Does Pregnancy Increase Cardiac Risk for LQT1 Patients With the KCNQ1-A341V Mutation?

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OBJECTIVES The purpose of this study was to assess the pregnancy-related cardiovascular risk in LQT1 patients.

BACKGROUND Only 1 study addressed this issue in genotyped patients and reported that the highest risk is for LQT2 patients.

METHODS This case-control study, performed in a cohort of patients from 22 families affected by LQT1 and all sharing the common KCNQ1-A341V mutation, involved 36 mutation carriers and 24 of their unaffected sisters for a total of 182 pregnancies.

RESULTS There were 3 (2.6%) cardiac events (2 cardiac arrests) in the 115 LQT1 pregnancies. Because they occurred only among the 27 mothers with previous symptoms, all off-therapy, the risk for asymptomatic patients is 11%, but decreases to 0 in symptomatic patients treated with beta-blockers. Carriers and control subjects did not differ for the incidence of miscarriage (10% vs. 15%). Cesarean sections (C-sections), elective or owing to fetal distress, were performed more often in carriers than in non-carriers (27% vs. 14%). Beta-blocker therapy did not influence the prevalence of fetal distress. Among the infants born to carriers, all those with fetal distress were carriers of the A341V mutation (10 of 10, 100%). Among the offspring of the carriers, 48 of 92 (52%) were mutation carriers, and of those, 15% died suddenly at age 14 ± 6 years.

CONCLUSIONS Women affected by the common KCNQ1-A341V mutation are at low risk for cardiac events during pregnancy and without excess risk of miscarriage; their infants delivered by C-section because of fetal distress are extremely likely to also be mutation carriers. Beta-blockers remain recommended. These conclusions likely apply to most LQT1 patients. (J Am Coll Cardiol 2006;48:1410–5) © 2006 by the American College of Cardiology Foundation

Congenital long QT syndrome (LQTS) is associated with prolongation of the QT interval on the electrocardiogram, recurrent syncope, and sudden cardiac death (1,2). Molecular diagnosis has allowed identification of at least 6 genetic subgroups. The 3 major subtypes (LQT1, due to mutations affecting KCNQ1, the gene encoding the IKs current; LQT2, due to mutations affecting KCNH2, the gene encoding the IKr current; and LQT3, due to mutations on SCN5A, the gene encoding the cardiac sodium channel) have their own clinical profile, despite some overlap (3,4–6). This includes markedly different genotype-phenotype correlations (7), ranging from natural history (8) to gene-specific triggers for cardiac events (9) and to response to therapy (9–11). Patients with LQT1 experience most of their cardiac events during exercise, especially swimming, or in condition of emotional stress, especially fear (9). This is the consequence of the impairment in the IKs current, which disrupts the normal ability to shorten ventricular repolarization during increases in sympathetic activity and heart rate (9). Thus, any condition that augments sympathetic activity can favor the occurrence of life-threatening arrhythmias in LQT1 patients. The counterpart of this concept is the efficacy in these patients of anti-adrenergic therapy, either beta-blocker (BB) therapy or left cardiac sympathetic denervation (9–12).

Pregnancy is associated with hormonal changes that prime cardiac receptors for adrenaline and other sympathomimetic neurotransmitters (13), whereas labor is also associated with a hyperadrenergic state due to pain, anxiety, and fear (14,15). This physiological background justifies concerns for additional risk of cardiac events in LQT1 pregnant women. An important and negative consequence of these concerns is that many women affected by LQTS do not dare to become pregnant or do so with fear.

However, except for 1 systematic study (16), the possibility of an increased risk during pregnancy for LQTS-affected mothers has been discussed only in isolated case reports (17–20). Rashba et al. (16) reported that the postpartum interval, specifically, was associated with a significant increase in risk for cardiac events among LQTS patients. However, an important limitation of that study—in light of the new knowledge concerning the different genotypes—was that it did not distinguish between the different LQTS subgroups. In the only study involving genotyped patients, Khositseth et al. (21) suggested that most of the cardiac events associated with pregnancy occur in LQT2 patients.

We have identified numerous South African families of Afrikaner descent who harbor the same mutation (KCNQ1-A341V) due to a founder gene effect (22,23). In this rather unique population we have retrospectively inves-
tigated the outcome of pregnancies to assess cardiovascular risk for both mothers and their infants.

The A341V represents a hot spot, because it has been found by investigators in Europe, America, and Asia. Moreover, we have demonstrated that this mutation is associated with an unusually high clinical severity (23). This suggests but does not prove that A341V might represent the “end-of-the-spectrum” and that it could be used to draw careful inferences on the “worst case scenario” for LQT1 patients.

**METHODS**

South African LQT1 female carriers of the KCNQ1-A341V mutation, who were 20 years or older at the commencement of the study, were identified from our LQTS database. They were all contacted by telephone and asked whether they would participate in the current study. Unaffected sisters of affected women who agreed to answer the same questions served as control subjects. The University of Stellenbosch Ethics Committee approved the study.

Each consenting subject received a self-administered, self-reported written questionnaire that contained questions relating to the age at the time of her first and last syncope attack, the number of successful pregnancies, the birthweight of the babies, the number of abortions or stillbirths, and whether they had received any form of anti-adrenergic therapy, such as beta-adrenergic blockers or left cardiac sympathetic denervation during pregnancy or in the peri-partum periods (defined as 40 weeks before and after pregnancy). Syncope was defined as complete loss of consciousness resulting in loss of postural tone and lasting for ≥1 min. Aborted cardiac arrest refers to subjects who reported having received cardiopulmonary resuscitation or electrical defibrillation.

All data reported in the questionnaire were subsequently verified by telephone with the mothers on 2 different occasions. Because the pregnancies occurred over a period of 36 years, it was possible to have information from general practitioners, obstetricians, pediatricians, or from the various hospitals only for the more recent ones and in most of the cases of fetal distress.

The mutation-carrier status of individuals born to the mothers who took part in the survey was determined from our database. The QT intervals were measured in standard lead II of the electrocardiogram (ECG) and were corrected for heart rate (QTc).

**Statistical analysis.** Differences among groups were analyzed by using the t test for unpaired data, the chi-square test, and the Fisher exact test (Prism software, version 3.02; Graphpad, San Diego, California), as appropriate. Data are presented as mean values ± 1 SD. A p value <0.05 was considered significant.

**RESULTS**

We identified and contacted 39 mutation carriers with previous pregnancies and 26 control subjects. Of these, 36 (92%) and 24 (92%), respectively, answered the questionnaire (Table 1). None of the non-responders died during/after pregnancy. The mean QTc interval of the mutation carriers (508 ± 59 ms, n = 36) was markedly longer (p < 0.0001) compared with that of the non-carriers (413 ± 16 ms, n = 24). Importantly, of the 36 LQTS-affected mothers, 27 (75%) had had cardiac events (7 had an aborted cardiac arrest and 20 had syncope). The mean age at the first and last reported cardiac event among the 27 symptomatic mutation carriers was 9.8 (range 2 to 18) and 29.6 (range 14 to 55) years, respectively.

The mean ages at first and last pregnancy were, respectively, 24 ± 4 and 32 ± 5 years among mutation carriers and 24 ± 4 and 31 ± 5 years among non-mutation carriers.

**Peri-partum syncope or cardiac arrest.** As expected, there were no cardiac events among the control subjects. This was not the case among the LQTS mutation carriers. There were no peri-partum maternal deaths, but 3 cardiac events (1 syncope and 2 aborted cardiac arrests) did occur among the carriers. The actual risk for the mothers during each full-term pregnancy was low, because there was 1 event (1/102 = 1%) during pregnancy and 2 (2/102 = 2%) within the first 9 months after delivery. However, a different pattern emerged when the risk for the individual mothers

| Table 1. Characteristics of Pregnancies of Carrier Versus Non-Carrier Mothers |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                             | Non-Carriers (n = 24)       | All Carriers (n = 36)       | Carriers βB+ (n = 8)        |
| QTc (ms)                    | 414 ± 18*                  | 508 ± 58*                  | 534 ± 78                   |
| Pregnancies                 | 67                         | 115                        | 15                         |
| Live births                 | 57/67 (85%)                | 102/115 (89%)              | 13/15 (87%)                |
| Miscarriages                | 10/67 (15%)                | 12/115 (10%)               | 2/15 (13%)                 |
| C-sections (% of live births)| 8/57 (14%)                 | 28/102 (27%)               | 9/13 (69%)†                |
| Fetal distress (% of C-sections)| 2/8 (25%)                | 10/28 (36%)               | 3/9 (33%)                  |
| *p < 0.0001 (unpaired t test); †p = 0.001 (Fisher exact test). |
| βB+ = beta-blocker therapy; βB− = without beta-blocker therapy; C-section = cesarean section; QTc = corrected QT. |
was examined on the basis of their previous clinical history and medication.

The 9 carriers who were asymptomatic before pregnancy had no cardiac events at all during their 30 pregnancies (mean 3.3/person). By contrast, among the 27 mutation carriers who had cardiac symptoms before becoming pregnant, 3 (11%) suffered cardiac events during or after their 85 pregnancies (mean 3.1/person). One carrier had a cardiac arrest during pregnancy (1 of 27 = 3.7%), whereas 2 reported 1 syncope and 1 cardiac arrest in the post-partum period (2 of 27 = 7.4%). No ECG was taken during these events, and therefore there is no documentation of the arrhythmias. None of these 3 patients were receiving βB therapy during pregnancy or in the post-partum period. None of the 3 cardiac events occurred during the first pregnancy. The 2 patients symptomatic after pregnancy suffered their cardiac events 3 and 4 months after delivery.

**Obstetrical and infant data.** A total of 182 pregnancies were reported in the 60 women (36 carriers and 24 of their unaffected sisters) (Table 1). Of these, the mutation carriers reported 115 pregnancies, of which 102 were live, full-term (38 to 40 weeks gestation) births; they occurred during a period of time spanning 56 years. Because diagnosis and therefore treatment of LQTS were rare in South Africa before 1975, most analyses on the differences between patients taking βB and those not taking βB were focused on the pregnancies ending from 1975 onward (Table 2). The incidence of miscarriage was similar in the 2 groups, because it was 10% (12 of 115) in pregnancies experienced by carriers and 15% (10 of 67) in the control group (p = NS). Among carriers there was also a stillbirth. With the exception of the latter, all the unsuccessful pregnancies ended in spontaneous abortion within the first 6 weeks of gestation. There were no reported therapeutic or elective abortions. Fifteen pregnancies were completed under βB, whereas 100 were in untreated carriers; the percentage of miscarriages is similar in both groups (13% and 10%, respectively).

Cesarean sections, all performed under general anesthesia and without any complication, were more common in LQTS mothers compared with control subjects (28 of 102, 27% vs. 8 of 57, 14%; p = 0.053) and among mutation carriers treated with βB compared with those not receiving therapy (9 of 13, 69% vs. 19 of 89, 21%; p = 0.001). However, this finding was influenced by the fact that until the 1970s most deliveries occurred at home and C-sections were limited to special cases. Among pregnancies after 1975, the prevalence of C-sections in mutation carriers treated or not with βB was not significantly different (9 of 13, 69% vs. 18 of 36, 50%; p = 0.2).

Fetal distress was the cause of C-section in 12 of 36 (33%) pregnancies: in 10 of 28 (36%) LQTS mothers and in 2 of 8 (25%) control subjects (NS). Because βB could facilitate fetal bradycardia, we considered the possibility that they could have caused a greater number of C-sections due to fetal distress among mothers in therapy. However, there was no difference between the prevalence of fetal distress among carriers receiving βB therapy and those not receiving βB therapy, both considering all of the pregnancies (33% vs. 37%, p = NS) and only those after 1975 (33% vs. 39%, p = NS). This rules out βB as a direct cause for fetal distress.

Among the mutation carriers, the probability of the occurrence of fetal distress was independent of both QTc duration and age at first cardiac event, even though a nonsignificant trend existed for QTc duration to be longer (511 ± 49 vs. 488 ± 53 ms, p = NS) and for cardiac events to occur earlier (4.4 vs. 6.1 years, p = NS) among the mothers destined to show signs of fetal distress.

Interestingly and importantly, among the infants from LQTS mothers, all those (10 of 10, 100%) who had suffered fetal distress were subsequently found to be mutation carriers. By contrast, only 38 of 92 (41%) infants born without fetal distress were mutation carriers. This represents a significantly different (p < 0.001) probability to be affected by LQTS according to the presence of fetal distress.

Apgar score was available in 6 of 10 babies born with fetal distress, and the mean value was 8 of 10 at 1 min after birth and 10 of 10 at 5 min after birth. In 3 of the 4 who had an unknown Apgar score, mothers referred to a pink skin color and a good and strong cry. Mean birth weight was lower among babies born to mothers taking βB (2.9 ± 0.6 kg vs. 3.3 ± 0.6 kg, p = 0.03). Mean gestational week was the same in the 2 groups (39 ± 1 vs. 39 ± 2).

Of the 102 full-term births in the LQTS group, 85 (83%) underwent molecular screening to determine their carrier status, whereas 10 had not yet undergone genetic testing. The remaining 7 children (7%), all untreated, died suddenly at an average age of 14 ± 6 years (range 3 to 21) and were considered to be mutation carriers. Among those genotyped, 41 were mutation carriers for a total of 48 (41 sudden deaths) of 92 tested (52%), whereas 44 (48%) were not. No information was available about the carrier/non-carrier status of the 12 aborted fetuses and the stillbirth. In

### Table 1. Characteristics of Pregnancies After 1975

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Carriers βB+</th>
<th>Carriers βB−</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total live births</td>
<td>13</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Live births post 1975 (% of all live births)</td>
<td>13/13 (100%)</td>
<td>36/89 (40%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C-sections post 1975 (% of all C-sections)</td>
<td>9/9 (100%)</td>
<td>18/19 (95%)</td>
<td>NS</td>
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<tr>
<td>C-sections post 1975 (% of live births after 1975)</td>
<td>9/13 (69%)</td>
<td>18/36 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Fetal distress (% live births after 1975)</td>
<td>3/13 (23%)</td>
<td>7/36 (19%)</td>
<td>NS</td>
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<tr>
<td>Fetal distress (% of C-sections after 1975)</td>
<td>3/9 (33%)</td>
<td>7/18 (39%)</td>
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Abbreviations as in Table 1.
this cohort of young individuals affected by LQT1, the incidence of sudden cardiac death was 15% (7 of 48).

**DISCUSSION**

This is the first report to provide comprehensive data concerning the risks and consequences of pregnancy for women affected by one of the most common mutations causing the LQT1 genetic subgroup of the LQTS (KCNQ1-A341V). The results of this case-control study also suggest rational strategies for the management of pregnant A341V-LQT1 women and their offspring.

The main findings were that A341V-LQT1 women are at low risk for cardiac events during pregnancy and the 9 months following delivery, that there is a trend for a higher risk among those who already had cardiac events before pregnancy, that there is no excess risk for miscarriage, and that the infants delivered by C-section because of fetal distress are extremely likely to also be mutation carriers.

Because the clinical manifestations of the A341V patients are indistinguishable from those of the LQT1 group at large, with the exception of an apparent greater clinical severity (23), it seems reasonable to expect that most of the findings reported here would also apply to most LQT1 women. If anything, the risks associated with pregnancy in LQT1 women might be even lower than those observed in the rather malignant A341V form of LQTS.

**LQTS and pregnancy-related cardiac events.** Because pregnancy is an emotionally stressful period and the postpartum period is associated with frequent sleep disruption, it had been presumed that patients affected by a disease such as LQTS—in which stress plays a significant role for the occurrence of life-threatening arrhythmias (1,9,24)—would be at increased risk during or after a pregnancy. This view seemed to be confirmed by the study by Rashba et al. (16) in which the postpartum period was associated with a significant increase in risk for cardiac events. They studied pregnancies in 111 probands and compared them with 105 affected (on the basis of a QTc duration >470 ms) family members and 134 unaffected family members. Probands, but not their affected family members, had a higher than expected incidence of cardiac events during the postpartum period. Their conclusion was limited by the fact that the data were obtained in LQTS patients irrespective of their genotype. Very recently, this limitation was partially overcome by Khositseth et al. (21), who observed that most of the arrhythmic events related to pregnancy in LQTS patients occurred in the LQT2 subgroup. Our findings, indicating a low risk among LQT1 patients, support that conclusion.

Because the present data demonstrate that A341V-LQT1 patients and probably most LQT1 patients with other mutations are at low risk for pregnancy-related cardiac events, it follows that the combined picture emerging by also using the data by Rashba et al. (16) and by Khositseth et al. (21) is indeed pointing to a genotype-phenotype difference such that this risk is relatively small for LQT1 patients and relatively large for LQT2 patients. No data are as yet available on the smaller LQT3 subgroup.

**Implications for the mothers.** These data allow us to reassure A341V-LQT1 women about the fact that they can approach pregnancy without undue anxiety. If they were asymptomatic before becoming pregnant, this risk is indeed minimal; if they already suffered cardiac events, their risk of a recurrence is around 10%. It is quite reasonable to expect that βB therapy—which is quite effective for LQT1 patients (7,9–11)—would further reduce or totally prevent arrhythmic episodes. Actually, in our population none of the previously symptomatic patients experienced a cardiac event while receiving βB therapy during or after pregnancy. Current knowledge, reinforced by the present data, indicates that every A341V-LQT1 patient who becomes pregnant, if not already under treatment, should be started on βB.

The probability of a miscarriage is not different compared with control women and is similar to that of the general population (25). Thus, there should be no specific fears for this possibility.

The probability of a C-section is greater in mutation carriers compared with control subjects and in mutation carriers receiving βB compared with those not receiving therapy. The latter is simply owing to the pregnancies that took place before 1975, when LQTS was very seldom diagnosed and treated and when C-sections were also unusual. After 1975, rates of 69% (βB therapy) and 50% (no βB therapy) are in line with South African private hospital practice of 65% (26). Even though βB could facilitate fetal bradycardia, they did not increase the prevalence of fetal distress. However, it is fair to say that it could be difficult to quickly distinguish between a bradycardia due to LQTS and a true obstetrical event. In doubt, the performance of a C-section seems a safe choice.

Indeed, our data raise the possibility that many of the C-sections performed in LQTS mothers are not necessary, because the fetal bradycardia—a major cause for the diagnosis of fetal distress—might simply reflect the presence of an infant affected by LQTS. This is supported by the fact that the Apgar score, when available, was normal in those affected babies born with a supposed fetal distress.

**Implications for the infants.** The transmission of the mutation to the infants of these 36 mutation carriers took place in 52% of cases, in accordance with autosomal dominant Mendelian inheritance. This strongly suggests that, within A341V-LQT1 patients, there is no excess loss of affected individuals either at conception, developmentally, or anywhere else during the course of pregnancy. Indeed, the abortion rate of 10% compares well with that of 15% within the control group and South Africa in general (25) and allows the conclusion that infants conceived by A341V-LQT1 mothers do not have a higher risk of dying in uterus. In contrast, the existing but largely anecdotal observations of stillbirths due to LQTS (27–29) foster the concept that
within the overall LQTS population, the prevalence of stillbirths might be higher within the LQT2 and LQT3 subgroups (30).

A practically important and unexpected observation was that within the group of affected mothers, all the infants with fetal distress were subsequently found to be mutation carriers. Because the ECG during the first few days of life might show spurious QT prolongation even in normal infants (31,32) and because genetic testing can take weeks or months (according to the knowledge of the mutation in the mother), fetal distress might be a key for a very strong suspicion that the newborn is indeed affected by LQTS. This in turn will allow the institution of the appropriate preventive strategies according to the guidelines of the European Society of Cardiology (32).

Finally, the present data support the existing concept that maternal βB treatment has no negative consequences for the infant and its development. Indeed, it does not increase the number of miscarriages and, even though the birth weight of these infants is lower than that of infants of LQTS mothers not receiving therapy, a mean weight of 2.9 kg is not enough to justify concern.

**Genetic implications.** The A341V is a relatively common LQT1 mutation and represents a mutational hotspot. It is unproven but likely that the observations made in the present study can be largely extrapolated to the entire LQT1 population. Indeed, A341V patients have their cardiac events primarily during physical and emotional stress, especially swimming, as we have described for the LQT1 population (9); also, their T waves match the morphology we had described for the LQT1 group (33), and they respond very well to βB, as do most LQT1 patients (11).

There is one potential difference between A341V and most LQT1 patients, but its nature is such that it does not affect the interpretation of the present results. Indeed, a surprising observation was that 74% of these women mutation carriers had cardiac events. This percentage of symptomatic patients is markedly higher than that reported in over 300 LQT1 patients (8) and, together with the 15% incidence of sudden death among the offspring of the mutation carriers, raises the intriguing possibility that A341V is a mutation of unusual severity. This is supported by our recent analysis of a large group of LQT1 patients all carrying the KCNQ1-A341V mutation (23).

**Conclusions.** In conclusion, A341V-LQT1 women should approach pregnancy without fear. They should all be treated with βB. The presence of fetal bradycardia is more likely to reflect the presence of LQTS than true fetal distress, and whenever fetal distress is diagnosed, it is quite likely that the infant will be a mutation carrier.

**Acknowledgment**

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**References**


