HeartRhythm

The Official Journal of the Heart Rhythm Society, The Cardiac Electrophysiology Society, and The Pediatric & Congenital Electrophysiology Society

Heart Rhythm Society SM

Top Stories: Pediatric Electrophysiology

Fetal long QT syndrome

Bettina F. Cuneo, MD

(Heart Rhythm 2025;22:285–286)

Clinical recognition of long QT syndrome before birth

Since the first report 30 years ago of inherited fetal long QT syndrome (LQTS) presenting as mild fetal bradycardia, more than 265 prenatal cases of LQTS have been reported.[1] The importance of prenatal recognition cannot be overestimated because of the significant risk for stillbirth or premature delivery and the value of primary prevention for the infant proband and LQTS-positive family members. Prenatal recognition is difficult without a family history because the most common sign of LQTS is a modestly decreased fetal heart rate (FHR) that does not even meet the obstetric definition of bradycardia. Although notable, the signature LQTS rhythms of torsades de pointes (TdP) and functional 2:1 atrioventricular block (AVB) occur in only about one-third of subjects.[1]

Characteristics of LQTS fetal bradycardia

A recent study compared the FHRs of LQTS-positive and LQTS-negative offspring with maternal or paternal LQTS with the goal of developing an FHR/gestational age algorithm identifying LQT1, LQT2, and LQT3 subjects before birth.[2] This study demonstrated that (1) FHRs of LQT3-positive subjects did not differ from LQT3-negative subjects; and (2) maternal β-blocker treatment worsened the sinus bradycardia of LQT1 and LQT2 fetuses but did not affect the FHR of LQTS-negative fetuses. Interestingly, LQT1 fetuses with non-nonsense and severe loss-of-function variants had lower FHRs than other LQTS1 variants. FHR < threshold correctly identified inherited LQT1 and LQT2 offspring with 75% accuracy, 71% sensitivity, and 81% specificity. Future studies of FHR to identify LQTS may show an even greater accuracy if fetal QTc, detected by fetal magnetocardiography (fMCG), is part of the algorithm. Larger studies are needed to test how well FHR < gestational age threshold identifies LQT1 and LQT2 subjects in ostensibly low-risk populations.

Fetal echocardiographic diagnosis of LQTS

While echocardiography measures the mechanical consequences of cardiac electrical activity and cannot identify repolarization abnormalities, detecting specific findings can suggest LQTS. Simultaneous fMCG and echocardiography performed at the University of Wisconsin–Madison uncovered beat-to beat-alternans in the isovolumic relaxation times (IVRT) in 3 LQTS fetuses with macroscopic T-wave alternans (TWA) and QTc >600 ms.[3] After birth, all had TWA on postnatal electrocardiography. One fetus with an inherited KCNH2 T613K pathogenic variant had *in utero* TdP. With the previously described findings of a prolonged IVRT, IVRT alternans is an echocardiographic marker for LQTS with a very prolonged QTc.

Risk stratification

Based primarily on retrospective multicenter data from 83 studies, known risk factors for perinatal death, which occurred in 20%, include fetal or neonatal QTc >600 ms (Figure 1), ventricular tachycardia (VT), TdP, or functional 2:1 AVB and a negative LQTS family history.[1] Confirmed *de novo* mutations were associated with longer neonatal QTc (receiver operating characteristic area under the curve 0.81, 95% confidence interval [CI] 0.72–0.89) and a significantly higher risk of VT/TdP (odds ratio [OR] 5.50, 95% CI 2.30–12.50); functional 2:1 AVB (OR 9.67, 95% CI 4.23–22.13); and death (OR 26.80, 95% CI 5.81–123.3).[1] FHR in sinus rhythm did not predict QTc, presence or development of TdP or functional 2:1 AVB, *de novo* vs inherited pathogenic variant, or outcome.[1]

Pregnancy management

Pregnancy management of the LQTS fetus is complex.[4] In the case of inherited LQTS, it is probably best to assume the fetus is affected given that the risk is 50%. Chorionic villus sampling

From the Departments of Pediatrics and Surgery, University of Arizona College of Medicine, Tucson, Arizona.

https://doi.org/10.1016/j.hrthm.2024.11.013
1547-5271/$-see front matter

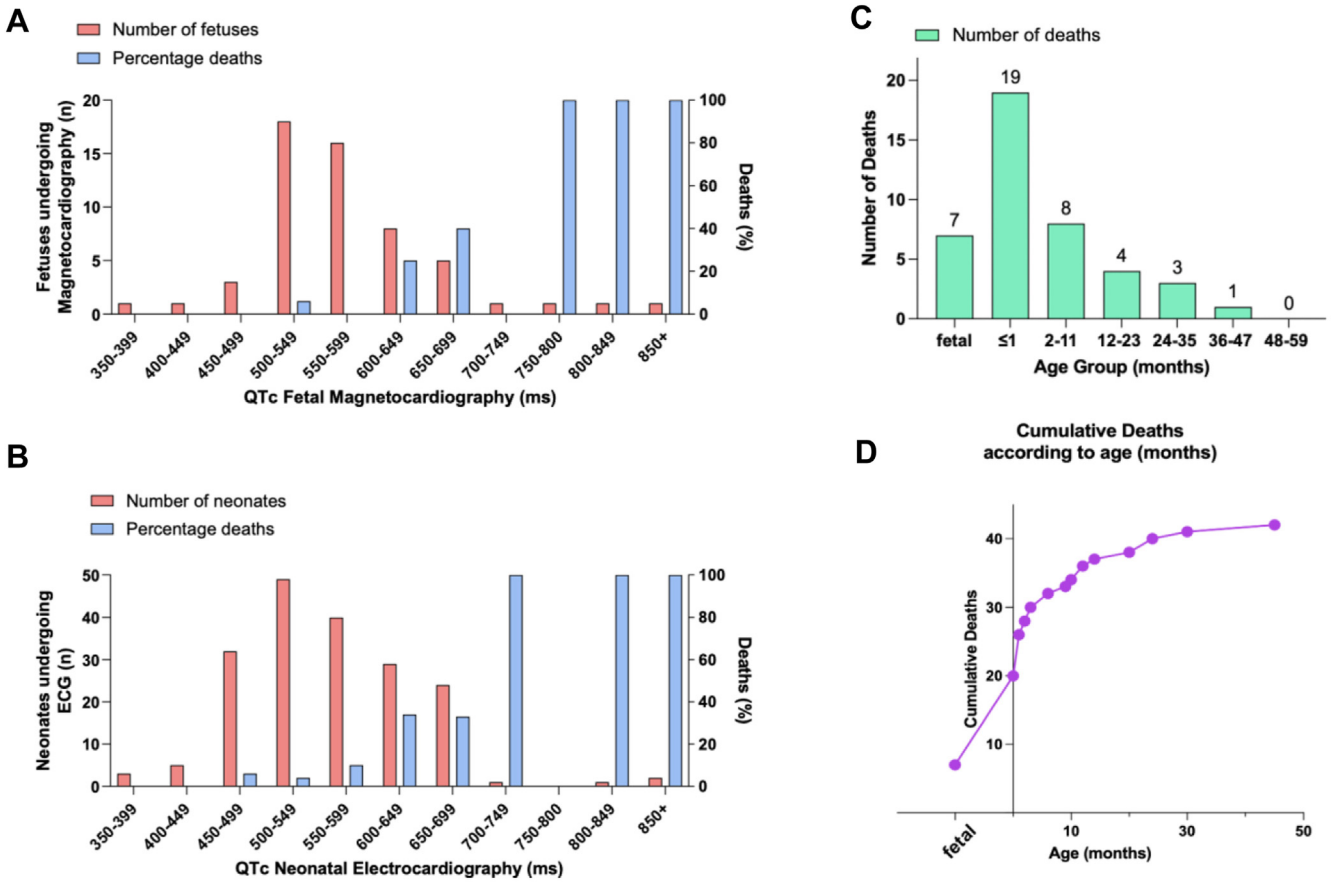

Figure 1

A: Number of fetuses undergoing magnetocardiography (n = 55, *pink bars*) and percent of deaths (n = 8, *blue bars*) grouped according to QTc duration. **B:** Number of neonates with QTc interval measured on postnatal electrocardiography (ECG) (n = 188, *pink bars*) and percent of deaths (n = 29, *blue bars*). **C:** Number of fetal and neonatal deaths based on age in months. **D:** Cumulative deaths of long QT syndrome subjects by age (in months). (Image reproduced from Chivers et al.[1])

(between 10 and 13 weeks) or amniocentesis (after 15 weeks) can be performed if the pathogenic variant is known or a *de novo* variant is suspected. Preimplantation genetic testing can identify affected embryos in couples undergoing *in vitro* fertilization because one of them carries a pathogenic LQTS variant. fMCG, especially in the early third trimester, is noninvasive and can confirm a fetal diagnosis and aid with risk stratification. If the mother is the affected partner, her electrophysiologist, maternal fetal medicine specialist, and fetal cardiologist can work together to ensure adequate maternal β-blocker treatment, optimal serum calcium, vitamin D, and magnesium levels, and regular fetal ultrasound/echocardiography surveillance for growth restriction, fetal well-being, and onset of LQTS signature rhythms.[4] QTc-prolonging medications must be avoided during pregnancy and delivery. The fetal cardiologist and maternal fetal medicine specialist closely collaborate if the fetus develops TdP, which is most likely to develop in *de novo* SCN5A or KCNH2 or inherited KCNH2 variants and occurs most commonly in the third trimester. Successful *in utero* treatment is possible with intravenous magnesium and lidocaine and oral β-adrenergic blocking agents to avert a preterm delivery and resolve hydrops if the latter is present.[5] Genetic testing after birth can be positive even if the infant's QTc is not prolonged. Cascade testing is recommended to detect affected but unsuspecting relatives.

Funding Sources: This study was funded by National Institutes of Health (NIH) RO1HD100929 and R21HD109564.

Disclosure: Ownership interest in HeartSounds Labs, Inc.

Authorship: The author attests she meets the current ICMJE criteria for authorship.

Address reprint requests and correspondence: Dr Bettina F. Cuneo, 1653 W. Campbell Avenue, Tucson, AZ 85724. E-mail address: Cuneo1@Arizona.edu

References

1. Chivers S, Ovadia C, Regan W, Zidere V, et al. Systematic review of long QT syndrome identified during fetal life. Heart Rhythm 2023;20:569–606.
2. Kaizer AM, Windo A, Clur S-AB, et al. Effects of cohort, genotype, variant and maternal β-blocker treatment of fetal heart rate predictors of inherited long QT syndrome. Europace 2023;25:1–11.
3. Roth DJ, Strasburger JF, Wakai RT. Fetal T-wave and isovolumetric relaxation time alternans can be identified by fetal echocardiography. Heart Rhythm 2024 Aug;5. S1547-5271(24)03118-7.
4. Wacker-Gussmann A, Eckstein GK, Strasburger JF. Preventing and treating torsades de pointes in the mother, fetus and newborn in the highest risk pregnancies with inherited arrhythmia syndromes. J Clin Med 2023;12:3379.
5. Putra M, Lee YM, Bucholz E, et al. Successful management of fetal torsades de pointes and long QT syndrome by a cardio-obstetrical team. JACC Case Reports 2023;27:102110.