Normalization of QT interval duration in a long QT syndrome patient during pregnancy and the postpartum period due to sex hormone effects on cardiac repolarization

Katja E. Odening, MD,* † Gideon Koren, MD, † Malcolm Kirk, MD, FHRS* 

From the *Cardiovascular Research Center, Division of Cardiology, Rhode Island Hospital, Alpert Medical School of Brown University, Providence, Rhode Island, and †Heart Center University of Freiburg, Department of Cardiology and Angiology I, Freiburg, Germany.

Introduction

In inherited long QT syndrome (LQTS), female sex is associated with a longer QT interval duration and a higher risk for potentially lethal polymorphic ventricular tachycardia (pVT) and sudden cardiac death than in males.1,2 The arrhythmogenic risk is particularly pronounced during the postpartum period—especially in patients with LQTS type 2—but relatively low during pregnancy,3 indicating a potential role for sex hormones in modulating cardiac repolarization and arrhythmogenesis in LQTS. In patients with the acquired, drug-induced LQTS variant, hormone-induced changes in QT interval duration during different phases of the menstrual cycle have been described, with a less pronounced drug-induced QT interval prolongation and hence shorter QT intervals during the luteal phase, when progesterone levels are high, than during the follicular phase with its high estradiol levels.4 Moreover, postmenopausal hormone replacement therapy in healthy women was found to prolong QT duration in women treated with estradiol alone but did not alter QT duration when combinations of estradiol and progesterone were used.5 However, despite the use of the heart rate–corrected QTc duration for risk stratification in LQTS patients,2 to date, the effects of sex hormones and their withdrawal during different phases of menstrual cycle, pregnancy, and postpartum on QT interval duration have not been investigated systematically in patients with inherited LQTS—except for 1 recent report on menstrual cycle–related changes in QT duration in 1 LQTS family.6

Case report

We here present the case and a series of electrocardiogram (ECG) recordings of a 37-year-old female LQTS patient, who was regularly followed in our arrhythmia outpatient clinic since 2002.

Initial presentation

In 1999, at the age of 21 years, the patient was initially diagnosed with epilepsy owing to several syncopal episodes and was consequently started on antiepileptic medication topiramate (100 mg twice daily) and carbamazepine (800 mg twice daily). Despite this treatment, she experienced 3 more syncopal episodes in 2000, all of which were triggered by auditory stimuli. The first of these syncopal episodes occurred in February 2000, when she was startled (by a knock on the door) while watching a horror movie. She was taken to a local emergency department and an ECG was notable for sinus rhythm and a prolonged heart rate–corrected QT interval (QTc) of 500 ms. The patient was consecutively diagnosed with LQTS. The second episode occurred in April 2000, when she was sleeping in a car and a noise woke her up. The third episode took place after she had already been placed on beta-blocker therapy (atenolol 25 mg once a day), when a jackhammer went off while she was at work.

Subsequently, given the failure of a standard beta-blocker therapy, a single-chamber implantable cardioverter-defibrillator (ICD; St. Jude Medical, Profile; St. Paul, MN) was implanted in August 2000 and the beta-blocker therapy was changed to metoprolol succinate 50 mg daily. At the time of the diagnosis and during the following years (2000–2002), all ECG recordings showed a QTc duration ranging from 500 to 575 ms. Following the ICD implantation, our patient experienced 1 inappropriate shock due to exercise-induced sinus tachycardia (188 beats/min), but has not experienced additional pVT episodes. In June 2003, her ICD was replaced (Medtronic, Marquis; Minneapolis, MN).
**KEY TEACHING POINTS**

- In patients with inherited long QT syndrome, heart rate-corrected QT interval (QTc) duration (and consequently arrhythmogenic risk) may vary pronouncedly with changing sex hormone levels.
- For adequate risk assessment, QTc duration should be assessed repetitively in female LQTS patients—ideally at different phases of the menstrual cycle, during pregnancy, and postpartum.
- One single measurement of a normal QTc does not exclude the diagnosis "long QT syndrome."

Although her medical history is suggestive of LQTS type 2, so far none of the known deleterious HERG/KCNH2 mutations were found, nor has any other known LQTS mutation been detected in any of the sequenced genes (FAMILON Comprehensive Test for the genes KCNQ1 [LQT1], KCNH2 [LQT2], SCN5A [LQT3], KCNE1 [LQT5], KCNE2 [LQT6], KCNJ2 [LQT7], CACNA1C [LQT8], CAV3 [LQT9], SCN4B [LQT10], AKAP9 [LQT11], SNTA1 [LQT12], and KCNJ5 [LQT13], reported sensitivity 75%, done in June 2012). However, a polymorphism in KCNE1 (Asp 85 Asn), the beta-subunit to KCNQ1/KvLQT1, was detected. This polymorphism may play a role in drug-induced LQTS and has been observed more frequently in LQTS patients, where it contributes to the clinical phenotype (QT duration, arrhythmogenic events). Her father and mother have normal QTc durations, and there have been no confirmed cases of sudden death in the family, although her maternal uncle died in his 20s, reportedly of a seizure, and a maternal cousin drowned at 16 years of age with no apparent cause. No ECG recordings had been acquired in these relatives.

**Presentation in our clinic**

We began treating the patient in 2002 in our outpatient arrhythmia clinic at Rhode Island Hospital. In the first 3 years, we regularly observed a prolonged QTc duration of greater than 500 ms in all of her ECG recordings. No further episodes of syncope occurred, nor were any pVTs detected by the ICD. Several months after her appointment in our hospital in May 2005, when her ECG showed a QTc duration of 575 ms (Figure 1A), she got pregnant, and she gave birth to a healthy girl at 29 weeks’ gestation (in March 2006).

At her follow-up appointment in November 2006, we observed for the first time a normalized QTc duration of 410 ms (Figure 1B). During several follow-up visits in 2007, her QTc duration continued to be normalized (May 2007, QTc of 400 ms; December 2007, QTc of 410 ms). We wondered about a possible explanation for this QTc normalization and realized that our patient was breastfeeding until March 2007. Additionally, she had a progesterone-releasing intrauterine device implanted in May 2006—and was hence under progesterone treatment while visiting our hospital in May 2007. The progesterone-releasing intrauterine device was removed in October 2007, and she subsequently became pregnant; shortly afterwards, in December 2007, she still had a normalized QTc duration (Figure 1C). From April until August 2008, she received weekly intramuscular 17α-hydroxyprogesterone caproate injections to prevent preterm birth; in August 2008, she delivered her second child 1 month prematurely. ECG controls in February, June, and August 2009, performed while the patient continued breastfeeding, continued to show normalized QTc intervals of around 400 ms. It was not until her follow-up visit in August 2011, when she was no longer breastfeeding or on hormone-based contraceptive, that her ECG showed a prolonged QTc duration of 497 ms (Figure 1D) for the first time since 2005.

**Discussion**

We here present the first series of ECG recordings of an individual LQTS patient with pronounced intra-individual changes of QTc duration (ie, a normalization of QTc) during pregnancy, while breastfeeding, and while using a progesterone-releasing intrauterine device. The ECG alterations strongly indicate a hormonal influence on QT interval duration in inherited LQTS.

**QTc interval normalization during pregnancy**

Although our patient had very long baseline heart rate-corrected QT intervals ranging from 500 to 575 ms, her QTc normalized during pregnancy (410 ms). This can likely be attributed to the effects of increased progesterone levels during pregnancy (ie, a normalization of QTc) during pregnancy, while breastfeeding, and while using a progesterone-releasing intrauterine device. The ECG alterations strongly indicate a hormonal influence on QT interval duration in inherited LQTS.
progesterone to the pregnancy-associated QT shortening/normalization observed in our patient.

Moreover, in our patient, a polymorphism in \( KCNE1/\) minK, the beta-subunit to KvLQT1 to form \( I_{Ks} \), was detected. This polymorphism is known to modulate the clinical phenotype in LQTS patients (QTc, arrhythmogenic events)\(^7\) in a sex-specific manner, with additional QT prolongation in male but not in female patients, suggesting

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**Figure 1**  
A: Electrocardiogram (ECG) recording from our patient in May 2005 showing a very long heart rate–corrected QT interval (QTc) of 575 ms (QT 560 ms, RR 960 ms). B: ECG recording from the same patient in November 2006 during the postpartum period while under progesterone-releasing intrauterine device treatment, showing for the first time a normalized QTc interval of 410 ms (QT 360 ms, RR 750 ms). C: ECG recording from our patient during pregnancy in December 2007, still showing a normalized QTc of 410 ms (QT 350 ms, RR 720 ms). D: ECG recording from the same patient after stopping breastfeeding in August 2011 showing—for the first time since 2005—again a QTc interval duration within her initial range of 497 ms (QT 500 ms, RR 990 ms). All traces were acquired at a speed of 25 mm/s.
that this polymorphism might be susceptible to differential sex hormonal influence and could thus contribute to progesterone’s particularly pronounced QT interval-shortening effects observed in this patient.

**QTc interval normalization during the postpartum phase**

During the postpartum phase, our patient continued to exhibit a normalized QTc duration. Two different hormonal mechanisms likely accounted for this observation: first, the progesterone-releasing intrauterine device our patient used for contraception during the postpartum phase after her first pregnancy; and second, the fact that she was breastfeeding during both postpartum periods. Progesterone-releasing intrauterine devices are known to increase local progesterone levels in the uterus as well as systemic serum progesterone levels (increase of serum progesterone concentration by 200 pg/mL, Mirena Data Sheet; Bayer). While using this intrauterine device, our patient hence continued to benefit from the QT-shortening effect of progesterone. During her second postpartum phase, our patient had ceased to use a progesterone-containing contraceptive, but she continued to have a shortened QTc interval; this is likely due to the fact that she was breastfeeding. In the early postpartum period, serum progesterone and estradiol levels are known to quickly decrease (Figure 2). Additionally, breastfeeding impedes normal ovarian cycles by disrupting the pulsatile release of gonadotropin-releasing hormone from the hypothalamus and of luteinizing hormone from the pituitary, which results in a reduced follicular estradiol production, thus maintaining the reduced estradiol serum level (Figure 2). We have previously demonstrated that physiological estradiol prolongs QT duration in transgenic LQT2 rabbit models. Consecutively, it is likely that the reduced estradiol levels during breastfeeding similarly contributed to the QTc normalization in our LQTS patient.

**Hormone effects on the arrhythmogenic risk**

It is known that the risk for arrhythmias in LQTS patients decreases during pregnancy and increases during the postpartum phase, although in these databases, breastfeeding status was not recorded. In our patient, we observed pronounced progesterone-related effects on QTc duration but no changes in the arrhythmogenic risk. Since pVTs are relatively rare events in LQTS patients, it is nearly impossible to clearly and conclusively identify potential pro- or antiarrhythmic effects in one single individual. Moreover, our patient did not have any pVTs since August 2000, when she got an ICD implanted and her beta-blocker dosage was increased.

In transgenic LQT2 rabbits, however, we have previously reported an antiarrhythmic, protective effect of progesterone that may contribute to the overall reduced arrhythmogenic risk in LQTS patients during pregnancy, and a proarhythmic effect of estradiol. To evaluate the antiarrhythmic effect of progesterone in human LQTS patients in detail, prospective case-control studies are thus warranted.

**Conclusion**

Here we report the case of an LQTS patient with pronounced intra-individual differences in QTc duration during phases of varying sex hormone levels—a shortening/normalization of QTc duration owing to increased progesterone levels during pregnancy and while using a progesterone-releasing intrauterine device, and owing to the pronounced reduction of the QTc-prolonging effect of estradiol when breastfeeding—indicating that it may be of clinical importance to consider the hormonal status of an LQTS patient when assessing QTc...
duration. Consecutively, to adequately assess the risk of an individual LQTS patient, it may be reasonable to analyze QTc intervals during different phases of the menstrual cycle, as well as during pregnancy and the postpartum phase.

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