	80.1 ± 7	82 ± 8.7	78 ± 6.9	0.35	0.16	0.39
Systolic BP, mmHg	116.0 ± 8.2	113.7 ± 7.6	117.5 ± 7.8	0.37	0.15	0.82
Diastolic BP, mmHg	71 ± 6.8	77 ± 10.7	72 ± 10	0.53	0.97	0.96
Maximum QTc interval (ms)	419 ± 26	433.3 ± 29	455.2 ± 36	0.14	<0.001[a]	0.01[a]
Minimum QTc interval (ms)	373.6 ± 27.5	374.1 ± 29.3	369.3 ± 33.9	0.99	0.84	0.78
Mean QTc interval	396.4 ± 26.1	403.7 ± 27.5	412.3 ± 33.6	0.55	0.08	0.45
QTc dispersion (ms)	45.7 ± 12	59.5 ± 20	87.6 ± 13.9	0.002[a]	<0.001[a]	<0.001[a]

Data expressed as mean ± SD,
BA, bile acids; BMI, body mass index; bpm, beats per min; BP, Blood pressure, min: minutes, ms, millisecond.
[a] The mean difference is significant at the 0.05 level.