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Influence of Pregnancy on the Risk for Cardiac Events in Patients With Hereditary Long QT Syndrome

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Background—The effects of pregnancy on women with the hereditary long QT syndrome are currently unknown. The appropriate medical management of pregnant patients with the long QT syndrome has not been established.

Methods and Results—The study was a retrospective analysis of the 422 women (111 probands affected with the long QT syndrome and 311 first-degree relatives) enrolled in the long QT syndrome registry who had one or more pregnancies. The first-degree relatives were classified as affected ($QTc > 0.47$), borderline ($QTc = 0.45$ to 0.47), and unaffected ($QTc < 0.45$). Cardiac events were defined as the combined incidence of long QT syndrome-related death, aborted cardiac arrest, and syncope. The incidence of cardiac events was compared during equal prepregnancy, pregnancy, and postpartum intervals (40 weeks each). Multivariate logistic regression analysis was performed by use of a mixed-effects model to identify independent predictors of cardiac events among probands. The pregnancy and postpartum intervals were not associated with cardiac events among first-degree relatives. The postpartum interval was independently associated with cardiac events among probands (odds ratio [OR], 40.8; 95% confidence interval [CI], 3.1 to 540; $P = .01$); the pregnancy interval was not associated with cardiac events. Treatment with β -adrenergic blockers was independently associated with a decrease in the risk for cardiac events among probands (OR, 0.023; 95% CI, 0.001 to 0.44; $P = .01$).

Conclusions—The postpartum interval is associated with a significant increase in risk for cardiac events among probands with the long QT syndrome but not among first-degree relatives. Prophylactic treatment with β -adrenergic blockers should be continued during the pregnancy and postpartum intervals in probands with the long QT syndrome. (*Circulation*. 1998;97:451-456.)

Key Words: pregnancy ■ long QT syndrome ■ cardiovascular diseases

Pregnancy is accompanied by a variety of cardiovascular changes in normal women, and these changes can cause clinical decompensation in patients with structural heart disease.¹ However, the effect of pregnancy on patients with cardiac rhythm disorders is not well characterized. Previous studies have focused primarily on patients with supraventricular arrhythmias, and an increase in symptoms during pregnancy has been described.^{2,3} In the case of the long QT syndrome (LQTS), the available information is limited to isolated case reports.⁴⁻⁶ It is consequently difficult to counsel patients with LQTS about the potential effects of pregnancy on their cardiovascular health. Moreover, the optimal medical management of patients with this repolarization disorder who become pregnant is currently unknown. The aim of the present study was to evaluate the effect of pregnancy on the incidence of cardiac events in women with hereditary LQTS.

Methods

Patients

The enrollment of families with LQTS into the international LQTS registry has been previously described.^{7,8} Since 1979, patients with suspected LQTS who were referred to the internationally dispersed investigators were considered for enrollment in the registry. Patients who were receiving medications known to prolong the QT interval were excluded from enrollment. The QT interval was measured with lead II of the ECG and corrected for heart rate according to the method of Bazett.⁹ Patients who had prolongation of the QTc interval > 0.44 seconds were enrolled in the registry as probands. In most cases, the probands had a personal history of syncope or cardiac arrest. The remainder of the probands had a family history of unexplained syncope or sudden cardiac death or had QT prolongation noted incidentally on a routine ECG. Every effort was made to enroll as many family members of each proband as possible; as a result, nearly 90% of the first-degree relatives were enrolled in the registry. Yearly follow-up information, with particular emphasis on cardiac events, was obtained for each patient.

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The other LQTS Investigators are listed in the "Appendix."

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The present study was designed as a retrospective analysis of 422 women enrolled in the registry who had had one or more pregnancies. The population consisted of 111 probands and 311 first-degree relatives. Among the probands, 92 (83%) had a personal history of cardiac events, 15 (13%) had a family history of cardiac events, and 4 (4%) had QTc >0.44 seconds without a personal or a family history of cardiac events. In 90% of the cases, the studied pregnancies occurred before the patients were enrolled in the registry; the information on cardiac events was obtained retrospectively from the patient or from medical records in these instances. Cardiac events were accepted for analysis if the date of the event could be definitively localized to a given month. Second-degree relatives were excluded from the study because of incomplete clinical information. The first-degree relatives were subdivided into three groups on the basis of a baseline ECG obtained at the time of enrollment into the registry: affected (QTc >0.47), borderline (QTc=0.45 to 0.47), and unaffected (QTc < 0.45).¹⁰

Definitions

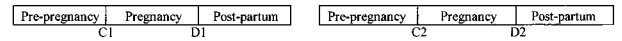
The date of delivery was recorded for each pregnancy. The pregnancy interval was defined as the 40 weeks preceding the date of delivery. The estimated date of conception was defined as the first day of the pregnancy interval. The prepregnancy interval was defined as the 40 weeks preceding the estimated date of conception. The postpartum interval was defined as the 40 weeks after the date of delivery, which was included in this interval. Equal prepregnancy, pregnancy, and postpartum intervals were used to eliminate the need to adjust for differential time exposure in determinations of the risk for cardiac events associated with each type of interval. The prepregnancy interval was used as a control period to determine whether the pregnancy or postpartum intervals were associated with an increase in risk for cardiac events.

Some patients had multiple pregnancies (Fig 1). In most cases, the time intervals did not overlap. When there was overlap between a postpartum interval and a subsequent prepregnancy interval, the prepregnancy interval was censored because it could not be used as a control period. If the second conception date occurred during a prior postpartum interval, the postpartum interval was also censored because it lasted <40 weeks. Stillbirths, spontaneous abortions, and elective abortions were excluded from the analysis (n=124) because the length of the pregnancy was not available, which precluded an accurate delineation of the prepregnancy interval in these instances.

Determination of Cardiac Risk

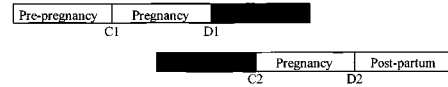
Cardiac events were defined as the combined incidence of LQTS-related death, aborted cardiac arrest, and syncope. Syncope was defined as a fainting spell with transient loss of consciousness. Unexpected, sudden (without warning as described by the family), natural death before 50 years of age, exclusive of a known cause, was

A. Pregnancy intervals do not overlap (N=710)



B. Pregnancy intervals overlap

1. Second conception occurs during first post-partum interval (N = 171)



2. Second conception occurs after first post-partum interval (N = 210)

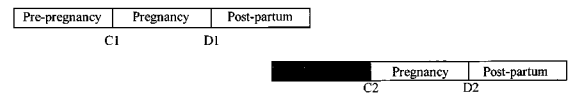


Figure 1. Criteria for censoring of pregnancy intervals. When patients had multiple pregnancies and overlaps occurred, intervals were censored as appropriate (shaded boxes; see text for details). All time intervals are 40 weeks in length. C1 and C2 indicate first and second conception dates; D1 and D2, first and second delivery dates.

categorized as probable LQTS-related death.⁸ Aborted cardiac arrest was defined as cardiac arrest that was terminated by electrical cardioversion. There were substantial differences in the absolute numbers of cardiac events experienced by individual patients; eg, one patient had >30 cardiac events during the pregnancy interval, whereas most patients had single events. Because this variability precluded a meaningful comparison of the absolute numbers of cardiac events during each interval, an ordinal classification system was used. The number of cardiac events that occurred during each time interval was quantified in three ways: any cardiac events, multiple cardiac events (≥ 2 events), and new-onset cardiac events. Probands and each of the three subtypes of first-degree relatives were analyzed separately. The number of patients who had cardiac events during any pregnancy was determined for each time interval for each of the three categories of cardiac events.

Statistical Analysis

The χ^2 test was used to compare the number of cardiac events during the prepregnancy, pregnancy, and postpartum intervals ($P < .05$ was considered significant). If a significant difference was present, McNemar's χ^2 test was used to localize the effect ($P < .016$ was considered significant with the Bonferroni correction). Fisher's exact test was used in cases in which the sample size was too small to permit use of the χ^2 test.

A mixed-effects logistic regression model was used for multivariate analysis (EGRET software). This analysis was restricted to the pro-

TABLE 1. Clinical Characteristics of the Patients

	Probands (n=111)	First-degree Relatives		
		Affected (n=105)	Borderline (n=72)	Unaffected (n=134)
Age at first pregnancy, y	25±5	23±5	23±4	24±5
No. of pregnancies				
Mean±SD	2.5±1.5	3.1±1.8	2.7±1.4	2.8±1.4
1, %	27	11	15	15
≥2, %	73	89	85	85
Cardiac events before first pregnancy, %	46	22	13	7
ECG Data,* ms				
RR interval	915±198	869±178	849±179	886±158
QTc interval	509±50	497±42	453±15	420±17

*ECGs were performed at the time of enrollment into the long QT syndrome registry.

bands because cardiac events were too infrequent among first-degree relatives to construct an appropriate model. The basic units for analysis were 40-week time intervals, classified as prepregnancy, pregnancy, or postpartum. The response (dependent variable) was the occurrence of any cardiac events during the interval. Two different types of explanatory variables (risk factors) were used: fixed effects and a random effect. The fixed effects considered included the type of interval (pregnancy, pregnancy, or postpartum), treatment with β -adrenergic blockers throughout the time unit, a history of cardiac events before the first prepregnancy interval, the QTc and RR intervals at enrollment into the registry, and the age at delivery of the first child ($P < .10$ required for inclusion in the model). The odds for having a cardiac event during the postpartum and pregnancy intervals were determined, with the prepregnancy interval used as a control. Because of the retrospective nature of the analysis, it is conceivable that more cardiac events were recognized during the pregnancy and postpartum intervals because the patients may have been more likely to receive medical attention at these times. The odds for having a cardiac event during the postpartum interval were also calculated with the pregnancy interval used as a control to minimize this potential source of bias.

We also hypothesized that the risk for cardiac events would vary between individuals, even after the fixed effects were accounted for. To quantify this variability, it was necessary to identify which time units were common to the same woman by including a "personal" risk factor for each woman. This risk factor was treated as random and was not estimated for each individual woman; the mean and SD of this effect were estimated for the population as a whole. The mean value of this random effect represents the average risk for cardiac events during the prepregnancy interval, whereas the SD quantifies the variability in risk that was present within the proband group.

Results

Clinical Characteristics

Probands had fewer pregnancies than first-degree relatives and more commonly had a history of cardiac events before the first pregnancy (Table 1). There was no difference in the average age at the time of the first pregnancy. The RR interval was longer among probands than first-degree relatives, possibly reflecting the greater prevalence of β -adrenergic blocker treatment among probands (see below). The degree of QTc interval prolongation did not differ significantly among probands and affected first-degree relatives.

Obstetrical History

Probands had more elective abortions than first-degree relatives, but there was no difference in the incidence of stillbirths or spontaneous abortions (Table 2). As expected, probands were more likely to be treated with β -adrenergic blockers during pregnancy. There were no reported fetal malformations after treatment with β -adrenergic blockers during pregnancy. Treatment with implantable cardioverter-defibrillators, left cervicothoracic sympathectomy, and permanent pacemakers was rare in this patient population.

Cardiac Events and Pregnancy

Three affected first-degree relatives died during the postpartum interval (presumed LQTS-related deaths). Two probands had an aborted cardiac arrest during the prepregnancy interval compared with two during the pregnancy interval and seven during the postpartum interval. Syncope accounted for the remainder of the studied cardiac events ($n=115$, 89% of all events).

TABLE 2. Obstetrical History

	First-degree Relatives			
	Probands (n=322)	Affected (n=341)	Borderline (n=222)	Unaffected (n=403)
Fetal Outcome, %				
Live birth	85	95	88	93
Spontaneous abortion	10	4	11	7
Elective abortion	4.7	0.0	0.5	0.5
Stillbirth	1.2	0.6	0.9	0.3
Treatments during pregnancy, %				
β -Adrenergic blockers	19.5	3.1	1.0	0.3
Left cervicothoracic sympathectomy	3.3	0.0	0.0	0.0
Permanent pacemaker	2.9	0.0	0.0	0.3
Implantable defibrillator	0.7	0.0	0.0	0.0

Values indicate the percentage of pregnancies with each characteristic.

Univariate Analysis

Any Cardiac Events

Twenty-six probands had cardiac events during the postpartum interval (23.4%) compared with 10 (9.0%) during the pregnancy interval and 4 (3.8%) during the prepregnancy interval ($P < .001$ for any difference among the three intervals; $P = .004$ for postpartum versus pregnancy or prepregnancy intervals) (Table 3). The excess of cardiac events among probands during the postpartum interval was not related to the immediate postpartum period; only 2 patients had cardiac events on the day of delivery, and the remainder of the events occurred throughout the 40-week interval. The numbers of probands who had cardiac events during the pregnancy and the prepregnancy intervals were not significantly different ($P = .10$). Eight affected first-degree relatives had cardiac events during the postpartum interval (7.6%) compared with 3 (2.9%) during the pregnancy interval and 1 (1.0%) during the prepregnancy interval (counts too small for a valid χ^2 test with the three groups; $P = .065$ for postpartum versus prepregnancy interval). Cardiac events were rare among borderline and unaffected first-degree relatives during all three intervals.

Multiple Cardiac Events

Ten probands (9.1%) had multiple cardiac events during the postpartum interval compared with 5 (4.5%) during the

TABLE 3. Incidence of Cardiac Events in Pregnant Long QT Syndrome Patients

	n	Percentage of Patients With Any Cardiac Events		
		Prepregnancy	Pregnancy	Postpartum
Probands*	111	3.8	9.0	23.4†
Affected	105	1.0	2.9	7.6
Borderline	72	0.0	2.8	0.0
Unaffected	134	0.0	2.2	0.8

* $P < .001$ for all three intervals simultaneously.

† $P < .004$ for postpartum vs pregnancy or prepregnancy interval.

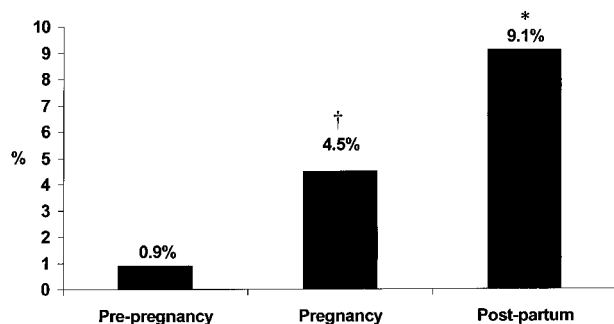


Figure 2. Percentage of LQTS probands with multiple cardiac events before, during, and after pregnancy. Multiple cardiac events were significantly more common among probands during the postpartum interval. The pregnancy interval was not associated with a significant increase in multiple cardiac events. * $P=.01$ vs the prepregnancy interval; † $P=.10$ vs the prepregnancy interval.

pregnancy interval and 1 (0.9%) during the prepregnancy interval ($P=.011$ for any differences; $P=.010$ for postpartum versus prepregnancy interval) (Fig 2). One first-degree relative with borderline QTc prolongation had multiple cardiac events during the pregnancy interval. No other multiple cardiac events were noted among first-degree relatives.

New-Onset Cardiac Events

Ten probands (9.0%) experienced their first cardiac event during the postpartum interval compared with 2 (1.8%) during the pregnancy interval and 0 during the prepregnancy interval (counts too small for a valid χ^2 test with the three groups; $P=.003$ for postpartum versus prepregnancy interval; $P=.018$ for postpartum versus pregnancy interval) (Fig 3). Two affected first-degree relatives had new-onset cardiac events during the postpartum interval compared with 1 during the pregnancy interval and 1 during the prepregnancy interval. Two first-degree relatives with borderline QTc prolongation had new-onset cardiac events during the pregnancy interval. There were no new-onset cardiac events among unaffected first-degree relatives during the prepregnancy, pregnancy, or postpartum interval.

Multivariate Analysis of Risk Factors for Cardiac Events Among Probands

Several risk factors were independently associated with cardiac events among probands (Table 4). The age at delivery of the first child, the QTc interval, and the RR interval did not enter into the model ($P>.10$). The odds for having a cardiac event

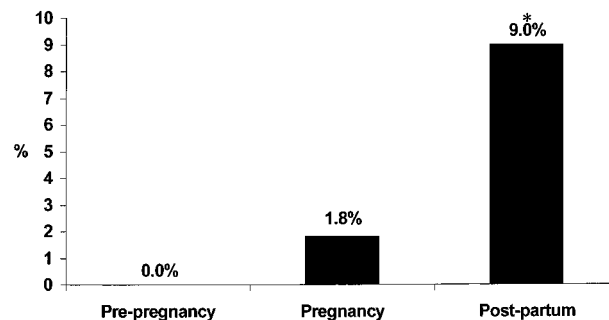


Figure 3. Percentage of LQTS probands with new-onset cardiac events before, during, and after pregnancy. New-onset cardiac events were significantly more common among probands during the postpartum interval. * $P<.02$ vs the pregnancy or prepregnancy interval.

during the postpartum interval were 40-fold greater than the odds for having a cardiac event during the prepregnancy interval ($P=.01$). The odds for having a cardiac event during the postpartum interval were 12-fold greater than the odds for having a cardiac event during the pregnancy interval (95% confidence interval [CI] 1.8 to 77.4; $P=.01$). Pregnancy was associated with more cardiac events than the prepregnancy interval, but this effect did not reach statistical significance (odds ratio [OR]=3.5; $P=.27$). A history of cardiac events before the first pregnancy was associated with a 9-fold increase in risk for subsequent cardiac events ($P=.01$). Treatment with β -adrenergic blockers was associated with a significant decrease in risk for cardiac events during the prepregnancy, pregnancy, and postpartum intervals (OR=0.023; $P=.01$). No interactions between these variables in the model were found.

The mean value of the random effect represents the average risk of having a cardiac event during the prepregnancy interval for a proband woman. The average risk of having a cardiac event during the prepregnancy interval was 0.0004, or 1 chance in 2500; however, this risk varied considerably among proband women. The probability of having a cardiac event would be 1 chance in 50 for a woman in the 97.5th percentile (2 SD greater than the mean), whereas a woman in the 2.5th percentile would have 1 chance in 100 000 of having a cardiac event. This variability between individuals was highly significant ($P<.001$) and was independent of the other clinical and ECG variables that were considered (fixed effects).

The ORs derived from our multivariate logistic regression model can be used to estimate the risk of pregnancy for individual patients, while recognizing the fact that the CIs are

TABLE 4. Multivariate Analysis of Risk Factors for Cardiac Events in 111 Probands

	No. of Intervals	Intervals With Cardiac Events, %	OR (95% CI)	P
Prepregnancy interval	171	2.3	1.0	
Pregnancy interval*	272	5.5	3.5 (0.4-32)	.27
Postpartum interval*	234	12.0	40.8 (3.1-540)	.01
β -Adrenergic blockers			0.023 (0.001-0.44)	.01
Cardiac events before first pregnancy			9.1 (1.7-47)	.01

*Compared with prepregnancy interval.

wide for all the variables that were studied. The combined odds is simply the product of the odds ratios of the coexisting factors. For a proband woman, the likelihood of having a cardiac event during the postpartum interval is [the average probability of having a cardiac event during the prepregnancy interval (0.0004)] \times [the odds of a cardiac event during the postpartum interval relative to the prepregnancy interval (40.8)]=0.02; ie, 1 chance in 50 pregnancies. Treatment with β -adrenergic blockers would be expected to lower the postpartum risk to 1 chance in 2500 pregnancies: [the average probability of having a cardiac event during the postpartum interval (0.02)] \times [the reduction in risk associated with β -adrenergic blockers (0.023)]=0.0004=1/2500.

Discussion

In the present study, probands with the hereditary LQTS were at significant risk for cardiac events during the postpartum interval. Nearly 10% of the probands in our study had their first cardiac event during the postpartum interval. Probands were also more likely to experience multiple cardiac events during the postpartum period. Treatment with β -adrenergic blockers was associated with a meaningful reduction in the risk for cardiac events among probands.

There are several potential reasons why pregnancy may contribute to an increased risk for cardiac events. It is well known that increases in sympathetic activity can precipitate malignant tachyarrhythmias in LQTS patients¹¹⁻¹³; the high levels of estrogen and progesterone that occur during pregnancy may amplify adrenergic responses.¹⁴⁻¹⁶ It is also conceivable that estrogen and progesterone could directly influence the number and function of the mutant ion channel proteins that have recently been linked to LQTS.¹⁷⁻¹⁹ Although the number and sensitivity of adrenergic receptors may be augmented as a consequence of the endocrinological changes of pregnancy, other factors may delay the expected increase in arrhythmic events until after pregnancy. One of the typical cardiovascular changes of pregnancy is an increased heart rate, particularly during the third trimester.¹ This phenomenon may be protective in LQTS patients, who exhibit exaggerated QT interval prolongation at slower heart rates.²⁰ The increase in arrhythmic events during the postpartum interval may therefore be related to a decrease in heart rate and an associated increase in the QT interval, which would allow antecedent changes in receptor function to become manifest. The psychological stress and altered sleep patterns associated with caring for a newborn infant could also contribute to an increase in adrenergically mediated cardiac events during the postpartum interval.

In accordance with previous data,⁸ a history of prior cardiac events was an independent predictor of future cardiac events in our population. Treatment with β -adrenergic blockers was independently associated with a meaningful decrease in the risk for cardiac events during the prepregnancy, pregnancy, and postpartum intervals; although the confidence intervals were wide, the smallest reduction in risk associated with β -adrenergic blocker therapy exceeds 50%. Taken together with previous observational data,^{12,13} this study strongly suggests that probands who become pregnant should be treated with β -adrenergic blockers. The effect of maternal treatment with β -adrenergic blockers during pregnancy has been studied extensively, primarily in patients who were treated for hyper-

tension during pregnancy.²¹⁻²³ Maternal treatment with propranolol was infrequently associated with neonatal bradycardia, respiratory depression, hypoglycemia, and intrauterine growth retardation in several small, uncontrolled studies.²⁴⁻³¹ Subsequent randomized trials have documented a decreased incidence of neonatal complications after maternal treatment with atenolol³² or metoprolol³³ for hypertension during pregnancy. In accordance with previous reports, we did not observe any fetal malformations after maternal treatment with β -adrenergic blockers. Most β -adrenergic blockers are secreted in breast milk, with higher concentrations reported for metoprolol and atenolol than for propranolol; however, adverse effects are uncommon in infants with normal renal and hepatic function.³⁴⁻⁴⁰ The decreased incidence of cardiac events among probands treated with β -adrenergic blockers certainly outweighs the low probability of harm to the infant.

In our population, probands were more likely to have a history of cardiac events before the first pregnancy than affected first-degree relatives (46% versus 22%). It is therefore not surprising that probands have more events than affected first-degree relatives during all three observation periods, because a history of cardiac events is a powerful predictor of subsequent events. Although the numbers of cardiac events were insufficient for multivariate analysis, affected first-degree relatives were more likely to have cardiac events during the postpartum interval compared with the prepregnancy interval ($P=.065$). Because prior cardiac events are also predictive of future cardiac events among first-degree relatives,⁸ it appears prudent to continue β -adrenergic blockers in symptomatic affected first-degree relatives who become pregnant. The decision to treat asymptomatic first-degree relatives with definite QT interval prolongation should be individualized, because these patients are at less risk for cardiac events. Cardiac events were very infrequent among first-degree relatives with borderline or unequivocally normal QT intervals; as a result, these patients do not require treatment with β -adrenergic blockers during the pregnancy and postpartum intervals.

Study Limitations

Several distinct genetic mutations have recently been identified in patients with LQTS.¹⁷⁻¹⁹ Patients with different mutations vary in their responses to a variety of physiological and pharmacological stimuli.⁴¹ Genetic heterogeneity may be partially responsible for the marked differences in risk for cardiac events that we observed among proband women. We do not yet have genotypic data on enough of our LQTS patients to determine whether the effect of pregnancy is influenced by the underlying genetic mutation.

Because of the retrospective nature of the analysis, it is conceivable that more cardiac events were recognized during the pregnancy and postpartum intervals, because the patients may have been more likely to receive medical attention at these times. An underestimation of the number of cardiac events during the prepregnancy interval would lead to an overestimation of the odds for a cardiac event during the postpartum interval. To minimize this potential source of error, we also determined the OR for cardiac events during the postpartum interval using the pregnancy interval as a control. The postpartum interval was independently associated with a

12-fold increase in the odds for a cardiac event relative to the pregnancy interval ($P=.01$). These data indicate that underreporting of cardiac events during the prepregnancy interval did not contribute to the increased odds for cardiac events during the postpartum interval among probands.

Conclusions

The postpartum period is associated with a significant increase in the incidence of cardiac events among probands with the LQTS. First-degree relatives with unequivocal QTc prolongation may also be at risk during the postpartum period, although not nearly to the same extent as probands. Pregnancy is safe for first-degree relatives with borderline or normal QT intervals. Probands and symptomatic first-degree relatives with definite QTc prolongation should continue prophylactic treatment with β -adrenergic blockers during the pregnancy and postpartum intervals.

Appendix

Other LQTS Investigators

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