

## Long QT Syndrome and Pregnancy

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- Objectives** This study was designed to investigate the clinical course of women with long QT syndrome (LQTS) throughout their potential childbearing years.
- Background** Only limited data exist regarding the risks associated with pregnancy in women with LQTS.
- Methods** The risk of experiencing an adverse cardiac event, including syncope, aborted cardiac arrest, and sudden death, during and after pregnancy was analyzed for women who had their first birth from 1980 to 2003 (n = 391). Time-dependent Kaplan-Meier and Cox proportional hazard methods were used to evaluate the risk of cardiac events during different peripartum periods.
- Results** Compared with a time period before a woman's first conception, the pregnancy time was associated with a reduced risk of cardiac events (hazard ratio [HR] 0.28, 95% confidence interval [CI] 0.10 to 0.76, p = 0.01), whereas the 9-month postpartum time had an increased risk (HR 2.7, 95% CI 1.8 to 4.3, p < 0.001). After the 9-month postpartum period, the risk was similar to the period before the first conception (HR 0.91, 95% CI 0.55 to 1.5, p = 0.70). Genotype analysis (n = 153) showed that women with the LQT2 genotype were more likely to experience a cardiac event than women with the LQT1 or LQT3 genotype. The cardiac event risk during the high-risk postpartum period was reduced among women using beta-blocker therapy (HR 0.34, 95% CI 0.14 to 0.84, p = 0.02).
- Conclusions** Women with LQTS have a reduced risk for cardiac events during pregnancy, but an increased risk during the 9-month postpartum period, especially among women with the LQT2 genotype. Beta-blockers were associated with a reduction in cardiac events during the high-risk postpartum time period. (J Am Coll Cardiol 2007;49:1092-8) © 2007 by the American College of Cardiology Foundation

The hereditary long QT syndrome (LQTS) is characterized by prolonged ventricular repolarization and a variable clinical course with arrhythmia-related recurrent syncope, aborted cardiac arrest (ACA), and sudden death (1). Mutations in several ion-channel genes are known to cause LQTS, the most common of which are found in potassium-channel *KCNQ1* (LQT1) and *hERG* (LQT2) genes, and in the sodium-channel *SCN5A* (LQT3) gene (2). Genotype-phenotype studies have highlighted the clinical course in the 3 major LQTS subgroups (3). However, there

have been only 3 studies evaluating the risks of pregnancy in patients with LQTS (4-6), with the report by Khositseth et al. (5) identifying the LQT2 genotype as a risk factor for postpartum cardiac events in a small number of women. The present study was designed to investigate the clinical course of LQTS in women throughout the childbearing years with a comparison with those who did and did not experience pregnancy, with additional focus on the risk associated with different LQTS genotypes and the prophylactic effectiveness of beta-blocker therapy during and after pregnancy.

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## Methods

**Study population.** The enrollment of subjects with LQTS into the International LQTS Registry has been previously described (1,7). A baseline electrocardiogram (ECG) was obtained on all subjects enrolled in the registry. The QT interval was measured in lead II of the ECG and corrected for heart rate according to the method of Bazett ( $QT_c = QT/\sqrt{RR}$ ). Yearly follow-up information, with particular emphasis on cardiac events, was obtained for each subject. All subjects or their guardians provided informed consent for acquisition of the clinical data and the genetic studies.

The study population consisted of women of childbearing age from the registry who were identified as having an LQTS-related gene mutation or were considered to be affected with LQTS on the basis of a  $QT_c > 470$  ms. The study subjects who were born between July 1946 and March 1985 (n = 1,094) were categorized as of May 2003 as either having 1 or more live births (n = 564) or as being nulliparous (n = 520). The live-birth category contained women who gave birth before 1980 (n = 173) and from 1980 to March 2003 (n = 391). This chronological subdivision was used because beta-blocker therapy was fully available by 1980, and pregnancy from 1980 onward is likely to reflect the modern era of medical management of LQTS. The nulliparous group contained women who had reached age 41 years and completed the defined childbearing period without giving birth or women who were younger than age 41 and had not yet had a child before March 2003.

The childbearing age range involved women ages 15 through 40. The LQTS Registry was accessed in October 2005 for the required data, thus providing a minimum of 30 months of follow-up information after March 2003. Data regarding cardiac events, beta-blocker usage, genotype data, and birth dates of children were collected. If the studied pregnancies occurred before the subject was enrolled in the registry, information was obtained retrospectively from the patient or from medical records.

**Risk and outcome events.** To evaluate the cardiac risk associated with pregnancy, peripartum time periods immediately before, during, and after pregnancy were divided into equal 9-month time intervals. The pregnancy interval was defined as the 9-month interval before the date of delivery. The estimated date of conception was defined as the first day of the pregnancy interval. The 9-month interval before the estimated date of conception was defined as the prepregnancy time interval. The postpartum interval was defined as the 9-month interval after the child's birth. The postpartum interval represents the time after the postpartum interval until the date of last follow-up or age 41, excluding the peripartum time periods of subsequent pregnancies. If a woman had more than 1 child, each time period for each pregnancy was analyzed. If 2 of the described time periods overlapped in a woman's history, both time periods were censored as previously described (4). Stillbirths, spontane-

ous abortions, and elective abortions were excluded from the analysis because the length of pregnancy was not available.

Outcome variables included LQTS-related death, aborted cardiac arrest, and syncope. Unexpected, sudden death without a known cause before age 41 was categorized as LQTS-related death (1). Aborted cardiac arrest was defined as cardiac arrest that was terminated by electrical cardioversion. Syncope was defined as transient loss of consciousness with abrupt onset and offset.

**Genotype data.** Standard genetic tests for LQTS mutations were performed in academic molecular-genetic laboratories associated with the registry. Among women in the study population with an LQTS-related mutation, only subjects with LQT1 (n = 82 from 53 families), LQT2 (n = 59 from 43 families), and LQT3 (n = 12 from 8 families) genotypes were identified. The remainder of the study population with  $QT_c > 470$  who did not have an LQTS-related mutation identified or did not have genetic testing performed were categorized as nongenotyped.

**Statistical analyses.** The probability of cardiac events was evaluated using the method of Kaplan and Meier with the log-rank statistic. The Cox proportional-hazards survivorship model (8) with allowance for time-dependent covariates (SAS version 9.1.3, SAS Institute Inc., Cary, North Carolina) was used to evaluate the independent risk of the peripartum time periods in predicting cardiac event end points among LQTS women from ages 15 through 40. In the analyses related to the end point, any cardiac event (syncope, ACA, or LQTS-related death),  $QT_c$ , and the presence of any cardiac event before age 15 (syncope or ACA) were included as covariates in the Cox model. In the analyses related to life-threatening events (ACA or LQTS-related death),  $QT_c$  and time-dependent interim syncope stratified by the time interval before the lethal event ( $\leq 2$  years,  $> 2$  years) were included as covariates in the Cox mode. The efficacy of beta-blocker therapy was evaluated as a time-dependent covariate in the Cox model. The SAS procedure PROC PHREG was used—it allows specification of time-dependent covariates by using a data-related step-like programming code that compares the timing of the time-dependent covariate with the survival time of the end point (9). Please see the Appendix for further details of the statistical analysis and an example of the programming code.

## Results

**Entire cohort. CLINICAL CHARACTERISTICS OF LQTS WOMEN.** The clinical characteristics of women who did not have a birth and women who had a live birth both before 1980 and from 1980 to 2003 are presented in Table 1. The nulliparous women had a shorter average follow-up time, a higher event rate before age 15, and a higher use of beta-blockers at age 15 than the 2 live-birth groups.

### Abbreviations and Acronyms

|                                     |
|-------------------------------------|
| <b>ACA</b> = aborted cardiac arrest |
| <b>CI</b> = confidence interval     |
| <b>ECG</b> = electrocardiogram      |
| <b>LQTS</b> = long QT syndrome      |

**Table 1** Clinical Characteristics of LQTS Women in the Nulliparous Group and in Those Who Had a Live Birth Before 1980 or From 1980 to 2003

| Variable   | Nulliparous Group (n = 520) | Live Birth <1980 (n = 173) | Live Birth ≥1980 (n = 391) |
|--|-----------------------------|----------------------------|----------------------------|
| QTc, ms  | 500 ± 60                    | 490 ± 50                   | 500 ± 50                   |
| Heart rate, beats/min                            | 73 ± 19                     | 70 ± 15                    | 72 ± 16                    |
| Cardiac event before age 15 yrs, %               | 38                          | 18                         | 28                         |
| Cardiac event after age 15 yrs, %                | 55                          | 49                         | 55                         |
| Number of cardiac events after age 15 yrs        | 2.6 ± 11                    | 2.6 ± 8.7                  | 2.7 ± 8.2                  |
| Death, %   | 7.4                         | 9.2                        | 4.3                        |
| Follow-up time age 15–40 yrs                     | 12.8 ± 8.2                  | 24.2 ± 4.7                 | 20.3 ± 6.3                 |
| Survival time age 15 to first cardiac event, yrs | 8.5 ± 7.9                   | 16.7 ± 10.2                | 13.3 ± 9.0                 |
| Time from age 15 to first live birth, yrs        |                             | 8.4                        | 11.0                       |
| Genotype, %                                      |                             |                            |                            |
| LQT1   | 10                          | 23                         | 21                         |
| LQT2   | 10                          | 11                         | 15                         |
| LQT3   | 2                           | 2                          | 3                          |
| Unknown  | 78                          | 64                         | 61                         |
| Therapy, %                                       |                             |                            |                            |
| Beta-blocker use at age 15 yrs                   | 25                          | 2                          | 9                          |
| ICD before age 15 yrs                            | 1                           | 0                          | 0                          |
| LCTSG surgery before age 15 yrs                  | 2                           | 0                          | 1                          |
| Pacemaker before age 15 yrs                      | 4                           | 0                          | 2                          |

Plus-minus values indicate mean ± SD.

ICD = implantable cardioverter-defibrillator; LCTSG = left cervicothoracic stellate ganglionectomy; LQTS = long QT syndrome.

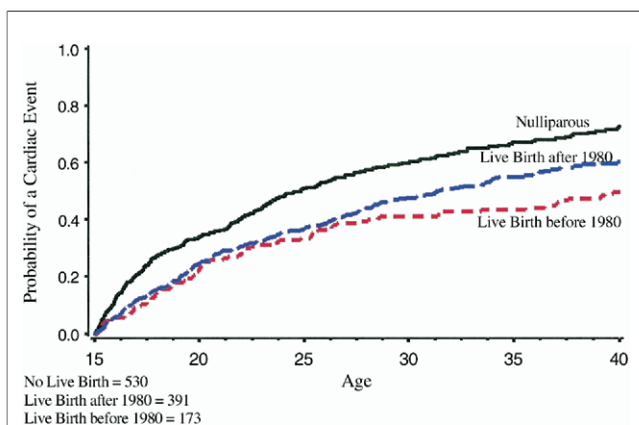
**LIVE BIRTH AND CARDIAC EVENTS.** Time-dependent cardiac event data for women between ages 15 and 40 are shown in Figure 1. Nulliparous women had a somewhat higher probability of experiencing a cardiac event than those who had a live birth before 1980 or from 1980 to 2003.

**Modern pregnancy cohort.** To describe the effects of pregnancy on the clinical course of women with LQTS in the modern era, the remainder of the article will involve only those women who had a live birth from 1980 to 2003 (modern cohort, n = 391).

**TIMING OF CARDIAC EVENTS.** Figure 2 shows the annualized cardiac event rate by time period for the modern cohort. The time periods include all times from ages 15 through 40. The pre-pre-first pregnancy period is the time from age 15 to the first prepregnancy period, the 9 months before the woman’s first pregnancy. In the case of multiple births, subsequent prepregnancy time periods were not analyzed because of a significant amount of overlapping and censoring of time periods. The annualized cardiac event rate was higher in the 9-month postpartum period (0.23 events/year) than in the other defined peripartum time periods. Aborted cardiac arrest and LQTS-related death account for 17% of the annualized events in the postpartum period. The annualized event rates for nonpostpartum time periods ranged from 0.04 to 0.09 events/year. Of note, no woman had her first cardiac event on the day of or within 1 day of her first live-birth delivery.

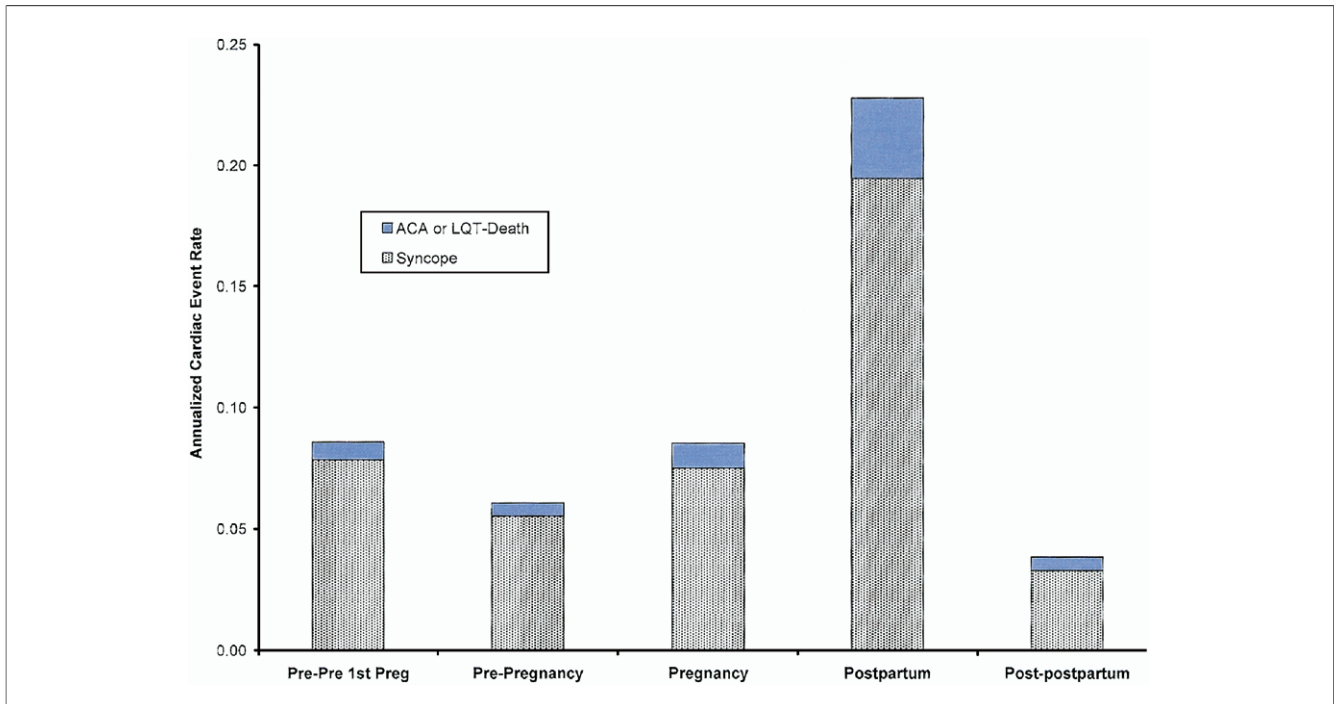
**THE POSTPARTUM PERIOD.** The cardiac event rate for the 4-year period after conception among LQTS women in the modern cohort is shown in Figure 3. The graph shows a meaningful increase in the probability of a first cardiac event during the first 6 months after childbirth, with a somewhat reduced increase in the probability of a first cardiac event thereafter.

**RISK OF CARDIAC EVENT BY PERIPARTUM TIME PERIODS.** In the Cox proportional-hazards survivorship analyses shown in Table 2, the hazard ratios were calculated using a reference comparison time period from age 15 to the start of the woman’s first pregnancy period. The pregnancy time period had a reduced risk for any cardiac event (hazard ratio



**Figure 1** Kaplan-Meier Curves

Kaplan-Meier curves for the cumulative probability of a first cardiac event from age 15 through age 40 in women who were nulliparous without a live birth, those who had a live birth before 1980, and those who had a live birth between 1980 and 2003.

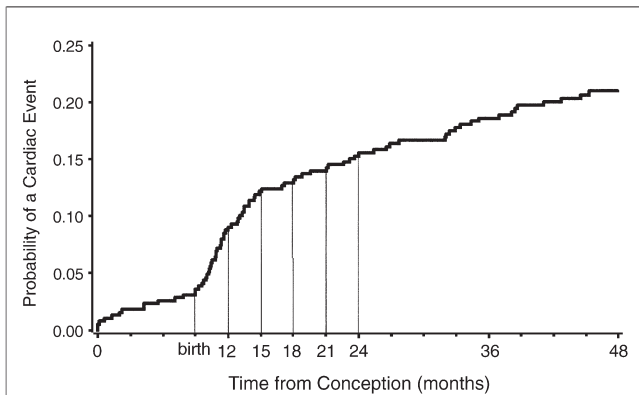


**Figure 2 Annualized Cardiac Event Rates**

Annualized cardiac event rates (syncope and aborted cardiac arrest [ACA]/long QT syndrome [LQTS]-related death) for defined pregnancy-related time periods for 391 women who had a live birth between 1980 and 2003. See text for definitions of time periods.

0.28, 95% confidence interval [CI] 0.10 to 0.76,  $p = 0.01$ ), whereas the postpartum period was associated with an increased risk for cardiac events (hazard ratio 2.7, 95% CI 1.8 to 4.3,  $p < 0.001$ ). The post-postpartum period had a risk similar to or lower than that associated with the first prepregnancy interval. As shown in Figure 4, the high rate of postpartum events was dominated by women with the LQT2 genotype. The LQT3 women seemed to have a somewhat different distribution of event rates in the various peripartum time periods, but the number of LQT3 women

is too small to compare peripartum event rates between LQT3 and the other 2 genotype groups. The post-postpartum period was associated with a low annualized event rate in all 4 groups, and this low rate is similar to or lower than that associated with the first prepregnancy interval. Using Kaplan-Meier survival analysis to compare the cumulative probability of cardiac events in genotyped women who had a live birth, those with the LQT2 genotype were more likely ( $p = 0.003$ ) to experience a cardiac event than women with the LQT1 genotype, although the QTc duration was similar in the 2 genotypes (data not shown).



**Figure 3 Cumulative Probability**

Cumulative probability of a first cardiac event during 48 months after first conception after age 15 in the 391 women who had a live birth between 1980 and 2003.

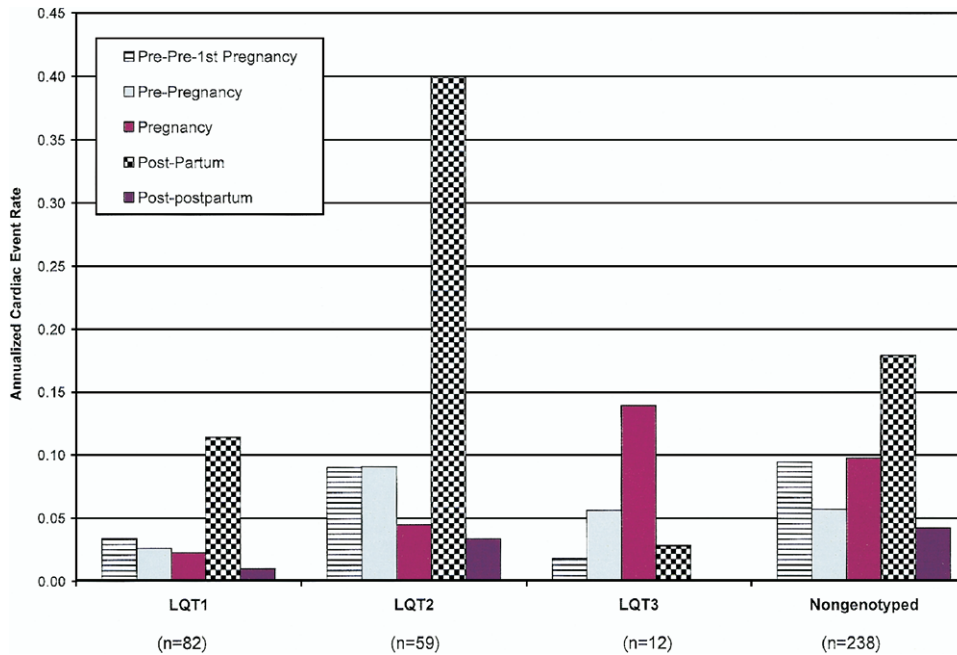
**Table 2 The Hazard Ratios for Any Cardiac Event and Life-Threatening Events (Aborted Cardiac Arrest or LQTS-Related Death) in the Pregnancy, Postpartum, and Post-Postpartum Time Periods for 391 Women With Live Births Between 1980 and 2003**

| Time Period     | Any Cardiac Event<br>(n = 214 of 391) |         | Life-Threatening Event<br>(n = 55 of 391) |         |
|-----------------|---------------------------------------|---------|---|---------|
|                 | Hazard Ratio<br>(95% CI)              | p Value | Hazard Ratio<br>(95% CI)                  | p Value |
| Pregnancy       | 0.28 (0.10–0.76)                      | 0.01    | 1.5 (0.49–4.5)                            | 0.49    |
| Postpartum      | 2.7 (1.8–4.3)                         | <0.001  | 4.1 (1.7–9.5)                             | 0.001   |
| Post-postpartum | 0.91 (0.55–1.5)                       | 0.70    | 1.9 (0.84–4.1)                            | 0.13    |

The reference for the hazard ratios is each woman's time from age 15 to the start of her first pregnancy. The hazard ratios for Any Cardiac Event are adjusted for QTc and cardiac events before age 15. The hazard ratios for Life-Threatening Events are adjusted for QTc and time-dependent syncope stratified by time before the lethal event.

CI = confidence interval; other abbreviations as in Table 1.





**Figure 4 Annualized Cardiac Event Rates**

Annualized cardiac event rates (syncope, aborted cardiac arrest, or long QT syndrome [LQTS] death) by genotype (LQT1, LQT2, LQT3, nongenotyped) for defined pregnancy-related time periods for 391 women who had a live birth. None of the 12 LQT3 women had a cardiac event during the post-postpartum period.

To better understand the risk of life-threatening events, the more serious events, ACA or LQTS-related death, were analyzed separately from syncope (Table 2). The risk for aborted cardiac arrest or LQTS-related death, whichever occurred first, was increased in the postpartum period ( $p = 0.001$ ), but the pregnancy and post-postpartum time periods were not associated with a significantly increased risk for life-threatening events.

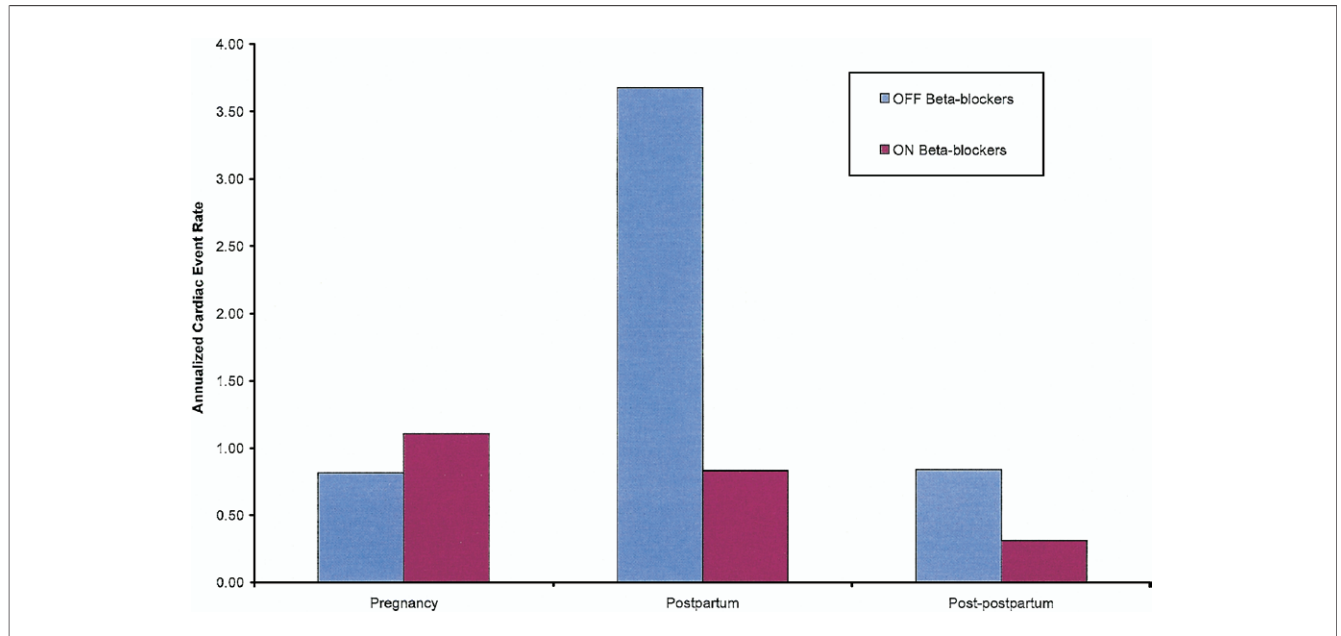
**EFFECT OF BETA-BLOCKER THERAPY.** Of the 391 women of the modern cohort, 104 were using beta-blockers at conception (27%), 116 at the time of childbirth (30%), and 128 at 9 months after giving birth (33%). Ninety percent of women who were using beta-blockers remained on the medication throughout these time points. In Figure 5, the effect of beta-blocker use by pregnancy time period is shown by comparing the annualized cardiac event rates of those who used beta-blockers with those who did not. Beta-blockers were associated with a reduction in annualized cardiac event rate during the high-risk postpartum time period, with an annualized event rate of 3.7 events/year in the absence of beta-blockers and 0.8 events/year with beta-blockers. In a Cox proportional-hazards survivorship analysis (Table 3), time-dependent beta-blocker use was associated with a significant reduction in cardiac events only in the postpartum period (hazard ratio 0.34, 95% CI 0.14 to 0.84,  $p = 0.02$ ). A significant beta-blocker effect was not seen for life-threatening events (hazard ratio 0.65,  $p = 0.60$ ), with the lack of signifi-

cance possibly caused by limited power, with only 15 life-threatening events in this secondary analysis.

## Discussion

Our findings indicate that among women with LQTS who gave birth, the 9-month postpartum time is associated with a 2.7-fold increased risk of experiencing a cardiac event and a 4.1-fold increased risk of experiencing a life-threatening event when compared with the preconception time period. After this transient high-risk postpartum period, the risk of cardiac events reverts to the baseline prepregnancy risk. The pregnancy period is associated with a reduced risk for cardiac events. The increased risk for cardiac events in the postpartum period was significantly reduced by beta-blockers. Furthermore, women with the LQT2 genotype are at a considerably higher risk for cardiac events during the postpartum period than those with LQT1 or LQT3 genotypes.

This study adds to the existing information on LQTS and pregnancy (4-6). With our larger population, we have studied the entire childbearing period from age 15 to 40 years and more precisely identified the postpartum risk for any cardiac event (mostly syncope), and also for life-threatening cardiac events (aborted cardiac arrest and LQTS-related sudden death). The benefit from beta-blocker therapy, especially in reducing the postpartum risk, is now well documented. Our findings confirm and extend the report of Khositseth et al. (5), who identified the



**Figure 5 Annualized Cardiac Event Rates**

Annualized cardiac event rates by beta-blocker use in the pregnancy, postpartum, and post-postpartum time periods for 391 women who had a live birth between 1980 and 2003. Beta-blockers were associated with a significant reduction ( $p = 0.01$ ) in the annualized cardiac event rate during the high-risk postpartum time period. See text for details.

particularly high postpartum cardiac risk in 14 women with the LQT2 genotype, and the recent report of Heradien et al. (6), who showed a low rate of cardiac events during pregnancy in 36 women with a specific LQT1 genotype.

The overall lower risk of experiencing a cardiac event among those who gave birth as contrasted with the women who were nulliparous may be attributable to several factors. Pregnancy brings women to health care providers, and this may be a factor contributing to more effective preventive management during pregnancy. Importantly, there may be a self-selection bias regarding pregnancy in our LQTS study population. Our analysis shows that although the nulliparous women did not have a longer QTc interval than those who gave birth, they did have more cardiac events before age 15 and more of them were using beta-blockers by age 15. These women may have chosen

not to become pregnant for this reason. Unfortunately, we are unable to adjust for this potential bias.

The postpartum interval was a particularly high-risk period. There are several influences that may be contributing to this phenomenon. Biologically, there are many unique physiological changes occurring during the postpartum period. Cardiac remodeling and increasing cardiac output are gradual processes during pregnancy, but in the postpartum period the decline in cardiac output is rapid, with cardiac output decreasing 37% from 8.8 to 5.4 l/min (10). Recently, Mone et al. (11) found normal pregnancy to be associated with a reversible decrease in myocardial contractility. They noted that systolic function is preserved throughout most of pregnancy by a decrease in afterload, with reduction in contractility and preload in the early postpartum period. These changes in hemodynamics in the postpartum period may be a contributing factor to cardiac arrhythmias and the increased postpartum cardiac event rate experienced by women with LQTS.

Rashba et al. (4) hypothesized that alterations in adrenergic activity in the peripartum period may cause an increase in postpartum cardiac events. It may be that the increase in sympathetic activity that occurs with the stress and disrupted sleep pattern when caring for a newborn is a factor that triggers malignant tachyarrhythmias in patients with LQT1 and LQT2 genotypes, as hypothesized by Schwartz et al. (12). In the current study, the risk was particularly accentuated in the LQT2 genotype, and this finding is in alignment with the recent report by Khositseth et al. (5). Interestingly, the LQT3

**Table 3 The Hazard Ratios for Any Cardiac Event for Time-Dependent Beta-Blocker Use During the Pregnancy, Postpartum, and Post-Postpartum Time Periods for 391 Women With Live Births Between 1980 and 2003**

| Time Period                     | Any Cardiac Event     |         |
|---------------------------------|-----------------------|---------|
|                                 | Hazard Ratio (95% CI) | p Value |
| Time-dependent beta-blocker use |                       |         |
| Pregnancy                       | 0.16 (0.02-1.3)       | 0.08    |
| Postpartum                      | 0.34 (0.14-0.84)      | 0.02    |
| Post-postpartum                 | 0.52 (0.14-1.9)       | 0.32    |

The hazard ratios are adjusted for QTc and cardiac events before age 15. CI = confidence interval.

women had a higher annualized event rate during pregnancy than in the postpartum period, but this finding is difficult to interpret because there were only 12 women with the LQT3 genotype who had live births.

Estrogen and progesterone levels are high during pregnancy and decrease well below normal levels when the mother breastfeeds her child. The profound decrease in estrogen and progesterone levels after delivery seems to be the initiating stimulus for lactation. This alteration in hormone levels could influence the adrenergic responses of the mutant ion channels in LQTS. Animal studies have provided several interesting findings. Protein expression of cardiac beta-1-adrenergic receptors have been shown to be downregulated in the presence of estrogen in ovariectomized animals (13). In animal studies, estrogen has weak antiarrhythmic effects and it may reduce the risk of the polymorphic ventricular antiarrhythmia (torsades de pointes) in LQTS patients (14). Therefore, deprivation of estrogen, such as that seen in the breastfeeding state, may increase adrenergic activity and cardiac myocyte excitability in the postpartum period and contribute to a higher probability of adverse cardiac events. Similarly, the hyperestrogenic state during pregnancy may be a factor associated with a reduced risk of cardiac events during this time period.

The increased risk of cardiac events during the postpartum period was significantly reduced among women using beta-blocker therapy. Beta-blockers are transmitted in the milk to the nursing infant, and although they can reduce the heart rate to some degree in the nursing infant, the benefit to the mother far outweighs the negligible risk to the nursing infant. We recommend that beta-blockers be prescribed to women with LQTS, with our findings most strongly documenting the benefit in the high-risk postpartum period that is dominated by the LQT2 genotype.

**Study limitations.** Potential recall bias is a concern. Study subjects may have recalled more cardiac events during the postpartum time period because of their concerns about their newborn infant. We only have 1 ECG recording on most women, so we do not have reliable data on the change in the QTc before, during, and after pregnancy. Unreported beta-blocker discontinuation may have occurred during times of pregnancy and lactation because of apprehension about taking medications during these time periods. In the analyses, beta-blocker therapy was modeled as a time-dependent covariate. This means that at each point in time (age), those on beta-blockers were compared with those not on beta-blockers within each covariate pattern. We know whether the subjects were prescribed beta-blockers, but we cannot be certain whether they actually took the beta-blocker on any given day. Thus, the reported efficacy of

beta-blockers may be an underrepresentation of the true efficacy of this therapy.

## Conclusions

The 9-month postpartum period is associated with a significantly increased risk of experiencing a cardiac event, especially in subjects with the LQT2 genotype. Beta-blocker use was associated with a reduction in cardiac events during the high-risk postpartum time period.

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## ▶ APPENDIX

For an example of the programming code used in the statistical analyses, please see the online version of this article.