Repolarization predictors of fetal long QT syndrome

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BACKGROUND Diagnosis of fetal long QT syndrome (LQTS) using fetal magnetocardiography (fMCG) is straightforward in cases of overt QTc prolongation accompanied by LQTS rhythms; however, cases of isolated QTc prolongation can be challenging.

OBJECTIVE The purpose of this study was to characterize repolarization in normal and phenotype-positive LQTS fetuses with the goal of using additional parameters of repolarization to improve the accuracy of fMCG diagnosis of LQTS.

METHODS fMCG recordings were taken from 37 phenotype-positive fetuses with confirmed LQTS and 132 normal controls. The normal fetuses were grouped into those with T and U waves and those with only T waves. We compared the repolarization characteristics of normal fetuses with only T waves with those of LQTS fetuses. We also compared the repolarization characteristics of normal fetuses with T and U waves with those of LQTS fetuses with 2-component T waves.

RESULTS Late-peaking T waves were strongly associated with LQTS (35/37 [95%]). No normal fetuses showed both QTc prolongation

(QTc >500 ms) and a late-peaking T wave. U waves were seen in 11 normal fetuses (8%) and resulted in waveforms that often mimicked those of the 19 LQTS fetuses with 2-component T waves. However, in normal fetuses the polarities of the T and U waves were the same, whereas in LQTS fetuses with 2-component T waves the polarities of the components usually were opposite.

CONCLUSION A late-peaking T wave in association with QTc prolongation is a distinctive, reliable indicator of fetal LQTS. U waves confound assessment of QTc; however, normal U waves usually can be distinguished from LQTS T waves based on polarity.

KEYWORDS Fetal arrhythmia; Fetal magnetocardiography; Fetus; Long QT syndrome; U wave

Introduction

Fetal magnetocardiography (fMCG), the magnetic analogue of fetal electrocardiography (ECG), has provided invaluable insight into the mechanisms of life-threatening fetal arrhythmia and has improved the diagnosis and clinical management of the disease.[1] A crucial advantage of fMCG is its ability to assess repolarization, a fundamental aspect of rhythm that cannot be assessed by echocardiography. This makes fMCG especially useful for evaluation of fetal long QT syndrome (LQTS), a leading cause of sudden death in early life, including prenatal life. Currently, fMCG is the only effective, noninvasive means of identifying LQTS *in utero.* However, the difficulty of making a diagnosis with fMCG can vary considerably from case to case. Generally, the diagnosis is based on prolongation of the heart rate–corrected QT interval (QTc) and the presence of LQTS rhythms, especially the 3 characteristic LQTS rhythms:

torsades de pointes, T-wave alternans, and functional second-degree atrioventricular (AV) block (ie, AV block due to overt QTc prolongation). Bradycardia and low-for-gestational-age fetal heart rate are also associated with LQTS but are less specific. The combination of QTc prolongation and an LQTS rhythm is highly predictive of LQTS; however, cases of isolated QTc prolongation are more difficult to evaluate. Family history is an important consideration, but a substantial fraction of cases are negative for family history[2] because of *de novo* mutations, inherited mutations with low penetrance, or incomplete family histories.

In addition to QTc prolongation and T-wave alternans, fetuses with LQTS often exhibit other forms of anomalous repolarization. The most common is a late-peaking T wave, which gives the waveform a distinctive appearance.[2] However, to our knowledge there is no accepted objective criterion for identifying late-peaking T waves. QRS-T discordance (ie, T wave and QRS complex having opposite polarity) has been noted anecdotally in fetal LQTS. Postnatally, QRS-T discordance results from conditions such as myocardial ischemia and myocarditis but can be normal in the precordial leads.

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KEY FINDINGS

- A late-peaking T wave in association with QTc prolongation is a distinctive, reliable indicator of fetal long QT syndrome (LQTS).

- U waves are seen in about 10% of normal fetuses and can confound assessment of QTc; In normal fetuses the T and U waves show the same polarity, whereas in LQTS fetuses with 2-component T waves the components typically show opposite polarity.

- QRS-T discordance is strongly associated with fetal LQTS but also is common in normal fetuses.

Perhaps the most difficult assessments are those involving repolarization waves with 2 distinct components. For LQTS fetuses, the second component usually is more peaked and has larger amplitude. Normal fetuses can also show a late waveform component in addition to the T wave. The late component usually is considered a U wave. U waves are not well understood but are presumed to arise from a source distinct from that of T waves. Typically, they are smaller than T waves; therefore, in most cases the 2-component T waves of LQTS fetuses can be distinguished from the TU waves of normal fetuses based on the relative amplitude of the components. However, if the components have similar amplitude, interpretation becomes subjective, and the presence of a U wave may result in a determination of QTc prolongation. Taggart et al[3] reported that misdiagnosis of LQTS is common and that U-wave inclusion is a leading cause of overdiagnosis.

Other than measurement of the QTc interval, repolarization in the fetus has not been extensively investigated. In this study, we characterized repolarization in normal and phenotype-positive LQTS fetuses with the goal of using additional parameters of repolarization to improve the accuracy of LQTS diagnosis.

Methods

The study protocol was approved by the University of Wisconsin–Madison Health Sciences Institutional Review Board. Informed consent was obtained from each subject. This study complied with the guidelines set forth in the Declaration of Helsinki.

Subjects

LQTS fetuses

The study cohort was derived from a group of 39 fetuses that underwent fMCG recording in the University of Wisconsin Biomagnetism Lab with confirmed LQTS based on genetic testing or a clinical diagnosis of LQTS (Figure 1). Two fetuses that tested positive for long QT syndrome type 1 (LQT1) variants were excluded because they were phenotype negative (ie, absence of QTc prolongation, LQTS rhythms,

and repolarization anomalies). The remaining 37 fetuses were studied at gestational age 20–37 weeks. Nine fetuses were studied serially; however, data from only the last session were used to avoid biasing the results. The LQTS rhythms of these fetuses, including QTc, were reported previously[4]; however, the repolarization anomalies that are the focus of this study—late-peaking T waves, QRS-T discordance, and 2-component T waves—were not described.

Normal fetuses

The control group comprised 132 fetuses from uncomplicated singleton pregnancies, studied at gestational ages 18–40 weeks. Forty-five fetuses were studied serially; however, data from only the last session were used to avoid biasing the results. Their waveform intervals, including QTc, and incidence of U waves were reported previously[5]; however, the T-wave and U-wave morphologies are characterized here in greater detail and are compared with those of the LQTS fetuses.

Data acquisition

The fMCG was recorded using a 37-channel (Magnes; 4D Neuroimaging, Inc, San Diego, CA) or 21-channel (model 624; Tristan Technologies, San Diego, CA) superconducting quantum interference device biomagnetometer, housed in a magnetically shielded room. Both devices have FDA 510(k) clearance.

The mother changed into nonmagnetic clothing and lay supine or slightly on her side if she experienced discomfort lying supine. At least 20 minutes of data were recorded from each normal fetus and at least 40 minutes of data from each LQTS fetus. The sensor was moved at least once during the data collection in order to capture a wider range of waveform configurations.

Signal processing and waveform averaging

A digital filter with 1- to 80-Hz passband was applied to band-limit the data. Signal processing was used to remove the maternal MCG and other interferences.[6] Averaging was used to increase the signal-to-noise ratio. Averaged waveforms for each channel were computed during periods of fetal quiescence, using the QRS complexes as triggers. Typically, 50–100 consecutive complexes were averaged, depending on the signal-to-noise ratio of the raw recording.
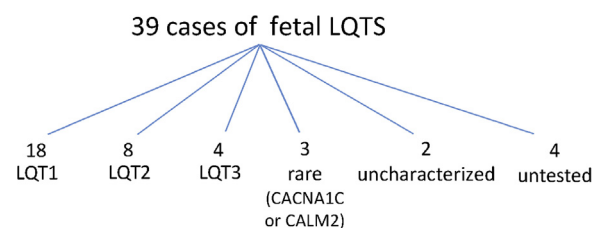

Figure 1   Genotype composition of the fetal long QT syndrome (LQTS) cohort. LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2; LQT3 = long QT syndrome type 3.

Repolarization anomalies

Repolarization anomalies were identified from inspection of the averaged waveforms by a board-certified pediatric cardiologist (JFS).

T-wave characteristics

We measured parameters that characterize the duration, amplitude, morphology, and polarity of the T wave. Fetuses with U waves were excluded from this analysis and were analyzed separately.

QTc

The heart rate–corrected QT interval (QTc) was computed using the Bazett formula: $QTc = QT/(RR)^{1/2}$. QTc prolongation was detected using a threshold of 500 ms based on previous studies.[2,5]

T/QRS amplitude ratio

T/QRS amplitude ratio was computed from measurement of the absolute amplitude (peak to peak) of the T wave and QRS complex in the channel with the largest T wave. Normalization of the T-wave amplitude by the QRS complex amplitude is commonly performed to account for subject-to-subject differences in factors such as fetal lie and maternal body mass index, which can affect signal strength.

Late-peaking T-wave morphology

Late-peaking T waves were identified by subjective assessment because of the lack of an accepted quantitative criterion. To devise a quantitative means of identifying late-peaking T waves, the results of subjective assessment were correlated with measurements of QT_{peak}/QT, where QT_{peak} is the time from the beginning of the QRS complex to the peak of the T wave using the channel with the largest T wave. A receiver operating characteristic curve was computed to objectively determine the value of QT_{peak}/QT yielding the highest predictive value.

QRS-T discordance

QRS-T discordance was assessed from the polarities of the T wave and QRS complex, using the channel with the largest T-wave amplitude. Discordance was not assessed in waveforms with flat T waves or equiphasic QRS complexes (complexes with positive and negative peak amplitudes equal to within 50%), for which the polarity of the QRS complex was ambiguous.

TU- and T′T-wave characteristics

We identified LQTS fetuses with 2-component T waves (T′T waves) and normal fetuses with 2 repolarization wave components (TU wave) due to the presence of a U wave. A U wave was taken to be a distinct waveform component occurring after or around the time the T wave returns to baseline. U waves shorter than half the height of the T wave were disregarded based on the assumption that a U wave is less likely to be significant if it is much smaller than the T wave. We denote the 2-component T waves of LQTS fetuses as T′T waves, where the primed component precedes the unprimed

component. With this nomenclature, the T wave remains the appropriate component for assessing the duration of repolarization. We measured parameters that characterize the duration, relative amplitude, and relative polarity of the components.

QTUc and QT′Tc

The QTU interval of each normal fetus was measured from the beginning of the QRS complex to the end of the U wave, and the heart rate–corrected QTU interval (QTUc) was computed using the Bazett formula. The QT′T interval of each LQTS fetus was measured from the beginning of the QRS complex to the end of the T wave, and the heart rate–corrected QT′T interval (QT′Tc) was computed using the Bazett formula.

U/T and T/T′ amplitude ratio

The relative amplitudes of the waves were assessed by measuring the ratio of the absolute amplitudes of the U and T waves of normal fetuses and the T and T′ waves of LQTS fetuses.

TU and T′T polarity

We assessed whether the polarity was the same or opposite for the T and U waves of normal fetuses and for the T′ and T waves of LQTS fetuses.

Statistical analysis

Continuous variables were compared using the Student t test. Categorical data were compared using the Fisher exact test. Analysis of variance was used to detect differences in continuous variables between LQTS fetuses with and those without ventricular arrhythmia and between fetuses with the 3 most common types of LQTS: type 1 (LQT1), type 2 (LQT2), and type 3 (LQT3). Due to the small number of planned comparisons, P values were not corrected for multiple comparisons. $P < .05$ was considered significant.

Results
T-wave characteristics

Figure 2 shows waveforms from typical normal and LQTS fetuses. The T-wave characteristics of the LQTS and normal fetuses are summarized in Table 1. QTc was much longer for the LQTS fetuses (590 ± 79 ms) than the normal fetuses (399 ± 54 ms). However, mean QTc of the LQTS fetuses was biased upward by several fetuses with severe disease—5 had QTc >690 ms. Median QTc of the LQTS fetuses was 558 ms. The LQTS fetuses were selected based on QTc prolongation (QTc >500ms), so a statistical comparison was not performed due to this bias. Only 2 normal fetuses (2%) showed QTc prolongation, with QTc values of 501 and 508 ms. Mean T/QRS amplitude ratio was 4 times higher for LQTS fetuses than normal fetuses. The lowest T/QRS ratio seen in any LQTS fetus was 0.031, whereas 38 normal fetuses (31%) showed ratios <0.031 with relatively flat T waves. Based on subjective assessment, waveforms with QT_{peak}/QT durations >0.78 were deemed late-peaking. The
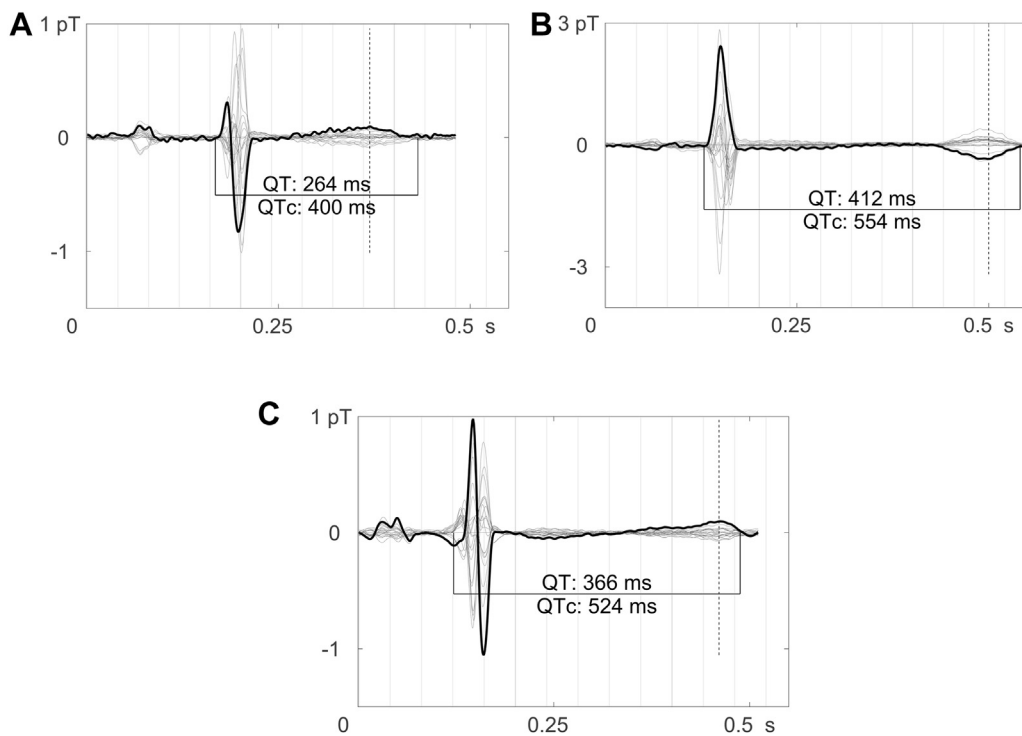
Figure 2   Superimposed multichannel, averaged fetal magnetocardiography waveforms (butterfly plot) from a typical normal fetus (**A**), a typical long QT syndrome (LQTS) fetus (**B**), and an LQTS fetus with below average QTc (**C**). The line weight is enhanced for the channel with the tallest T wave. **A:** Normal fetus at 31 weeks' gestation, with QTc = 400 ms, RR = 436 ms, T/QRS amplitude ratio = 0.059, and QT_{peak}/QT = 0.74. **B:** LQT1 fetus at 35 weeks' gestation, with QTc = 555 ms, RR = 553 ms, T/QRS amplitude ratio = 0.26, and QT_{peak}/QT = 0.87. The T-wave characteristics of the waveforms in **A** and **B** are approximately equal to that of the cohort mean. **C:** LQT1 fetus at 31-4/7 weeks' gestation, with QTc = 524 ms, RR = 487 ms, T/QRS amplitude ratio = 0.05, and QT_{peak}/QT = 0.93. Although the waveforms in **B** and **C** are considered late-peaking, variation in T-wave morphology is evident. The T wave is late-appearing and symmetrical in **B** but is more diffuse but shows a very late peak due to skewness in **C**.

combination of QT_{peak}/QT >0.78 and QTc >500 ms was seen in 35 LQTS fetuses (95%) and was not seen in any normal fetus. Receiver operating characteristic analysis (not shown) showed that the highest predictive value was obtained for a threshold of QT_{peak}/QT $= 0.82$, which yielded sensitivity 86% and specificity 85% for identification of long QT syndrome. QRS-T discordance was strongly associated with LQTS (88%); however, it also was common in normal fetuses (54%).

Waveforms from a normal fetus with a U wave and an LQTS fetus with a 2-component T wave are shown in Figure 3. They are similar in appearance and both show apparent prolongation of repolarization. This was reflected in the similarity of the parameter values in Table 2. However, a critical difference was seen for T-U and T′-T polarity. In normal fetuses the polarities of the U wave and T wave were always the same, whereas in LQTS fetuses the polarities of the T and T′ waves usually were opposite.

TU- and T′T-wave characteristics
Eleven normal fetuses (8%) showed U waves, and 19 LQTS fetuses (51%) showed 2-component T waves (Table 2).

Phenotype–genotype correlations
We previously showed that QTc differs among fetuses with LQT1, LQT2, and LQT3.[4] However, none of the other

Table 1   T-wave characteristics of normal and LQTS fetuses

	n	Gestational age (wk)	QTc (ms)	QTc >500 ms	T/QRS amplitude	QT_{peak}/QT	QT_{peak}/QT >0.78 and QTc >500 ms	QRS-T discordance[†]
Normal	121	29.8 ± 5.8	399 ± 54	2 (2)	0.05 ± 0.03	0.65 ± 0.16	0 (0%)	40 (54)
LQTS	37	30.7 ± 4.5	590 ± 79	37 (100)	0.20 ± 0.19	0.88 ± 0.06	35(95%)	22 (88)
P value			—	—	<.001*	<.001*		<.01*

Values are given as mean ± SD or n (%) unless otherwise indicated.

QT_{peak}/QT was not assessed in 33 normal fetuses with flat T waves.

LQTS = long QT syndrome; NS = not significant.

*Statistically significant.

†QRS-T discordance was not assessed in 12 LQTS fetuses because the QRS complex was equiphasic and in 47 normal fetuses because the QRS complex was equiphasic or the T wave was flat.

Table 2   TU-wave characteristics of normal fetuses and T'T-wave characteristics of LQTS fetuses

	n	Gestational age (wk)	QTUc or QT'Tc	QTUc or QT'Tc >500ms	U/T or T/T' amplitude	T-U or T'-T same polarity
Normal	11	33.7 ± 4.5	QTUc: 519 ± 22 ms	QTUc >500 ms: 9 (82)	U/T amplitude: 1.15 ± 0.35	T-U same polarity: 11 (100)
LQTS	19	32.3 ± 3.6	QT'Tc: 567 ± 55 ms	QT'Tc >500 ms: 19 (100)	T/T' amplitude: 1.53 ± 0.72	T'-T same polarity: 6 (32)
P value			—	—	NS	<.001*

Values are given as mean ± SD or n (%) unless otherwise indicated.
LQTS = long QT syndrome; NS = not significant.
*Statistically significant.

repolarization parameters examined here, such as T/QRS ratio, QT_{peak}/QT, and QRS-T discordance, showed an association with LQTS type or ventricular arrhythmia. In particular, fetuses in the LQTS cohort exhibited a late-peaking T-wave morphology, regardless of LQTS type.

Discussion

QTc data for LQTS and normal fetuses have been reported previously, but this study is the first to investigate LQTS and normal fetuses for differences in repolarization characteristics other than QTc. An important outcome was the quantification of parameters of repolarization that can help distinguish LQTS and normal fetuses. The main findings are as follows. (1) A late-peaking T wave in association with QTc prolongation is a distinctive, reliable indicator of fetal LQTS. (2) U waves confound assessment of QTc; however, in normal fetuses with U waves, the T and U waves show the same polarity, whereas in LQTS fetuses with 2-component T waves the wave components typically show opposite polarity (ie, are biphasic). (3) QRS-T discordance is strongly associated with fetal LQTS but also is common in normal fetuses. These findings can improve the accuracy of LQTS diagnosis.

The combination of QTc prolongation and a late-peaking T wave is highly predictive of fetal LQTS. This implies that QTc prolongation is primarily due to lengthening of the ST interval as opposed to an increase in T-wave dispersion. Fetuses with borderline QTc prolongation (490 ms < QTc <510 ms) and a normal-peaking or flat T wave are likely to be negative for LQTS, especially if the family history is negative. A potential cause of borderline QTc prolongation is low levels of maternal magnesium, potassium, and other electrolytes. Fetuses with suspected LQTS should be assessed for electrolyte imbalance, discontinue QTc-prolonging medications, and undergo frequent monitoring for onset of LQTS rhythms, including low-for-gestational-age fetal heart rate. Serial fMCG monitoring has been shown to detect torsades de pointes events missed by routine echocardiographic surveillance.[4]

Moss et al[7] first described T-wave morphologies of the 3 most prevalent types of LQTS. The T waves are normal-appearing and broad-based in LQT1, low-voltage and notched in LQT2, and late-appearing and peaked in LQT3. Here we found that late-peaking T waves were present in the LQTS fetuses regardless of LQTS type. Notched T waves are seen only rarely[4] and were not evident in our LQT2 subjects. Our results suggest that the T-wave morphology of different LQTS types is relatively similar in the fetus and becomes more differentiated postnatally.

The prominence of the late-peaking T waves of LQTS fetuses is enhanced by their large amplitude in
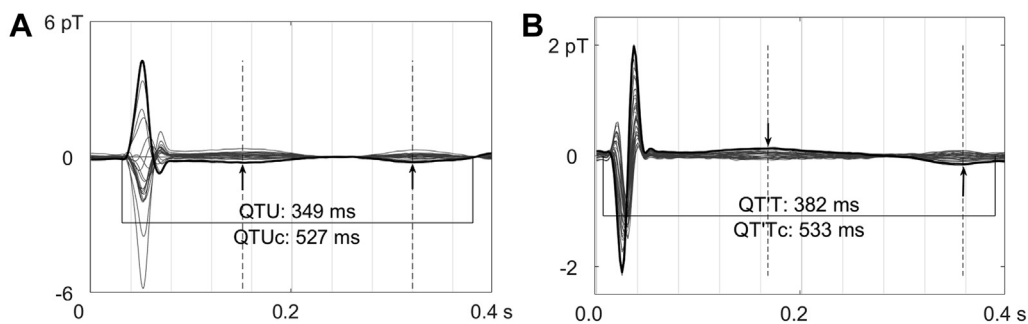

Figure 3   Superimposed multichannel, averaged fetal magnetocardiography waveforms (butterfly plot) from a normal fetus with a U wave (**A**) and a long QT syndrome (LQTS) fetus with a 2-component T wave (**B**). The line weight is enhanced for the channel with the tallest T wave. The normal fetus was 30 weeks' gestation, with QTc = 388 ms, RR = 439 ms, and U/T amplitude ratio = 0.92. The LQTS fetus was 30 weeks' gestation, with QTc = 590 ms, RR = 514 ms, and T/T' amplitude ratio = 1.16. *Arrows* indicate the polarities of the wave components and show that they are the same for the normal fetus and opposite for the LQTS fetus.

comparison to the typically flat T waves of normal fetuses. The T/QRS amplitude ratio was approximately 4 times higher for LQTS fetuses than normal fetuses. Strand et al[5] speculated that the flat T waves of normal fetuses result because some areas of the fetal heart repolarize from base to apex, whereas others repolarize from apex to base, causing cancellation. The larger amplitude of the late-peaking T waves of LQTS fetuses may result from reduced cancellation associated with the altered electrophysiology. Given the limited signal-to-noise ratio of fMCG, this improves the success rate and accuracy of QTc measurement and other assessments of repolarization in LQTS fetuses.

A main motivation for this study is the difficulty of diagnosing LQTS when a U wave is present. U waves are relatively common in normal fetuses and can confound assessment of QTc because inclusion of the U wave often results in determination of QTc prolongation. However, we found that in LQTS fetuses with 2-component T waves the 2 waves usually show opposite polarity, whereas in normal fetuses with U waves the T and U waves show the same polarity. This is consistent with what is seen postnatally. Cellular mechanisms for biphasic T waves and other complex morphologies seen in LQTS patients have been demonstrated by Emori and Antzelevitch.[8]

QRS-T discordance is strongly associated with LQTS; however, its utility as a diagnostic parameter is diminished because it occurs in a surprisingly high percentage of normal fetuses. One possible explanation for this finding is the sensitivity of fMCG to tangential vs radial currents and the orientation of the fetus. If the probe is above the maternal surface and the fetus is facing directly up or down, then the fMCG is most sensitive to currents in the frontal plane. However, if the fetus is lying on its side, which is most often the case, then the fMCG is most sensitive to currents in the sagittal plane. The configuration of the fMCG would then be closest to ECG leads V_1 and V_2, which commonly show inverted T waves.

Study limitations
The dependence of T-wave morphology on fetal lie is a potential confounder. This was mitigated by making recordings using multiple sensor positions and orientations and by referencing the amplitude and polarity of the T wave relative to that of the QRS complex. LQTS subgroup analysis, such as phenotype–genotype correlations, was limited by the modest number of subjects.

Conclusion
The results of this study can help improve the predictive value of fMCG for diagnosis of fetal LQTS and help resolve ambiguities caused by U waves.

Funding Sources

Disclosures
The authors have no conflicts of interest to disclose.

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