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Determination of fetal heart rate short term variation from umbilical artery Doppler waveforms

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Contribution

What are the novel findings of this work?

Short term fetal heart rate variation from computerized cardiotocography is a sensitive predictor of fetal hypoxemia; however, this technology is not universally available. This study demonstrates that fetal heart rate variation can be determined directly from umbilical artery Doppler waveforms obtained using standard clinical ultrasound equipment.

What are the clinical implications of this work?

These findings have the potential to extend the utility of umbilical artery Doppler as a fetal monitoring tool by allowing concurrent evaluation of a surveillance modality that has an important role in the management of pregnancies with fetal growth restriction.

Abstract

Objectives: To evaluate the feasibility of using umbilical artery (UA) Doppler waveforms to measure fetal heart rate short term variation (STV) across gestation.

Methods: A prospective longitudinal study was conducted at two study sites in 195 women with pregnancies considered low risk. Pulsed wave Doppler of the UAs was performed at a 4-weekly interval between 14-40 weeks of gestation using a standardized imaging protocol. Up to 12 consecutive UA Doppler waveforms were analyzed using an off-line processing software. Fetal heart rate STV was calculated using average R-to-R intervals extracted from the waveforms and baseline corrected for fetal heart rate.

Results: Baseline corrected short term fetal heart rate variation increased significantly with gestational age (conditional $R^2 = 0.37$, $p < 0.0001$) and was inversely correlated with fetal heart rate (conditional $R^2 = 0.54$, $p < 0.0001$). The short term variation ranged (median (interquartile range)) from 3.5 (2.9-4.1) ms at 14-20 weeks' gestation to 6.3 (4.8-7.7) ms at 34-40 weeks' gestation. The change in short term heart rate variation did not differ between study sites, different models of ultrasound machine or individual sonographers.

Conclusions: Umbilical artery Doppler waveforms offer a robust and feasible method to derive short term variation of the fetal heart rate. It needs to be emphasized that the umbilical-Doppler derived short term variation is not interchangeable with measurements derived with computerized cardiotocography. Accordingly, further investigations need to validate associations with outcome to determine the value of concurrent fetal cardiovascular and heart rate evaluation that are possible with the technique described here.

Introduction

Fetal heart rate monitoring by cardiotocography (CTG) is used for surveillance of patients considered to be risk for fetal hypoxemia. Heart rate variability and activity-related accelerations are reflective of the gestational maturation of the nervous and cardiovascular systems. Fetuses that develop hypoxia show abnormalities of short term variation (STV) in the fetal heart rate (FHR), which can be identified on a traditional CTG, but may be inconsistently recognize on visual interpretation and therefore go undetected[1]. Computerized analysis of the CTG (cCTG) based on the Dawes-Redman criteria, measures time domains between fetal heart beats, together with detecting fetal activity, and derives several parameters that are interpreted in the context of gestational age[2]. Among the various parameters that can be derived from the cCTG, the STV in milliseconds has emerged as a sensitive predictor of fetal acidemia, especially in pregnancies complicated by FGR[1,2,3]. In the multicenter randomized trial of umbilical and fetal flow in Europe (TRUFFLE) that evaluated monitoring techniques for early-onset FGR, the daily risk of developing an abnormal cCTG and/or recurrent FHR decelerations was 5%[3]. However, cCTG trends alone were unable to exclusively predict hypoxia and acidosis reliably emphasizing the importance of concurrent monitoring with UA and ductus venosus Doppler[4]. Professional societies uniformly agree that FGR surveillance requires a combination of UA and fetal Doppler with some type of CTG, ideally cCTG, to accurately predict and thereby prevent an abnormal fetal acid-base status at birth by timely delivery of the growth restricted fetus[5,6].

While the recommendations of utilizing cCTG are limited to health systems where this technology is available, the recommendation to use UA Doppler is universal in monitoring of the fetus with suspected FGR. However, significant differences exist in the predictive performance of UA Doppler in early- and in late-onset FGR[7]. UA Doppler recordings do however permit analysis of time intervals between standardized points of the flow velocity waveform to derive the FHR. Accordingly, serial measurement of these time intervals between heart beats permits calculation of the short term FHR variation, analogous to the cCTG. The purpose of this study is to evaluate the feasibility of deriving short term FHR variation from UA Doppler waveforms obtained from a cohort of fetuses considered low risk for fetal hypoxia.

Methods

Recruitment and data collection:

We conducted a prospective longitudinal ultrasound study in women recruited in the first trimester of pregnancy. Fetal biometry, amniotic fluid volume and UA Doppler studies were obtained on a 4-weekly interval between 14-40 weeks of gestation. The study was approved by the Institutional Review Boards of The Hospital for Sick Children (Toronto, ON, Canada) (REB Number 1000051548), Mount Sinai Hospital (Toronto, ON, Canada) (REB Number 15-0279-A), and Johns Hopkins University (Baltimore, MD, USA) (IRB Number: 00082717). Inclusion criteria were maternal age between 18 and 45 years, body mass index (BMI) < 45 kg/m^2, healthy singleton pregnancy, and no significant maternal comorbidities such as type 1 diabetes or hypertension. Datasets were excluded when a major fetal abnormality was detected, the patient withdrew at any point during the study, or the birth weight was less than the 5th centile (based on neonatal sex and gestational age (in completed weeks))[8].

Ultrasound examinations were performed by certified research sonographers using either a Philips iU22 (Philips Healthcare, Andover, MA, USA) or GE Voluson e10 (GE Healthcare, Chicago, IL, USA) ultrasound scanner. Flow velocity waveforms were recorded with pulsed Doppler ultrasound at the fetal end, mid cord and placental end in both UAs. These images were collected to measure UA wave reflections using a method previously developed by our group[9]. Waveform acquisition was standardized to periods of fetal quiescence and stable cardiac output to obtain at least six uniform waveforms with high signal to noise ratio and clear resolution of the envelope[10]. The sweep speed was adjusted to display at least 12 consecutive waveforms.

Signal extraction:

UA flow velocity signals were extracted to calculate the time interval between the onset of the systolic velocity component of the consecutive waveforms[11]. Briefly, saved ultrasound DICOM images were transferred for off-line processing using an in house Python 2.7 derived software. Header information was used to automatically identify the region containing the Doppler sonogram and convert pixel row and column to velocity and time. Background speckle was removed from the region containing the Doppler spectrum. The maximum-velocity envelope was traced by the pixel intensity defined threshold. Poor quality regions of the waveform were manually censored from further analysis. This signal was used as input into an algorithm that automatically identifies the initial rise in blood velocity corresponding to the R-wave at the beginning of systole[12]. The algorithm converts the waveform into a slope sum function signal to enhance the upslope of the waveform and uses adaptive thresholding and local search strategies to accurately detect the onset of the R-wave. Small adjustments to the R-wave positions were automatically made by an algorithm seeking to maximize the similarity between the consecutive blood velocity waveforms corresponding to each cardiac cycle[9].

From every two adjacent R-wave positions we can extract an R-to-R interval in milliseconds (**Figure 1**). The complete set of R-to-R intervals recorded over the entire exam can then be used to derive a metric of fetal heart rate variability. Analogous to published analytic approaches we corrected for the impact of the slow heart rate baseline drift on the variability of the R-R intervals with the following steps:

1) The subset of R-to-R intervals from each DICOM was converted to heart rate in beats per minute (bpm).
2) The subset of heart rates within each DICOM was adjusted by an additive factor to bring the average heart rate to 150 bpm.
3) This subset of baseline-corrected heart rates was converted back to R-to-R intervals in milliseconds.

The standard deviation of all of the baseline corrected R-to-R intervals per visit were used as a metric of fetal heart rate variation.

Statistical analysis:

Data were analyzed using the R software package (www.r-project.org). The fetal heart rate and heart rate variation data were analyzed using a linear mixed effect model with gestational age (in completed weeks) as the fixed effect and a heteroscedastic random effect where intersubject variation varied linearly with gestational age. Total variation was modeled as a sum of interfetal variation and intrafetal variation with the parameters estimated using the reduced maximum likelihood algorithm. Sonographers were included as covariates to assess if the change in heart rate variation with age was different between sites or between sonographers.

Results

Of the 221 women who consented to participate in the study, 195 underwent ultrasound examinations throughout gestation and were included in the study population (one had a major fetal abnormality, 11 withdrew, and 14 had neonates who were SGA). The clinical characteristics of these participants are summarized in **Table 1**. The 195 participants provided a total of 1070 visits (average of 5.5 visits per participant) with an average of 59 cardiac cycles from the UAs per visit. Between the two study sites, a total of eight different sonographers performed the experiments, with 85% of the visits conducted at Mount Sinai Hospital (n=910).

As gestation advanced, the baseline corrected heart rate variation increased significantly ($p < 0.0001$, **Figure 2**). The intrafetal standard deviation of the heart rate variation was 2.07 ms and the interfetal effect accounted for an additional 0.36 ms of variation. The change in heart rate variation with gestational age did not differ between study sites ($p = 0.3$) or between sonographers ($p = 0.1$). The fetal heart rate decreased significantly with gestational age ($p < 0.0001$) and was inversely correlated with the baseline corrected heart rate variation ($p < 0.0001$) (**Figure 3**).

Discussion

In this study, we demonstrated that short term FHR variation can be measured from UA Doppler waveforms collected using standard clinical ultrasound equipment. Consistent with studies performed using cCTG[13,14], heart rate variation measured in our cohort of low risk fetuses increased significantly with gestational age and within the expected range. Similar to the cCTG methodology, we have corrected the R-to-R intervals to account for differences in baseline FHR between subjects. The baseline corrected FHR variation showed the expected inverse correlation with FHR. There were no statistically significant differences in measurements between study sites or sonographers. These observations support the feasibility of using the output from Doppler waveforms as a robust method to extract clinically-meaningful data on FHR variation.

While cCTG provides a consistent and objective method for antepartum fetal surveillance, specifically in the context of FGR, it is not universally available as the equipment is distinct from a standard CTG or NST machine. For women who have ultrasound performed, the current method of deriving short term FHR variation requires a separate location and potentially a separate clinic visit and additional midwifery/medical staffing to complete fetal health assessment[1,5]. Moreover, its benefit beyond CTG in determining fetal acidosis has not been established[4]. The cCTG method of obtaining short term FHR variation requires continuous data acquisition throughout a monitoring session, so as to obtain FHR variation data only during periods of active fetal sleep. The cCTG device therefore distinguishes the true physiologic decrease in FHR variation during quiet sleep from the abnormal decrease associated with fetal hypoxemia and acidemia in FGR[15]. In contrast, our approach samples the FHR data sparsely through the ultrasound visit and selectively during periods of fetal quiescence which may overlap with sleep cycles. Despite these practical differences in data capture, our technique yields values for short term FHR variation that are within the range of those previously published

during normal gestational maturation of the fetus. The values of STV in the present study tended to be lower than those measured by cCTG, most likely due to data acquired when the fetus is less active to facilitate high quality Doppler tracings. With the physiologic maturation of fetal behavior, continuous fetal activity transitions into definitive rest activity cycles after 32 weeks gestation with significant differences in heart rate variability between states[16]. Accordingly we can expect that UA-derived STV during periods of quiescence will diverge more from cCTG measurements beyond this gestational age. This difference will require independent validation of the predictive cutoffs for fetal status and will be the subject of future investigation. Another difference is that using Doppler ultrasound we are able to resolve individual R-to-R intervals, while the Dawes-Redman criteria instead measures STV by averaging over epochs of 1/16th of a minute. Maturation of the fetal heart characteristics in normal fetuses is characterized by increased sophistication of the central and autonomic nervous system to process sensory inputs, regulatory outputs and increasing complexities of fetal behavior. The result is a steady increase in STV, bursts of high variation, heart rate reactivity and a decreasing basal heart rate due to vagal tone[17,18]. Our cohort exhibited a steady increase of FHR variation with advancing gestational age, where most of the measurement variability was intrafetal and therefore consistent with normal brain maturation. Therefore we believe that our approach to derive the FHR variation using UA Doppler holds promise as an alternative to measure short term FHR variation and compliments the assessment of fetal well-being with UA Doppler.

Our study is limited to observations in normal fetuses without verification of acid-base status at the time of the ultrasound examination. Without access to a cCTG apparatus at our study sites, we were unable to perform a comparison between our measurements of STV and those acquired from the Dawes-Redman analysis. However, our intention at this stage is merely to demonstrate the feasibility of deriving short term FHR variation data from clinically-derived UA waveforms. In this context the strength of our study lies in the large sample size of individual high quality UA Doppler measurements. Moreover, we accessed longitudinal observations that

further validated this method since intrafetal changes over time demonstrated physiologic maturation of FHR variation. It is likely that the differences in the technique to derive the STV will require consideration in the construction of UA-Doppler derived reference ranges.

Our principal findings confirm that extraction of FHR and its STV in milliseconds is feasible from UA Doppler data. The broader implication of our findings is that currently available ultrasound equipment can be used to derive multi-modal fetal well-being assessment information (i.e. a biophysical profile, UA Doppler and short term FHR variation) from one single examination, customized to recognizing the pertinent features of either the context of early-onset (UA and fetal Doppler alone) or late-onset (biophysical profile and short term FHR variation) FGR. The possibility of extracting this additional information at the time of the routine ultrasound evaluation may obviate the need for more intensive inpatient monitoring in cases of FGR. While we used data from the UAs, other arterial Doppler waveforms collected during a clinical visit, such as those from the middle cerebral artery, could be used to determine heart rate variation. We were unable to control for fetal state; however, our results suggest we should consider Doppler waveforms collected throughout the exam.

The TRUFFLE trial confirmed that the integration of UA, ductus venosus and cCTG monitoring provided the most favorable perinatal outcome in early onset FGR[6,19]. When concurrent monitoring with fetal Doppler and cCTG is performed, 11-51% of pregnancies are delivered for STV criteria[19]. This highlights the potential importance of concurrent availability of Doppler and STV data, especially in the surveillance of early onset FGR. We would like to emphasize that the UA-Doppler derived STV is not interchangeable with measurements derived with the cCTG for the reasons stated above. Further research is required to establish the relationship between UA Doppler derived short term FHR variation and acid-base status at the time of testing, in separate populations of suspected FGR pregnancies with early-onset or late-onset disease. Given the simplicity of obtaining UA Doppler waveforms, we believe our data open up an exciting new era of integrated fetal health assessment in FGR that is both customized for gestational age and achieved in a single testing visit.

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Conflict of interest: none

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Figure captions

Figure 1. Representative umbilical artery Doppler waveform with maximum velocity envelope traced (red) and start of R-wave (blue). The R-to-R interval (ms) is annotated above each waveform.

Figure 2. Baseline corrected heart rate variation over gestation ($p < 0.0001$). A best fit line based on the fixed factors of the mixed-effects model and a 95% confidence ribbon is shown.

Figure 3. Baseline corrected heart rate variation is inversely correlated with fetal heart rate ($p < 0.0001$). A best fit line based on the fixed factors of the mixed-effects model and a 95% confidence ribbon is shown.

Table 1. Characteristics of the study subjects meeting the inclusion criteria.

Characteristic	Mean [Range]
Maternal age at delivery (years)	34 [18-43]
Maternal prepregnancy body mass index (kg/m^2)	25.6 [17.4-43.6]
Gestational age at delivery (weeks)	38 [31-41]
Birth weight (g)	3244 [1410-4630]
Infant female sex (%)	48%