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Cardiotocography and Beyond: A Review of One-Dimensional Doppler Ultrasound Application in Fetal Monitoring

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Abstract

One-dimensional Doppler ultrasound (1D-DUS) provides a low-cost and simple method for acquiring a rich signal for use in cardiovascular screening. However, despite the use of 1D-DUS in cardiotocography (CTG) for decades, there are still challenges that limit the effectiveness of its users in reducing fetal and neonatal morbidities and mortalities. This is partly due to the noisy, transient, complex and non-stationary nature of the 1D-DUS signals. Current challenges also include lack of efficient signal quality metrics, insufficient signal processing techniques for extraction of fetal heart rate and other vital parameters with adequate temporal resolution, and lack of appropriate clinical decision support for CTG and Doppler interpretation. Moreover, the almost complete lack of open research in both hardware and software in this field, as well as commercial pressures to market the much more expensive and difficult to use Doppler imaging devices, has hampered innovation. This paper reviews the basics of fetal cardiac function, 1D-DUS signal generation and processing, its application in fetal monitoring and assessment of fetal development and wellbeing. It also provides recommendations for future development of signal processing and modeling approaches, to improve the application of 1D-DUS in fetal monitoring, as well as the need for annotated open databases.

1. Introduction

1.1. Background

Despite the advances in maternal and fetal healthcare, complications during birth still accounts for 40% of perinatal and maternal deaths of a total of over 287000 worldwide (World Health Organization, 2009). Globally 18.4 babies in every 1000 total births were stillborn as in 2015, mostly in Low- and Middle-Income Countries (LMICs) (World Health Organization, 2016). A variety of factors contribute to fetal and maternal compromise, which can be categorized as either pathophysiological or infrastructural. Among the

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pathophysiological causes, asphyxia, infection, congenital anomalies and prematurity contribute the most to stillbirth, particularly in LMICs (McClure *et al.*, 2017). The most common congenital defect is Congenital Heart Disease (CHD), with an incidence of around 1% of live births, which is the leading cause of morbidity and mortality in childhood due to structural defects (Bruneau & Srivastava, 2014; Ferencz *et al.*, 1985). Pathological fetal development such as Intrauterine Growth Restriction (IUGR), with a global incidence of between 3% and 7% (Romo *et al.*, 2009), also significantly contributes to perinatal morbidity and mortality and associated with 8-fold increased risk of stillbirth, compared to non-IUGR cases (Creasy & Resnik, 2008; Bukowski, 2010; Gardosi *et al.*, 2013).

Early detection of these pathologies is critical to prevention of perinatal morbidity and mortality, while providing tremendous medical, psychological and economic benefits (Merz, 2004; Hameed & Sklansky, 2007). However, insufficient infrastructure and a shortage of skilled healthcare personnel are the key causes of failures in health risk identification, referral and intervention rates, particularly in low-resource and rural regions (Woods, 2008; Stroux *et al.*, 2016). The high incidence of global perinatal mortality indicates the critical need for more accurate and affordable methods of identifying risks to fetal health.

One of the fundamental approaches to monitoring fetal health and development is through fetal cardiovascular function assessment. For example Fetal Heart Rate (FHR) and FHR variability (FHRV) provide markers that assist in the detect of hypoxia and CHD. FHRV is also associated with gestational age and therefore facilitates discrimination of healthy versus pathological fetal development, such as IUGR (Van Leeuwen *et al.*, 2004; Ueda *et al.*, 2009; Warrick *et al.*, 2010; Freeman *et al.*, 2012; Van Leeuwen *et al.*, 2003; Hoyer *et al.*, 2013). Current fetal heart assessment approaches are ranging from simple but with low specificity such as Cardiotocography (CTG), to expensive and highly specialized such as fetal echo-cardiography. The latter is based on ultrasound imaging and provides a more comprehensive fetal heart assessment, which is however relatively expensive and is only useful when performed by heavily trained experts, and in the context particular maternal and fetal indications (Caserta *et al.*, 2008). CTG, on the other hand, is an inexpensive and less specialized method for fetal cardiac activity assessment, which is routinely performed during pregnancy and labor for monitoring of FHR and the response to uterine contractions. Noninvasive one-dimensional Doppler Ultrasound (1D-DUS) is usually used in CTG for FHR monitoring. Similarly, it is used for in-home fetal monitoring devices, which can cost as little as $17 and can be performed by nonexperts, e.g. pregnant women (Martinez *et al.*, 2018; Stroux *et al.*, 2017; Valderrama *et al.*, 2018). These low-cost devices can be easily adapted to connect to mobile devices such as smart phones, for recording and processing, motivating their use in mobile-health (mhealth) systems for risk screening in low-resource environments (Stroux *et al.*, 2016; Stroux & Clifford, 2016). Table 1 summarizes available methods for non-invasive fetal monitoring, their affordability, training burden and availability in LMICs.

Although CTG is well-established, several randomized controlled trials have questioned its effectiveness in reducing perinatal morbidity and mortality (Alfirevic *et al.*, 2013; Steer, 2008). Despite its high negative predictive value, its high false positive rate has also caused unnecessary interventions (Alfirevic *et al.*, 2013; Kwon & Park, 2016). Insufficient standards

of CTG interpretation and poor inter- and intra-observer agreement in assessing FHR patterns contribute to this issue (Kwon & Park, 2016; Steer, 2008). In addition, due to the complex and changing nature of the 1D-DUS signal, variable signal quality and lack of well-defined fiducial points in the waveform, it has proved difficult to extract an accurate beat to beat heart rate from the signal. Therefore an averaging process is performed, often resulting in a less useful FHRV signal (Jezewski *et al.*, 2017; Lee *et al.*, 2009b). Technical improvements of the hardware apparatus, the introduction of new cost-effective techniques, and the development of clinical support systems have been recently investigated to address the issues of prevention of unnecessary interventions and perinatal morbidity and mortality (Marzbanrad *et al.*, 2014a; Stroux & Clifford, 2016). A new application of 1D-DUS has been also introduced for assessment of fetal heart function beyond the FHR, through identification of fetal heart valve movements, further facilitating monitoring of fetal well-being and development (Marzbanrad, 2015; Marzbanrad *et al.*, 2017, 2014d).

1.2. Scope and structure of review

This review covers the use of 1D-DUS for human fetal monitoring in current clinical practice and its issues, recent advances in the field, and future directions. Following this introduction, basics of fetal circulation, heart development and function are described in section 2. A background on the function of 1D-DUS modality for fetal monitoring is presented in section 3. In section 4, the main open and closed access databases for CTG recordings and 1D-DUS (raw) data are outlined. Section 5 discusses the importance of assessing 1D-DUS signal quality for reliable fetal monitoring and presents the techniques for quality assessment in previous studies. Various current and potential applications of 1D-DUS in fetal monitoring are discussed in section 6, including fetal movement and heart rate monitoring, cardiac valve movement detection and assessment of fetoplacental circulation. Further applications of 1D-DUS in identification of various pathological conditions are presented in section 7. The final section summarizes the current challenges and future directions of 1D-DUS application in fetal monitoring.

2. Fetal circulation

The embryonic human heart starts developing in the third week of pregnancy and becomes functional by the end of the eighth week (Archer & Manning, 2009). During its critical development (3rd-7th weeks), it changes from a simple tube to a four chamber structure. Although the heart is capable of blood-pumping in the 3rd week, the heartbeat has only been auscultated by Doppler from 10 weeks of gestation onwards, and monitored after 18 weeks by non-invasive fetal electrocardiogram (fECG) or magnetocardiogram (fMCG) (Sameni & Clifford, 2010; Van Leeuwen *et al.*, 2004; Kimura *et al.*, 2012; Peters *et al.*, 2001). A developed human fetal heart consists of four chambers, similar to the heart after birth: right atrium and ventricle as well as left atrium and ventricle (See Figure 1). To ensure the blood flows in the right direction, the heart has atrioventicular valves, which open from the atria into the ventricles. These are known as the tricuspid and mitral valves, located on the right and left sides of the heart, respectively. There are also two semilunar valves which open from the ventricles into the aorta and pulmonary artery (OpenStaxCollege, 2015). All of the oxygen and nutrition are supplied maternally via the placenta. The fetal blood detours away

from the non-operational lungs, via two openings: the Foramen ovale between the right and left atria and the Ductus Arteriosus linking the aorta and pulmonary artery. Normally these openings close around 30 minutes after the newborns first breaths (Feinstein *et al.*, 1993). The lungs do inflate and deflate (although not continuously) in utero, moving amniotic fluid through the lungs and creating breathing patterns, amplitude changes on the recording device as well as beat interval modulation. The movement is thought to exercise the lungs and increase surfactant. At birth, when the lungs inhale air for the first time, the pulmonary vascular pressure decreases and the left atrial pressure exceeds that of the right hand side. This makes the septum primum (the thin wall of inter-atrial septum) fuse with the septum secundum (a muscular tissue growing to the right of the septum primum), forcing the foramen ovale to close. The tissue around this then starts to seal (Homma & Sacco, 2005). Abnormalities in this process can be detected via heart sounds or ultrasound. Nevertheless, the cardiac valve and wall motion are the same preand postnatally.

Normal cardiac rhythm originates from an action potential at the sinoatrial (SA) node (the pacemaker) (OpenStaxCollege, 2015). The action potential from the SA node causes atrial contractions during systole (fECG P-wave), then travels via the atrioventricular (AV) node, while spreading through the bundle branches and Purkinje fibers along the ventricle walls, causing ventricular contraction (fECG QRS complex) (OpenStaxCollege, 2015). It is followed by the ventricular diastole, when the action potential leaves the ventricles and the ventricular wall repolarizes (fECG T-wave), as depicted in Figure 2 (OpenStaxCollege, 2015).

The normal FHR range is around 120 to 160 bpm, being controlled by the Autonomic Nervous System (ANS) and baroreceptors, i.e. the pressure sensors in the aortic arch and carotid arteries, and brain stem (Von Steinburg *et al.*, 2013; Baker *et al.*, 2009; Blackburn, 2013). The ANS includes sympathetic and parasympathetic branches innervating atria, ventricles and the SA node. The parasympathetic input (vagal stimulation) reduces the FHR through decreasing the rate of the SA node stimulation and transmission to the ventricles. The sympathetic nervous system, on the contrary, can increase the FHR. The balance between parasympathetic and sympathetic inputs mediates the FHR baseline, while its continuous recalibration generates the FHR variability (FHRV). Earlier maturation of the sympathetic system causes a higher FHR in the preterm fetus, while with advancing gestational age the parasympathetic development decreases the FHR. The fluctuations in vagal impulse and sympathetic reflexes constantly change the FHR, while the normal baseline variability reflects the balanced parasympathetic and sympathetic control and proper oxygenation (Blackburn, 2013; Von Steinburg *et al.*, 2013).

The FHR is also controlled by the baroreceptors. If the blood pressure increases, the vagal nerve receives a stimulus to slow the FHR to lower the pressure. Decreasing blood pressure reduces the parasympathetic tone leading to an increase in FHR and blood pressure. The chemoreceptors located in the carotid bodies of the carotid arteries and in the aortic bodies of the aortic arch, sense a decrease in circulating oxygen (hypoxemia) and compensate by increasing the FHR and cardiac output. Hypoxemia, or an increase in carbon dioxide (hypercapnia), however triggers a vagal response to decrease FHR and increase blood pressure, as typically observed in a cord compression event. The FHRV can be affected by

several factors such as gestational age, fetal movement, fetal sleep state, acidemia (low blood pH) and hypoxia (decreased oxygen in tissue) and even the maternal physiological and psychological state (Mantel *et al.*, 1991; Ivanov *et al.*, 2009; Marzbanrad *et al.*, 2015b; Stroux & Clifford, 2016; Monk *et al.*, 2000).

3. 1D-DUS basics

An ultrasound probe has a piezoelectric transducer which transmits and receives ultrasound waves by transforming the electrical charge into mechanical energy and vice versa. The frequency range of ultrasound waves is higher than the human audible limit (i.e. 20 kHz). The common types in clinical use include pulsed and continuous wave transducers. Several modes are available in medical applications, including the brightness mode (B-mode) producing an image of a selected scanned plane in the body, also known as 2D mode, and M-mode which emits pulses in rapid succession producing an ultrasound video. These modes have been commonly used for fetal echo-cardiography. The 1D-DUS transducers for fetal monitoring commonly operate in continuous Doppler mode with a frequency of 1–4 MHz, as employed in previous studies (Stroux & Clifford, 2016; Marzbanrad, 2015; Sato *et al.*, 2007; Shakespeare *et al.*, 2001; Yumoto *et al.*, 2005). This type of probe continuously generates and receives, using a two-crystal transducer to fulfill both functions. Doppler mode refers to the probe's capability to measure the change in frequency between the emitted and the observed signal, reflected from the moving structures on the ultrasound beam path. This enables estimation of the velocities of the moving cardiac structures, and in the application of fetal monitoring, the identification of heart valve and wall motion, as illustrated in Figure 3.

The shift in frequency is called the Doppler effect and is written as:

$$f_D = \frac{2f_o}{c} V cos(\theta) \quad (1)$$

where f_D is the measured change in frequency (Hz), f_o the frequency of emitted ultrasound (Hz), c the speed of sound in soft tissue (m/s), V the velocity of the reflecting target (m/s) and its angle with the ultrasound beam (Hill *et al.*, 2004). The Doppler mode for FHR assessment is also described as auscultation Doppler, since the resultant Doppler signal is usually translated into audible cardiac sounds. To distinguish clearly from the 2D ultrasound such as B-mode, which is commonly associated with medical ultrasound imaging, the signal is also referred to as one-dimensional (Stroux & Clifford, 2016).

For the fetal Doppler, the expected fetal cardiac information is composed of blood flow, cardiac wall and valve motion, while cardiac tissue motion is dominating with higher intensity (Tutschek *et al.*, 2003). These movements are also differentiable based on their different velocities, resulting in different Doppler frequencies (Marzbanrad, 2015). The ventricular motion could be recorded from early on in gestation (12 weeks onwards) by tissue Doppler echo-cardiography, whereas the detection rate of valve motion increases with gestational age (Tutschek *et al.*, 2003).

4. Databases

The field of ultrasound-based fetal heart rate assessment has been limited by the lack of public databases and open source algorithms so far. Since the commercial 1D-DUS devices in clinical practice have been designed as closed systems, the raw signals are not accessible. There are also very limited publicly available databases of Doppler FHR data.

As summarized in table 2, there is however the CTU-UHB Intrapartum Cardiotocog-raphy Database 2, which contains 552 CTG traces, all carefully selected from 9164 recordings collected between 2010 and 2012 at the University Hospital in Brno, Czech Republic (Chudáček *et al.*, 2014). The CTG recordings were from no longer than 90 minutes before the actual delivery, and at most 90 minutes long. Each recording contains FHR time series and a uterine contraction signal, both sampled at 4 Hz. Each CTG is also accompanied by maternal, delivery, and fetal clinical details. There are two limitations with this database; firstly it was recorded intrapartum only, and secondly it did not provide the raw fetal 1D-DUS signal. Many CTG databases were also used in previous studies, but without public access. Some of these databases are summarized in tables 2 and 4, which include CTG tracings collected from healthy and growth restricted fetuses in second and third trimesters. The largest of these databases is a set of 1163 IUGR and 1163 control cases at 23–42 weeks of gestation in the UK (Stroux *et al.*, 2017). This database is a subset of the Oxford database collected by Dawes, Redman and colleagues over the last three decades, which now contains CTG from 22,790 women in labor (at more than 36 weeks of gestation) together with paired umbilical blood analyses (Dawes *et al.*, 1992a; Georgieva *et al.*, 2017). Another large but closed access CTG database with more than hours of tracing just prior to delivery was used in a study on discrimination of normal and at-risk populations from fetal HRV (Warrick & Hamilton, 2014). It consisted of 5320 normal cases, 10 cases with neonatal depression and 99 with metabolic acidosis, from two US hospitals. However these closed databases contained FHR tracings without the raw 1D-DUS signals.

Several studies used raw 1D-DUS signals to either improve FHR estimation or extract additional information, such as fetal movement, mechanical activity of the fetal heart or other physiological parameters, as detailed in section 6. The databases used in these studies are all closed access, and with various devices working at different ultrasound frequencies ranging from 1 MHz to 3.3 MHz. Details of these databases are summarized in table 3.

5. 1D-DUS quality assessment

Despite the benefits and wide use of 1D-DUS in fetal monitoring, the data quality is often affected by noise, the movement of the probe against the skin, and maternal and fetal movements. Changes in the position of the probe or the fetus affect the alignment of the ultrasound beam with the fetal heart, causing non-stationarity. Ensuring the quality of data is essential particularly in mobile-health applications, and it needs to be validated at data acquisition point. Timely feedback on the quality of recordings enables retaking the data if required, avoiding decision and actions based on unreliable data and having a measure of confidence while interpreting the output. The importance of DUS signal quality assessment

for FHR monitoring, was investigated in several studies (Valderrama *et al.*, 2018; Stroux & Clifford, 2013, 2014, 2016; Magenes *et al.*, 2001; Marzbanrad *et al.*, 2015a).

The pattern and the quality of the 1D-DUS signal were found to be variable, even on a beat-to-beat basis (Marzbanrad *et al.*, 2014a), as shown in figure 4 for different time windows of a single 30-minute recording from a single subject. The figure shows that not all cardiac wall or valve movements are detectable from every beat of 1D-DUS. It was recently demonstrated how closely the accuracy of FHR analysis depends on the signal quality, showing the necessity of quality assessment while data collection (Stroux & Clifford, 2013). It was recommended by Magenes et al. to remove CTG signals with low quality before applying methods for detecting fetal anomalies (Magenes *et al.*, 2001). While Magenes et al. assessed the quality based on the FHR (Magenes *et al.*, 2001), recent studies have been more focused on the 1D-DUS signal features (Stroux & Clifford, 2016; Marzbanrad *et al.*, 2015a). One of these features is Sample Entropy (SampEn) which was investigated by Stroux, to analyze reoccurring patterns, together with wavelet features as the percentage of energy at different resolution levels to evaluate the localized signal power (Stroux & Clifford, 2016). In the system developed by Stroux et al., a mobile-phone was mounted on the 1D-DUS probe, therefore features derived from the phone's in-built accelerometer could also be analyzed to characterize the probe movements, as a possible contributor to the signal quality. All these features were used for classification, through logistic regression (LR) and Support Vector Machines (SVM) (Stroux & Clifford, 2016). Using a database of 17 one-minute recordings evaluated by three annotators as good or poor quality, an accuracy of 96.18% was achieved by SVM, based on all cardiac input features, while the best performance on the test set using a LR was 95.41%, based on the cardiac as well as accelerometer features.

The study by Stroux was followed by another work, which proposed a templatebased method using only the 1D-DUS-based features (Valderrama *et al.*, 2017). It used Empirical Mode Decomposition (EMD) to detect the fetal heart beats and to segment the recording into short, time-aligned temporal windows. A template was initially derived for each 15-second window by averaging the signal in all beats in the window, then the template was updated by averaging only the beats which were highly correlated with the initial template. The DUS signal quality index (SQI) was calculated by correlating the segments in each window with the corresponding running template using four different pre-processing steps. The template-based SQIs were combined with additional features based on SampEn and power spectral density and the quality was classified using SVM. Using a combination of these features, this method achieved a median out of sample classification accuracy of 85.8% on the test set. This method was promising not only for classifying (annotated) good and bad quality data, but also the borderline (mostly clean and mostly noisy) signals. Although this study was on the same dataset used by Stroux (Stroux & Clifford, 2016), different statistical validation approaches where used, which limited direct comparison. While Stroux trained on two thirds of the data set and held out one third for testing, Valderrama et al. used stratified five-fold cross validation with bootstrapping (repeated 100 times), with subject stratification across different folds in each repetition.

Another study analyzed the 1D-DUS signal quality specifically for the application of valve motion detection (Marzbanrad *et al.*, 2015a). In this work, simultaneous 1D-DUS and fECG

were recorded for one minute from 57 fetuses and annotated by four independent reviewers. The method was based on various quality features of the high frequency component of the 1D-DUS signal associated with valve motion. The DUS signal was decomposed by wavelet analysis and the normalized envelope of the signal was segmented into cardiac cycles using the corresponding R-R intervals from fECG. Twelve features were selected mainly based on the signal properties in the valve motion ranges compared to the remaining time intervals (Khandoker *et al.*, 2009; Marzbanrad *et al.*, 2014d). The features included the power density, number of peaks, average of the peak amplitude and variance in the valve motion range compared to the values in the remaining ranges. Other features included Kurtosis, skewness, Hjorth parameters, SampEn and Singular Value Decomposition (SVD) based features (Marzbanrad *et al.*, 2015a). Naive Bayes (NB) classifier was used to classify the signal quality as poor or good and the performance was tested by 10-fold cross validation, which showed an average classification accuracy of 86% on training and 84% on test data (Marzbanrad *et al.*, 2015a).

Despite the promising methods proposed so far, the Doppler quality assessments have all been evaluated only on healthy cases. It would be crucial to validate these techniques for various arrhythmias and heart anomalies to investigate if the abnormalities would confound the quality assessment. All studies so far have been based on data collected in a hospital setting by medical professionals. It is important, however, to also build a database recorded by non-experts when considering the application of 1D-DUS in low-resource settings. In addition, further investigation is recommended for making the quality assessment computationally efficient to be able to provide real-time feedback to the user.

6. 1D-DUS applications for fetal monitoring

The main role of fetal monitoring techniques is to evaluate antepartum and intrapartum fetal risks which indicate the need for intervention. These methods are aimed at reducing the risk of stillbirth and damage to the fetal nervous system (Signore *et al.*, 2009; Ramanathan & Arulkumaran, 2009; Devoe, 2008; Malcus, 2004). The risks include, but are not limited to, placental insufficiency, perinatal hypoxia and asphyxia leading to Hypoxic-Ischemic Encephalopathy (HIE), IUGR and congenital abnormalities, and have a particularly high prevalence in LMICs (McClure *et al.*, 2017). Available monitoring techniques can be categorized into internal (invasive) and external (noninvasive) methods. Invasive methods often involve rupture of membranes therefore typically employed during labor, while non-invasive methods are more suitable for antenatal screening. Electronic fetal monitoring using 1D-DUS has been established as a widely used non-invasive technique even for low risk pregnancies (Grivell *et al.*, 2010). Although it is typically used for FHR estimation as in CTG, other applications have also been proposed including fetal movement monitoring (Wróbel *et al.*, 2014; Maeda, 2013), fetal cardiac valve motion identification (Marzbanrad, 2015; Shakespeare *et al.*, 2001) and umbilical artery circulation assessment (Thuring *et al.*, 2015), which will be briefly discussed in the following sections.

6.1. Fetal movement monitoring

Fetal movement counting is one of the oldest and simplest techniques, aiming at identifying the reduced fetal movement. Traditionally this has been based on maternal perception, which is however inaccurate as confused by uterine contractions or aortic pulsation and dependent of the gestational age, the fetal size or the amount of amniotic fluid (Johnson *et al.*, 1990). The analysis of the fetal movement activity (actogram) is also important for detection of the nonreactive recording (Wróbel *et al.*, 2014; Jezewski *et al.*, 2002). The most reliable method for the detection of movement, its type and volume, is through ultrasound imaging, which is however costly and specialized. Wrobel et al., showed that the fetal movement can also be obtained using 1D-DUS (Wróbel *et al.*, 2014). Fetal movement activity can be extracted from 1D-DUS using bandpass filtering, since it generally corresponds to lower frequency bands compared to heart wall and valve movements (e.g. the movement speed of 1–3 cm/s is reflected at 20–80 Hz range if the transducer operates at 2 MHz) (Wróbel *et al.*, 2014; Maeda, 1990). Wrobel et al. proposed an algorithm estimating an adaptive classification threshold, rather than the fixed threshold which was used in other studies (Wróbel *et al.*, 2014; Maeda, 1990). This technique could ensure detection of up to 89% of movement perceived by the mother, while resulting in 84% incorrectly detected episodes (Wróbel *et al.*, 2014). However, the latter does not necessarily represent incorrect detection, since only about 30% of the actual fetal movements can be perceived by the mother. Further investigation is required using ultrasound imaging as a reliable gold standard to evaluate the accuracy of the 1D-DUS-based actogram.

6.2. Fetal heart rate monitoring

The FHR provides a reliable evaluation of the function and development of the ANS, which regulates the heart beat dynamics. The most accurate measurement of FHR is through direct fECG, which is invasive. Noninvasive fECG through the maternal abdomen has been an alternative fECG approach for potential antenatal use and has been a challenging area of research (Sameni & Clifford, 2010; Clifford *et al.*, 2014; Kimura *et al.*, 2012; Behar *et al.*, 2016; Lewis, 2003). The obtained signal by this method contains a weak fECG with a low signal to noise ratio, because of the small size of the fetal heart and several low conductive layers through which the signal passes to reach the maternal abdomen surface. Furthermore, fECG is not the only recorded signal, but is mixed with the maternal ECG overlapping in the time and frequency domain. It is also contaminated by maternal respiration, motion artifacts and uterine contractions. Fetal movement also has an influence depending on the orientation of the fetus. Moreover, limitation of clinical knowledge about the fetal cardiac function, compared to that of adult's have limited the advancement in this field (Sameni & Clifford, 2010; Clifford *et al.*, 2014). Some commercial noninvasive fECG devices have been recently entered the market, such as the Monica fetal monitor from Monica Healthcare (UK) and the Meridian monitor from MindChild Medical (USA). However, they are still at an early stage with studies being limited by the number of patients and population size, hence further studies and development are required.

The most widely used antepartum and intrapartum FHR monitoring approach remains Doppler ultrasound and is performed using CTG. A recent study compared noninvasive fECG and 1D-DUS for FHR monitoring, not only in terms of FHR specifically, but also the

clinically important indices describing the instantaneous FHRV (Jezewski *et al.*, 2017). The FHR comparison showed no measurement bias between the acquisition methods, while the mean absolute difference was 1.2 bpm, which does not practically affect the visual assessment of the FHR signal. However, inconsistencies of several percent were reported for acceleration (7.8%) and particularly deceleration (54%) patterns (Jezewski *et al.*, 2017). The authors explained the inconsistencies for deceleration as the effect of signal loss for FHR by DUS which is on average twice higher than for FHR by fECG. In addition, the autocorrelation technique, commonly used for FHR estimation in CTG, is often unable to follow the rapid decrease of FHR signal related to deceleration. Nevertheless, the ability of clinical parameters to distinguish between normal and abnormal groups was not affected by choice of the acquisition method (Jezewski *et al.*, 2017).

CTG is usually performed through a non-stress test (NST) to examine the reactivity of the FHR, i.e. showing at least two accelerations of more than 15 bpm from the baseline (110–160 bpm) lasting more than 15 seconds, within the 20 minute test. However, the absence of accelerations may be due to fetal sleep (Bobby *et al.*, 2003). In practice, if the fetus does not show reactivity after 40 minutes, further assessment is performed by contraction stress test (CST), e.g. through intravenous admission of dilute Oxytocin or Vibroacoustic stimulation (Arora & Bhatnagar, 2015). Another factor involved with false positive results is the gestational age. Reactivity typically appears between 28 to 30 weeks and 50% of the normal fetuses in 24–28 weeks and 15% in 28–32 weeks of pregnancy fail to show reactivity in FHR (Malhotra *et al.*, 2014; Lavin Jr *et al.*, 1984; Druzin *et al.*, 1985). Possible causes for nonreactive FHR include prolonged fetal sleep, prematurity, preexisting neurologic damage or other abnormal conditions (Walton & Peaceman, 2012). While the false negative rate of this method is low 0.3%, the false positive rate is around 50% (Devoe, 2008). False negative results may severely affect the health outcomes of the fetus and the mother, while false positive results may lead to inappropriate and potentially risk-bearing procedures and an additional burden on resources.

The effectiveness, reliability and reproducibility of CTG have been the matters of controversy, since the current antenatal CTG has not significantly improved the perinatal outcome (Grivell *et al.*, 2010; Steer, 2008). The issues include insufficient standards of CTG interpretation leading to poor inter- and intra-observer agreement in interpretation of FHR traces (Kwon & Park, 2016; Steer, 2008). The complexity and changing nature of the 1D DUS, the variable signal quality and lack of well-defined fiducial points in the waveform (as shown in figure 4), also lead to inaccurate FHR estimates. More promising results compared to standard CTG could be demonstrated using computer-assisted interpretation methods, to improve the accuracy and reduce the variation in interpretation (Grivell *et al.*, 2010; Stroux & Clifford, 2016).

The rest of this section reviews the FHR estimation methods using 1D-DUS recordings.

6.2.1. Auto-correlation based methods—The early methods for FHR estimation from 1D-DUS in the 1980s were based on correlation providing relatively robust FHR with acceptable accuracy compared to invasive fECG (Tuck, 1982; Lawson *et al.*, 1983). Autocorrelation-based approaches have been the basis for both cardiotocographs and

handheld Doppler devices while being improved progressively (Peters *et al.*, 2004). They basically uncover the regular patterns by comparing the signal with its delayed versions, considering that the fetal cardiac activity has an almost periodic nature. To measure the repetitive patterns, the signal and its delayed versions are multiplied sample-wise and their product is summed over the analysis window. The autocorrelation function decreases the noise contribution and highlights the periodicity of the input signal. This periodicity can reflect the mean interval between cardiac events, to measure the FHR. The conventional autocorrelation approach has been improved in several ways, including processing time reduction for handheld devices (Hua *et al.*, 2005), decreasing the number of missed FHR samples (Voicu *et al.*, 2010), exploring signal envelope alternatives for correlation assessment (Kret & Ka lużyński, 2006), assessing optimal parameter settings, such as the auto-correlation window and overlap size (Voicu *et al.*, 2014; Lee *et al.*, 2009a), and the evaluation of a number of different correlation approaches (auto-, cross-correlation, correlation coefficient and YIN, a fundamental frequency estimator for speech and music) (Voicu *et al.*, 2010).

One of the properties of autocorrelation approaches used in the commercial Doppler-based fetal monitors, is averaging over a certain period, e.g. providing FHR values every 250 msec. The choice of sampling interval is based on a maximum expected fetal heart rate of 240 bpm (Jezewski *et al.*, 2008). The averaging nature of correlation-based approaches also masks the detailed and short term HRV. The diagnostic potential of HRV markers can be improved by higher accuracy of the HRV, which is achievable by fECG or fMCG (Hoyer *et al.*, 2013). Several researchers studied the effect of averaging on heart rate variability measures, which are significantly lower compared to variability measures computed from the fECG (Jezewski *et al.*, 2011; Roj *et al.*, 2010; Lawson *et al.*, 1983). In contrast to fECG and fMCG, where the R-peaks are distinctive markers, 1D-DUS reflects the mechanical activity of the heart including various valve or heart wall motion events, which complicates detection of a unique fiducial point for each cardiac cycle. As shown in figure 4, considerable variation in the signal pattern is often observed depending on the orientation of the fetal heart with respect to the ultrasound beam which may vary even during a single one-minute recording(Marzbanrad *et al.*, 2014a). The beat-to-beat intervals can be estimated from 1D Doppler recordings in two ways: post-processing the evenly sampled autocorrelation trace by eliminating duplicate samples; or the segmentation of the Doppler signal prior to heart rate estimation (Stroux & Clifford, 2016). The latter is sensitive to noise (Peters *et al.*, 2004), since for the correlation-based approaches, there is a potential trade-off between susceptibility to noise and beat-to-beat accuracy (Lee *et al.*, 2009a). Jezewski et al. combined measurements in multiple cycles to improve the robustness to noise with a segmentation process translating the trace into beat-to-beat intervals (Jezewski *et al.*, 2011).

6.2.2. HMM and HSMM methods—Despite the non-stationarity and dynamic spectral characteristics, 1D-DUS can be used for fetal auscultation similar to a phonocardiogram. The signal represents the sequential physiological process of the cardiac heart cycle in phenotypical manner which bears a resemblance to heart sounds captured during acoustic auscultation. Recently, given the success on heart sound data (Ricke *et al.*, 2005; Schmidt *et al.*, 2010; Springer *et al.*, 2016), Stroux and Clifford proposed the use of a Hidden Markov

Model (HMM) approach for segmenting the 1D-DUS signal into heart cycles, as a preprocessing step for heart rate variability and intrauterine growth studies (Stroux & Clifford, 2016). This segmentation procedure involved a preprocessing step for removing spikes in the signal, i.e. the samples greater than a certain threshold within the analysis window of a minimum of one beat. The signal was bandpass filtered (between 25Hz and 600Hz, for ultrasound transducer frequency of 3.3 MHz) to minimize the influence of fetal movement and blood flow, occurring at lower and higher frequencies respectively. An extended version of HMM, namely Hidden Semi-Markov Model (HSMM) was then employed which is based on the state duration probabilities and have been successfully used in speech recognition (Vaseghi, 1995) and heart sound segmentation (Schmidt *et al.*, 2010; Springer *et al.*, 2014). In the HSMM, the probability of staying in a state is governed by the duration densities rather than self-transition probabilities used in conventional HMM (Rabiner, 1989). The signal envelope representing the signal's amplitude component was used as feature, using three different time domain, frequency domain and time-frequency domain envelopes, namely, homomorphic, wavelet and the power-spectral density (PSD). The primary cardiac oscillations in a cycle and the interval between successive oscillations were used as the states. The training process of HSMM was by the Baum-Welch algorithm and the optimal state path was estimated by Viterbi approach. Comparing against manual annotations, the percentage of estimates within the 10% tolerance limit for excellent, intermediate and poor quality signals was reported as 100%, 92% and 59% for autocorrelation and 97%, 91% and 71% for HSMM approach. Therefore good performance of both methods for intermediate to excellent signal qualities and a superior performance of HSMM for poor quality signals were observed (Stroux & Clifford, 2016). One limitation of the study by Stroux and Clifford was the use of manual annotation for benchmarking whose accuracy may be affected by signal quality. This could be improved by comparing the accuracy of the HSMM segmentation against a more robust and simultaneously acquired measure of cardiac activity such as fECG or fMCG. Furthermore, the dataset was recorded from 17 healthy patients, while a larger dataset is recommended especially for earlier gestation weeks, e.g. lower than 35 weeks.

HMM has also been the basis of several methods for automated identification of opening and closing of fetal heart valves from 1D-DUS recordings, as reviewed in the next section (Marzbanrad *et al.*, 2014a,d; Marzbanrad, 2015).

6.3. Identification of fetal cardiac valve motion

The Doppler shift of the ultrasound beam which is reflected from the moving valves of the fetal heart and collected by the transducer, uncovers the opening and closure of the fetal cardiac valves. Using 1-D DUS signal, the timings of cardiac valve movements can be estimated with less expertise and cost compared to the echocardiography. The valve motion timings are the main bases for estimating the mechanical and electromechanical indices of the fetal heart illustrated in figure 5. Considering the synchronous operation of both sides of the fetal heart, in this figure the semilunar and atrioventricular valve motions are expressed as the aorta and mitral valve movements, respectively. From the intervals shown in figure 5, the Myocardial Performance Index (MPI) is calculated as (ICT + IRT)/VET, which is a parameter for measuring global myocardial function and a useful highly sensitive parameter

of dysfunction in fetal pathologies (Mahajan *et al.*, 2015). A modified index was recently proposed as (ICT + IRT)/VFT, which has been shown significantly decreasing with gestational age, while no significant correlation of MPI with gestational ages was found (Khandoker *et al.*, 2016). From a clinical standpoint, PEP, ICT, IRT, VET are the most useful cardiac intervals for assessing fetal development and wellbeing, as sensitive markers of the functional state of the fetal myocardium, cardiac performance and ANS function, and can reflect the early development of hypoxemia and acidosis (Tongprasert *et al.*, n.d.; Hassan *et al.*, 2013; Velayo *et al.*, 2011; Mensah-Brown *et al.*, 2010; Cruz-Martínez *et al.*, 2012; Yumoto *et al.*, 2005; Marzbanrad *et al.*, 2016).

The frequency content of DUS which is associated with cardiac valve motion is higher compared to the cardiac wall motion and the movement of other organs, hence could be identified based on its spectral and temporal characteristics (Shakespeare *et al.*, 2001; Marzbanrad, 2015), as shown in figure 4. Early studies in the 1980s proposed noninvasive methods which mainly aimed to analyze the systolic time interval, while using fECG as reference (Murata *et al.*, 1978; Sampson, 1980; Organ *et al.*, 1980; Koga *et al.*, 2001). All of these methods were based on bandpass filtering to extract the high frequency component of the DUS, from which the valve movements were identified ‘manually’ by experts. There were three main issues with these methods. Firstly, due to the noisiness and variability of the DUS data on a beat-to-beat basis, as well as the wide changes in the signal contents and spectral characteristics over time (figure 4), bandpass filters could not effectively provide the component originated by the valve motion. Secondly, manual identification of beat-to-beat opening and closing of valves was time consuming, required special expertise and was subject to inter and intra observer and visual errors. Finally, these techniques required simultaneous fECG as reference. Improvement in the aforementioned aspects has been essential to make this technique more reliable and applicable with less required expertise, as discussed in the next sections.

6.3.1. Extraction of the valve-motion-related component of1D-DUS—Several studies suggested applying advanced signal processing techniques to extract the information content of the DUS signal (Shakespeare *et al.*, 2001; Kupka *et al.*, 2004; Khandoker *et al.*, 2009; Marzbanrad *et al.*, 2014d). Shakespear et al. used Short Time Fourier Transform (STFT) analysis of the DUS signal and showed that the component with a higher frequency was linked to valve movement (Shakespeare *et al.*, 2001). However, the frequency range of the valve motion related component was not constant over time and there were some instances where the valve motion was not detectable from the spectrogram (Shakespeare *et al.*, 2001). Considering the nonstationarity and transient nature of the DUS signal as well as the wide changes in the signal content and spectral characteristics over time, it was proposed by Khandoker et al., to apply the multi-resolution wavelet analysis to the DUS signal (Khandoker *et al.*, 2009). Using the wavelet analysis, valve movements were visualized as peaks in the detailed signal (at level 2 wavelet decomposition, for an ultrasound frequency of 1.15 MHz). Other studies proposed to use EMD, which is a data-driven algorithm used for decomposing nonlinear and nonstationary time series (Marzbanrad *et al.*, 2014d; Valderrama *et al.*, 2017). Using EMD, the first intrinsic mode function (IMF), i.e. the highest frequency component, was locally extracted out of the 1D-DUS signal and used to detect the valve

movements, as validated against simultaneous echo-cardiography images (Marzbanrad *et al.*, 2014d).

6.3.2. Automated identification of valve motion events—The first method which was proposed for automated valve motion detection was based on HMM and used a simultaneous 1D-DUS and noninvasive abdominal ECG recordings (Marzbanrad *et al.*, 2013b). The 1D-DUS signal was first decomposed into the first IMF using EMD, and the peaks of its envelope were detected. The interval from each fECG R-peak to the following peaks of the first IMF before the next R-peak were selected as observation samples. The aorta and mitral opening and closing, together with their transition were assumed as hidden states. The opening and closure of the valves were then automatically assigned to the IMF peaks using HMM. Fetal echocardiography images and expert annotation were used for training and validation (Marzbanrad *et al.*, 2013b). This method was further extended using a multi-dimensional HMM approach to incorporate multiple features, such as peak amplitudes (Marzbanrad *et al.*, 2014b), and combining Support Vector Machine (SVM) with HMM (hybrid SVM-HMM) to classify the 1D-DUS features as valve motion events (Marzbanrad *et al.*, 2014d; Ganapathiraju *et al.*, 2000). Since HMM is based on probability models, a probabilistic output of SVM was obtained using Platt's method to provide the posterior probability of classifying the sample, i.e. $P(class|input)$ (Platt *et al.*, 1999). The transition probability from HMM and the emission probability distribution estimated from the output of the Platt's SVM through the Bayes' rule, were used to estimate the sequence of events using Viterbi algorithm (Marzbanrad *et al.*, 2014d).

One of the challenges of valve motion detection is the nonstationarity of the 1D-DUS signal and its variable pattern, observed for both inter and intra subjects/recordings, which primarily depends on the orientation of the fetal heart to the transducer (as shown in figure 4). For example, the peak corresponding to aortic valve opening could be smaller or larger than the peak representing the mitral closure over a single or across multiple recordings. Therefore instead of using a common training set for all existing patterns of the 1D-DUS, a cluster-based method was proposed (Marzbanrad *et al.*, 2014a). The study found six different patterns for the 1D-DUS high frequency component which were actually variable on a beat to beat basis and found to be different for the early to late gestation. After clustering the signals, the hybrid SVM-HMM was trained for each cluster separately. To identify the events, each beat-to-beat interval of signal was first matched to the clusters to which it had the minimum Euclidean distance. Then the sequence of events which were attributed to the peaks of the signal, were identified by the Viterbi algorithm using the trained SVM-HMM specific to the corresponding cluster. Applying this method resulted in a higher average precision and recall (pr: 83.4% and re: 84.2%), compared to the hybrid SVM-HMM without clustering (pr: 79.0% and re: 79.8%) and HMM approach (pr: 77.4% and re: 77.9%) (Marzbanrad, 2015; Marzbanrad *et al.*, 2014a).

6.3.3. Valve motion detection without fECG reference—Simultaneously recorded fECG has been a crucial component of the automated valve motion identification methods for segmentation into cardiac cycles, since the features (timings) are calculated with respect to the R-peaks (Marzbanrad *et al.*, 2014d,a). However simultaneous recording of abdominal

ECG with DUS signal and separation of fECG from a noisy mixture of maternal ECG and other interfering signals and artifacts add extra costs and complications. An automated valve motion detection method without using fECG was investigated to address those issues (Marzbanrad *et al.*, 2014e). This method used the first IMF (high frequency) of 1D-DUS decomposition as linked to valve motions and the fourth IMF (low frequency) related to the cardiac wall motions. The latter were used for segmentation into cardiac cycles as a substitute for fECG R-waves. The mitral and aortic valve motion events were automatically identified by hybrid SVM-HMM and the results were compared to the method with fECG as reference. The calculated fetal ICT (mitral closing to Aorta opening) with this method was in agreement with the average ICT measured by the method with fECG reference (Marzbanrad *et al.*, 2014d), with correlation coefficient: r = 0.9 and bias = 0.5 msec, while 95% limits of agreement were −2.7 to 3.7 msec). However larger differences were found for beat to beat measurements with and without using fECG (6.1 ± 3.8 msec). A more accurate beatby-beat estimation of valve movements, could be achieved using improved segmentation methods.

6.4. Doppler velocimetry for fetoplacental circulation

Doppler assessment of umbilical artery involves the use of continuous or pulsed wave Doppler to determine arterial flow in a segment of umbilical cord, which is identified using (2D) B-mode ultrasound. The pattern of the waveform is then evaluated mostly through the ratio of Systolic/Diastolic (S/D) and the resistance index, based on quantifying the end diastolic velocity relative to the peak systolic velocity. The presence of diastolic flow has a higher impact than S/D value, e.g. the absence or reversed end diastolic flow is associated with increased incident of perinatal morbidity and mortality and 80% and 46% risk of hypoxia and acidosis, respectively (Westergaard *et al.*, 2001; Karsdorp *et al.*, 1994; Nicolaides *et al.*, 1988). Using Doppler velocimetry is recommended in pregnancies complicated by hypertension and IUGR (Alfirevic & Neilson, 2009).

Thuring et al., have recently shown in a series of studies that objective analysis of the Doppler sound spectrum based on measures relevant to human auditory perception can provide a more sensitive indicator of changes in the umbilical artery blood flow than the traditional waveform analysis (Thuring *et al.*, 2015, 2014, 2013). The DUS auditory measures were defined by the frequency band where the spectral energy had dropped 15 dB from its maximum level. It was then evaluated before and after two doses of 12 mg Betamethasone, where the audio measure reflected the changes more sensitively than the traditional waveform-based pulsatility index (PI) (Thuring *et al.*, 2014).

7. Application of 1D-DUS in pathological conditions

The main application of 1D-DUS is FHR monitoring, which is common practice in developed countries, most often during or prior to labor. It is principally aimed at accurate identification of fetal metabolic acidemia and hypoxia with risk of deterioration, and to plan for expedited or immediate delivery (Nageotte, 2015). FHR monitoring is also used antenatally, particularly for progressive health monitoring of the IUGR fetus and to detect fetal health risks (Kouskouti *et al.*, 2017; Murray, 2017).

7.1. Perinatal hypoxia

Hypoxia and resulting ischemia (tissue damage) leading to HIE, occurs in one to three per 1000 live full-term births, 15–20% of which leads to neonatal death, with an additional 25% leading to severe and permanent neuropsychological consequences (Graham *et al.*, 2008; Lai & Yang, 2010; Vannucci & Perlman, 1997). Prenatal factors associated with increased risk of hypoxia include maternal smoking, severe preeclampsia and birth defects, while intrapartum factors include fetal tachycardia and late decelerations, maternal fever, chorioamnionitis and primary cesarean section (Ogunyemi *et al.*, 2016). CTG has been often used as a promising method for identification of perinatal hypoxia in clinical practice and research. As outlined in table 1, its availability is still limited in low-resource-settings. It is important to note that the studies reviewed in this section were conducted on different databases with various type and number of cases and over different stages ranging from several hours before and during labor. Without a unified common database, the performance of these methods cannot be appropriately compared.

The heart rate of a normally oxygenated fetus after 32 weeks of gestation has episodes of accelerations at least every 60–80 min (i.e. reactivity), associated with fetal movements. In case of progressive hypoxia, decelerations will occur before the absence of accelerations. Significant hypoxia results in a decrease in fetal cerebral blood flow, which changes the sympathetic and parasympathetic control of the fetal heart, leading to low FHR or a deceleration. However, most of the deceleration patterns are not associated with any significant hypoxia or acidosis (Nageotte, 2015). There are certain clinical markers including: late deceleration with minimum occurring more than 30 seconds after uterine contraction peak and delayed return to the baseline, variable decelerations, loss of variability and elevation of the FHR baseline, sustained bradycardia and the sinusoidal FHR traces (Nageotte, 2015). These characteristics categorize the tracings in category III associated with abnormal and indicative of hypoxic risk, according to the threetiered classification of FHR, introduced by the American College of Obstetricians and Gynecologists (ACOG), the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the Society for Maternal-Fetal Medicine (American College of Obstetricians and Gynecologists, 2010). In this classification category I is attributed to normal tracings not associated with fetal asphyxia, with a baseline FHR of 110–160, moderate variability, no late or variable decelerations. Category II includes bradycardia with variability, tachycardia, minimal variability, no variability with no recurrent decelerations, marked variability, absence of induced accelerations even after fetal stimulation, recurrent variable decelerations with minimal or moderate baseline variability, prolonged decelerations lasting more than two minutes, but less than ten minutes, recurrent late decelerations with moderate variability, variable decelerations with other characteristics such as slow return to baseline, overshooting the baseline, or shoulders (Hooper & Elsamadicy, 2014; American College of Obstetricians and Gynecologists, 2010).

Visual inspection of FHR patterns for manual detection of hypoxia is of low specificity and subject to intra- and inter-observer variability (Hamilton & Warrick, 2013). A recent study found algorithm-assisted FHR interpretation potentially improving the management of category II FHR for prevention of neonatal metabolic acidemia, however, only around half

of the infants born with metabolic acidemia could be potentially identified and have delivery expedited, even under ideal circumstances (Clark *et al.*, 2016). Automated methods have been proposed to detect hypoxia through its effect on the autonomic regulation which can be characterized by FHRV features (Chudáček *et al.*, 2011; Van Laar *et al.*, 2008; Dong *et al.*, 2014). These contributing features include temporal features and spectral power at different bands of FHRV (Georgoulas *et al.*, 2006b), statistical parameters such as standard deviation of RR-intervals (Boardman *et al.*, 2002), nonlinear features including Lempel-Ziv complexity (LZC), and Higuchi fractal dimension (HFD) (Chudáček *et al.*, 2011; Spilka *et al.*, 2012). It has been shown that SVM with temporal and spectral features can identify the neonatal risk of metabolic acidosis following fetal hypoxia, with specificity of 85% and sensitivity of 70% (Georgoulas *et al.*, 2006b).

The relationship between the uterine pressure (UP) and the FHR also provides crucial information to assess contraction-deceleration timing (Warrick *et al.*, 2012). A system-identification approach was also proposed which modeled the spectral power of FHRV and UP in an input-output system and the features from the model was used for classification by SVM, resulted in 50% sensitivity and 7.5% false positives (Warrick *et al.*, 2010). The non-stationary features have shown outperforming stationary spectral features (Dong *et al.*, 2014). Taking into account the nonstationarity of FHRV signals, wavelet analysis of FHRV (Salamalekis *et al.*, 2002; Georgoulas *et al.*, 2006a), EMD (Krupa *et al.*, 2009) and classification based on the normalized compression distance (NCD) related to Kolmogorov Complexity and mutual information have been also proposed to detect hypoxia (Santiago-Mozos *et al.*, 2013). The latter resulted in 92% sensitivity and 85% specificity (Santiago-Mozos *et al.*, 2013).

Other promising approaches were based on time-frequency measures (Dong *et al.*, 2014), including quadratic time-frequency distributions (TFDs), estimating the instantaneous frequency (IF) and corresponding instantaneous amplitude (IA) (Boashash *et al.*, 2013; Dong *et al.*, 2014). Dong et al., used IF and IA components of HRV signal components and matrix decomposition of the time-frequency distributions through singular value decomposition and nonnegative matrix factorization as features. Classification by SVM resulted in 93.3% and 98.3%, sensitivity and specificity, respectively (Dong *et al.*, 2014). However it is important to note that the aforementioned studies were conducted on different databases with various type and number of cases and over different stages ranging from several hours before and during labor. Without a unified common database, the performance of these methods cannot be appropriately compared.

Despite a lack of evidence on benefit of the antenatal CTG, it is often performed where the fetus is at-risk due to antepartum haemorrhage, preeclampsia, preterm premature rupture of the membranes and unexplained prematurity (Murray, 2017). There are certain pathological traces which are associated with significant fetal morbidity and necessitates further assessment of the umbilical and middle cerebral arteries, or the Ductus venosus if delivery is not to be undertaken (Murray, 2017). These traces show recurrent decelerations, either spontaneous or following mild uterine activity on an otherwise unreactive trace, a bradycardia, or, in the absence of the ability to test Doppler indices, the trace that is unreactive for over 120 min. (Murray, 2017).

As described in section 6.3.2, 1D-DUS can also provide more information beyond the FHR and its variability, such as systolic and diastolic time intervals, based on valve motion timings, which can be potentially useful in characterizing hypoxia. For example, PEP shortens with acute hypoxemia, while becoming prolonged during sustained and severe hypoxemia (Organ *et al.*, 1980; Mensah-Brown *et al.*, 2010). A study on lamb fetuses found a highly significant negative correlation between ICT and maximum first derivative of the left ventricular pressure waveform, under the hypoxemia condition (Satoh *et al.*, 2007).

7.2. Fetal development and IUGR

7.2.1. Gestational age estimation—Gestational Age (GA) estimation is essential for antenatal diagnosis, monitoring fetal growth and detecting IUGR, predicting the delivery date, management of pre-term and post-term pregnancies, and can ultimately prevent fetal and neonatal mortality (Bhutta *et al.*, 2014; Chauhan *et al.*, 2014; Alexander *et al.*, 1996; Taipale & Hiilesmaa, 2001). It has been traditionally estimated based on the Last Menstrual Period (LMP), which is the most affordable method but subject to human errors and biologically associated errors (Dietz *et al.*, 2007; Lynch & Zhang, 2007; Mahendru *et al.*, 2016). A more accurate and reliable growth assessment is through obstetric ultrasound imaging, which is clinically established as the gold standard (Papageorghiou *et al.*, 2014; Lynch & Zhang, 2007). Various physical measurements are used for this purpose including Biparietal Diameter (BPD) and Crown-Rump Length (CRL)(Papageorghiou *et al.*, 2014; Dietz *et al.*, 2007; Lynch & Zhang, 2007). However, they are affected by genetic variations, fetal sex and inherent variability in the fetal growth process, pathological conditions, unsuitable positioning of the fetus and the quality of the images, as well as operator and technical errors (Kullinger *et al.*, 2016; Lynch & Zhang, 2007; Callen, 2011; Hunter, 2009). Moreover its use is limited in low income countries due to the high cost of the equipment and a lack of trained healthcare professionals (McClure *et al.*, 2014; Wang *et al.*, 2011).

An alternative method of GA estimation is through FHR (Tetschke *et al.*, 2016; Hoyer *et al.*, 2013; Cha *et al.*, 2001), which can be measured with affordable devices and less prior skill (Stroux *et al.*, 2014; Tezuka *et al.*, 1998). Unlike ultrasound imaging techniques which are based on the physical development, FHR provides a marker for neuro-physiological development of the fetus, reflecting the ANS control of the cardiovascular system. Various linear, nonlinear time-domain, frequency-domain and complexity measures of FHRV were found related to fetal development (Tetschke *et al.*, 2016; Schneider *et al.*, 2006; Hoyer *et al.*, 2013; Van Leeuwen *et al.*, 2003; Hoyer *et al.*, 2009; Wallwitz *et al.*, 2012). Linear time domain FHRV measures such as SDNN (standard deviation from normal-to-normal beats) and RMSSD (root mean square of successive differences) and also complexity of the FHR increase with advancing gestation (Hoyer *et al.*, 2009). They indicate an increase in sympathetically-mediated control of the FHR with fetal maturation, improving predictability of stable FHR patterns (Hoyer *et al.*, 2009). Van Leeuwen et al. reported changes in the power spectra of FHRV with fetal development and emerging behavioral states during pregnancy (Van Leeuwen *et al.*, 2003). Schneider et al. introduces AIF (Autonomic Information Flow), which is a complexity measure of the information transfer in the underlying physiological system, such as the ANS and found it increasing with gestational age (Schneider *et al.*, 2006). However, the fetal maturation process is complex and non-

linear, particularly with developing fetal behavioral states (Schneider *et al.*, 2008; Tetschke *et al.*, 2016; Hoyer *et al.*, 2017). For example, active awake neuro-behavioral state stimulates sympathetic activation, increasing mean fHR, affecting sympatho-vagal balance and reducing FHR complexity (Schneider *et al.*, 2008; Hoyer *et al.*, 2017).

While in most of the earlier studies fetal development was modeled by linear characteristic curves using univariate regression models, recent works focus on complex multivariate and non-linear analysis of FHR which can better characterize the complex FHR patterns (Hoyer *et al.*, 2013; Tetschke *et al.*, 2016; Hoyer *et al.*, 2017). Hoyer et al. has proposed a Fetal Autonomic Brain Age Score (FABAS) which leverages the FHR patterns in a multivariate analysis using fMCG recordings (Hoyer *et al.*, 2013). This score was shown to reflect increasing fluctuation range, complexity, and pattern formation based on skewness, power spectral VLF (very low frequency 0.02–0.08 Hz)to LF (low frequency 0.08–0.2 Hz) ratio, generalized multiscale entropy and pNN5. Hoyer et al. also suggested the use of FABAS to detect growth-retarded fetuses (based on 11 IUGR cases). The fetuses were selected to be in active sleep state by three independent clinicians (Hoyer *et al.*, 2013), while this criteria is difficult to implement in practice. Following the development of FABAS, the authors recently proposed a random forest approach to model the fetal maturation for a more accurate prediction of GA than other linear, multivariate regression approaches (Tetschke *et al.*, 2016). These methods however use fMCG and fECG (not available in LMICs, see table 1) for accurate measurement of FHRV parameters since it requires high temporal resolution of FHR (to the beat-to-beat level) which may not be achieved by CTG. The relationship between CTG and fMCG or fECG-based FHRV is still an important issue to be investigated, although they are generally consistent when calculated over oneminute windows (Jezewski *et al.*, 2017). FHR patterns are also influenced by many other factors, arrhythmias, and even by the maternal psychological and physiological conditions, particularly in mid- and late-gestation (Marzbanrad *et al.*, 2015b; Ivanov *et al.*, 2009; Mantel *et al.*, 1991; Monk *et al.*, 2000).

As discussed in the previous section, 1D-DUS can provide additional information beyond the FHR, about the mechanical activity of the fetal heart. Fetal cardiac valve intervals derived from 1D-DUS were recently found as alternative measures of fetal development (Marzbanrad *et al.*, 2016, 2017). An automated method was proposed to assess the fetal physiological development using the component intervals between fetal cardiac valve timings and the Q-wave of fECG. These intervals were estimated automatically from 1D-DUS and noninvasive fECG and used to model the fetal development in a stepwise regression process. The estimated GA was validated against the gold standard gestational age identified by CRL (Marzbanrad *et al.*, 2017). The valve interval-based method was found to be comparable to CRL method (with average error of 2.7 weeks), outperforming the model based on FHRV, also less affected by arrhythmias such as tachycardia and bradycardia compared to FHRV (Marzbanrad *et al.*, 2017).

7.2.2. IUGR detection—One of the main implications of assessing fetal development is in early detection of IUGR. Several studies used FHR to detect IUGR, as summarized in table 4. As shown in the table, these studies were based on various (closed access) databases, which limited direct comparison of the techniques. One of the time domain FHR features

used for this purpose is short-term variability (STV) which has been found to be lower in IUGR cases (Schneider *et al.*, 2006; Fanelli *et al.*, 2013) and used in predicting the delivery time (Dawes *et al.*, 1992b; Ferrario *et al.*, 2009b). Other timedomain FHRV measures include mean and baseline FHR (Ferrario *et al.*, 2007, 2009a,b; Buscicchio *et al.*, 2010), Long-term Irregularity (LTI) (Ferrario *et al.*, 2007; Fanelli *et al.*, 2013; Ferrario *et al.*, 2009a) and Interval Index (II) (Ferrario *et al.*, 2007; Fanelli *et al.*, 2013; Ferrario *et al.*, 2009a,b). Using fMCG, Schneider et al. (Schneider *et al.*, 2006) found SDNN and RMSSD both significantly lower in IUGR population (39 cases) than controls (29 cases). The method is however expensive and not available in LMICs (table 1). Ferrario et al. also analyzed the frequency domain features of FHR based on CTG, but did not find them different for IUGR cases (Ferrario *et al.*, 2007, 2009a,b). However, Anastasiadis et al. used fMCG and found LF and HF to be discriminative (Anastasiadis *et al.*, 2003), and Schneider et al. reported significantly lower total power (*TP*) and *LF/HF* for IUGR cases compared to control (Schneider *et al.*, 2006).

Several studies used complexity measures such as entropy measures as potential markers for IUGR (Ferrario *et al.*, 2006, 2009b). Ferrario et al. used Multiscale Entropy (MSE) and LZC based on CTG recordings to differentiate IUGR cases from healthy small for gestational age fetuses (Ferrario *et al.*, 2006). They later found SampEn and Approximate Entropy (ApEn) not discriminative, using the same data (Ferrario *et al.*, 2007, 2009a). The maximum Lyapunov exponent (MLE) as an estimate of predictability of a dynamic system, was reported to be significantly lower for IUGR cases than control (Kikuchi *et al.*, 2006). The authors also showed Detrend Fluctuation Analysis (DFA) can be used to separate IUGR cases from normal controls (Kikuchi *et al.*, 2008). It was further supported by Ferrario et al., who found significantly higher DFA values of long-term scaling exponents for IUGR cases (Ferrario *et al.*, 2009b).

Several studies leveraged the use of a signal processing technique called Phase-Rectified Signal Averaging (PRSA), which characterize the cardiac acceleration and deceleration capacity (Bauer *et al.*, 2006). The Averaged Acceleration Capacity (AAC) and Average Deceleration Capacity (ADC) were used as IUGR markers (Lobmaier *et al.*, 2012; Huhn *et al.*, 2011; Graatsma *et al.*, 2012), while Fanelli et al., also computed the acceleration and deceleration phase-rectified slope (APRS and DPRS) compared to both AAC and ADC (Fanelli *et al.*, 2013). These studies reported at least one of the PRSA based markers useful in discriminating IUGR cases from control, while slightly outperforming STV. There was however a disagreement in details about which of the three markers were the best performing. Fanelli et al., found only APRS ($p = 1.12e-9$) and DPRS ($p = 9.57e-12$) to be discriminative while both AAC ($p = 0.2$) and ADC ($p = 0.06$) failed to distinguish IUGR from control (Fanelli *et al.*, 2013).

While the CTG-based studies on IUGR are limited by the use of small databases (as summarized in table 4), Stroux et al. recently used a dataset of CTG recordings from 1163 IUGR and 1163 controls for IUGR classification, which is the largest on its kind (Stroux *et al.*, 2017; Stroux & Clifford, 2016). Using STV, Long Term Variability (LTV) as features, they classified IUGR cases by LR (Stroux & Clifford, 2016). The achieved sensitivity (Se) and specificity (Sp) in a population of 23 to 34 weeks gestation were Se:63% and Sp:81%

for LTV, Se:63% and Sp:78% for STV and Se:67% and Sp:70% for AAC. It was different for the population with 35 to 42 weeks gestation, where Se:55% and Sp:70% for LTV, Se: 63% and 60% for STV, and Se:52% and Sp:74% for AAC were obtained, showing that the method was most effective when used before 34 gestation weeks (Stroux & Clifford, 2016). The author also proposed to use the behavioral state dependent CTG metrics for IUGR classification, considering that active and quiet sleep states are associated with high and low HRV, respectively (Stroux *et al.*, 2017; Stroux & Clifford, 2016). The included features were based on LTV and STV metrics, averaged over episodes with high or low variability, the total number and average duration of high and low variability episodes, the number of minutes in high or low variability, the onset of the first high variability episode, and the gestational age estimated at time of recording (Stroux *et al.*, 2017). A lower percentage of high variability (active sleep) was reported for IUGR compared to the normal population, in particular before 35 gestational weeks, possibly due to delayed or compromised sleep state. The FHR variability features were more discriminative earlier in gestation (before 35 weeks) for both male and female fetuses. The LTV in active sleep was superior to STV (AUC of 72% vs. 71%) and the most predictive measure was the number of minutes in high variation per hour (AUC of 75%). The model combining multiple features including gestational age, long-term and short-term variability in high variation episodes, the average duration in high variation and the number of high episodes in the trace improved the discriminative performance to 76% on the test set for 23–34 weeks of gestation (Stroux *et al.*, 2017).

Overall, FHRV markers with trace characteristics and additional surrogate information on sleep states can contribute to the detection of early-onset IUGR; while not that suitable for classifying late-onset IUGR (Stroux *et al.*, 2017; Stroux & Clifford, 2016). While this large scale study was limited to the population of UK residents largely consisting of caucasian subjects, and the data were collected in a hospital setting, it provided good evidence that IUGR screening is indeed possible with low-cost FHR monitoring systems, which could be applied in LMICs. Such an approach could be further improved, using signal quality assessment (discussed in section 5), improving the temporal resolution of the FHR derived from 1D-DUS and using additional features such as fetal cardiac valve intervals (Marzbanrad *et al.*, 2017).

7.3. Fetal arrhythmias and heart anomalies

Approximately 10 to 20% of referrals to fetal cardiologists are due to fetal arrhythmias (Wacker-Gussmann *et al.*, 2014). Although they affect a small percentage (0.6–2.0%) of pregnancies, certain types of arrhythmias account for a high morbidity and mortality, contributing to 3–10% of fetal demise, unexplained fetal hydrops, and prematurities (Crotti *et al.*, 2013; Wacker-Gussmann *et al.*, 2014). They are usually identified as presenting an abnormal fetal heart rate or rhythm during fetal Doppler-based auscultation at routine antenatal assessment (Hornberger & Sahn, 2007). For example, fetal bradycardia is characterized by sustained FHR <110 bpm over at least 10 minutes. Gestational age should also be considered and persistent heart rates below the third percentile of FHR for GA may be a marker for significant conduction disease (Wacker-Gussmann *et al.*, 2014; Hornberger & Sahn, 2007). Fetal tachycardia is defined as sustained FHR >160 bpm, with some types typically showing as high as 200 bpm. Fetal hydrops, premature delivery, and perinatal

morbidity and mortality can be associated with tachycardias (Wacker-Gussmann *et al.*, 2014). However a recent study showed relatively low inter-observer agreement in interpretation based on CTG (by six clinicians), as tachycardia and bradycardia were detected with agreement proportion of 0.56 and 0.49, respectively (Rei *et al.*, 2016).

Most lethal fetal cardiac rhythm disturbances are due to depolarization and repolarization abnormalities occurring with normal and regular rhythm (WackerGussmann *et al.*, 2014). Currently, diagnosis of arrhythmias relies on fetal echocardiographic modalities such as M-mode and pulsed Doppler (Strasburger & Wakai, 2010). However they cannot provide the cardiac time interval waveforms, such as P wave, QRS duration, QT interval. In some types of arrhythmias, such as blocked atrial bigeminy, atrial flutter (AF), and long QT syndrom, the mechanical rhythm does not accurately reflect the electrical rhythm (Wiggins *et al.*, 2013; Crotti *et al.*, 2013; Wacker-Gussmann *et al.*, 2014). In fact in some of the most serious electrophysiological abnormalities, the sinus rhythm is present with normal heart rate or rhythm, which cannot be detected without fMCG or fECG. Nevertheless, some arrhythmias still cause persistent FHR alteration from the normal range for gestation (Wacker-Gussmann *et al.*, 2014).

Recent advances in identification of fetal cardiac valve motion from 1D-DUS can provide additional markers beyond the FHR, to detect fetal cardiac anomalies (Marzbanrad *et al.*, 2014c; Marzbanrad, 2015). Particularly in conjunction with fECG, valve motion intervals can provide electromechanical features to assess the fetal heart function. One of these intervals is the myocardial performance index (MPI : ($ICT + IRT$)/VET) which can characterize the systolic and diastolic function of the fetal heart (Tei, 1995) (figure 5). Recently K-index (($ICT + IRT$)/VET) has been also proposed and shown as a better marker for various CHD types (Khandoker *et al.*, 2016, 2017). Evaluated for 8 cases with conduction pathway abnormalities, 6 structural anomalies, versus 57 control cases, the conventional MPI did not show any significant change from conductive CHD to structural CHD fetuses, while K-index showed significantly lower values for structural CHD cases compared to conductive CHD and normal cases (Khandoker *et al.*, 2017). However, conduction-based CHD cases were found to be within the confidence interval of normal K-index (Khandoker *et al.*, 2017). A pilot study on assessment of fetal physiological development using cardiac valve intervals demonstrated distinctive effect of certain structural and conductive cardiac abnormalities, on deviation of the estimated physiological age from the ultrasound imaging-based gestational age (Marzbanrad *et al.*, 2017). Overall, a combination of fECG with 1D-DUS, can provide a better characterization of conductive, mechanical or electromechanical abnormalities of the fetal heart. This requires further improvements in extraction of fECG morphological information and cardiac valve motion identification from these two modalities.

8. Summary of current challenges and future directions

This review concludes with five notable issues, and possible solutions to push the field forward and enable the full utilization of a low-cost signal that is routinely recorded during pregnancy, the world over.

- Fetal cardiac 1D-Doppler has been used for CTG in clinical practice for decades as an affordable technique for the assessment of fetal wellbeing. However, as discussed in section 4, devices have been limited to black-box proprietary products, without providing documentation of techniques, or any access to raw data for further development and improvement. Building a database open to researchers and providing open-source algorithms are particularly crucial, since the current application of 1D-DUS in electronic FHR has been found to be largely ineffective in reducing perinatal morbidity and mortality (Alfirevic *et al.*, 2013; Steer, 2008). Substantial public gold standard databases are required and should particularly include raw Doppler signals. Such databases would ideally also contain simultaneous fECG, fMCG or echocardiography recordings and multiple expert annotations on onset and offset of relevant features in the signals. Other clinical information such as gestational age during recording and at birth, neonatal outcome Apgar score, maternal health data (e.g. smoking status, blood pressure, medications, drug usage, family history, etc.), and demographics would also be helpful for developing accurate and generalizable clinical decision support systems. Such databases are required for development and comparison of different signal processing techniques for extraction of fetal vital parameters and classification of abnormalities.
- Considering the noisy and non-stationary nature of 1D-DUS signal, it is essential to evaluate the signal quality before extraction of fetal vital parameters. As discussed in section 5, development of real-time signal quality feedback might also assist the operator with acquisition of reliable data through a real-time feedback system. This has not been sufficiently studied until recently (Marzbanrad *et al.*, 2015a; Stroux & Clifford, 2016; Valderrama *et al.*, 2017) and requires further development of signal quality metrics. It not only requires raw Doppler signals, but also quality annotation or benchmarking with another approved modality.
- Most of the current methods for estimation of FHR from 1D-DUS are based on conventional autocorrelation techniques (see section 6.2.1), which only provide averaged FHR with limited accuracy and temporal resolution. Moreover, this approach is not well documented, being the main approach in proprietary systems, therefore inhibiting reproducibility. As detailed in section 6.2.2, recent advances have shown that FHR estimation from 1D-DUS can approximate the beat-to-beat resolution observed in the fECG (Jezewski *et al.*, 2017). Further development of signal processing approaches is likely to improve the temporal resolution of FHR analysis, enabling measurement of detailed fetal HRV parameters and assessment of sympathetic and parasympathetic function and development of the fetal ANS.
- Simultaneous acquisition of 1D-DUS and abdominal ECG recordings has shown to be promising for enabling more accurate extraction of fECG from the abdominal mixture (Sato *et al.*, 2007). Furthermore, additional features beyond the FHR can be extracted from 1D-DUS, such as fetal cardiac valve opening and closing (Marzbanrad *et al.*, 2013a, 2014a), as reviewed in section 6.3.2. Recent

studies showed the feasibility of estimating fetal cardiac valve intervals and their effectiveness in assessing the fetal development and wellbeing (Marzbanrad *et al.*, 2017; Khandoker *et al.*, 2017). This could be further pursued, using simultaneous fetal echocardiography and precise expert annotation of valve motion events. Combining Doppler and fECG modalities also enables assessment of electrical, mechanical and electromechanical activity of the fetal heart, to better characterize structural and conductive abnormalities, as discussed in section 7.3. Considering the challenges in CTG interpretation and relatively low inter-observer agreement (Kwon & Park, 2016), developing automated decision support systems is also recommended for future developments. Fusion of multiple modalities, and extraction and integration of information should be explored to develop better predictive markers.

- Finally, despite the extensive use of 1D-DUS in CTG, its characteristics and patterns have not been well studied. Future research can focus on modeling the 1DDUS signals, to better explain variable signal patterns. The models should ideally simulate possible fetal orientation with respect to the ultrasound probe, fetal movement and maturation process, as well as pathological conditions. Modeling and simulation of 1D-DUS signals can also facilitate development and improvement of extracting fetal cardiac parameters such as FHR and valve motion intervals.

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References

Alexander Greg R, Himes John H, Kaufman Rajni B, Mor Joanne, & Michael Kogan. 1996 A United States national reference for fetal growth. Obstetrics & Gynecology, 87(2), 163–168. [PubMed: 8559516]

Alfirevic Z, & Neilson JP. 2009 Doppler ultrasound for fetal assessment in high risk pregnancies (Review).

Alfirevic Zarko, Devane Declan, & Gyte Gillian ML. 2013 Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. The Cochrane Library.

American College of Obstetricians and Gynecologists. 2010 Practice bulletin no. 116: Management of intrapartum fetal heart rate tracings. Obstetrics and gynecology, 116(5), 1232. [PubMed: 20966730]

Anastasiadis PG, Kotini A, Anninos P, Adamopoulos A, Sigalas J, & Koutlaki N 2003 Chaotic and periodic analysis of fetal magnetocardiogram recordings in growth restriction. Prenatal diagnosis, 23(5), 405–409. [PubMed: 12749039]

Archer Nick, & Manning Nicky. 2009 OSH Fetal Cardiology.

Arora Puneeta Kaur, & Bhatnagar Beena. 2015 Vibroacoustic stimulation test as adjunct to non-stress test for antepartum fetal well-being. Comparision of Vibroacoustic Stimulation Test & Non Stress Test in High Risk Pregnancies.

Baker L, Beaves M, Trickey D, & Wallace E 2009 Fetal surveillance: a practical guide. Melbourne: RANZCOG.

Bauer Axel, Kantelhardt Jan W, Bunde Armin, Barthel Petra, Schneider Raphael, Malik Marek, & Schmidt Georg. 2006 Phase-rectified signal averaging detects quasi-periodicities in non-stationary data. Physica A: Statistical Mechanics and its Applications, 364, 423–434.

Behar Joachim, Andreotti Fernando, Zaunseder Sebastian, Oster Julien, & Clifford Gari D. 2016 A practical guide to non-invasive foetal electrocardiogram extraction and analysis. Physiological measurement, 37(5), R1. [PubMed: 27067431]

Bhutta Zulfiqar A, Das Jai K, Bahl Rajiv, Lawn Joy E, Salam Rehana A, Paul Vinod K, Sankar , M Jeeva, Blencowe Hannah, Rizvi Arjumand, Chou Victoria B, et al. 2014 Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? The Lancet, 384(9940), 347–370.

Blackburn Susan. 2013 Maternal, fetal, & neonatal physiology: a clinical perspective. 4th edn. Elsevier.

Boardman Anita, Schlindwein Fernando S, Thakor Nitish V, Kimura Tetsu, & Geocadin RG. 2002 Detection of asphyxia using heart rate variability. Medical and biological engineering and computing, 40(6), 618–624. [PubMed: 12507311]

Boashash Boualem, Azemi Ghasem, & O'Toole John M. 2013 Time-frequency processing of nonstationary signals: Advanced TFD design to aid diagnosis with highlights from medical applications. IEEE Signal Processing Magazine, 30(6), 108–119.

Bobby Paul, et al. 2003 Multiple assessment techniques evaluate antepartum fetal risks. Pediatric annals, 32(9), 609. [PubMed: 14508894]

Bruneau Benoit G, & Srivastava Deepak. 2014 Congenital Heart Disease. Circulation research, 114(4), 598–599. [PubMed: 24526674]

Bukowski Radek. 2010 Stillbirth and fetal growth restriction. Clinical obstetrics and gynecology, 53(3), 673–680. [PubMed: 20661051]

Buscicchio Giorgia, Gentilucci Lucia, & Tranquilli Andrea L. 2010 Computerized analysis of fetal heart rate in pregnancies complicated by gestational diabetes mellitus, gestational hypertension, intrauterine growth restriction and premature rupture of membranes. The Journal of Maternal-Fetal & Neonatal Medicine, 23(4), 335–337. [PubMed: 20121394]

Callen Peter W. 2011 Ultrasonography in obstetrics and gynecology. Elsevier Health Sciences.

Caserta Luigi, Ruggeri Zaira, D'Emidio Laura, Coco Claudio, Cignini Pietro, Girgenti Alessandra, Mangiafico Lucia, & Giorlandino Claudio. 2008 Two-dimensional fetal echocardiography: where we are. Journal of prenatal medicine, 2(3), 31. [PubMed: 22439025]

Cha Kyung Joon, Park Young Sun, Ryu Je Seon, Yoon Sang Soon, Hwang Jung Hae, Chung Sung Ro, Moon Hyung, & Park Moon Il. 2001 Development of Algorithm for Estimation of Gestational Age using each Variable of Fetal Heart Rate. Korean Journal of Obstetrics and Gynecology, 44(11), 2016–2024.

Chauhan Suneet P, Beydoun Hind, Chang Eugene, Sandlin Adam T, Dahlke Josh D, Elena Igwe, Magann Everett F, Anderson Kristi R, Abuhamad Alfred Z, & Ananth Cande V. 2014 Prenatal detection of fetal growth restriction in newborns classified as small for gestational age: correlates and risk of neonatal morbidity. American journal of perinatology, 31(03), 187–194. [PubMed: 23592315]

Chudáček V, Spilka Jirí, Jankuu ,P, Kouckỳ Michal, Lhotská Lenka, & Michal Huptych. 2011 Automatic evaluation of intrapartum fetal heart rate recordings: a comprehensive analysis of useful features. Physiological Measurement, 32(8), 1347. [PubMed: 21765204]

Chudáček V, Spilka Jirí, Burvsa Miroslav, Jankuu P, Hruban L, Huptych Michal, & Lhotská Lenka. 2014 Open access intrapartum CTG database. BMC pregnancy and childbirth, 14(1), 16. [PubMed: 24418387]

Clark Steven L, Hamilton Emily F, Garite Thomas J, Timmins Audra, Warrick Philip A, & Smith Samuel. 2016 The limits of electronic fetal heart rate monitoring in the prevention of neonatal metabolic acidemia. American Journal of Obstetrics and Gynecology.

Clifford Gari D, Silva Ikaro, Behar Joachim, & Moody George B. 2014 Non-invasive fetal ECG analysis. Physiological measurement, 35(8), 1521. [PubMed: 25071093]

Creasy RK, & Resnik R 2008 Chapter 34: Intrauterine growth restriction Maternal-fetal medicine: principles and practice (6th ed.), Saunders, Philadelphia, 635–650.

Crotti Lia, Tester David J, White Wendy M, Bartos Daniel C, Roberto Insolia, Besana Alessandra, Kunic Jennifer D, Will Melissa L, Velasco Ellyn J, Bair Jennifer J, et al. 2013 Long QT syndrome–associated mutations in intrauterine fetal death. Jama, 309(14), 1473–1482. [PubMed: 23571586]

Cruz-Martínez R, Figueras F, Bennasar M, García-Posadas R, Crispi F, HernándezAndrade E, & Gratacós E 2012 Normal reference ranges from 11 to 41 weeks? gestation of fetal left modified myocardial performance index by conventional Doppler with the use of stringent criteria for delimitation of the time periods. Fetal diagnosis and therapy, 32(1–2), 79–86. [PubMed: 22759646]

Dawes GS, Lobb M, Moulden M, Redman CWG, & Wheeler T 1992a Antenatal cardiotocogram quality and interpretation using computers. BJOG: An International Journal of Obstetrics & Gynaecology, 99(10), 791–797.

Dawes GS, Moulden M, & Redman CWG. 1992b Short-term fetal heart rate variation, decelerations, and umbilical flow velocity waveforms before labor. Obstetrics & Gynecology, 80(4), 673–678. [PubMed: 1407893]

Devoe Lawrence D. 2008 Antenatal fetal assessment: Contraction stress test, nonstress test, vibroacoustic stimulation, amniotic fluid volume, biophysical profile, and modified biophysical profile- An overview. Pages 247–252 of: Seminars in perinatology, vol. 32 Elsevier.

Dietz Patricia M, England Lucinda J, Callaghan William M, Pearl Michelle, Wier Megan L, & Kharrazi Martin. 2007 A comparison of LMP-based and ultrasoundbased estimates of gestational age using linked California livebirth and prenatal screening records. Paediatric and Perinatal Epidemiology, 21(s2), 62–71. [PubMed: 17803619]

Dong Shiying, Boashash Boualem, Azemi Ghasem, Lingwood Barbara E, & Colditz Paul B. 2014 Automated detection of perinatal hypoxia using time–frequency-based heart rate variability features. Medical & biological engineering & computing, 52(2), 183–191. [PubMed: 24272142]

Druzin, Maurice L, Fox A, Kogut E, Carlson C, et al. 1985 The relationship of the nonstress test to gestational age. Am J Obstet Gynecol, 153(4), 386–9. [PubMed: 3901768]

Fanelli Andrea, Magenes Giovanni, Campanile Marta, & Signorini Maria G. 2013 Quantitative assessment of fetal well-being through CTG recordings: a new parameter based on phase-rectified signal average. IEEE Journal of Biomedical and Health Informatics, 17(5), 959–966. [PubMed: 25055375]

Feinstein Nancy, Torgersen Keiko L, & Atterbury Jana. 1993 Fetal Heart Monitoring: Principles and Practices. Kendall Hunt.

Ferencz Charlotte, Rubin Judith D, Mccarter Robert J, Brenner Joel I, Neill Catherine A, Perry Lowell W, Hepner Seymour I, & Downing John W. 1985 Congenital Heart Disease: Prevalence at Livebirth the Baltimore-Washington Infant Study. American Journal of Epidemiology, 121(1), 31–36. [PubMed: 3964990]

Ferrario M, Signorini MG, Magenes G, et al. 2007 Comparison between fetal heart rate standard parameters and complexity indexes for the identification of severe intrauterine growth restriction. Methods of information in medicine, 46(2), 186–190. [PubMed: 17347753]

Ferrario Manuela, Signorini Maria G, & Magenes Giovanni. 2006 New indexes from the Fetal Heart Rate analysis for the identification of severe intra uterine growth restricted fetuses. Pages 1458–1461 of: Engineering in Medicine and Biology Society, 2006. EMBS'06. 28th Annual International Conference of the IEEE IEEE.

Ferrario Manuela, Signorini Maria G, & Magenes Giovanni. 2009a Complexity analysis of the fetal heart rate variability: early identification of severe intrauterine growth-restricted fetuses. Medical & biological engineering & computing, 47(9), 911–919. [PubMed: 19526262]

Ferrario Manuela, Magenes Giovanni, Campanile Marta, Carbone Imma F, Di Lieto Andrea, & Signorini Maria G. 2009b Multiparameter analysis of heart rate variability signal for the investigation of high risk fetuses. Pages 4662–4665 of: Engineering in Medicine and Biology Society, 2009. EMBC 2009. Annual International Conference of the IEEE IEEE.

Freeman Roger K, Garite Thomas J, Nageotte Michael P, & Miller Lisa A. 2012 Fetal heart rate monitoring. Lippincott Williams & Wilkins.

Ganapathiraju Aravind, Hamaker Jonathan, & Picone Joseph. 2000 Hybrid SVM/HMM architectures for speech recognition Pages 504–507 of: INTERSPEECH. Citeseer.

Gardosi Jason, Madurasinghe Vichithranie, Williams Mandy, Malik Asad, & Francis André. 2013 Maternal and fetal risk factors for stillbirth: population based study. Bmj, 346, f108. [PubMed: 23349424]

Gembruch Ulrich, Shi Chun-yan, & Smrcek Jan M. 2000 Biometry of the fetal heart between 10 and 17 weeks of gestation. Fetal diagnosis and therapy, 15(1), 20–31. [PubMed: 10705210]

Georgieva Antoniya, Redman Christopher WG, & Papageorghiou Aris T. 2017 Computerized data-driven interpretation of the intrapartum cardiotocogram: a cohort study. Acta obstetricia et gynecologica Scandinavica, 96(7), 883–891. [PubMed: 28369712]

Georgoulas George, Stylios Chrysostomos, & Groumpos Peter. 2006a Feature extraction and classification of fetal heart rate using wavelet analysis and support vector machines. International Journal on Artificial Intelligence Tools, 15(03), 411–432.

Georgoulas George, Stylios D, & Groumpos P. 2006b Predicting the risk of metabolic acidosis for newborns based on fetal heart rate signal classification using support vector machines. IEEE Transactions on biomedical engineering, 53(5), 875–884. [PubMed: 16686410]

Gon calves, Hernâni, Bernardes João, & Ayres-de Campos, Diogo. 2013 Gender-specific heart rate dynamics in severe intrauterine growth-restricted fetuses. Early human development, 89(6), 431–437. [PubMed: 23369693]

Graatsma EM, Mulder EJH, Vasak B, Lobmaier SM, Pildner Von Steinburg S, Schneider KTM, Schmidt G, & Visser GHA. 2012 Average acceleration and deceleration capacity of fetal heart rate in normal pregnancy and in pregnancies complicated by fetal growth restriction. The Journal of Maternal-Fetal & Neonatal Medicine, 25(12), 2517–2522. [PubMed: 22725720]

Graham Ernest M, Ruis Kristy A, Hartman Adam L, Northington Frances J, & Fox Harold E. 2008 A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. American journal of obstetrics and gynecology, 199(6), 587–595. [PubMed: 19084096]

Grivell Rosalie M, Alfirevic Zarko, Gyte Gillian ML, & Devane Declan. 2010 Antenatal cardiotocography for fetal assessment. The Cochrane Library.

Hameed Afshan B, & Sklansky Mark S. 2007 Pregnancy: maternal and fetal heart disease. Current problems in cardiology, 32(8), 419–494. [PubMed: 17643825]

Hamilton Emily F, & Warrick Philip A. 2013 New perspectives in electronic fetal surveillance. Journal of perinatal medicine, 41(1), 83–92. [PubMed: 23565511]

Hassan Wassim A, Brockelsby Jeremy, Alberry Medhat, Fanelli Tiziana, Wladimiroff Juriy, & Lees Christoph C. 2013 Cardiac function in early onset small for gestational age and growth restricted fetuses. European Journal of Obstetrics & Gynecology and Reproductive Biology, 171(2), 262–265. [PubMed: 24176539]

Hill Christopher Rowland, Bamber Jeff C, & Ter Haar GR. 2004 Physical principles of medical ultrasonics. The Journal of the Acoustical Society of America, 116(5), 2707–2707.

Homma Shunichi, & Sacco Ralph L. 2005 Patent foramen ovale and stroke. Circulation, 112(7), 1063–1072. [PubMed: 16103257]

Hooper Dwight E, & Elsamadicy Emad. 2014 Review of Category I, II, and III Fetal Heart Rate Classifications. Journal of Family Medicine Obstetrics, 8(1).

Hornberger Lisa K, & Sahn David J. 2007 Rhythm abnormalities of the fetus. Heart, 93(10), 1294–1300. [PubMed: 17890709]

Hoyer Dirk, Heinicke Esther, Jaekel Susann, Tetschke Florian, Paolo Dania Di Pietro, Haueisen Jens, Schleußner Ekkehard, & Schneider Uwe. 2009 Indices of fetal development derived from heart rate patterns. Early Human Development, 85(6), 379–386. [PubMed: 19188032]

Hoyer Dirk, Tetschke Florian, Jaekel Susan, Nowack Samuel, Witte Otto W Schleußner Ekkehard, & Schneider Uwe. 2013 Fetal functional brain age assessed from universal developmental indices obtained from neuro-vegetative activity patterns. PloS One, 8(9), e74431. [PubMed: 24058564]

Hoyer Dirk, Żebrowski Jan, Cysarz Dirk, Gon calves, Hernâni Pytlik, Adelina Amorim-Costa, Célia Bernardes, João Ayres-de Campos, Diogo Witte, Otto W, Schleußner Ekkehard, et al. 2017

Monitoring fetal maturationobjectives, techniques and indices of autonomic function. Physiological Measurement, 38(5), R61. [PubMed: 28186000]

Hua Xiao, Kaiqing Luo, & Zhenxi Zhang. 2005 A new algorithm for detecting fetal heart rate using ultrasound Doppler signals. Ultrasonics, 43(6), 399–403. [PubMed: 15823314]

Huhn EA, Lobmaier S, Fischer T, Schneider R, Bauer A, Schneider KT, & Schmidt G 2011 New computerized fetal heart rate analysis for surveillance of intrauterine growth restriction. Prenatal diagnosis, 31(5), 509–514. [PubMed: 21360555]

Hunter Linda A. 2009 Issues in pregnancy dating: Revisiting the evidence. Journal of Midwifery & Womens Health, 54(3), 184–190.

Ivanov Plamen Ch, Ma Qianli DY, & Bartsch Ronny P. 2009 Maternal–fetal heartbeat phase synchronization. Proceedings of the National Academy of Sciences, 106(33), 13641–13642.

Jezewski J, Wrobel J, Horoba K, Gacek A, & Sikora J 2002 Fetal heart rate variability: clinical experts versus computerized system interpretation. Pages 1617–1618 of: Engineering in Medicine and Biology, 2002. 24th Annual Conference and the Annual Fall Meeting of the Biomedical Engineering Society EMBS/BMES Conference, 2002. Proceedings of the Second Joint, vol. 2. IEEE.

Jezewski Janusz, Kupka Tomasz, & Horoba Krzysztof. 2008 Extraction of fetal heartrate signal as the time event series from evenly sampled data acquired using Doppler ultrasound technique. IEEE Transactions on Biomedical Engineering, 55(2), 805–810. [PubMed: 18270022]

Jezewski Janusz, Roj Dawid, Wrobel Janusz, & Horoba Krzysztof. 2011 A novel technique for fetal heart rate estimation from Doppler ultrasound signal. Biomedical engineering online, 10(1), 92. [PubMed: 21999764]

Jezewski Janusz, Wrobel Janusz, Matonia Adam, Horoba Krzysztof, Martinek Radek, Kupka Tomasz, & Jezewski Michal. 2017 Is abdominal fetal electrocardiography an alternative to Doppler ultrasound for FHR variability evaluation? Frontiers in physiology, 8.

Johnson TR, Jordan Elizabeth T, & Paine Lisa L. 1990 Doppler recordings of fetal movement: II. Comparison with maternal perception. Obstetrics and gynecology, 76(1), 42–43. [PubMed: 2193268]

Karsdorp VHM, Van Vugt JMG, Van Geijn HP, Kostense PJ, Arduim D, Montenegro N, & Todros T 1994 Clinical significance of absent or reversed end diastolic velocity waveforms in umbilical artery. The Lancet, 344(8938), 1664–1668.

Khandoker Ahsan H, Kimura Yoshitaka, Ito Takuya, Sato Naoaki, Okamura Kunihiro, & Palaniswami Marimuthu. 2009 Antepartum non-invasive evaluation of opening and closing timings of the cardiac valves in fetal cardiac cycle. Medical & Biological Engineering & Computing, 47(10), 1075–1082. [PubMed: 19711109]

Khandoker Ahsan H, Marzbanrad F, Kimura Y, Al Nuaimi Saeed, & Palaniswami M. 2016 Assessing the development of fetal myocardial function by a novel Doppler myocardial performance index. Pages 3753–3756 of: Engineering in Medicine and Biology Society (EMBC), 2016 IEEE 38th Annual International Conference of the IEEE.

Khandoker Ahsan H, Al-Angari Haitham M, Marzbanrad F, & Kimura Y. 2017 Investigating fetal myocardial function in heart anomalies by Doppler myocardial performance indices. Pages 2197–2200 of: Engineering in Medicine and Biology Society (EMBC), 2017 39th Annual International Conference of the IEEE IEEE.

Kikuchi Akihiko, Shimizu Toshiyuki, Hayashi Akiko, Horikoshi Tsuguhiro, Unno Nobuya, Shiro Kozuma, & Taketani Yuji. 2006 Nonlinear analyses of heart rate variability in normal and growth-restricted fetuses. Early human development, 82(4), 217–226. [PubMed: 16242867]

Kikuchi Akihiko, Unno Nobuya, Kozuma Shiro, & Taketani Yuji. 2008 Detrended fluctuation analysis of heart rate variability in normal and growth-restricted fetuses. Gynecologic and obstetric investigation, 65(2), 116–122. [PubMed: 17917463]

Kimura Yoshitaka, Sato Naoaki, Sugawara Junichi, Velayo Clarissa, oshiai H Teturo, Nagase Satoru, Ito Takuya, Onuma Yukari, Katsumata Asami, Okamura Kunihiro, et al. 2012 Recent Advances in Fetal Electrocardiography. Open Medical Devices Journal, 4, 7–12.

Koga Tsuyoshi, Athayde Neil, & Trudinger Brian. 2001 The fetal cardiac isovolumetric contraction time in normal pregnancy and in pregnancy with placental vascular disease: the first clinical report

using a new ultrasound technique. British Journal of Obstetrics and Gynaecology, 108(2), 179–185. [PubMed: 11236118]

Koga Tsuyoshi, Athayde Neil, & Trudinger Brian. 2003 A new ultrasound technique to measure the isovolumetric contraction time as an index of cardiac contractility: fetal lamb validation. Journal of the Society for Gynecologic Investigation, 10(4), 194–199. [PubMed: 12759147]

Kouskouti Christina, Regner Kerstin, Knabl Julia, & Kainer Franz. 2017 Cardiotocography and the evolution into computerised cardiotocography in the management of intrauterine growth restriction. Archives of gynecology and obstetrics, 1–6.

Kovács Ferenc, Horváth Csaba, Balogh Ádám T, & Hosszú Gábor. 2011 Fetal phonocardiography-Past and future possibilities. Computer methods and programs in biomedicine, 104(1), 19–25. [PubMed: 21146247]

Kret TOMASZ, & Kałużyński Krzysztof. 2006 The fetal heart rate estimation based on continuous ultrasonic Doppler data. Biocybernetics and Biomedical Engineering, 26, 49–56.

Krupa BN, Ali , MA Mohd, & Zahedi E. 2009 The application of empirical mode decomposition for the enhancement of cardiotocograph signals. Physiological measurement, 30(8), 729. [PubMed: 19550027]

Kullinger Merit, Haglund Bengt, Kieler Helle, & Skalkidou Alkistis. 2016 Effects of ultrasound pregnancy dating on neonatal morbidity in late preterm and early term male infants: a register-based cohort study. BMC Pregnancy and Childbirth, 16(1), 335. [PubMed: 27799069]

Kupka T, Jezewski J, Matonia A, Horoba K, & Wrobel J 2004 Timing events in Doppler ultrasound signal of fetal heart activity. Pages 337–340 of: Engineering in Medicine and Biology Society, 2004. IEMBS'04. 26th Annual International Conference of the IEEE, vol. 1. IEEE.

Kwon Ji Young, & Park In Yang. 2016 Fetal heart rate monitoring: from Doppler to computerized analysis. Obstetrics & gynecology science, 59(2), 79–84. [PubMed: 27004196]

Lai Ming-Chi, & Yang San-Nan. 2010 Perinatal hypoxic-ischemic encephalopathy. BioMed Research International, 2011.

Lavin Justin P, Jr, Miodovnik , Menachem, & Barden Tom P. 1984 Relationship of nonstress test reactivity and gestational age. Obstetrics & Gynecology, 63(3), 338–344. [PubMed: 6700856]

Lawson GW, Belcher R, Dawes GS, & Redman CWG. 1983 A comparison of ultrasound (with autocorrelation) and direct electrocardiogram fetal heart rate detector systems. American journal of obstetrics and gynecology, 147(6), 721–722. [PubMed: 6638120]

Lee Chang Su, Masek Martin, Lam Chiou Peng, & Tan Keng T. 2009a Advances in fetal heart rate monitoring using smart phones. Pages 735–740 of: Communications and Information Technology, 2009. ISCIT 2009. 9th International Symposium on IEEE.

Lee Chang Su, Masek Martin, Lam Chiou Peng, & Tan Keng T. 2009b Towards higher accuracy and better noise-tolerance for fetal heart rate monitoring using Doppler ultrasound. Pages 1–6 of: TENCON 2009–2009 IEEE Region 10 Conference. IEEE.

Lewis Michael J. 2003 Review of electromagnetic source investigations of the fetal heart. Medical engineering & physics, 25(10), 801–810. [PubMed: 14630467]

Lobmaier SM, Huhn EA, Pildner Von Steinburg S, Müller A, Schuster T, Ortiz JU, Schmidt G, & Schneider KT. 2012 Phase-rectified signal averaging as a new method for surveillance of growth restricted fetuses. The Journal of Maternal-Fetal & Neonatal Medicine, 25(12), 2523–2528. [PubMed: 22630786]

Lynch Courtney D, & Zhang, 6 2007 The research implications of the selection of a gestational age estimation method. Paediatric and perinatal epidemiology, 21(s2), 86–96. [PubMed: 17803622]

Maeda K 2013 Quantitative Analysis of Fetal Actocardiogram: Update. J Health Med Informat, 4(140), 2.

Maeda Kazuo. 1990 9 Computerized analysis of cardiotocograms and fetal movements. Bailliere's clinical obstetrics and gynaecology, 4(4), 797–813.

Magenes G, Signorini MG, & Sassi R 2001 Automatic diagnosis of fetal heart rate: comparison of different methodological approaches. Pages 1604–1607 of: Engineering in Medicine and Biology Society, 2001. Proceedings of the 23rd annual international conference of the IEEE, vol. 2. IEEE.

Magenes G, Bellazzi R, Fanelli A, & Signorini MG. 2014 Multivariate analysis based on linear and non-linear FHR parameters for the identification of IUGR fetuses. Pages 1868–1871 of:

Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE IEEE.

Mahajan Aditi, Henry Amanda, Meriki Neama, Hernandez-Andrade Edgar, Fatima Crispi, Linda Wu, & Welsh Alec W. 2015 The (Pulsed-Wave) Doppler fetal myocardial performance index: technical challenges, clinical applications and future research. Fetal diagnosis and therapy, 38(1), 1–13. [PubMed: 25926030]

Mahendru Amita A, Wilhelm-Benartzi Charlotte S, Wilkinson Ian B, McEniery Carmel M, Johnson Sarah, & Lees Christoph. 2016 Gestational length assignment based on last menstrual period, first trimester crown-rump length, ovulation, and implantation timing. Archives of Gynecology and Obstetrics, 294(4), 867–876. [PubMed: 27469987]

Malcus Peter. 2004 Antenatal fetal surveillance. Current Opinion in Obstetrics and Gynecology, 16(2), 123–128. [PubMed: 15017340]

Malhotra Narendra, Malhotra Jaideep, Mathur Vanaj, Tomar Sakshi, Singh Kuldeep, Rao JP, Gupta Samiksha, & Malhotra Neharika. 2014 Antenatal Assessment of Fetal Well-being. Ultrasound in Obstetrics & Gynecology, 227.

Mantel Rob, van Geijn Herman P, Ververs Inge AP, & Copray Frans JA. 1991 Automated analysis of near-term antepartum fetal heart rate in relation to fetal behavioral states: The Sonicaid System 5000. American Journal of Obstetrics and Gynecology, 165(1), 57–65. [PubMed: 1853916]

Martinez Boris, Ixen Enma Coyote, Hall-Clifford Rachel, Juarez Michel, Miller Ann C, Francis Aaron, Valderrama Camilo Ernesto, Stroux Lisa, Clifford Gari D, & Rohloff Peter. 2018 mHealth intervention to improve the continuum of maternal and perinatal care in rural Guatemala: a pragmatic, randomized controlled feasibility trial. Reproductive Health, In Press.

Marzbanrad F, Kimura Y, Funamoto K, Oshio S, Endo M, Sato N, Palaniswami M, & Khandoker AH 2014a Model-Based Estimation of Aortic and Mitral Valves Opening and Closing Timings in Developing Human Fetuses. Biomedical and Health Informatics, IEEE Journal of, 20(1), 240–248.

Marzbanrad F, Khandoker AH, Endo M, Kimura Y, & Palaniswami M 2014b (8). A multi-dimensional Hidden Markov Model approach to automated identification of fetal cardiac valve motion. Pages 1885–1888 of: Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE.

Marzbanrad Faezeh. 2015 Modeling fetal cardiac valve intervals and fetal-maternal interactions. Ph.D. thesis, The University of Melbourne.

Marzbanrad Faezeh, Kimura Yuichi, Funamoto Kiyoe, Sugibayashi Rika, Endo Miyuki, Ito Takao, Palaniswami Marimuthu, & Khandoker Ahsan H. 2013a Automated estimation of fetal cardiac timing events from Doppler ultrasound signal using hybrid models. Biomedical and Health Informatics, IEEE Journal of, 18(4), 1169–1177.

Marzbanrad Faezeh, Khandoker Ahsan H, et al. 2013b Automated Identification of fetal cardiac valve timings. Pages 3893–3896 of: Engineering in Medicine and Biology Society (EMBC), 2013 35th Annual International Conference of the IEEE IEEE.

Marzbanrad Faezeh, Kimura Yoshitaka, Palaniswami Marimuthu, & Khandoker Ahsan H. 2014c Application of automated fetal valve motion identification to investigate fetal heart anomalies. Pages 243–246 of: Healthcare Innovation Conference (HIC) IEEE.

Marzbanrad Faezeh, Kimura Yoshitaka, Funamoto Kiyoe, Sugibayashi Rika, Endo Miyuki, Ito Takuya, Palaniswami Marimuthu, & Khandoker Ahsan H. 2014d Automated estimation of fetal cardiac timing events from Doppler ultrasound signal using hybrid models. Biomedical and Health Informatics, IEEE Journal of, 18(4), 1169–1177.

Marzbanrad Faezeh, Kimura Yoshitaka, Endo Miyuki, Palaniswami Marimuthu, & Khandoker Ahsan H. 2014e Automated Measurement of Fetal Isovolumic Contraction Time from Doppler Ultrasound Signals without using Fetal Electrocardiography. Pages 485–488 of: Computing in Cardiology Conference (CinC), 2014 IEEE.

Marzbanrad Faezeh, Kimura Yoshitaka, Endo Miyuki, Palaniswami Marimuthu, & Khandoker Ahsan H. 2015a Classification of Doppler Ultrasound Signal Quality for the Application of Fetal Valve Motion Identification. Computing in Cardiology Conference (CinC), 2015, 42, 365–368.

Marzbanrad Faezeh, Kimura Yoshitaka, Palaniswami Marimuthu, & Khandoker Ahsan H. 2015b Quantifying the Interactions between Maternal and Fetal Heart Rates by Transfer Entropy. PloS One, 10(12), e0145672. [PubMed: 26701122]

Marzbanrad Faezeh, Khandoker Ahsan, Kimura Yushitaka, Palaniswami Marimuthu, & Clifford Gari D. 2016 Estimating Fetal Gestational Age Using Cardiac Valve Intervals. In: Computing in Cardiology Conference (CinC) IEEE.

Marzbanrad Faezeh, Khandoker Ahsan H, Yoshitaka Kimura, Marimuthu Palaniswami, & Clifford Gari D. 2017 Assessment of Fetal Development Using Cardiac Valve Intervals. Frontiers in Physiology, 8, 313. [PubMed: 28567021]

McClure Elizabeth M, Nathan Robert O, Saleem Sarah, Esamai Fabian, Garces Ana, Chomba Elwyn, Tshefu Antoinette, Swanson David, Mabeya Hillary, Figuero Lester, et al. 2014 First look: a cluster-randomized trial of ultrasound to improve pregnancy outcomes in low income country settings. BMC Pregnancy and Childbirth, 14(1), 1. [PubMed: 24383788]

McClure EM, Garces A, Saleem S, Moore JL, Bose CL, Esamai F, Goudar SS, Chomba E, Mwenechanya M, Pasha O, et al. 2017 Global Network for Women's and Children's Health Research: probable causes of stillbirth in low-and middle-income countries using a prospectively defined classification system. BJOG: An International Journal of Obstetrics & Gynaecology.

Mensah-Brown Nana Aba, Wakai Ronald T, Cheulkar Bageshree, Srinivasan Shardha, & Strasburger Janette F. 2010 Assessment of left ventricular pre-ejection period in the fetus using simultaneous magnetocardiography and echocardiography. Fetal diagnosis and therapy, 28(3), 167–174. [PubMed: 20975278]

Merz E 2004 Ultrasound in Obstetrics and Gynecology. Georg Thieme Verlag.

Monk Catherine, Fifer William P, Myers Michael M, Sloan Richard P, Trien Leslie, & Hurtado Alicia. 2000 Maternal stress responses and anxiety during pregnancy: effects on fetal heart rate. Developmental Psychobiology, 36(1), 67–77. [PubMed: 10607362]

Mosher John C, Flynn Edward R, Quinn A, Weir A, Shahani U, Bain RJP, Maas P, & Donaldson GB. 1997 Fetal magnetocardiography: methods for rapid data reduction. Review of scientific instruments, 68(3), 1587–1595.

Murata YUJI, Martin CHESTERB, Ikenoue T, & Lu PS. 1978 Antepartum evaluation of the pre-ejection period of the fetal cardiac cycle. Am J Obstet Gynecol, 132, 278–284. [PubMed: 707568]

Murray Henry. 2017 Antenatal foetal heart monitoring Best Practice & Research Clinical Obstetrics & Gynaecology, 38, 2–11. [PubMed: 27866937]

Nageotte Michael P. 2015 Fetal heart rate monitoring Pages 144–148 of: Seminars in Fetal and Neonatal Medicine, vol. 20 Elsevier. [PubMed: 25769203]

Nicolaides KH, Bilardo CM, Soothill PW, & Campbell S 1988 Absence of end diastolic frequencies in umbilical artery: a sign of fetal hypoxia and acidosis. BMJ: British Medical Journal, 297(6655), 1026. [PubMed: 3142596]

Ogunyemi Dotun, Madan Ichchha, Hage Natalie, Crossley Heather, & Qu Lihua. 2016 Neonatal Hypoxia in Term Infants: Obstetrical Predictors and Perinatal Consequences [24H]. Obstetrics & Gynecology, 127, 72S.

OpenStaxCollege. 2015 Anatomy and Physiology II

Organ LW, Bernstein A, & Hawrylyshyn PA. 1980 The pre-ejection period as an antepartum indicator of fetal well-being. American journal of obstetrics and gynecology, 137(7), 810. [PubMed: 7405972]

Papageorghiou AT, Kennedy SH, Salomon LJ, Ohuma EO, Cheikh Ismail L, Barros FC, Lambert A, Maria Carvalho, Jaffer YA, Bertino E, et al. 2014 International standards for early fetal size and pregnancy dating based on ultrasound measurement of crown–rump length in the first trimester of pregnancy. Ultrasound in Obstetrics & Gynecology, 44(6), 641–648. [PubMed: 25044000]

Peters Chris HL, ten Broeke Edith DM, Andriessen Peter, Vermeulen Barbara, Berendsen Ralph CM, Wijn Pieter FF, & Oei , S Guid. 2004 Beat-to-beat detection of fetal heart rate: Doppler ultrasound cardiotocography compared to direct ECG cardiotocography in time and frequency domain. Physiological measurement, 25(2), 585. [PubMed: 15132321]

Peters M, Crowe J, Pi?ri JF, Quartero H, Hayes-Gill B, James D, Stinstra J, & Shakespeare S. 2001 Monitoring the fetal heart non-invasively: a review of methods. Journal Of Perinatal Medicine, 29(5), 408–416. [PubMed: 11723842]

Platt John, et al. 1999 Probabilistic outputs for support vector machines and comparisons to regularized likelihood methods. Advances in large margin classifiers, 10(3), 61–74.

Rabiner Lawrence R. 1989 A tutorial on hidden Markov models and selected applications in speech recognition. Proceedings of the IEEE, 77(2), 257–286.

Ramanathan Gowri, & Arulkumaran Sabaratnam. 2009 Antenatal Fetal Surveillance. Obstetrics and Gynecology for Postgraduates, 1.

Rei Mariana, Tavares Sara, Pinto Pedro, Machado Ana P, Monteiro Sofia, Costa Antónia, Costa-Santos Cristina, Bernardes João, & Ayres-De-Campos Diogo. 2016 Interobserver agreement in CTG interpretation using the 2015 FIGO guidelines for intrapartum fetal monitoring. European Journal of Obstetrics & Gynecology and Reproductive Biology, 205, 27–31. [PubMed: 27566218]

Ricke Anthony D, Povinelli Richard J, & Johnson Michael T. 2005 Automatic segmentation of heart sound signals using hidden Markov models Pages 953–956 of: Computers in Cardiology, 2005 IEEE.

Roj Dawid, Wróbel Janusz, Horoba Krzysztof, Przyby la Tomasz, & Kupka Tomasz. 2010 Improving the periodicity measurement in fetal heart activity signal. Journal of Medical Informatics & Technologies, 16.

Romo A, Carceller R, & Tobajas J 2009 Intrauterine growth retardation (IUGR): epidemiology and etiology. Pediatric endocrinology reviews: PER, 6, 332–336. [PubMed: 19404231]

Sadler Tomas W. 2004 Langmans Essential Medical Embryology. 9.

Salamalekis E, Thomopoulos P, Giannaris D, Salloum I, Vasios G, Prentza A, & Koutsouris D 2002 Computerised intrapartum diagnosis of fetal hypoxia based on fetal heart rate monitoring and fetal pulse oximetry recordings utilising wavelet analysis and neural networks. BJOG: An International Journal of Obstetrics & Gynaecology, 109(10), 1137–1142. [PubMed: 12387467]

Sameni Reza, & Clifford Gari D. 2010 A review of fetal ECG signal processing; issues and promising directions. The open pacing, electrophysiology & therapy journal, 3, 4.

Sampson Milo B. 1980 Antepartum measurement of the preejection period in high-risk pregnancy. Obstetrics & Gynecology, 56(3), 289–290. [PubMed: 7422166]

Santiago-Mozos Ricardo, Garcia-Vizuete Beatriz, Lillo-Castellano Jose Maria, RojoAlvarez José Luis, & Martin-Caballero Carlos. 2013 On the early detection of perinatal hypoxia with information-theory based methods. Pages 425–428 of: Computing in Cardiology Conference (CinC), 2013 IEEE.

Sato Michiyoshi, Kimura Yoshitaka, Chida Shinichi, Ito Takuya, Katayama Norihiro, Okamura Kunihiro, & Nakao Mitsuyuki. 2007 A novel extraction method of fetal electrocardiogram from the composite abdominal signal. Biomedical Engineering, IEEE Transactions on, 54(1), 49–58.

Satoh Shoji, Yumoto Yasuo, Fujita Yasuyuki, Kinukawa Naoko, & Nakano Hitoo. 2007 Noninvasive measurement of isovolumetric contraction time by Doppler cardiography can be substituted for fetal cardiac contractility: evaluation of a fetal lamb study. Early human development, 83(4), 263–267. [PubMed: 16860948]

Schmidt SE, Holst-Hansen Claus, Graff Claus, Toft Egon, & Struijk Johannes J. 2010 Segmentation of heart sound recordings by a duration-dependent hidden Markov model. Physiological measurement, 31(4), 513. [PubMed: 20208091]

Schneider Uwe, Fiedler Anja, Liehr Mario, Kähler Christiane, & Schleussner Ekkehard. 2006 Fetal heart rate variability in growth restricted fetuses. Biomedizinische Technik, 51(4), 248–250. [PubMed: 17061950]

Schneider Uwe, Frank Birgit, Fiedler Anja, Kaehler Christiane, Hoyer Dirk, Liehr Mario, Haueisen Jens, & Schleussner Ekkehard. 2008 Human fetal heart rate variability-characteristics of autonomic regulation in the third trimester of gestation. Journal of perinatal medicine, 36(5), 433–441. [PubMed: 18605969]

Serra V, Moulden M, Bellver J, & Redman CWG. 2008 The value of the short-term fetal heart rate variation for timing the delivery of growth-retarded fetuses. BJOG: An International Journal of Obstetrics & Gynaecology, 115(9), 1101–1107. [PubMed: 18715432]

Shakespeare SA, Crowe JA, Hayes-Gill BR, Bhogal K, & James DK. 2001 The information content of Doppler ultrasound signals from the fetal heart. Medical and Biological Engineering and Computing, 39(6), 619–626. [PubMed: 11804166]

Signore Caroline, Freeman Roger K, & Spong Catherine Y. 2009 Antenatal testing–a reevaluation: executive summary of a Eunice Kennedy Shriver National Institute of Child Health and Human Development workshop. Obstetrics and gynecology, 113(3), 687. [PubMed: 19300336]

Spilka Jirí, Chudáček V, Koucký Michal, Lhotská Lenka, Huptych Michal, Jankuu P, Georgoulas George, & Stylios Chrysostomos. 2012 Using nonlinear features for fetal heart rate classification. Biomedical Signal Processing and Control, 7(4), 350–357.

Springer David B, Tarassenko Lionel, & Clifford Gari D. 2016 Logistic regression-HSMM-based heart sound segmentation. IEEE Transactions on Biomedical Engineering, 63(4), 822–832. [PubMed: 26340769]

Springer DB, Brennan T, Zuhlke LJ, Abdelrahman HY, Ntusi N, Clifford GD, Mayosi BM, & Tarassenko L. 2014 Signal quality classification of mobile phonrecorded phonocardiogram signals. Pages 1335–1339 of: Acoustics, Speech and Signal Processing (ICASSP), 2014 IEEE International Conference on IEEE.

Steer Philip J. 2008 Has electronic fetal heart rate monitoring made a difference? Pages 2–7 of: Seminars in Fetal and Neonatal Medicine, vol. 13 Elsevier. [PubMed: 18271079]

Strasburger Janette F, & Wakai Ronald T. 2010 Fetal cardiac arrhythmia detection and in utero therapy. Nature reviews cardiology, 7(5), 277–290. [PubMed: 20418904]

Stroux L, & Clifford GD. 2014 (6). The Importance of Biomedical Signal Quality Classification for Successful mHealth Implementation. In: 2014 Tech4Dev International Conference UNESCO Chair in Technologies for Development: What is Essential?

Stroux L, King NE, Fathima S, Hall-Clifford R, Rohloff P, & Clifford GD. 2014 A low-cost perinatal monitoring system for use in rural Guatemala. Pages 1–4 of: Appropriate Healthcare Technologies for Low Resource Settings (AHT 2014). IET.

Stroux Lisa, & Clifford GD 2016 A Perinatal Monitoring System for Low-resource Settings. Ph.D. thesis, University of Oxford.

Stroux Lisa, & Clifford Gari D. 2013 Affordable Multisensor Perinatal Monitoring Concept The importance of signal quality indices for successful mHealth implementation. “Second WHO Global Forum on Medical Devices: Priority Medical Devices for Universal Health Coverage, Geneva, Switzerland”.

Stroux Lisa, Martinez Boris, Coyote Ixen, Enma King, Nora Hall-Clifford, Rachel Rohloff Peter, & Clifford Gari D. 2016 An mHealth monitoring system for traditional birth attendant-led antenatal risk assessment in rural Guatemala. Journal of medical engineering & technology, 40(7–8), 356–371. [PubMed: 27696915]

Stroux Lisa, Redman Christopher W, Georgieva Antoniya, Payne Stephen J, & Clifford Gari D. 2017 Doppler-based fetal heart rate analysis markers for the detection of early intrauterine growth restriction. Acta Obstetricia et Gynecologica Scandinavica, 96(11), 1322–1329. [PubMed: 28862738]

Taipale Pekka, & Hiilesmaa Vilho. 2001 Predicting delivery date by ultrasound and last menstrual period in early gestation. Obstetrics & Gynecology, 97(2), 189–194. [PubMed: 11165580]

Tei C 1995 New non-invasive index for combined systolic and diastolic ventricular function. Journal of cardiology, 26(2), 135–136. [PubMed: 7674144]

Tetschke Florian, Schneider Uwe, Schleussner Ekkehard, Witte Otto W, & Hoyer Dirk. 2016 Assessment of fetal maturation age by heart rate variability measures using random forest methodology. Computers in biology and medicine, 70, 157–162. [PubMed: 26848727]

Tezuka Naohiro, Saito Hidekazu, & Hiroi Masahiko. 1998 Comparison of the accuracy of gestational age estimation from fetal heart rate and crown-rump length. Primary Care Update for OB/GYNS, 5(4), 193.

Thuring Ann, Brännström , K Jonas, Ewerlöf Maria, Hernandez-Andrade Edgar, Ley David, Lingman Göran, Liuba Karina, Maršál Karel, & Jansson Tomas. 2013 Operator auditory perception and spectral quantification of umbilical artery Doppler ultrasound signals. PloS one, 8(5), e64033. [PubMed: 23700452]

Thuring Ann, Brännström , K Jonas, Jansson Tomas, & Maršál Karel. 2014 Audio spectrum analysis of umbilical artery Doppler ultrasound signals applied to a clinical material. Acta obstetricia et gynecologica Scandinavica, 93(12), 1320–1324. [PubMed: 25168261]

Thuring Ann, Källén Karin, Brännström KJ, Jansson Tomas, & Maršál K. 2015 Doppler Audio Signal Analysis as an Additional Tool in Evaluation of Umbilical Artery Circulation. Ultraschall in der Medizin-European Journal of Ultrasound.

Tongprasert Fuanglada, Srisupundit Kasemsri, Luewan Suchaya, Traisrisilp Kuntharee, Jatavan Phudit, & Tongsong Theera. Fetal isovolumetric time intervals as a marker of abnormal cardiac function in fetal anemia from homozygous alpha thalassemia-1 disease. Prenatal Diagnosis.

Tuck DL. 1982 Improvement in Doppler ultrasound human foetal heart rate records by signal correlation. Medical and Biological Engineering and Computing, 20(3), 357–360. [PubMed: 7109732]

Tutschek B, Zimmermann T, Buck T, & Bender HG. 2003 Fetal tissue Doppler echocardiography: detection rates of cardiac structures and quantitative assessment of the fetal heart. Ultrasound in obstetrics & gynecology, 21(1), 26–32. [PubMed: 12528157]

Ueda Keiko, Ikeda Tomoaki, Iwanaga Naoko, Katsuragi Shinj, Yamanaka Kaoru, Neki Reiko, Yoshimatsu Jun, & Shiraishi Isao. 2009 Intrapartum fetal heart rate monitoring in cases of congenital heart disease. American journal of obstetrics and gynecology, 201(1), 64–e1. [PubMed: 19481721]

Valderrama CE, Marzbanrad F, Stroux L, Martinez B, Hall-Clifford R, Liu C, Katebi N, Rohloff P, & Clifford GD 2018 (Sept). Improving the Quality of Point of Care Diagnostics with Real-Time Machine Learning in Low Literacy LMIC Settings. In: ACM SIGCAS Conference on Computing and Sustainable Societies (COMPASS 2018).

Valderrama Camilo E, Marzbanrad Faezeh, Stroux Lisa, & Clifford Gari D. 2017 Template-based Quality Assessment of the Doppler Ultrasound Signal for Fetal Monitoring. Frontiers in physiology, 8.

Van Laar JOEH, Porath MM, Peters CHL, & Oei SG. 2008 Spectral analysis of fetal heart rate variability for fetal surveillance: review of the literature. Acta obstetricia et gynecologica Scandinavica, 87(3), 300–306. [PubMed: 18307069]

Van Leeuwen, Peter Geue, Daniel Lange, Silke Hatzmann, Wolfgang, & Grönemeyer Dietrich. 2003 Changes in the frequency power spectrum of fetal heart rate in the course of pregnancy. Prenatal Diagnosis, 23(11), 909–916. [PubMed: 14634977]

Leeuwen Van, Peter Lange, Silke Klein, Anita Geue, Daniel, & Grönemeyer Dietrich HW. 2004 Dependency of magnetocardiographically determined fetal cardiac time intervals on gestational age, gender and postnatal biometrics in healthy pregnancies. BMC pregnancy and childbirth, 4(1), 1. [PubMed: 15005809]

Vannucci Robert C, & Perlman Jeffrey M. 1997 Interventions for perinatal hypoxic–ischemic encephalopathy. Pediatrics, 100(6), 1004–1114. [PubMed: 9374573]

Vaseghi SV. 1995 State duration modelling in hidden Markov models. Signal processing, 41(1), 31–41.

Velayo Clarissa, Sato Naoaki, Ito Takuya, Chisaka Hiroshi, Yaegashi Nobuo, Okamura Kunihiro, & Kimura Yoshitaka. 2011 Understanding congenital heart defects through abdominal fetal electrocardiography: case reports and clinical implications. Journal of Obstetrics and Gynaecology Research, 37(5), 428–435. [PubMed: 21272152]

Voicu Iulian, Girault Jean-Marc, Roussel Catherine, Decock Aliette, & Kouame Denis. 2010 Robust estimation of fetal heart rate from US Doppler signals. Physics Procedia, 3(1), 691–699.

Voicu Iulian, Ménigot Sébastien, Kouamé Denis, & Girault Jean-Marc. 2014. New estimators and guidelines for better use of fetal heart rate estimators with Doppler ultrasound devices. Computational and mathematical methods in medicine, 2014.

Von Steinburg Stephanie Pildner, Boulesteix Anne-Laure, Lederer Christian, Grunow Stefani, Schiermeier Sven, Hatzmann Wolfgang, Schneider Karl-Theodor M, & Martin Daumer. 2013 What is the normal fetal heart rate? PeerJ, 1, e82. [PubMed: 23761161]

Wacker-Gussmann Annette, Strasburger Janette F, Cuneo Bettina F, & Wakai Ronald T. 2014 Diagnosis and treatment of fetal arrhythmia. American journal of perinatology, 31(07), 617–628. [PubMed: 24858320]

Wallwitz Ulrike, Schneider Uwe, Nowack Samuel, Feuker Janine, Bauer Stephan, Rudolph Anja, & Hoyer Dirk. 2012 Development of integrative autonomic nervous system function: an investigation based on time correlation in fetal heart rate patterns. Journal of Perinatal Medicine, 40(6), 659–667. [PubMed: 23093257]

Walton Janelle R, & Peaceman Alan M. 2012 Identification, assessment and management of fetal compromise. Clinics in perinatology, 39(4), 753–768. [PubMed: 23164176]

Wang Wenjuan, Alva Soumya, Wang Shanxiao, & Fort Alfredo. 2011 Levels and trends in the use of maternal health services in developing countries.

Warrick PA, & Hamilton EF 2014 (Sept). Discrimination of normal and at-risk populations from fetal heart rate variability. Pages 1001–1004 of: Computing in Cardiology 2014.

Warrick Philip A, Hamilton EF, Kearney RE, & Precup D. 2010 Classification of normal and hypoxic fetuses using system identification from intrapartum cardiotocography. IEEE Trans Biomed Eng, 57, 771–9. [PubMed: 20659819]

Warrick Philip A, Hamilton Emily F, Kearney Robert E, & Doina Precup. 2012 A machine learning approach to the detection of fetal hypoxia during labor and delivery. AI Magazine, 33(2), 79.

Westergaard HB, Langhoff-Roos J, Göran Lingman, Karel Marsal, & Svend Kreiner. 2001 A critical appraisal of the use of umbilical artery Doppler ultrasound in high-risk pregnancies: use of meta-analyses in evidence-based obstetrics. Ultrasound in obstetrics & gynecology, 17(6), 466–476. [PubMed: 11422966]

Wiggins Delonia L, Strasburger Janette F, Gotteiner Nina L, Bettina Cuneo, & Wakai Ronald T. 2013 Magnetophysiologic and echocardiographic comparison of blocked atrial bigeminy and 2: 1 atrioventricular block in the fetus. Heart Rhythm, 10(8), 1192–1198. [PubMed: 23619035]

Woods Robert. 2008 Long-term trends in fetal mortality: implications for developing countries. Bulletin of the World Health Organization, 86(6), 460–466. [PubMed: 18568275]

World Health Organization. 2009 Maternal and perinatal health.

World Health Organization. 2016 The neglected tragedy of stillbirths.

Wróbel Janusz, Kupka Tomasz, Horoba Krzysztof, Matonia Adam, Roj Dawid, & Jeżewski J. 2014 Automated detection of fetal movements in Doppler ultrasound signals versus maternal perception. Journal of Medical Informatics & Technologies, 23.

Yumoto Yasuo, Satoh Shoji, Fujita Yasuyuki, Koga Tsuyoshi, Kinukawa Naoko, & Nakano Hitoo. 2005 Noninvasive measurement of isovolumetric contraction time during hypoxemia and acidemia: Fetal lamb validation as an index of cardiac contractility. Early human development, 81(7), 635–642. [PubMed: 15970405]

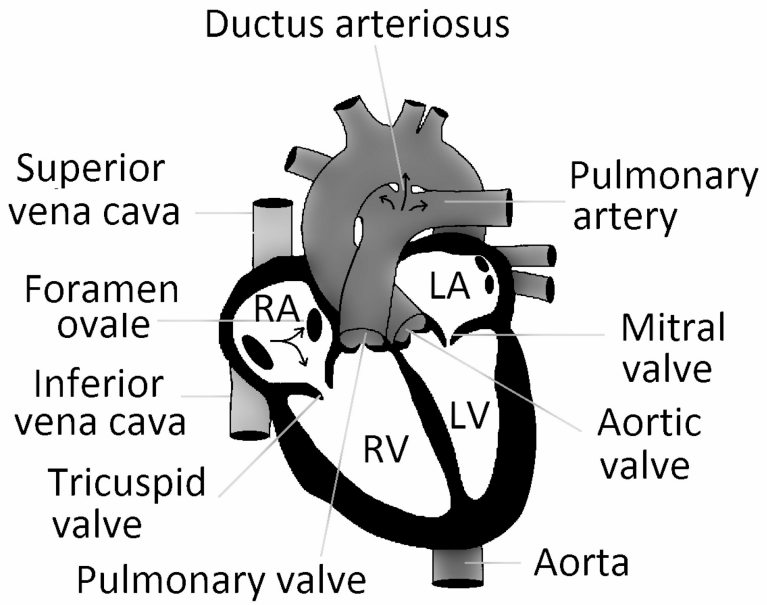

Figure 1:
The anatomic structure of the fetal heart is illustrated. Note the existence of the foramen ovale, which bypasses the lungs and moves blood from the right atrium of the heart to the left atrium. The foramen ovale closes in most newborns around 30 minutes after the first breaths, however, conditions such as patent foramen ovale, observable through echo-cardiography, can persist into adulthood (Sadler, 2004). Adapted from (Marzbanrad, 2015) under the Creative Commons Attribution 4.0 International License (CC BY 4.0).

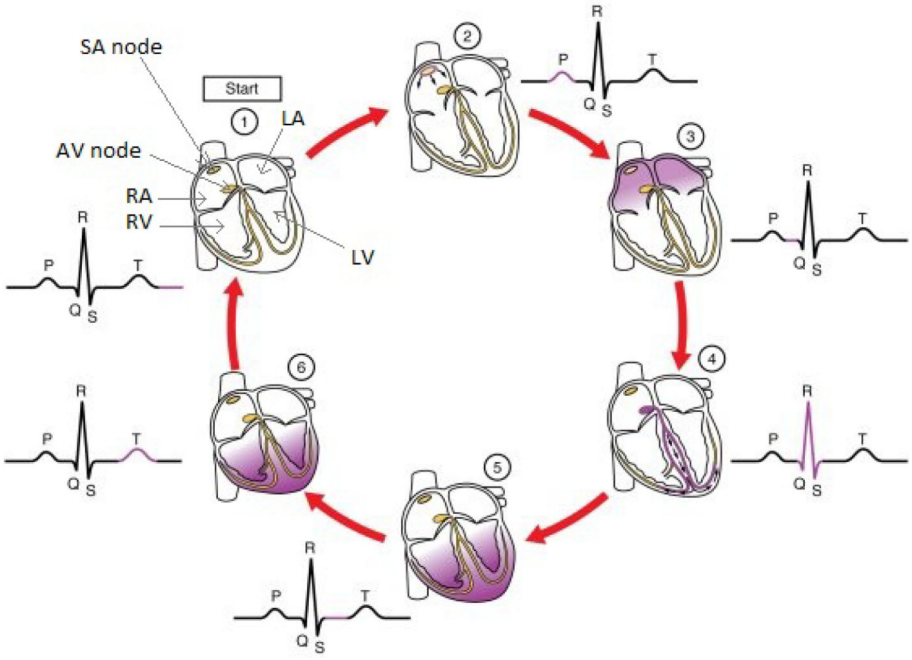

Figure 2:

The ECG tracing corresponding to the electrical and mechanical events in a cardiac cycle is illustrated. Image was downloaded for free at https://openstax.org/details/books/anatomy-and-physiology and modified under the Creative Commons Attribution 4.0 International License (CC BY 4.0) (OpenStaxCollege, 2015).

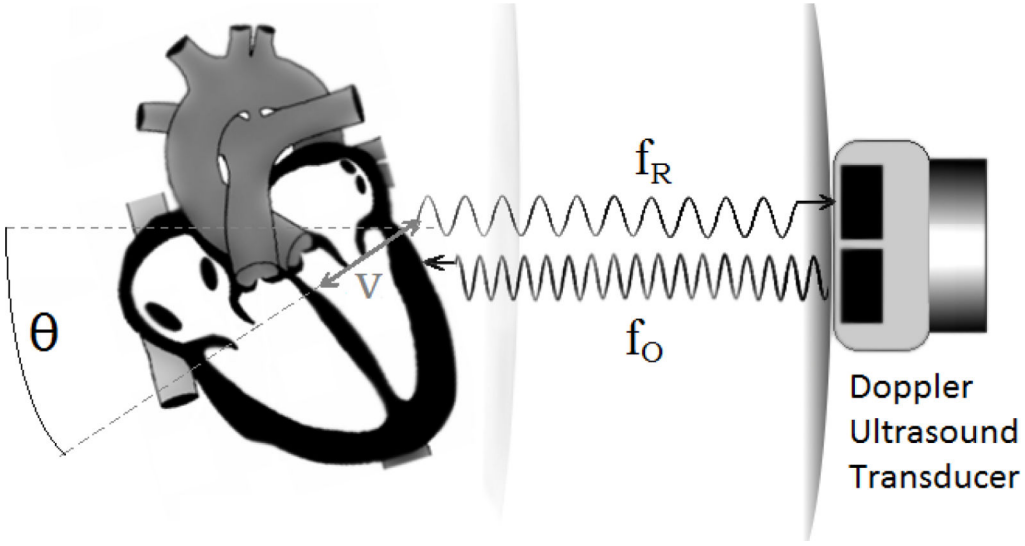

Figure 3:

If the 1D-DUS transducer is placed on the maternal abdomen and directed towards the fetal heart, movement of cardiac walls and valves can be captured. It emits ultrasound waves with frequency f_o and receives the reflected signal with frequency f_R, where the reflected wave has a different frequency due to the Doppler shift. The shift in frequency depends on the velocity V, direction and angle of the movement with respect to the ultrasound beam, θ, and the speed of sound in soft tissue, c, as detailed in equation 1.

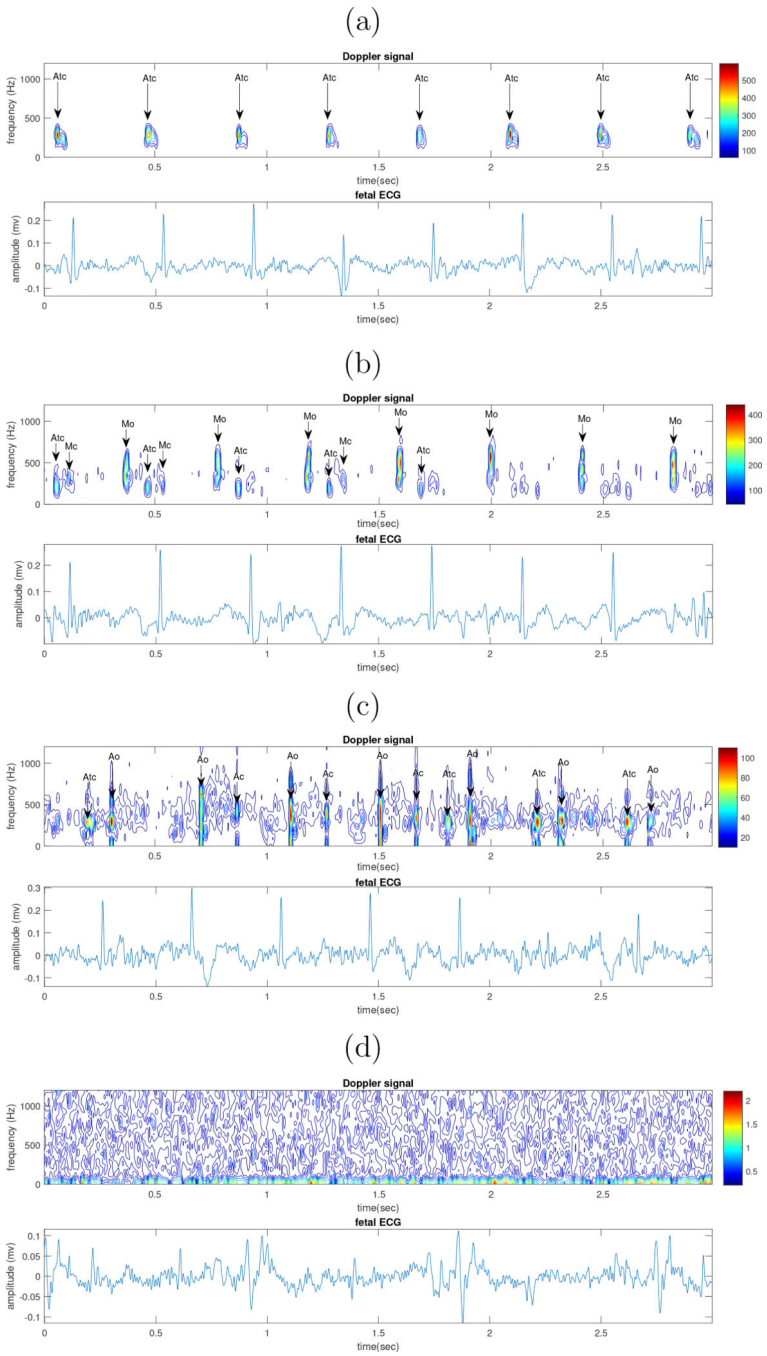

Figure 4:

The 1D-DUS spectrogram is shown with simultaneous fECG for different time windows of a 30-minute recording. Figures (a)-(d) show the variability of the 1D-DUS even on a beat-to-beat basis, mainly due to fetal movements and changes in fetal heart-transducer orientation. In window (a), atrial contraction (Atc) is predominant, while mitral opening (Mo) and closing (Mc) are detectable in window (b), different from window (c) where aorta opening (Ao) and closing (Ac) are visible and none of the cardiac events are captured in window (d). The figures are annotated manually based on the spectro-temporal patterns and timings using

fECG R-peaks as reference. The source data including 1D-DUS (AngelSounds JPD-100S with ultrasound frequency of 3.3 MHz) and noninvasive fECG were recorded at University Hospital of Leipzig in Germany and made available under an open access license.

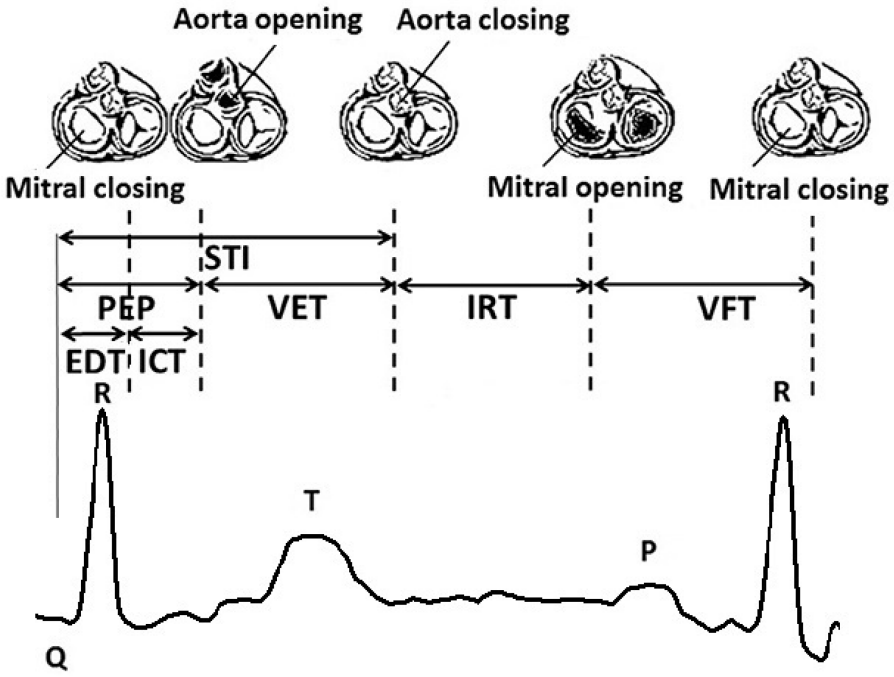

Figure 5:

An illustrative example of fetal cardiac intervals: Systolic Time Interval (STI), Electromechanical Delay Time (EDT), Isovolumic Contraction Time(ICT), Pre-Ejection Period (PEP), Ventricular Ejection Time (VET), Diastolic Time Interval (DTI), Isovolumic Relaxation Time (IRT), Ventricular Filling Time (VFT). The image is adapted from (Marzbanrad *et al.*, 2017), and licensed under Creative Commons Attribution 4.0 International (CC BY 4.0).

Table 1:

Summary of available methods for non-invasive fetal monitoring, their affordability, training burden and availability in LMICs.

Methods	Equipment cost	Training burden	Availability in LMIC	Gestational age
1D-DUS (hand-held)	Low	Low (Stroux *et al.*, 2016)	Available	≳ 20 weeks (Peters *et al.*, 2001)
1D-DUS (Car-diotocogrpahy)	High	Moderate	Limited	During Labor
Echocardiography	High	High	Limited	≳ 11 weeks * (Gembruch *et al.*, 2000)
Non-invasive fECG	Low	Moderate	Limited, under development	≳ 18 weeks with dip from 28th to 37th weeks (Sameni & Clifford, 2010)
FMCG	High	High	Unavailable	≳ 18 weeks (Mosher *et al.*, 1997)
Phonocardiography	Low	Low	Limited, under development (noise prone)	≥30 weeks (Kov´acs *et al.*, 2011)

* According to a study by Gembruch et al., on 136 normal singleton fetuses, the heart four-chamber view and great arteries can be adequately visualized in 44% of the fetuses at 10 weeks of gestation, in 75% at 11 weeks of gestation, in 93% at 12 weeks of gestation and in 100% of the fetuses at 1317 weeks of gestation. Before 14 weeks of gestation transvaginal sonography is superior to the transabdominal sonography, while after 14 weeks of gestation transabdominal sonography can accurately demonstrate the heart structure (Gembruch *et al.*, 2000).

Table 2:

Summary of the substantial CTG databases used in the literature is presented in chronological order, which however do not include raw 1D-DUS data.

Study	Access	Subjects	Site	Application
Stroux *et al.* (2017); Stroux & Clifford (2016)	closed	1163 IUGR and 1163 control cases at 23–42 weeks of gestation	Oxford, UK	FHR analysis markers for the detection of early IUGR
Georgieva *et al.* (2017)	closed	22,790 women in labor, ≥36 weeks of gestation	Oxford, UK	Using CTG and clinical features to automatically identify the fetuses at risk of intrapartum hypoxia.
(Warrick & Hamilton, 2014)	closed	Intrapartum recordings from 5320 normal cases, 10 cases with neonatal depression and 99 with metabolic Acidosis	United States	discrimination of normal and at-risk populations from fetal HRV.
(Chudáček *et al.*, 2014)	open	552 intrapartum CTG selected from 9164 cases, ≥37 weeks of Gestation	Brno, Czech Republic	Providing an open-access CTG database for research on intrapartum CTG signal processing and analysis.

Table 3:

Summary of the 1D-DUS databases used in the literature in the past 20 years is presented in chronological order. All databases are closed access.

Study	Device	Subjects	Site	Application
Valderrama *et al.* (2018); Stroux & Clifford (2016)	Angel-Sounds JPD100s hand-held, frequency of 3.3 MHz	146 fetuses, GA: 2nd and 3rd trimester	Rural Guatemala	improving the quality of point of care diagnostics in LMICs.
Valderrama *et al.* (2017); Stroux & Clifford (2016)	Angel-Sounds hand-held JPD100s, frequency of 3.3 MHz	17 fetuses, GA: 20 to 40 weeks	Oxford, UK	signal quality assessment and improving FHR mon-itoring
Marzbanrad *et al.* (2017, 2014a,a)	Corometrics 5700 Ultrasound transducer, frequency of 1.15 MHz	57 healthy fetuses and 30 cases with fetal arrhythmia or heart anomalies between 16 to 41 weeks	Sendai, Japan	Signal quality assessment, fetal heart valve movement detection and assessing fetal development
Wróbel *et al.* (2014)	not specified	11 recordings, GA: 26 to 41 weeks	Katowice, Poland	fetal movement detection
Lee *et al.* (2009b)	FD2-P hand-held, frequency of 2 MHz	Synthetic and limited fetal recordings (numbers not speci-fied)	Mount Lawley, Australia	Improving FHR monitoring
Yumoto *et al.* (2005); Satoh *et al* (2007)	FD-390 Hand Held, frequency of 2.5 MHz	12 fetal lambs, GA: 128 to 135 days	Kyushu, Japan	measurement of isovolumetric contraction time (ICT)
Kupka *et al.* (2004)	fetal monitor MT430, frequency of 2 MHz	12 antepartum and 3 intrapartum recordings	Poland	fetal heart valve movement detec-tion
Koga *et al.* (2003)	continuous-wave ultrasound transducer, frequency of 2.5 MHz	116 normal fetuses, between 20 and 40 weeks of gestation, with 8 longitudinal measurements > 3 times in pregnancy 2nd half and 55 potentially compromised fetuses	Western Sydney, Australia	Assessment of isovolumetric contraction time (ICT)
Shakespeare *et al.* (2001)	Sonicaid (modified), frequency of 1.5 MHz	21 patients (22 recordings)	Nottingham, UK	Fetal heart valve movement detection

Table 4:

Summary of the literature on identification of IUGR fetuses using FHR parameters is presented in chronological order. Fetal magenetocardiogram (fMCG) and electrocardiogram (fECG) studies have been included as well as 1D-DUS for comparison.

Study	Modality	Method	Database	Main findings
Stroux *et al.* (2017); Stroux & Clifford (2016)	1D-DUS/ CTG	Multiparameter behavioral state dependent metrics: LTV and STV averaged over high or low variability episodes, no. and average duration of high and low variability episodes, no. of minutes in high or low variability, onset of the first high variability episode, and estimated GA	1163 IUGR and 1163 control cases at 23–42 weeks of gestation	LTV in active sleep was superior to STV (AUC of 72% vs. 71%). The number of minutes in high variation per hour (AUC of 75%) was the most predictive. The combined model improved the performance to 76%.
Magenes *et al.* (2014)	1D-DUS/CTG	multivariate: time domain (Rcov, STV, LTV), regu- larity/complexity (ApEn, Lempel Ziv, SE) and PRSA (APRS, DPRS)	60 IUGR at 32.27 ± 2.79 weeks and 60 control cases at 34.78 ± 0.53 weeks of gestation	LR performed on ApEn, LTI, LZC and RCO achieved 92.5% accuracy of IUGR detection, with 93% sensitivity and 91.5% Specificity
Gon¸calves *et al.* (2013)	1D-DUS/CTG	Linear and entropy methods: mean FHR, LF, HF and MF, LF/(MF+HF) ApEn, SampEn, MSE.	15 severe IUGR fetuses at 28–37 gestation weeks and 18 controls at 29–38 gestation weeks	significantly lower mFHR was only evident in IUGR males and lower entropy in IUGR females. Lower LF/(MF+HF) for IUGR females but not for males. Better detection of IUGR for male fetuses.
Hoyer *et al.* (2013)	fMCG	FABAS: a multivariate model including: amplitude, skewness, generalized MSE, pNN5 and VLF/LF	428 normal (113 quiet sleep, 286 active sleep, 29 active awake), and 19 IUGR cases, at 21- 40 gestation weeks	Classification of quiet and active sleep states (93.1%) and reduced fABAS for 11 IUGR fetuses preselected in active sleep.
Fanelli *et al.* (2013)	1D-DUS/CTG	PRSA, DPRS depending on the slope sign of the PRSA curve.	61 IUGR and 61 control cases at 3435 weeks of gesta- tion	better discrimination by APRS (AUC=0.823) and DPRS (AUC=0.837) than STV (AUC=0.816). Significantly different STV, Delta, LTV, for IUGR.
Lobmaier *et al.* (2012)	1D-DUS/CTG	AAC to assess the dynamic capacity of the fetal ANS, and STV	39 IUGR and 43 control cases, at 2638 weeks of gesta- tion	AAC differentiates better than STV, with higher AUC (97% vs. 85%), PPV (90% vs. 77%) and NPV (90% vs. 81%)
Graatsma *et al.* (2012)	fECG	STV, AAC, ADC using PRSA	30 small for GA, at 27–36 weeks and 90 control fetuses, 2140 gestation weeks	In small fetuses, both AAC and ADC z-scores were lower than the STV z-scores.
Huhn *et al.* (2011)	1D-DUS/CTG	Transformed PRSA, AAC	74 IUGR and 161 normal cases at 2836 gestation weeks	Lower AAC and STV for IUGR. AUC of 81.4% for AAC and 70.5% for STV.
Buscicchio *et al.* (2010)	1D-DUS/CTG	baseline FHR, no. of small and large accelerations, no. of decelerations, duration of high and low variation in minutes, LTV, STV, no. of fetal movements per hour	100 gestational diabetes cases on diet therapy and 100 on insulin therapy, 100 gestational hypertention, 100 IUGR, 100 premature rupture of membranes, 100 controls, all 35–36 gestation weeks	Baseline FHR, the duration of episodes of low variation and STV were significantly higher in all abnormal cases than in controls; significantly reduced fetal movement for IUGR, hypertention and premature rupture of membranes.
Ferrario *et al.* (2009b)	1D-DUS/CTG	time domain and frequency domain FHRV, and complexity parameters: ApEn, SampEn, MSE, LZC, DFA	25 recordings from 6 IUGR cases, at 28–34 weeks, 4 subjects (13 recordings) with altered fluximetric indices	IUGR cases without fluximetry alterations, had reduced HRV amplitude and regularity, lower spectral components and complexity.

Study	Modality	Method	Database	Main findings
Ferrario *et al.* (2006, 2009a)	1D-DUS/CTG	LZC and MSE with k-mean cluster analysis	23 severe IUGR, 19 non-severe IUGR and 17 control fetuses, at 27 to 34 weeks of gestation	LZC and MSE are significantly different for severe IUGR vs. non-sever and control (Se=77.8% and Ac=82.4%).
Kikuchi *et al.* (2008)	1D-DUS/CTG	DFA	68 IUGR fetuses, at 24 to 40 weeks, and 119 control fetuses at 22 to 41 weeks of gestation	α_2 exponent values of IUGR were significantly higher than control
Serra *et al.* (2008)	1D-DUS/CTG	STV	257 IUGR cases within 24 hours of delivery (26–42 weeks)	Decreasing STV was correlated with earlier deliveries and worse postnatal outcome.
Ferrario *et al.* (2007)	1D-DUS/CTG	Time and frequency domain FHRV, LZC, ApEn, SampEn	23 severe IUGR, 19 non-severe IUGR and 17 control fetuses, at 27 to 34 weeks of gestation	Only LZC, DELTA and STV were discriminative, no improvement by adding ApEn and SampEn
Schneider *et al.* (2006)	fMCG	linear and nonlinear FHRV parameters	36 IUGR and 29 control fetuses, at 28 to 39 weeks of gestation	Significantly lower SDNN, RMSSD, TP and LF/HF for IUGR
Kikuchi *et al.* (2006)	1D-DUS/ CTG	Nonlinear FHRV: attractor reconstruction, largest Lyapunov exponents and correlation dimension	69 IUGR fetuses, at 24 to 40 weeks, and 119 control fetuses at 22 to 41 weeks of gestation	Decreased variability, less chaotic FHR dynamics and decreased complexity for IUGR.
Anastasiadis *et al.* (2003)	fMCG	chaotic and periodic heart rate dynamics	11 IUGR and 19 control fetuses at 34 to 37 weeks of gestation	Significantly lower correlation dimension and higher LF, HF powers for IUGR.