Oral contraceptive use and the risk of cardiac events in patients with long QT syndrome

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BACKGROUND In prior clinical studies of patients with long QT syndrome (LQTS), pregnancy was associated with fewer cardiac events (CEs) compared to before or after pregnancy. In recent animal studies involving rabbits with LQTS mutations, progesterone had favorable effects on CEs compared to estrogen. The effect of oral contraceptive therapy with its high progesterone/estrogen ratio on the risk of CEs in patients with LQTS has not been examined.

OBJECTIVE To study the effect of oral contraceptive use on the risk of CEs in patients with LQTS.

METHODS We studied 174 patients from the Rochester-based LQTS Registry who responded to a questionnaire about their oral contraceptive use. We used time-dependent Cox regression to estimate the hazard ratio for recurrent CEs when patients were using vs not using oral contraceptives during nonpregnancy periods. For this recurrent events analysis, the Prentice-Williams-Peterson model was used and the time origin was defined as the onset of menarche. We adjusted for the baseline corrected QT interval, history of CEs before menarche, age at menarche onset, number of births, time-dependent β-blocker therapy, and LQTS genotype.

RESULTS No differences in the risk of CEs for the times patients with LQTS were using vs not using oral contraceptives was found in the general population with LQTS (hazard ratio 1.01; $P = .95$) or in analyses of LQTS subsets ($P > .2$).

CONCLUSION Oral contraceptive therapy use did not affect LQTS-related CEs in the study population. Oral contraceptives did not show beneficial or harmful effects in this patient group.

KEYWORDS Long QT syndrome; Oral contraceptive therapy; Sex hormones; Progesterone; Estrogen; Cardiac events; I_{Ks} channels; I_{Kr} channels; Pregnancy

ABBREVIATIONS ACA = aborted cardiac arrest; **CE** = cardiac event; **HR** = hazard ratio; **I_{Kr}** = rapid component of cardiac K^+ channel; **I_{Ks}** = slow component of cardiac K^+ channel; **LQTS** = long QT syndrome; **LQT#** = long QT syndrome genotype #; **OC** = oral contraceptive; **PWP** = Prentice-Williams-Peterson; **QTc** = corrected QT

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Introduction

The inherited long QT syndrome (LQTS) is a genetic cardiac channelopathy caused by ion-channel mutations. These mutations result in delayed ventricular repolarization and are detected by a prolonged QT interval on the electrocardiogram. Symptoms in LQTS are known as cardiac events (CEs) and include syncope, aborted cardiac arrest (ACA), and sudden cardiac death. In long QT syndrome genotype 1 (LQT1) and long QT syndrome genotype 2 (LQT2), the delayed rectifier K^+ channels are affected. Mutations in *KCNQ1* gene, encoding for the slow component of cardiac K^+ channel (I_{Ks}), result in LQT1,[1,2] and mutations in the *KCNH2* gene, encoding for the rapid component of cardiac K^+ channel (I_{Kr}), result in LQT2.[3,4]

Earlier studies in LQTS found that pregnancy was not associated with CEs in probands or first-degree relatives[5] and was associated with a significant reduction of CEs when compared to the time before first conception.[5,6] Pregnancy correlates with a high progesterone/estrogen ratio, suggesting a protective role for progesterone in this disorder. Similarly, a few in vivo and in vitro studies have examined the effect of sex hormones on I_{Ks} and I_{Kr}, with consistent findings suggesting that estrogen may cause QT interval prolongation while progesterone does not.[7–11]

Hormonal therapy studies in female patients with LQTS are limited. This study is the first to examine the effects of oral contraceptive (OC) therapy on the risk of CEs in female patients with LQTS. We compared CEs between patients

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who are and those who are not receiving OC therapy to evaluate the effect of this hormonal therapy on the clinical course of patients with LQTS. The results of this study provide new information regarding OC medications with their high progesterone/estrogen ratio as well as address safety concerns that might be associated with OC use in patients with LQTS.

Methods

Study population

This study included patients from the Rochester-based LQTS Registry who responded to a questionnaire about their OC use (n = 175). Study packages were mailed to eligible patients in September 2010 (n = 340). Questionnaires were sent out to female patients who met the following criteria: (1) who were born between 1950 and 1992, with the starting date reflecting the time when the use of OC medications became popular and the 1992 year limit to ensure that patients who received the questionnaire were at least 18 years of age; (2) who were genotype positive for LQT1 or LQT2 or clinically diagnosed with corrected QT (QTc) interval $\geq$450 ms and are identified clinically as LQTS in the registry; and (3) who were alive and gave consent to the study. One patient with missing age at menarche (time origin for the analysis) was excluded. The total number of patients included in the study was 174.

This study was approved by the University of Rochester Medical Center Research Subjects Review Board.

Time origin and follow-up

The time origin was selected as the date of menarche to restrict CE counts to a time period when OC use was a likely possibility and to preclude controls (ie, patients who are not taking OCs) from coming from premenarche time periods. Follow-up time during pregnancy periods was excluded by temporarily removing pregnant patients from the risk set for 2 reasons: (1) patients are usually free of OC use during pregnancy, and (2) the risk of CEs during pregnancy has been shown to be low, possibly owing to the hormonal changes during pregnancy.[5,6] Follow-up was censored at the age of 40 years to minimize the confounding effect of other cardiovascular diseases and hormonal changes after this age.

End points

The study end point was the occurrence of 1 or more syncopal events or ACA, that is, first and recurrent events after the onset of menarche. No deaths occurred in this study population during follow-up as a consequence of the retrospective design.

Statistical analysis

We compared patients who responded to the questionnaire vs those who did not respond by using the Wilcoxon test for continuous variables and the χ^2 test for categorical variables. The clinical characteristics of the study population were summarized by mean $\pm$ SD for continuous variables and by frequencies and proportions for categorical variables. The analysis of the primary end point was based on the conditional PWP non-gap–time model (Prentice, Williams, and Peterson, 1981), an extension of the stratified Cox model,[12] allowing for time-dependent strata with separate nonparametric baseline hazard functions for each recurrent event. The PWP model was used to estimate the hazard ratio (HR) for recurrent CEs (first and subsequent) for patients on vs off OC therapy after the onset of menarche. OC use was modeled as a time-dependent variable to account for the changing status of OC use (being on to going off and vice versa). The HR was adjusted for the history of CEs before menarche, baseline QT interval corrected for heart rate, age at menarche onset, number of births, and a time-dependent variable for β-blocker use to adjust for LQTS therapy.

All statistical tests were 2-sided tests with $P = .05$. Analyses were performed with SAS software (version 9.3, SAS Institute, Cary, NC).

Results

Baseline clinical characteristics

Patients who responded to the OC questionnaire (n = 175) were compared with those who did not respond (n = 165) (Table 1). Comparison of both groups showed no significant differences in variables relevant to LQTS severity, including family history, baseline QTc interval measurements, and nonpharmacological therapy. For nonresponders, we have no information about specific variables requested by this questionnaire, such as age at menarche and onset of OC use, and therefore we were unable to compare these variables.

Clinical characteristics for the study population, patients who responded to the questionnaire and included in this study (n = 174; 1 patient was missing age at menarche), are summarized in Table 2. There were 129 genotype-positive patients, 20 genotype-negative patients, and 25 patients with unknown information about their genotype. Sixty-two patients (36%) were genotype positive for LQT1, 65 (37%) patients were genotype positive for LQT2, 1 patient (0.57%) had LQT4, and 1 patient (0.57%) was genotype positive for both LQT10 and LQT11. Only 18 (14%) patients had CEs before menarche, while 41 (24%) patients had a family history of sudden cardiac death. The average baseline QTc interval was 492 ms, and it ranged from 380 to 670 ms. Of all 174 patients included in the study, there were 147 patients who reported OC use at any time compared to 27 patients who never used OC.

Multivariate time-dependent analyses

LQTS in the general study population

The results of the covariate-adjusted PWP model for recurrent CEs in female patients with LQTS are summarized in Table 3. The HR is reported relative to going off OC medications. There is no difference in the risk of CEs (syncope or ACA) for the times patients with LQTS were using vs those not using OCs (HR 1.01; 95% confidence interval 0.71–1.44; $P = .95$). The HRs are adjusted for baseline QTc interval, CEs before menarche, age at menarche onset, number of births, LQT1 (vs LQT2) genotype, and time-dependent β-blocker use.