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ELECTROPHYSIOLOGY

CASE REPORT: CLINICAL CASE

Low Baseline Fetal Heart Rate Leads to Diagnosis of Long QT Syndrome Type 1

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ABSTRACT

A low baseline fetal heart rate at 20 weeks' gestation was detected in a fetus without cardiac structural anomalies. Fetal echocardiography and magnetocardiography were used to diagnose congenital long QT syndrome. It was confirmed in the neonate, and the same pathogenic variant in *KCNQ1* was subsequently identified in the mother. (J Am Coll Cardiol Case Rep 2024;29:102183) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 28-year-old primigravida presented for a routine fetal anatomic survey at 20 weeks' gestational age (GA). During this ultrasound, fetal heart rates (FHRs) of 109-115 beats/min were noted (which is below the 3rd percentile for the GA; the 50th percentile for this GA is 150 beats/min).[1] The heart appeared structurally normal, and the fetal anatomy was otherwise unremarkable.

LEARNING OBJECTIVES

- To recognize the variable presentations of congenital LQTS.
- To describe the clinical implications of fetal LQTS.

PAST MEDICAL HISTORY

The mother had no pertinent medical or surgical history. She denied history of fetal loss, syncope, seizures, or cardiac disease. Her standard prenatal panel was normal, and she declined genetic screening. There was no personal or family history of known arrhythmias, syncope, or sudden cardiac death.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for FHR below 3rd percentile for GA with 1:1 atrioventricular (AV) conduction includes transient effects from umbilical cord compression, immune-mediated (anti-Ro/SSA antibody) sinus bradycardia and sinus bradycardia secondary to maternal hypothyroidism, exposure to maternal medications (such as methadone or other

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ABBREVIATIONS AND ACRONYMS

AV = atrioventricular

ECG = electrocardiography

FHR = fetal heart rate

fMCG = fetal magnetocardiography

GA = gestational age

LQTS = long QT syndrome

LVIVRT = left ventricular isovolumic relaxation time

TdP = torsades de pointes

agents), fetal central nervous system anomalies, long QT syndrome (LQTS), other familial inherited arrhythmia syndromes (such as mutations in the *HCN4*, *NKX2.5*, and *SCN5A* genes), sick sinus syndrome, and myocarditis.

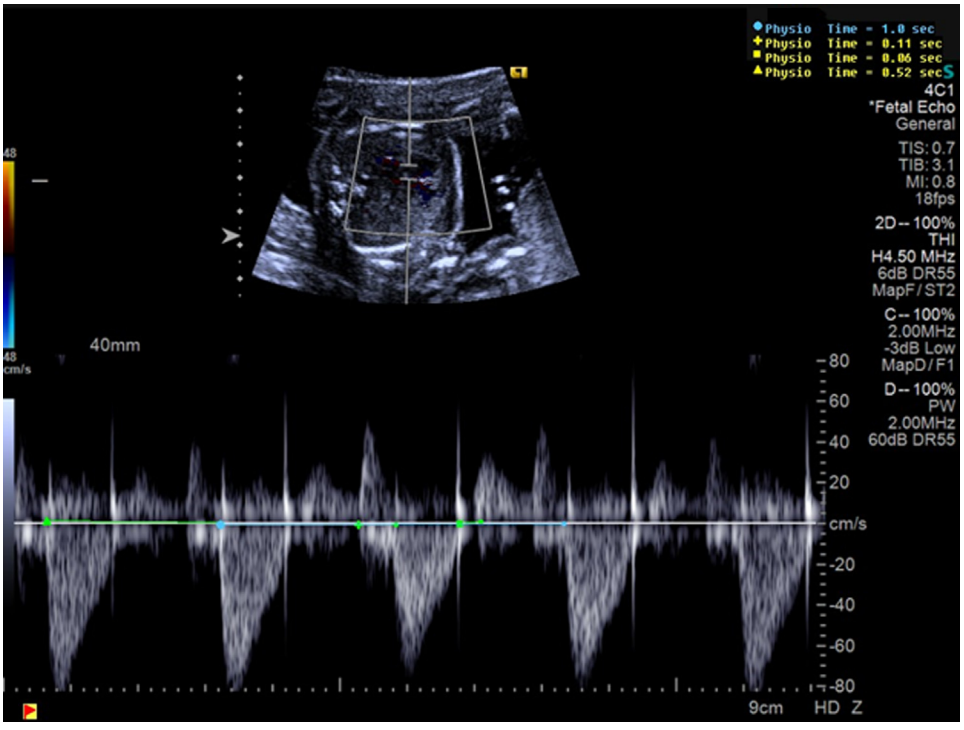
INVESTIGATIONS

Maternal evaluation included normal thyroid stimulating hormone, normal electrolytes, normal 25,OH vitamin D level, negative anti-SSA/SSB antibodies, and no known medication use that could cause fetal bradycardia. A fetal echocardiogram (Figure 1) at 20 3/7 weeks' GA demonstrated an FHR below the 3rd percentile for GA (115-122 beats/min) with a normal AV interval but a prolonged left ventricular isovolumic relaxation time (LVIVRT). No AV block, ventricular ectopy, or cardiac structural anomalies were appreciated. Maternal and paternal electrocardiography (ECG) demonstrated normal QTcs of 452 ms and 385 ms, respectively. Given the concern for possible LQTS based on the FHR below 3rd percentile for GA and prolonged LVIVRT (60 ms and normalized [N]-LVIVRT 12%, with N-LVIVRT ≥11.3% at ≤20 weeks as the best cutoff for LQTS),[2] the mother underwent a fetal magnetocardiogram (fMCG) at 23 weeks' GA. This confirmed a low baseline FHR (118 beats/min) and a prolonged QTc of 499-515 ms (>95th percentile for GA)[3] (Figure 2).

MANAGEMENT

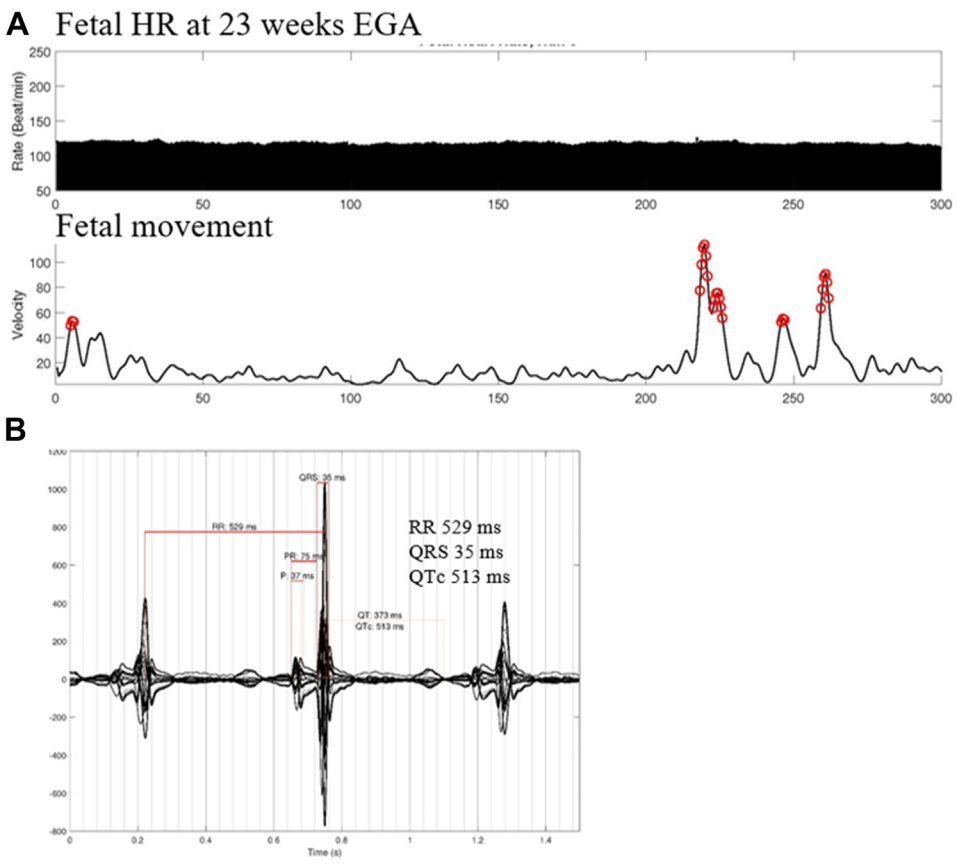
Weekly FHR assessments via in-office Doppler (before 32 weeks' GA) and nonstress tests (after 32 weeks' GA) were recommended to evaluate for AV block or torsades de pointes (TdP), with a plan to repeat the fMCG in the third trimester. Interestingly, the majority of nonstress tests performed after 32 weeks' GA were

FIGURE 1 Fetal Echocardiography at 20 3/7 Weeks' Gestational Age



Sinus vs atrial rhythm at 115 to 122 beats/min (fetal heart rate below 3rd percentile for gestational age [GA]); mechanical PR by pulsed Doppler = 110 ms. Left ventricular isovolumic relaxation time (LVIVRT) 60 ms; normalized LVIVRT 12%.

FIGURE 2 fMCG Fetal Heart Rate Trend Graph and Signal-Averaged fMCG Tracing at 23 0/7 Weeks' GA



(A) Sinus bradycardia, 113 beats/min. The heart rate tracings are nonreactive despite occasional fetal movement. (B) Cardiac time intervals show prolongation of the QTc. EGA = estimated gestational age; fMCG = fetal magnetocardiography; GA = gestational age.

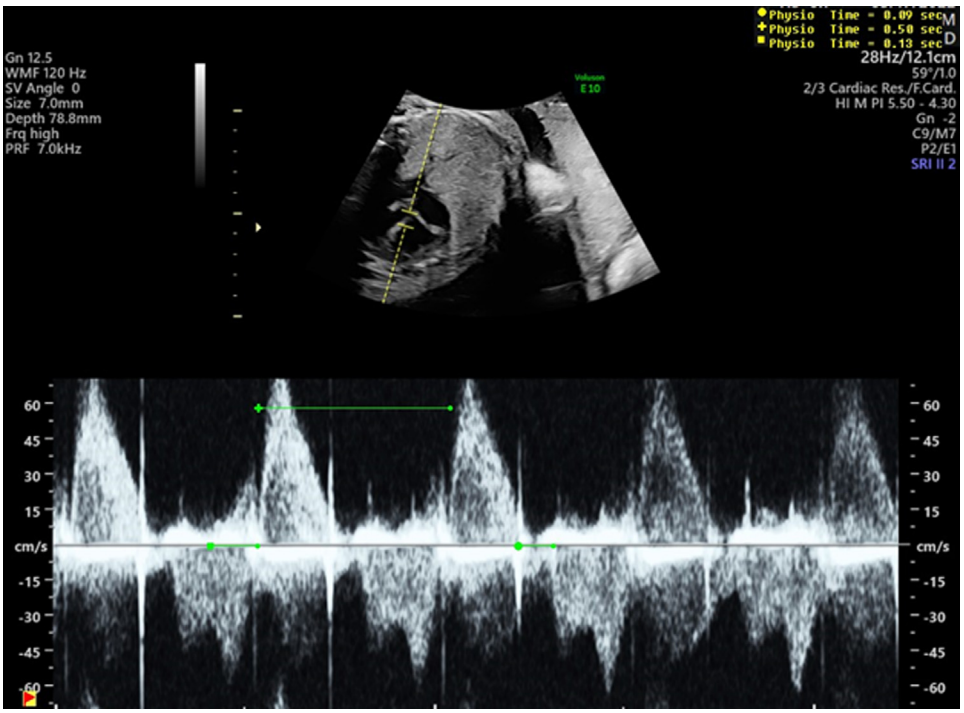
reactive and reassuring. The mother was provided with a home FHR monitor and asked to report values <80 beats/min or >180 beats/min. She checked daily and reported no values in those ranges. She was also counseled to avoid QT-prolonging medications.

The fetus had a normal growth course, without evidence of hydrops or other hemodynamic compromise. The FHR ranged from 110 to 120 beats/min (Supplemental Figure 1), with third-trimester N-LVIVRTs of 18% (**Figure 3**). The follow-up fMCG at 31 weeks' GA showed an average QTc of 533 ms with late-peaking T waves, supporting the diagnosis of LQTS as cause of the low FHR (**Figure 4**). At that time, 5-second fetal rhythm strips demonstrated QT prolongation (**Figure 5**).

The mother had an otherwise uncomplicated pregnancy and underwent a primary cesarean delivery at 39 weeks GA for breech presentation. The neonatal birth weight was 4,060 g, and the initial heart rate was 129 beats/min. The baby was admitted to the Neonatal Intensive Care Unit for monitoring. ECG on the first day of life demonstrated a QTc of 507 ms, and T-wave morphology was consistent with LQTS type 1. Propranolol was initiated at 1 mg/kg/day in divided doses and advanced to 2 mg/kg/day. The infant remained hemodynamically stable and was discharged home at 4 days of age.

Genetic testing subsequently confirmed a pathogenic variant in *KCNQ1* (p.Ser566Tyr rs199472804), which was consistent with the infant's phenotype. Parental testing identified the same *KCNQ1* variant in the mother, who did not have a known history of LQTS, an LQTS sentinel event, or a prolonged QTc on ECG.

FIGURE 3 Fetal Echocardiography at 35 4/7 Weeks' Gestational Age



Sinus vs atrial rhythm at 120 to 122 beats/min; mechanical PR by pulsed Doppler = 130 ms. Left ventricular isovolumic relaxation time (LVIVRT) 90 ms; normalized LVIVRT 18%.

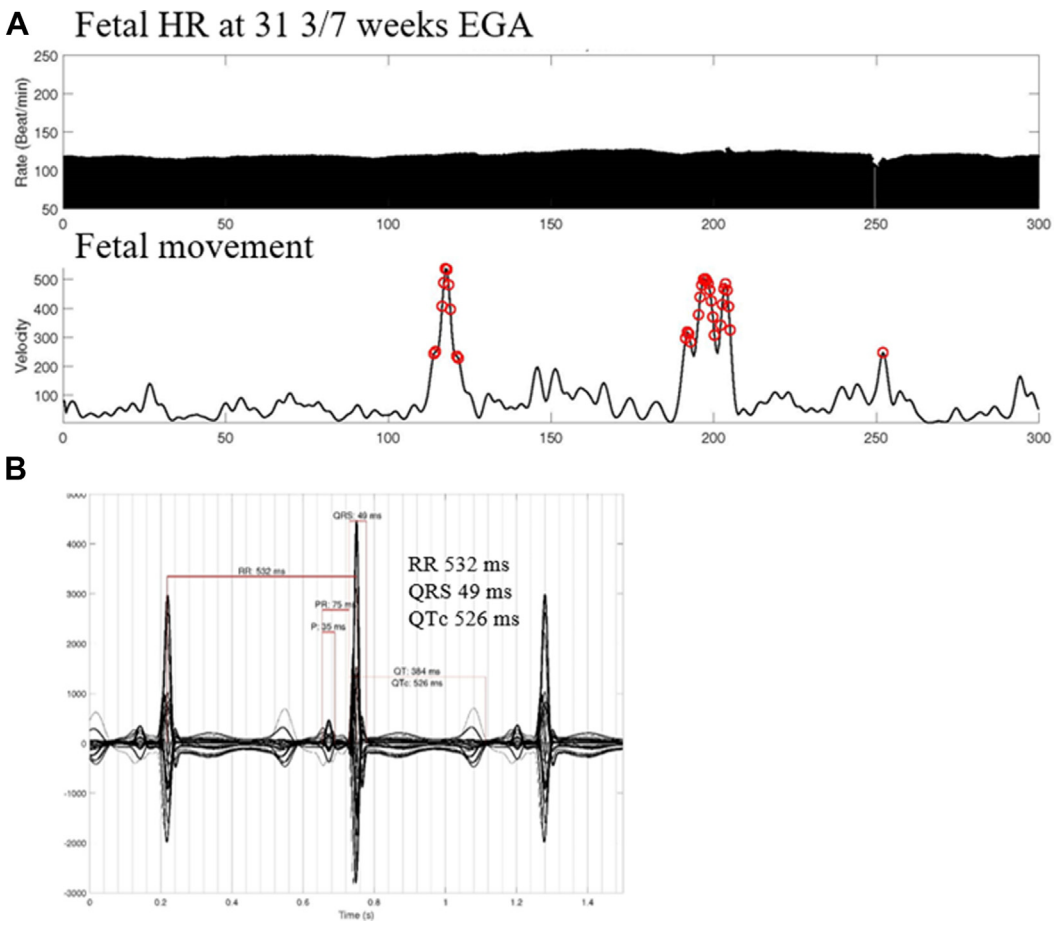
DISCUSSION

Congenital LQTS is a hereditary channelopathy that may be unrecognized until a sentinel event occurs; it is rarely diagnosed prenatally. However, recognition that FHRs of fetuses affected by LQTS are lower than those of unaffected fetuses (66% of affected fetuses have baseline FHRs at the 3rd percentile or lower for GA[1]) is improving prenatal detection. Channelopathy gene mutations have been found in 8.8% of intrauterine fetal demises and around 10% of sudden infant death syndrome cases.[4] Owing to its association with adverse perinatal events and life-threatening arrhythmias, as well as the success of primary intervention, prompt diagnosis and treatment of congenital LQTS are crucial to improving patient outcomes.

The fetal presentation of LQTS is variable, with lower baseline FHRs being the most common presentation. It is important to note that the American College of Obstetrics and Gynecology (ACOG) defines the normal fetal heart rate as 110 to 160 beats/min.[5] However, this range does not take into account variations in fetal heart rate due to GA, notably the progressive decrease in the mean basal fetal heart rate with advancing gestation.[6] As a marker for LQTS, a mean FHR of <133 beats/min in the third trimester has a high specificity (>97%) but low sensitivity (<50%).[7]

Management of fetal arrhythmias is rhythm-specific and relies on transplacental antiarrhythmic drug therapy. Although isolated FHRs below 3rd percentile for GA tend to be well tolerated and do not require treatment, the progression from bradycardia to other arrhythmias, fetal hydrops, or fetal heart failure may require initiation of antiarrhythmic agents.[8] TdP, which can be seen in cases of fetal LQTS, is usually treated with magnesium sulfate, beta-blockers, lidocaine, or mexiletine.[8] It is important to avoid terbutaline in labor, because its use has been associated with TdP. The fetus in this case, who had isolated FHR below 3rd percentile for GA, no premature ventricular contractions, and no evidence of TdP, was not thought to have a risk profile that would warrant in utero beta-blocker therapy based on

FIGURE 4 fMCG Fetal Heart Rate Trend Graph and Signal-Averaged fMCG Tracing at 31 3/7 Weeks' GA



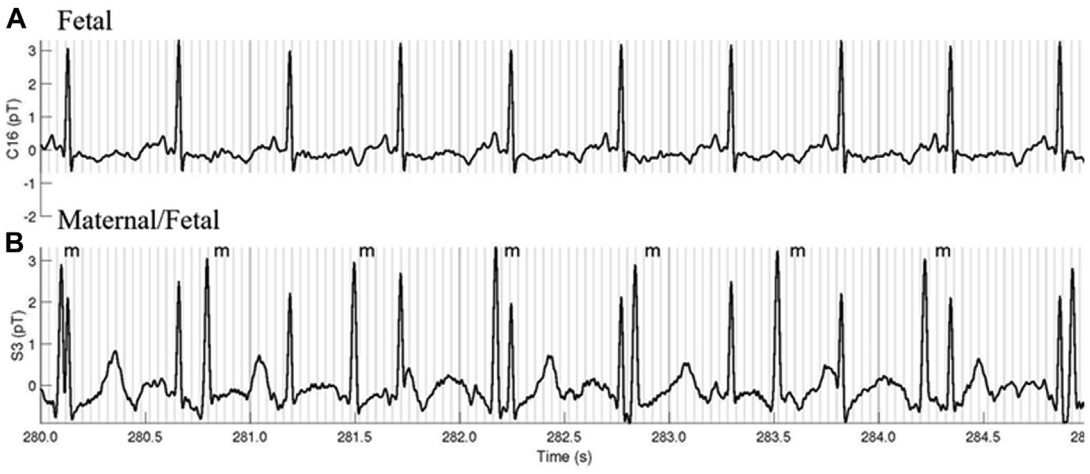
(A) Sinus bradycardia, 112 beats/min. Note the low heart rate variability, which would make it challenging to monitor this fetus with standard nonstress testing. (B) Cardiac time intervals show QTc of 526 ms. EGA = estimated gestational age; fMCG = fetal magnetocardiography; GA = gestational age.

current guidelines.[9] In addition, available data suggest that only fetal QTc >600 ms is highly predictive of fetal or neonatal death or TdP.[3] Isolated FHR below 3rd percentile for GA is most commonly seen in LQTS type 1, and no studies to date have demonstrated fetal mortality in this group.

Although fetal echocardiography is the main modality of assessing fetal cardiac structure, function, and rhythm, fetal ECGs can be obtained only through magnetocardiography or noninvasive abdominal fetal ECG. However, these modalities are only available at selected institutions. As such, both the variable presentation of congenital LQTS and the inaccessible diagnostic tools may explain why the majority of patients diagnosed with congenital LQTS are diagnosed after birth.[10] However, recognizing an FHR below 3rd percentile for GA as abnormal and referring for cardiology evaluation may increase the proportion of patients diagnosed antenatally.

Antenatal diagnosis has the potential to improve outcomes because LQTS can be associated with fetal and neonatal death and with adverse maternal outcomes. Invasive fetal testing through amniocentesis can confirm genetic mutations and establish a diagnosis before birth, and when a genetic variant is recognized, cascade testing can identify other family members (most notably the mother) who may be at risk of cardiac events.[11] For patients who wish to avoid the risks associated with amniocentesis, although those risks are low, noninvasive

FIGURE 5 Maternal and Fetal Rhythm: Study 2 at 31 3/7 Weeks' Gestational Age



(A) Fetal magnetocardiography 5-second rhythm tracing demonstrated characteristic late peaking of the T-wave with QRS-T discordance. (B) Maternal and fetal magnetocardiography are not separated here. m = the maternal QRS complexes.

assessments such as a combination of FHR checks, N-LVIVRT measurements, and fMCG plays an important role in fetal assessment. The hemodynamic changes of pregnancy pose an increased cardiac risk (predominantly to patients with LQTS type 2), with labor and delivery potentially triggering LQTS sentinel events due to the adrenergic stimuli and the use of QT-prolonging medications such as oxytocin and ondansetron.[11] As such, pregnant and postpartum patients diagnosed with LQTS can receive appropriate cardiac monitoring and care in these high-risk periods.

FOLLOW-UP

The infant otherwise had an uneventful hospital course and continued to receive care with pediatric cardiology after discharge. Her propranolol dose remained 2 mg/kg/day in divided doses at her 2-month appointment, and her most recent QTc was 470 to 480 ms. Cardiology care was strongly recommended to the infant's mother and her twin sister as well. The family moved out of the state and is now receiving care in a different health system.

CONCLUSIONS

Antenatal diagnosis of congenital LQTS, though challenging, can have a significant impact in improving outcomes for both the fetus and the mother. In the case presented here, recognizing an isolated FHR below the 3rd percentile for GA led to an important diagnosis for the infant and her mother, who would not otherwise have known that she possessed a potentially lethal cardiac electrophysiologic abnormality.

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KEY WORDS **bradycardia, cardiac channelopathy, pregnancy, fetal magnetocardiography**

APPENDIX **For a supplemental figure, please see the online version of this paper.**