Diagnostic opportunities of transabdominal fetal electrocardiography

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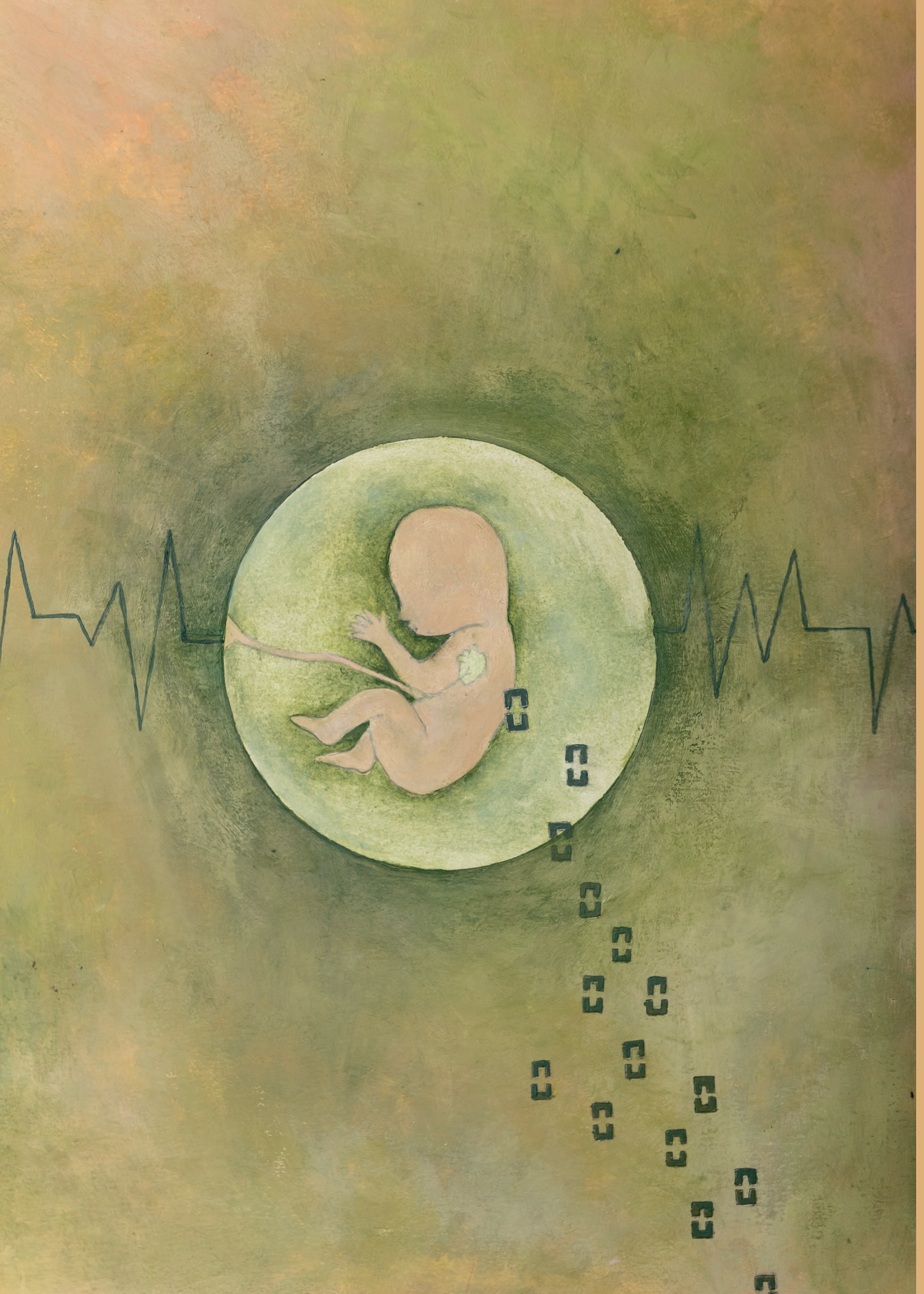

Chapter 1

General introduction

GENERAL INTRODUCTION

Approximately 140 million births occur globally every year according to the World Health Organization.[1] Although most pregnancies and deliveries are uncomplicated, timely recognition and intervention of fetal compromise is crucial. After previous reports of the relatively high perinatal mortality rate in the Netherlands compared to other European countries[2], recent data have shown a strong decrease in mortality rates.[3] Current perinatal mortality rate in the Netherlands is 3.9 per 1000 live births.[4]

Although perinatal mortality rates are generally low in high-income countries, most of these deaths are preventable. Evaluation of Dutch perinatal data available from the Perinatal Registry of The Netherlands (PRN) revealed that in 85% of cases of perinatal mortality, at least one of the following four conditions was present: birth asphyxia, preterm birth, fetal growth restriction and/or congenital anomalies.[5] Therefore, these are referred to as the "Big Four".[5] Timely detection of these conditions may result in further decrease of perinatal mortality rates. This allows for closer monitoring during pregnancy and delivery. Moreover, planning of the optimal timing of delivery in an environment with the required treatment facilities is possible. As the fetus remains a relative inaccessible patient until birth, the obstetrician is challenged to adequately estimate fetal wellbeing. Current fetal surveillance methods available in clinical practice have limited diagnostic value in the identification of fetal compromise. Improving fetal surveillance during pregnancy and labor is therefore still a topic of debate. The search for new fetal monitoring modalities is ongoing in order to globally reduce perinatal morbidity and mortality to a bare minimum.

The challenge of fetal monitoring

The fetal heart rate (FHR) is currently the only reliable physiological parameter which is readily available since other hemodynamic parameters of the fetus such as blood pressure are not within reach during pregnancy. FHR monitoring by means of cardiotocography (CTG) has been the method of choice in clinical practice since the introduction of the first commercially available electronic fetal monitoring systems in 1968.[6] This non-invasive method simultaneously registers the FHR by means of Doppler Ultrasound (DU) as well as uterine activity by means of an external strain gauge pressure transducer, the tocodynamometer. The ultrasound transducer operates in pulsed-wave Doppler mode and is placed on the maternal abdomen, in the vicinity of the fetal heart. From the received Doppler signal, fetal heart periodicity is determined using algorithms which use an autocorrelation function to obtain an estimate of the FHR.[7,8] The DU transducer as well as the tocodynamometer are fixated on the maternal abdomen using an elastic band, which is often considered as uncomfortable by the pregnant woman. Furthermore, relocation of the DU transducer is repeatedly needed due to signal loss upon fetal movement or when the transducer has shifted due to maternal movement.

The primary goal of introducing continuous FHR monitoring was to reduce the risk of perinatal mortality and morbidity. Unfortunately, due to the poor specificity of the CTG technology and high rate of false positive tests, nonreassuring FHR patterns do not necessarily signify fetal hypoxia.[9,10] Furthermore, CTG evaluation is based on visual interpretation by the physician, leading to high inter- and intra-observer variability.[11–13] As a result, the rate of operative vaginal deliveries and caesarean deliveries increased with the introduction of CTG, without a decrease in perinatal mortality and morbidity.[12] Despite these known shortcomings of the CTG technology, it is the only available method for antepartum fetal monitoring due to its non-invasive nature. There is hence an urgent need for a more reliable non-invasive fetal monitoring method which can be applied during both pregnancy and labor.

Non-invasive fetal electrocardiography

Electrophysiological monitoring by means of non-invasive fetal electrocardiography (NI-fECG) is a patient-friendly method for external monitoring of the FHR as well as uterine activity, by means of conventional electrodes which are placed on the maternal abdomen. NI-fECG relies on electrophysiological signals to deliver beat-to-beat information on the FHR, calculated on the R-R interval of the fetal ECG. Uterine activity is measured by means of the electrohysterogram (EHG), which registers the myometrial electrical activity. Evaluation of the EHG technology falls outside the scope of this thesis and has previously been reported on by Vlemminx.[14] Her research shows that EHG has a higher sensitivity than tocodynamometry in detecting uterine contractions during labor, especially in obese women.[15]

Cremer first reported the use of the NI-fECG technology as early as 1906, by means of abdominal and intravaginal electrodes.[16] Although the potential clinical value of this method has been acknowledged over time, technical challenges in separating the fetal signal from the relatively large maternal signal and background noise prohibited its further development for clinical use. With the arrival of computer technology in the second half of the 20th century, new tools

arose to address this issue. Recent advances in computer software and signal processing techniques gradually led to the development of specific algorithms to surpass these obstacles. More details concerning the background of NI-fECG measurements can be found in chapter 3 – technical background.

Since the NI-fECG technology delivers beat-to-beat FHR, it enables the use of quantitative measures such as spectral power analysis to objectively evaluate fetal heart rate variability (FHRV), which is an important parameter of fetal wellbeing. Furthermore, it introduces the opportunity to evaluate fetal ECG waveform characteristics in the future, delivering additional information on fetal wellbeing. In this thesis we explore the possibilities of the NI-fECG technology for antepartum and intrapartum fetal monitoring, as well as for diagnosing congenital heart disease in utero.

This thesis is subdivided into two parts: fetal monitoring and fetal diagnostics. Application of the NI-fECG in each of the "Big Four" conditions will be discussed. In Part I, we focus on how NI-fECG can be deployed for fetal monitoring during labor, as well as antepartum fetal monitoring in certain high-risk pregnancies. In Part II we explore the role of ECG waveform changes in increasing the detection rates of congenital heart disease in the future, by initially looking at differences in the electrical heart axis.

Part I: fetal ECG for fetal monitoring

In the Netherlands, fetal monitoring by means of CTG during pregnancy and labor is applied only in the hospital setting, which concerns primarily medium- and high-risk pregnancies. Most of these hospitalized women have a predisposed risk to a pregnancy complicated by one of the "Big Four" conditions and therefore close fetal surveillance is warranted.

Birth asphyxia is an important cause of perinatal mortality and morbidity which is caused by oxygen deprivation during labor.[17–19] Since specificity of CTG monitoring is poor, additional methods were developed over time to more accurately predict the fetal status in this event. Fetal scalp blood sampling (FBS) was introduced to reduce unnecessary interventions, although the evidence for this is weak.[20] In this case, a blood sample is taken from the fetal scalp in the case of a nonreassuring CTG during labor to identify the presence of acidosis. However, it delivers only momentary information about the fetal status and repeated sampling is therefore necessary to monitor possible changes in the fetal condition.[21] This method is only applicable once fetal membranes have ruptured and in the presence of sufficient cervical dilatation. It is an invasive technique with risks of infection and fetal bleeding. Leakage of cerebrospinal fluid following FBS has even been described in one case.[22] Furthermore, critics question if a blood sample derived from peripheral tissue accurately reflects oxygenation of central organ systems.

The fetal scalp electrode (FSE) was introduced in 1972. This invasive method uses a spiral electrode which is inserted through the birth canal and attached to the fetal scalp. It registers a single-lead fetal ECG and accurately calculates the FHR based on the R-R interval. FSE is considered as the gold standard for FHR detection but due to its invasive nature, it is not routinely applied in every hospital. There is an increased risk of injuring the fetal scalp as well as intra-uterine infection and this method can only be applied once fetal membranes have ruptured.[23]

In the 1990s, ST analysis of the fetal electrocardiogram (STAN, Neoventa Medical AB, Mölndal, Sweden) was developed to deliver continuous information of the fetal status. This method automatically detects ST-segment changes of the fetal ECG measured with a FSE, which, in case of a nonreassuring CTG, are associated with metabolic acidosis. STAN was proven to reduce the rate of operative deliveries and FBS. However, the intended reduced risk of metabolic acidosis was not observed.[24]

NI-fECG provides beat-to-beat information on the FHR to analyze FHRV, e.g. in the frequency domain, which allows assessment of the underlying autonomic control as explained in more detail in chapter 3 – technical background. Van Laar et al. studied the effect of severe acidemia during labor on FHRV indices.[25] They found increased normalized low-frequency power (reflecting sympathetic and parasympathetic tone) and decreased normalized high-frequency power (reflecting parasympathetic tone) in the last 30 minutes prior to delivery. These findings are in line with the physiological response to stress, indicating sympathetic predominance during fetal distress.

The relatively low prevalence of perinatal asphyxia in the Netherlands (0.88%) led to a small sample size in the aforementioned study of van Laar et al.[25,26] The next step would be to implement the NI-fECG technology for intrapartum monitoring in daily clinical practice, enabling a large database in which we can gain further insight in the autonomic response to fetal distress during labor. Therefore, in chapter 5 we compare the performance measures of the NI-fECG

technology against those of DU as reported in the literature, to validate this technology for clinical use.

Preterm birth is defined as delivery prior to 37 weeks of gestation. It is the most important cause of neonatal mortality and morbidity worldwide with approximately 15 million infants delivered preterm every year.[27] Preterm birth can either be iatrogenic on fetal or maternal indication or spontaneous following preterm premature rupture of membranes (PPROM) or spontaneous contractions.[28] Although the cause of preterm birth is often unknown, several risk factors have been identified, among which multiple gestation.[29] Multiple gestation is the most common high-risk condition in obstetric medicine where preterm birth is highly prevalent. In chapter 7 we describe a case in which we show the potential value of NI-fECG in multiple gestation, by successfully recording both individual fetuses in a twin pregnancy.

When a preterm birth threatens between 24 and 34 weeks of gestation, corticosteroids are administered to enhance fetal lung maturation. The use of corticosteroids is associated with an overall reduction in perinatal mortality and morbidity.[30] Betamethasone is the most frequently used corticosteroid, administered by means of two intramuscular injections with a time interval of 24 hours. Previous research using CTG has shown that betamethasone transiently decreases FHRV.[31,32] It is important to distinguish if this transient decrease in FHRV is drug-induced since it can be misinterpreted as fetal distress, causing unnecessary iatrogenic preterm birth. However, beat-to-beat information on the FHR is lacking in CTG measurements since the FHR is averaged over several heartbeats, preventing reliable spectral analysis of FHRV. Verdurmen et al. previously reported on the effect of betamethasone on FHRV using NI-fECG measurements.[33] However, due to insufficient data quality they were unable to find significant results. With the improvement of the data processing algorithm, the amount of data available for analysis could be increased. In chapter 6 we re-evaluated the effect of betamethasone on FHRV with this larger dataset.

Fetal growth restriction (FGR) is a condition in which the fetus fails to reach its full growth potential.[34] FGR is associated with stillbirth, increased perinatal morbidity, mortality and long-term severe neurodevelopmental and cardiovascular diseases.[35,36] A gold standard for diagnosing FGR is lacking. FGR was primarily defined as an estimated fetal weight below the 10th percentile, leading to the inclusion of small infants with and without placental dysfunction. Therefore, new definitions for FGR include Doppler indices to reflect placental function.[37] In pathological FGR, the placenta fails to adequately deliver oxygen and nutrients to the developing fetus causing stunting of fetal growth.[38] It is known that growth-restricted fetuses with placental insufficiency are associated with a poorer perinatal outcome.[39]

FGR poses various challenges in clinical practice. First, FGR often remains undetected in the antenatal period, especially in low-risk pregnancies. Second, if identified, pregnancies complicated with FGR require close fetal monitoring in order to detect fetal compromise upon which optimal timing for the delivery has to be planned. Here the risks of iatrogenic premature birth have to be weighed against the risks of prolonged hypoxia in utero. However, despite careful antenatal examinations using Doppler assessment of the umbilical artery and middle cerebral artery, biophysical profile scoring and CTG, the optimal surveillance method still needs to be identified.[36,40–43]

A reduction in FHRV in growth-restricted fetuses has been described in CTG-based studies.[44–46] Since FHRV is an important indicator of fetal wellbeing, it is routinely used in clinical practice to evaluate the fetal status. FHRV gradually decreases with progressive fetal deterioration. Profound reductions in FHRV visible in CTG recordings are a rather late sign in the process of fetal deterioration.[44,47] Frequency-domain analysis of the FHRV by means of spectral analysis, as mentioned earlier in this chapter, reflects autonomic control. Therefore, altered autonomic regulation in a state of chronic hypoxia as in FGR may be reflected by spectral FHRV estimates. In chapter 8 we performed a prospective study comparing spectral estimates between adequately grown fetuses and growth-restricted fetuses to test this hypothesis.

Part II: fetal ECG for diagnostic purposes

Congenital heart disease (CHD) is the most common congenital anomaly worldwide, with a reported prevalence of 8 per 1000 live births.[48–50] It is a major cause of neonatal morbidity and mortality.[48–56] About 20-30% of all CHDs are considered severe as they require urgent intervention.[52–54] Despite the decrease in mortality rates over the last decades due to improved diagnostic and treatment techniques, CHD remains the leading cause of infant mortality in developed countries.[57,58] Prenatal detection of CHD is advantageous since it allows for close monitoring during pregnancy, planning the delivery in a center with the required treatment facilities and it enables parents to choose for pregnancy termination if the diagnosis is made before 24 weeks of gestation.

In the Netherlands antenatal screening for CHD is performed by means of the fetal anomaly scan around 20 weeks of gestation. Since the introduction of national screening programs around Europe, the detection rate for CHD in the low-risk population has increased up to 50%–60%.[53,55,59,60] However, the detection rate is strongly correlated with the severity of the CHD and highly dependent on the sonographer's experience.[61] In specialized tertiary care centers with experienced sonographers, the general detection rate rose up to 89%.[62] However, only 10% of infants born with CHD are born to mothers with known risk factors, and therefore end up in tertiary care.[63] Most CHDs occur in the low-risk population, where at least 4 out of 10 cases of severe CHD are still missed.[53,55,59,60]

In pediatric and adult ECGs, it is already known that characteristic ECG patterns are associated with structural heart defects.[64] Therefore, it is feasible that characteristic waveform changes associated with certain CHD are also present in fetal ECG recordings. Development of a non-invasive diagnostic method from which this information can be obtained might be a major step towards increasing the prenatal diagnosis of CHD when combining it with the fetal anomaly scan. In chapter 9 to 11 we describe our initial results in the usage of the fetal ECG to aid in the diagnosis of CHD.

OUTLINE OF THIS THESIS

This thesis concerns the diagnostic opportunities of the NI-fECG technology. The innovative fECG systems used for our research are the result of a close collaboration between the Máxima Medical Center (MMC) and Eindhoven University of Technology (TU/e) in the field of fundamental perinatology. From this research collaboration, the spin-off company Nemo Healthcare B.V. originated that developed the fECG systems. In this thesis, we explore clinical implications for transabdominal fetal electrocardiography related to the "Big Four" conditions associated with perinatal mortality: birth asphyxia, preterm birth, fetal growth restriction and/or congenital anomalies.

The goal of the research elaborated in this thesis is to answer the following questions:

- Is the non-invasive fetal electrocardiogram a valid technology for intrapartum feto-maternal monitoring in daily clinical practice?

- Are the changes in fetal heart rate variability following betamethasone administration as measured with time-domain indices comparable to those measured with frequency-domain indices?
- Is the non-invasive fetal electrocardiogram able to monitor two individual fetuses by means of one abdominal electrode patch in twin gestation?
- Are there differences in cardiac deformation values and power spectral estimates of fetal heart rate variability between appropriate for gestational age fetuses and growth-restricted fetuses?
- Can we determine reference values for the electrical heart axis in healthy fetuses between 18 and 24 weeks of gestation?
- Is the electrical heart axis deviated in certain congenital heart diseases?

Chapter 2 provides physiological background information concerning the fetal heart and its autonomic regulation.

Chapter 3 provides technical background concerning the non-invasive fetal electrocardiogram and spectral analysis of fetal heart rate variability.

Part I: fetal ECG for fetal monitoring

Chapter 4 provides an overview of the current literature available on the use of feto-maternal monitoring during labor by means of non-invasive fetal electrocardiography.

Chapter 5 presents the results of a multicenter observational study that reports on the performance measures of a non-invasive fetal electrocardiography device during labor, validated against the fetal scalp electrode. Measurements were obtained using a wireless electrode patch on the maternal abdomen.

Chapter 6 presents the results of a secondary analysis of a prospective cohort study that describes the effect of betamethasone on fetal heart rate variability, by applying spectral analysis on non-invasive fetal electrocardiography recordings.

Chapter 7 describes a case of a twin pregnancy in which non-invasive fetal electrocardiography allows for monitoring of the fetal heart rate and ECG of both individual fetuses.

Chapter 8 presents the results of a prospective study in which cardiac deformation values measured with speckle tracking echocardiography and

spectral estimates measured with non-invasive fetal electrocardiography are compared between growth-restricted fetuses and appropriate for gestational age fetuses.

Part II: fetal ECG for diagnostic purposes

Chapter 9 provides reference values for the electrical heart axis in healthy fetuses between 18 and 24 weeks of gestation.

Chapter 10 presents the results of a case-cohort study in which we compared the electrical heart axis in certain congenital heart diseases with our reference values for healthy fetuses as described in chapter 9.

Chapter 11 describes a case report in which a bundle branch block was suspected prenatally based on a non-invasive fetal electrocardiography recording. The diagnosis was confirmed postnatally at the age of 2 years by means of an ECG.

Chapters 4 to 11 have been either published or submitted for publication. Therefore, each chapter is written to be self-contained which causes some overlap in the introduction and methods section of these chapters.

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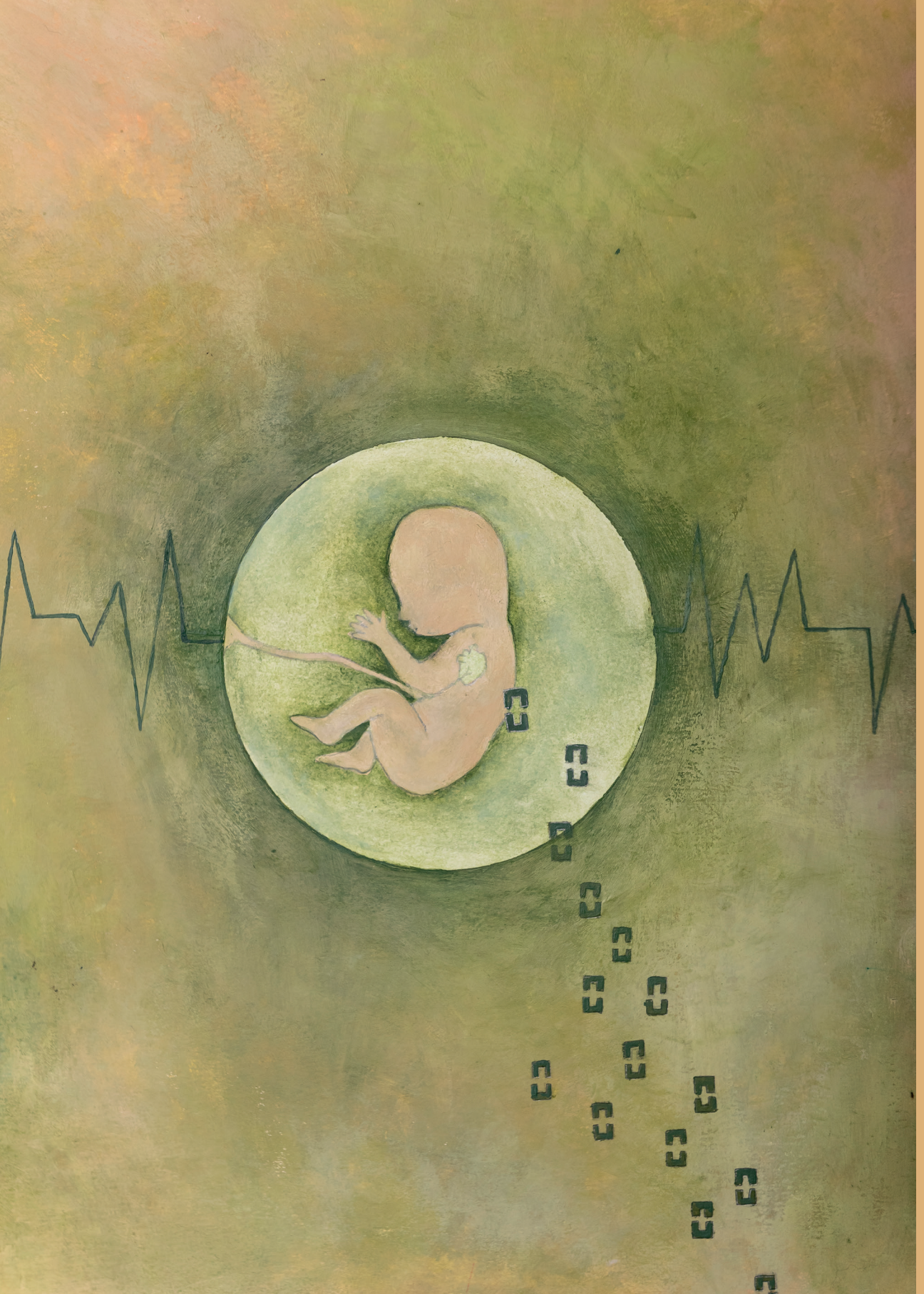


Chapter 2

Physiological background

Embryology of the fetal heart

The heart is the first organ to function during embryonic development. It starts beating merely three weeks after fertilization.[1] Development of the fetal heart commences in the cardiogenic area around 19 days after fertilization, near the head of the embryo, from one of the three primary germ layers called the mesoderm.[1,2] From this area, two endocardial tubes are formed which fuse to form a single primitive heart tube, with five distinct regions which later form the various regions of the developed heart. Between day 23 and 28 after fertilization, cardiac looping and rotation to the right side of the midline takes place. From day 28, internal septa start to form separating the heart in two atria and two ventricles.[1,2] Atrioventricular valves are formed between weeks five and eight after fertilization and semilunar valves are formed between weeks five and nine. Finally, development of the cardiac conduction system, the coronary circulation and innervation by the autonomic nervous system takes place. By day 50, the heart structure resembles its mature form.[3]

The fetal circulatory system

In utero the fetus receives oxygenated blood from the placenta through the umbilical cord. The oxygenated blood flows from the umbilical vein partly through the liver and partly through the ductus venosus into the vena cava inferior. From here the oxygen-rich blood is transported to the right side of the fetal heart where it is mixed with deoxygenated blood from the body. The fetal heart has two cardiac shunts leading to a parallel circulation. The first is the foramen ovale, which connects the right and left atrium. The second is the ductus arteriosus between the pulmonary trunk and the aorta. These cardiac shunts allow the majority of the mixed blood to bypass the non-functional lungs of the fetus and pass to the brain and fetal body. In utero, the pulmonary resistance is high as the fetal lungs are filled with amniotic fluid. This allows a larger part of the blood to flow from the pulmonary trunk through the ductus arteriosus into the aorta. Deoxygenated blood is transported through the umbilical arteries to the placenta where it gets reoxygenated. After birth a change from a parallel to a serial circulation occurs. With the first breath of a newborn the lungs get distended, lowering the resistance in the pulmonary circulation causing more blood flow through the lungs and returning to the left atrium. Consequently the pressure in the left atrium increases, causing the foramen ovale to close. When the umbilical cord is clamped, the peripheral resistance increases leading to a higher pressure in the aorta. The ductus arteriosus closes in the first days after birth due to a higher oxygen saturation in the blood causing the smooth muscle cells in the wall of the ductus to contract.

The cardiac conduction system

The human heart is made up of cardiac muscle cells, which have the unique capability of generating their own electrical impulse. There are two types of cardiac muscle cells: the myocardial contractile cells (99%) and the myocardial conducting cells (1%). The latter form the conduction system of the heart and are responsible for propagating the electrical impulse which triggers coordinated contraction of the myocardial contractile cells. The cardiac conduction system is built up from the following components: the sinoatrial node, the atrioventricular node, the atrioventricular bundle, the atrioventricular bundle branches and the Purkinje cells.[4]

The sinoatrial (SA) node is located in the superior and posterior wall of the right atrium and functions as the pacemaker of the heart. Electrical impulses initiated by the SA node travel throughout the atria towards the atrioventricular (AV) node through specialized internodal pathways. This causes the atria to contract from superior to inferior, pumping the blood towards the ventricles through the atrioventricular valves. Connective tissue prevents the electrical impulse from spreading directly into the myocardial cells of the ventricles except at the AV node. The AV node is situated within the AV septum in the inferior part of the right atrium. The AV node causes an essential delay in impulse transmission. From here, the impulse travels through the common AV bundle and thereafter through both AV bundle branches, located in the interventricular septum and descending upon the cardiac apex. Here they connect with the Purkinje fibers, which extend from the apex of the heart toward the base of the heart. When the electrical impulse triggers the Purkinje fibers, myometrial contraction starts at the apex and travels upward towards the base of the heart, allowing the blood to be pumped into the aorta and pulmonary trunk.

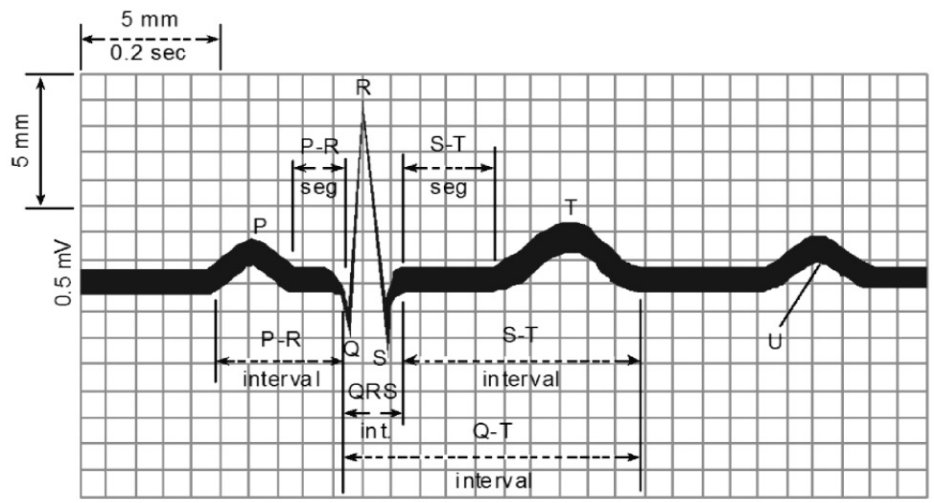
The electrocardiogram

The electrical impulse generated by the cardiac conduction system can be recorded by means of the electrocardiogram (ECG), using surface electrodes on the human body. Each combination of two different electrodes forms a lead, which registers the propagation of the electrical activity in different directions. Electrical activity which propagates towards the electrode causes a positive deflection and electrical activity propagating away from the electrode causes a negative deflection. In adults, the surface electrodes are placed in a standardized manner producing a 12-lead ECG. The physiological activation of the myocardium by the cardiac conduction system produces a typical ECG tracing which reflects each part of the cardiac cycle. The P-wave represents

the depolarization of the left and right atrium leading to atrial contraction. The P-wave is followed by the QRS-complex, composed of three successive waves representing ventricular depolarization from the ventricular septum towards the ventricular free walls and then the basal parts of the ventricles. Finally, the T-wave represents ventricular repolarization. Figure 1 shows an example of one heartbeat as seen on an ECG.

Since the fetus is inaccessible during pregnancy, surface electrodes are placed on the maternal abdomen. More background on the NI-fECG technology and its challenges can be found in chapter 3 – Technical background.

Figure 1. Example of one heartbeat as seen on an ECG.



Adapted from: The Complete Study Guide to Learning the Electrocardiogram.[5]

Fetal autonomic nervous system

As in adults, the fetal autonomic nervous system (ANS) is involved in the regulation of nearly all organs, among which the cardiovascular system. It consists of the sympathetic and parasympathetic nervous system, which both have a counteracting effect on the fetal heart rate (FHR) through complex interactions.[6] The sympathetic nervous system serves as the cardiac pacemaker, while the parasympathetic nervous system has an inhibitory effect on the heart.

Studies have shown a non-synchronous maturation of both branches of the ANS. Development of the sympathetic branch appears first and occurs steadily

throughout gestation.[6,7] Maturation of the parasympathetic nervous system predominantly takes place in the term period and reaches adult levels after birth.[7] During intra-uterine life, cardiovascular control is therefore predominantly influenced by the sympathetic nervous system.

Fetal heart rate variability (FHRV) reflects autonomic cardiovascular control and is an important indicator of fetal wellbeing. It is internationally used as part of standard clinical practice to assess the fetal status through fetal monitoring techniques. Spectral analysis is one method to quantify FHRV and is further explained in detail in chapter 3. When FHRV falls within normal range, it is a good indicator of fetal wellbeing.[8] Decreased variability is associated with fetal acidosis and low Apgar score.[8] FHRV is influenced by several confounding factors which should be taken into account when interpreting FHRV patterns. First, the ANS matures when gestational age advances as explained earlier in this chapter. This is reflected by an increase in absolute spectral estimates with increasing gestational age.[9,10] Second, several drugs commonly used in obstetrics, among which betamethasone for fetal lung maturation, are known to (transiently) influence FHRV.[11–13] Third, ANS activity is modulated by fetal behavioral states. The development of states occurs gradually as gestational age progresses. From 23 weeks of gestation body movements become clustered into rest-activity cycles.[14] These gradually change into fetal behavioral states which are fully developed after 34 weeks of gestation.[15] In total, four behavioral stages can be distinguished.[16] In the quiet sleep state (1F) there is little movement and FHR is stable. Relatively small changes occur in the FHR pattern. During the active sleep or REM sleep (2F) repeated body movements and continuous eye movements are present. Large changes in the FHR are seen during this state. The other 2 states are quiet awake (3F) and active awake (4F), which occur less frequently. During 3F there are continuous eye movements, but gross body movements are absent. The FHR is stable but has a wider oscillation bandwidth than during 1F. In 4F rigorous continuous activity is seen with an unstable FHR pattern.[16]

In hypoxia, the ANS is activated to compensate for the oxygen shortage through various mechanisms. If acute hypoxia occurs during labor when blood flow through the placenta and umbilical cord decreases following uterine contractions, both sympathetic and parasympathetic tone increase, mediated by the chemoreceptor reflex. Parasympathetic effects on the heart mediated by vagal nerve stimulation cause variable decelerations. There are several theories concerning the pathway. Fetal movements cease and FHR decreases

(i.e., deceleration) to lower oxygen consumption, which is modulated by the parasympathetic nervous system. By reducing the FHR, end-diastolic filling time is prolonged thereby increasing end-diastolic volume. This results in maintenance of the cardiac output and perfusion pressure.[17] On the other hand, uterine contractions initially cause compression of the umbilical vein before compression of the umbilical artery due to the difference in intravascular pressure. This leads to an increase in fetal blood return during the short period that the umbilical artery is still open, followed by a rapid drop in FHR caused by baroreceptor-mediated activation of the vagal nerve following complete cord occlusion.[18,19] Activation of the sympathetic branch of the ANS leads to peripheral vasoconstriction to redistribute the blood flow favoring vital organs such as the brain and fetal heart.[20] In fetuses, the sympathetic branch predominates due to the non-synchronous maturation of both branches as discussed earlier. Therefore, the increase in FHRV seen in this stage is mainly due to sympathetic activation.[21] These adaptation mechanisms controlled by the ANS are comparable to the adult physiological response to stress.[22] In chronic hypoxia, e.g. in the presence of uteroplacental dysfunction, sympathetic suppression occurs while the parasympathetic contribution to fetal cardiac control remains stable.[23,24] This leads to a decrease in FHRV which is a rather late sign of fetal acidosis and is associated with poor fetal outcome.[25–27]

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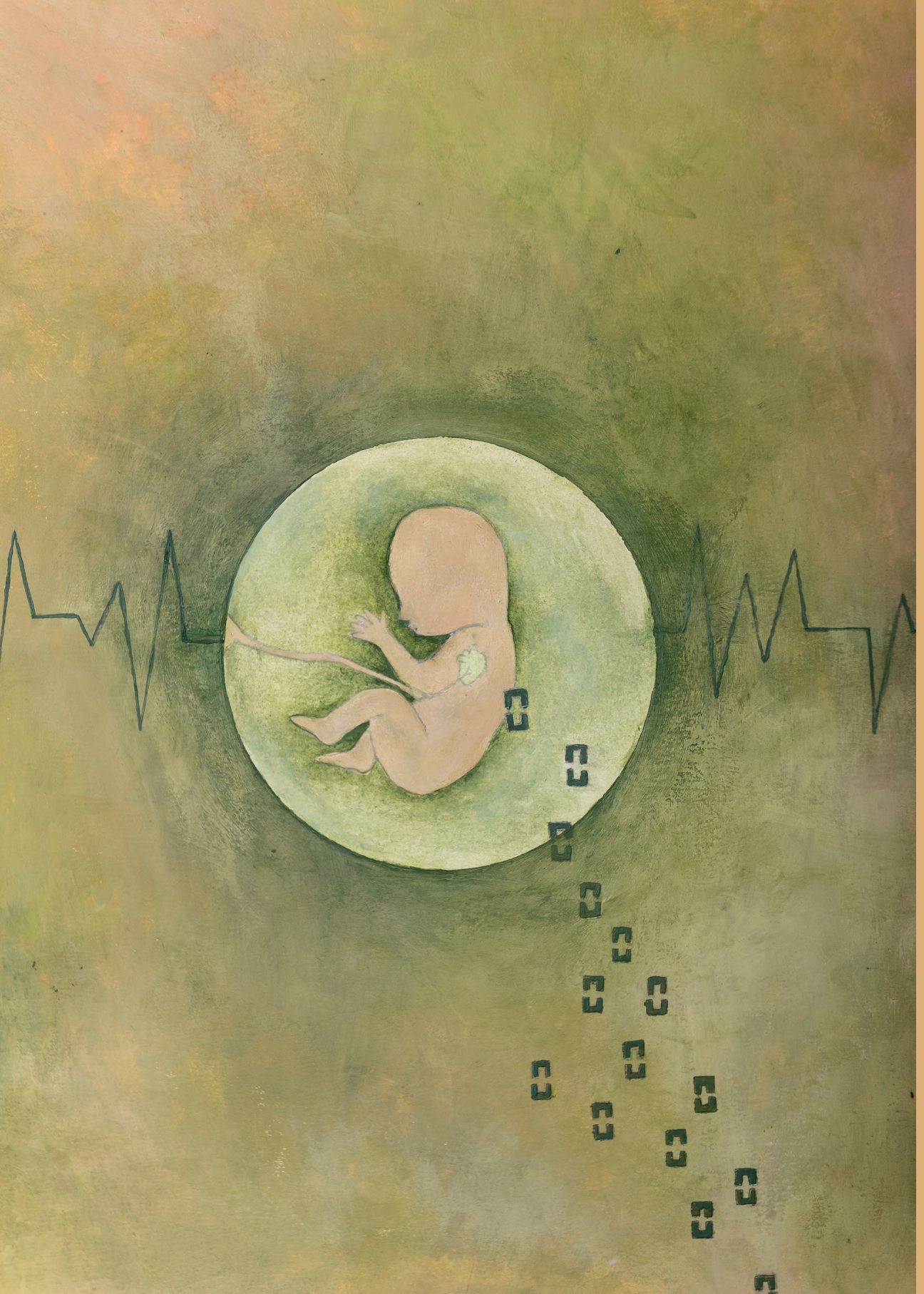


Chapter 3

Technical background

The fetal electrocardiogram

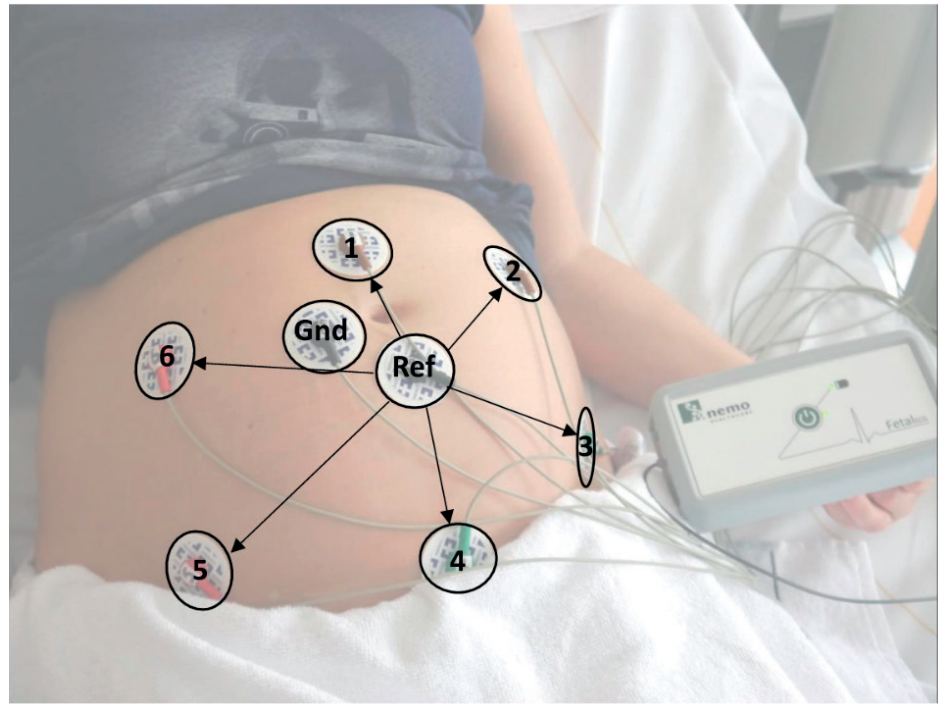
During labor the fetal electrocardiogram (fECG) can be directly obtained through an invasive manner, by means of a single electrode screwed in the top skin layer of the fetal scalp, the fetal scalp electrode (FSE).[1] This method can only be applied after fetal membranes are ruptured and is contra-indicated in the case of maternal HIV or hepatitis infection due to the risk of fetal transmission and suspected fetal bleeding disorder. Furthermore, it has an increased risk of complications such as trauma and infection.

A non-invasive method of recording the fECG is by means of electrodes placed on the maternal abdomen. In contrast to the FSE, this method can be applied throughout pregnancy. Although the non-invasive fetal electrocardiography (NI-fECG) technology was first described over a century ago by Cremer et al., development lagged behind the development of DU and FSE technology due to multiple technical difficulties.[2]

Signals recorded by abdominal electrodes are largely corrupted by several physiological interferences, such as the maternal ECG, abdominal muscle activity and the electrohysterogram, and non-physiological electrical interferences, leading to a low signal-to-noise ratio (SNR). The degree of SNR changes throughout pregnancy, being the lowest between 28 and 32 weeks of gestation with the development of the vernix caseosa. In this period the fetus is surrounded by a protective layer which causes electrical isolation of the fetus until dissolvement of the vernix around 32 weeks of gestation. The electrical isolation lowers the amplitude of the fetal ECG, thus lowering the SNR.[3,4]

The NI-fECG recordings used in this thesis are performed with either six (chapter 5 and 7) or eight (chapters 6, 8 throughout 11) self-adhesive electrodes including one reference and one ground electrode. Before application of the abdominal electrodes, the abdominal skin was washed with water and soap and then prepared using medical abrasive paper in order to lower skin impedance. The abdominal electrodes are placed in a fixed configuration on the maternal abdomen (Figure 1). The potential-difference between each electrode and the reference electrode is measured. As explained in chapter 2 – physiological background, electrical activity which propagates towards the electrode causes a positive deflection and electrical activity propagating away from the electrode causes a negative deflection. Each electrode thus records a different ECG waveform depending on the orientation of the fetal heart relative to that electrode which influences the projection of the cardiac electrical activity (heart vector) onto that electrode.[5] This multi-lead approach allows for recombination of leads to reconstruct the standard Einthoven leads, as used in adult cardiology.

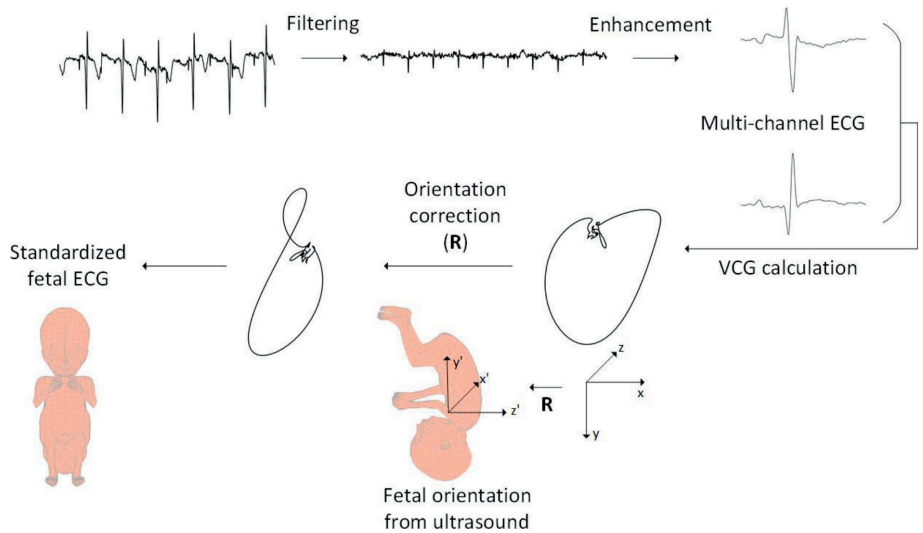
Figure 1. Placement of the abdominal electrodes in a fixed configuration.



Adapted from Lempersz et al. The standardized 12-lead fetal electrocardiogram of the healthy fetus in midpregnancy: A cross-sectional study.[6]

Unlike the recording of an adult ECG, where the position of the recording electrodes is fixed relative to the heart, the fetus is able to move around freely in utero. Fetal movements are reflected by a rotation of the vectorcardiogram (VCG). The VCG is a three-dimensional representation of the heart vector during one cardiac cycle.[7] In addition, fetal movement causes variation in the distance between the electrodes and the fetal heart causing attenuation or amplification of the fetal ECG signal. The VCG also allows for detection of changes in the fetal orientation in utero. When the fetal orientation is known, the VCG can be rotated accordingly and a normalized VCG can be obtained which aids in the calculation of a standardized ECG (Figure 2).

Figure 2. Schematic illustration of signal processing to obtain standardized fetal ECG.



Adapted from Lempersz et al. The standardized 12-lead fetal electrocardiogram of the healthy fetus in midpregnancy: A cross-sectional study.[6]

The fECG recordings undergo several preprocessing steps in order to obtain a beat-to-beat FHR or fetal ECG complex. First the maternal ECG is suppressed using a dynamic template subtraction technique.[8] Then by spatially combining the remaining signals to filter out electrophysiological interferences from e.g. muscle activity, the SNR was enhanced.[9] In this enhanced signal, fetal QRS complexes were identified using a method as described by Warmerdam et al. from which a beat-to-beat FHR is calculated.[10]

Power spectral analysis

Fetal heart rate variability (FHRV), which reflects R-R interval fluctuations, is a known marker for fetal wellbeing as discussed in chapter 2.[11] The clinical relevance of altered FHRV was noted as early as 1965 when Hon and Lee discovered that FHRV changes preceded changes in FHR in fetal distress. FHRV can be quantified in both the time and frequency domain. More knowledge and experience is available on the physiological background of frequency domain indices.[11] However, time domain analysis is often easier to perform.

Short-term variability (STV) and long-term variability (LTV) are examples of time-domain indices. STV reflects changes in successive R-R intervals and is calculated

based on the difference between successive inter-beat intervals.[12,13] When beat-to-beat FHR is unavailable such as during conventional CTG monitoring, STV is calculated by measuring the variation between adjacent epochs. LTV gives a measure for the overall variability and is calculated as the difference between the maximum and minimum inter-beat interval within a one-minute period.[13]

Power spectral analysis (PSA) is a method to quantify FHRV in the frequency domain. It reduces the FHR signal into a sum of its component sine and cosine waves.[14] PSA was first introduced by Akselrod in 1981, who found a link between oscillatory components of FHR and autonomic cardiac regulation.[15] High-frequency (HF) oscillations are associated with respiratory activity and regulated by the parasympathetic nervous system. Low-frequency (LF) oscillations represent a combination of the sympathetic and parasympathetic branches of the ANS and reflect the baroreceptor reflex.[11,15]

The HF band ranges from 0.4-1.5 Hz in both fetuses and newborns since the parasympathetic branch of the ANS acts in a higher frequency range in newborns compared to adults. The LF band ranges from 0.04-0.15 Hz.[11,16–19] Spectral estimates can be calculated in both absolute and normalized units. The advantage of using normalizing units is that relative changes in HF-power and LF-power are not masked by changes in total power.[11]

In this thesis, a continuous wavelet transform (CWT) with a fifth order symlet wavelet is used for spectral analysis. CWT enables a simultaneous time and frequency analysis, making CWT suitable for analysis of the non-stationary frequency content of a FHR signal.[20]

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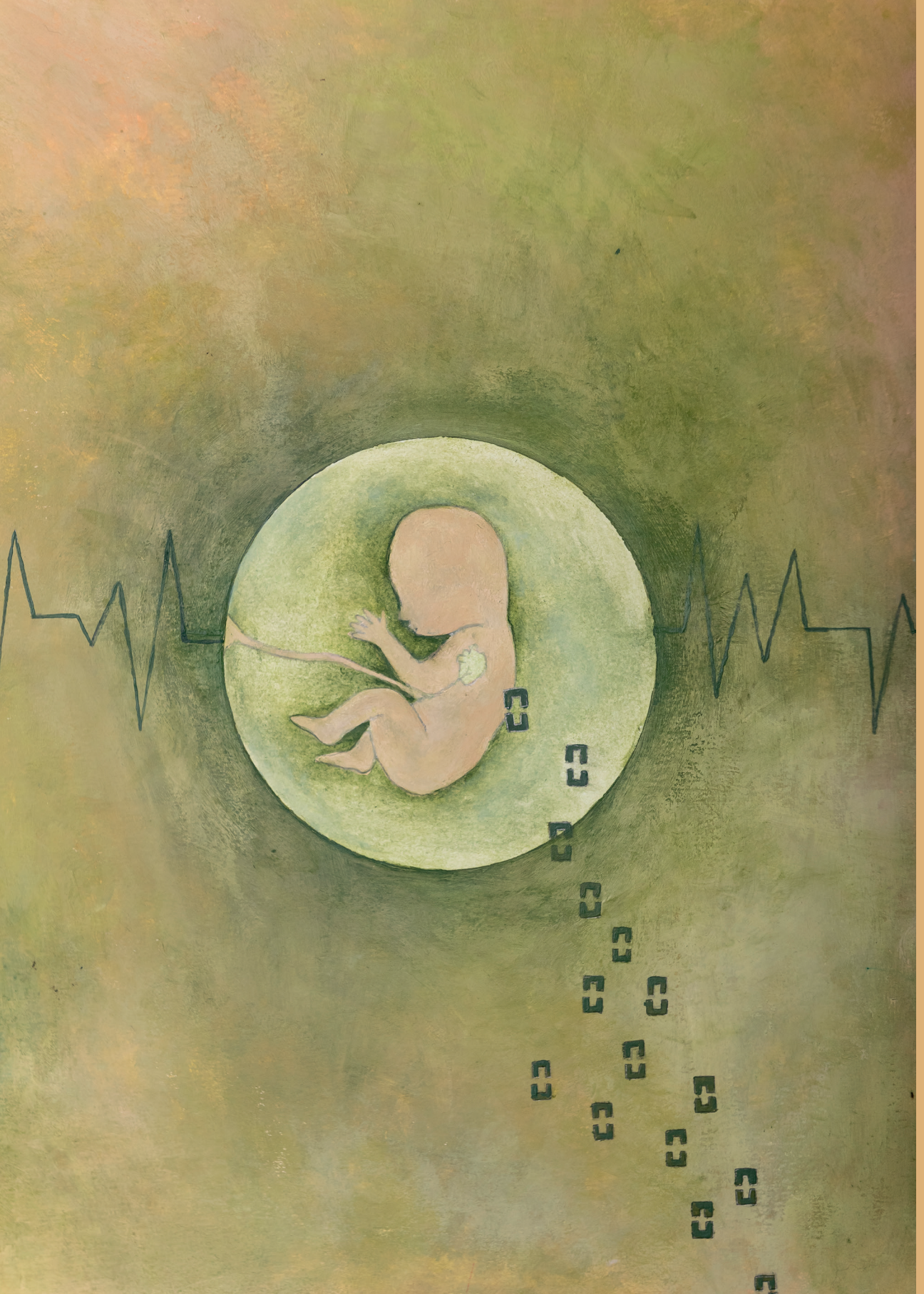
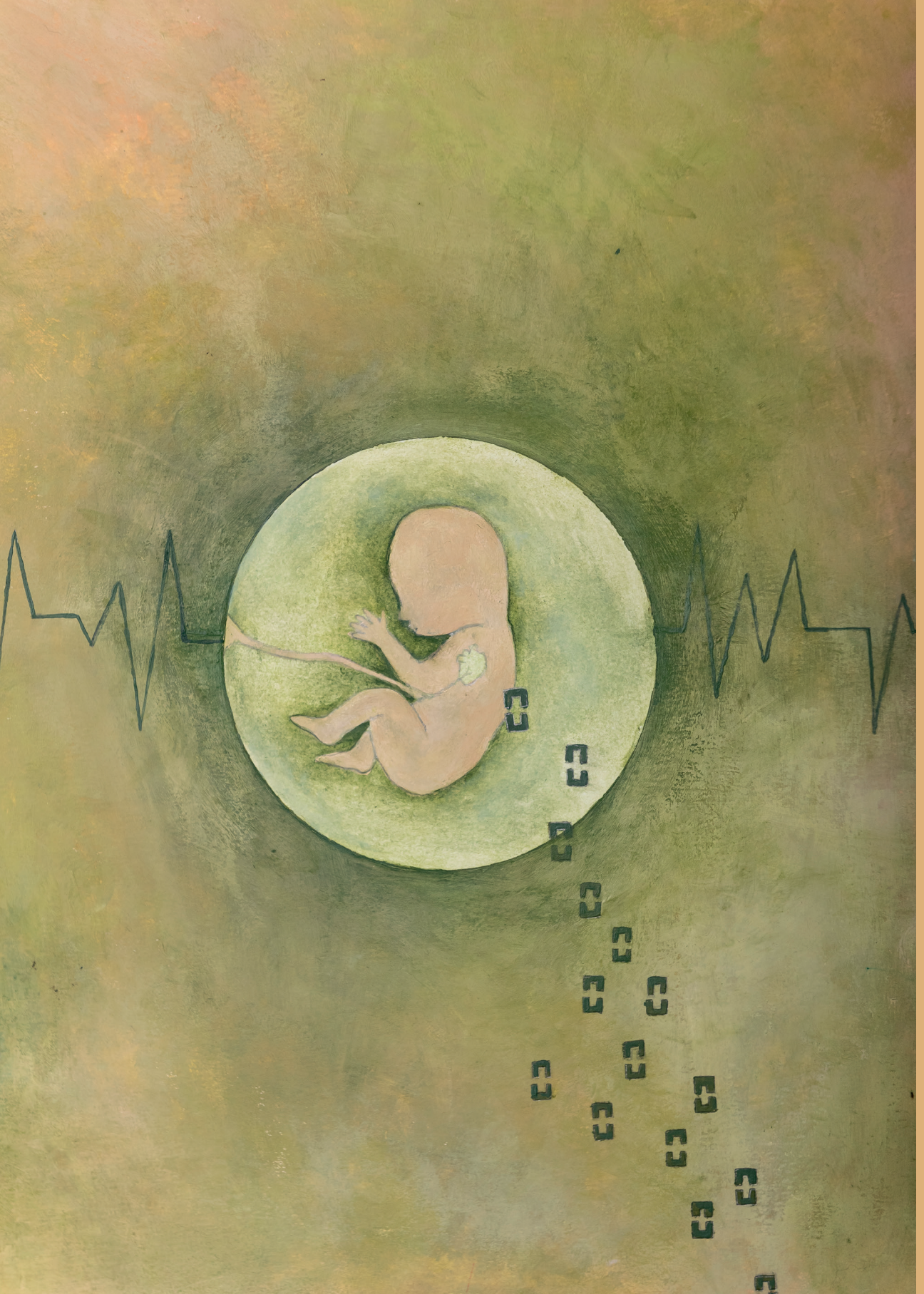


Part I

Fetal ECG for fetal monitoring



Chapter 4

The noninvasive fetal electrocardiogram during labor: a review of the literature

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ABSTRACT

Importance: The introduction of the cardiotocogram (CTG) during labor has not been found to improve neonatal outcome. The search for a more reliable, less invasive and patient-friendly technique is ongoing. The non-invasive fetal electrocardiogram (NI-fECG) has been proposed as one such alternative.

Objectives: To review the literature on the performance of NI-fECG for fetal monitoring during labor.

Evidence acquisition: Following the PRISMA guidelines a systematic search in MEDLINE, EMBASE and Cochrane Library was performed. Studies involving original research investigating the performance of NI-fECG during labor were included. Animal studies and articles in languages other than English, Dutch or German were excluded. The QUADAS-2 checklist was used for quality assessment. A descriptive analysis of the results is provided.

Results: Eight articles were included. Pooled analysis of the results of the separate studies was not possible due to heterogeneity. All studies demonstrate that it is possible to apply NI-fECG during labor. Compared to Doppler ultrasound, NI-fECG performs equally well or better in most studies.

Conclusions and Relevance: NI-fECG for fetal monitoring is a promising non-invasive and patient-friendly technique that provides accurate information. Future studies should focus on signal quality throughout labor, with the aim to further optimize technical development of NI-fECG.

INTRODUCTION

The cardiotocogram (CTG) for fetal heart rate and contraction monitoring during labor was introduced in the early 1970's to identify fetuses with hypoxia and to reduce neonatal morbidity and mortality.[1] Unfortunately, neonatal outcome has not improved after the introduction of the CTG.[1]

The two most commonly used techniques to acquire fetal heart rate (FHR) for CTG monitoring is via a non-invasive method using Doppler Ultrasound (DU), or with a more invasive method, the fetal scalp electrode (FSE). DU uses a transducer placed on the maternal abdomen and held in place with an elastic band. An advantage of the DU is that it is a non-invasive method that can be used before membranes have been ruptured. Unfortunately, DU is sensitive to signal loss with reported percentages ranging from 5.2% up to 40%.[2-4] This signal loss can partially be due to maternal and fetal movements, a high BMI of the mother and irregularities of the FHR i.e. decelerations, extrasystolic beats, and other cardiac arrythmias.[3-6] Furthermore, this method and the means of attaching the DU device to the maternal abdomen can be experienced as uncomfortable.[7] Invasive monitoring via FSE is a more reliable method and is considered the gold standard for FHR monitoring. However, this method carries an increased risk for complications, such as trauma and infection and can only be applied after membranes have been ruptured and with sufficient dilation.[8,9]

Overall, the specificity of CTG monitoring is poor.[1] Multiple techniques have been added to increase the detection rate of fetal hypoxia, i.e. fetal blood sampling (FBS) and ST waveform analysis (STAN). However, previous studies have demonstrated that these methods do not significantly decrease neonatal morbidity and mortality.[10-16]

The search for other monitoring techniques that can gather accurate information in a safe and patient-friendly way, is still ongoing. Non-invasive fetal electrocardiography (NI-fECG) may be an alternative to conventional monitoring techniques. The NI-fECG retrieves electrophysiologic signals of fetal and maternal heart rate (MHR), as well as the electrohysterogram (EHG) via electrodes placed on the maternal abdomen. This technique provides more information than FHR alone as it also provides beat-to-beat information that can be used to assess fetal heart rate variability. Furthermore, the NI-fECG provides a complete fetal ECG waveform that could be assessed for morphologic changes possibly indicating fetal hypoxia. In contrast to STAN, the NI-fECG provides a

multilead fetal ECG and therefore may overcome the current shortcomings in ST waveform analysis.[17-19]

NI-fECG is not a new technique, as first recordings were made in the early 1900s.[20] However, difficulties in acquiring and processing the electrophysiologic signals limited development of this technique. Recently, NI-fECG has gained renewed interest due to technical improvements. Over the last years more research has been performed on NI-fECG as an alternative for intrapartum fetal monitoring.

This paper aims to provide a review of the existing literature on the performance of NI-fECG as a method for fetal monitoring during labor.

MATERIALS AND METHODS

This review was registered in Prospero (#CRD42019124807). A systematic search in the electronic databases MEDLINE (1966-Present), EMBASE (1974-Present) and Cochrane library was performed until the 24th of April 2019. The search was conducted following the PRISMA guidelines by two independent researchers (LN and CL) and one trained medical librarian (BdV) from the Máxima Medical Center, Veldhoven, The Netherlands. The following search terms were used: fetus, electrocardiography, cardiotocography, fetal monitoring, non-invasive, labor, intrapartum (full electronic search is available in appendix A). The main outcome measures of interest were accuracy and reliability of the NI-fECG during labor compared to DU and/or FSE.

We only included original research. If there was any overlap between studies, we used the original article. Animal studies and articles in languages other than English, Dutch or German were excluded.

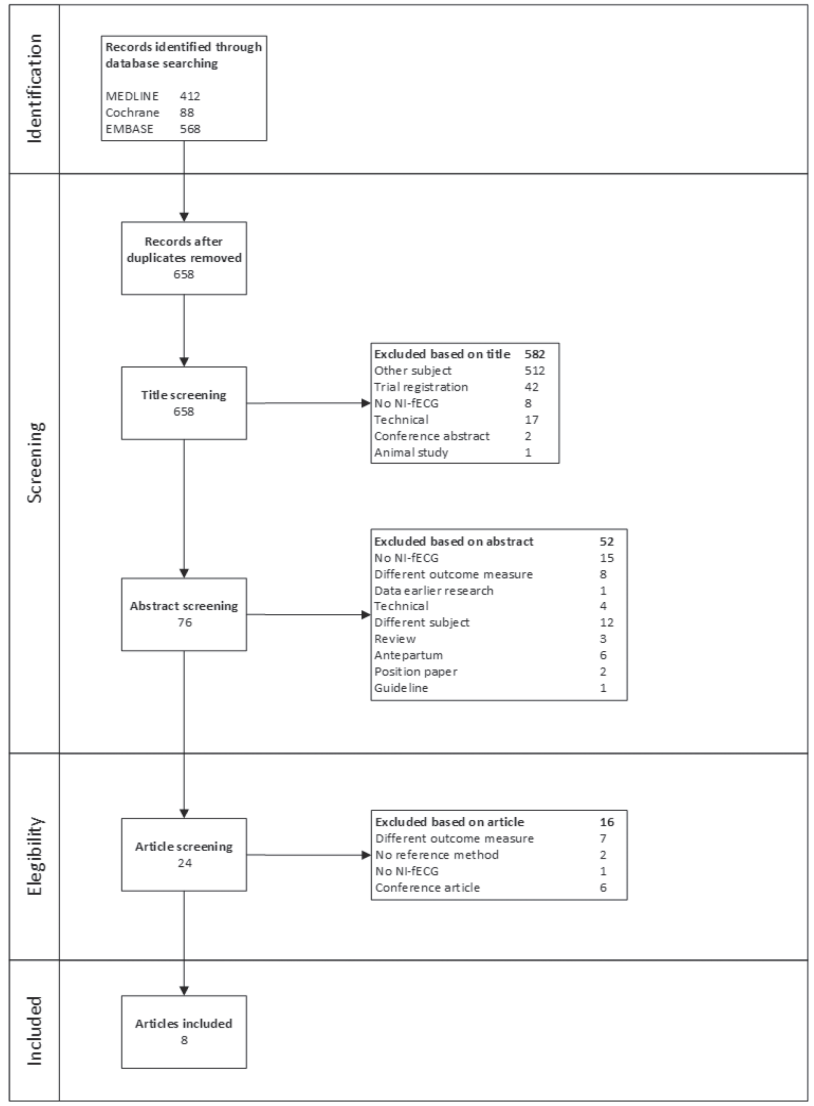
Articles were initially screened by title and abstract by two independent reviewers (LN and CL). When found appropriate, the full text was evaluated. Furthermore, references of the selected articles were checked for eligible articles. Disagreements were resolved by discussion.

The QUADAS-2 checklist was used as reference for quality assessment of the included studies.[21]

RESULTS

A total of eight out of 658 articles were included in this review after removal of duplicates, title and abstract screening, reading the full text articles and screening reference lists of the included articles. Seven articles describe a prospective study and one article a retrospective study. Figure 1 summarizes the screening and article selection process.

Figure 1. Flowchart article screening and selection process.



Pooled analysis of the results of the separate studies was not possible due to heterogeneity. Table 1 shows a summary of the quality assessment of the included articles. A summary of the eight included articles is enclosed in appendix B.

Table 1. Quality assessment of the eight included articles according to Quadas-2.[21]

	Risk of bias				*Applicability concerns*		
Study	**Patient selection**	**Index test**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Reference standard**
Breuker et al. 1976	?	+	+	+	+	-	+
Frank et al. 1992	-	+	+	+	+	-	+
Stampalija et al. 2012	+	+	-	-	+	-	-
Reinhard et al. 2012	+	+	-	+	+	-	+
Cohen et al.2012	-	+	+	-	+	+	+
Reinhard et al. 2013	+	+	-	+	+	-	+
Ashwal et al. 2017	+	+	+	+	+	+	+
Euliano et al. 2017	?	+	+	?	+	+	+

Accuracy

Accuracy is defined as the difference in FHR output from the investigational product (NI-fECG or DU) compared to the reference method (FSE) expressed in root mean square error (bpm). This definition of accuracy was reported in three included studies, using the FSE as the gold standard. Euliano et al. and Cohen et al. reported an overall accuracy of about 5 bpm for NI-fECG. For DU, overall accuracy was reported as 10.9 (± 5.8) bpm by Cohen et al. and 14.3 (± 8.2) bpm by Euliano et al.[22,23]

No difference in accuracy of NI-fECG between labor stages was found by Euliano et al, whereas Cohen et al. found a slight decrease in accuracy to 7.9 (± 4.2) bpm for the second stage of labor.[22,23]

Ashwal et al. reported a higher accuracy of 1.47 (± 0.82) bpm for NI-fECG and 5.39 (± 3.82) bpm for DU, using non-continuous segments for analysis.[24] Although they used segments from each stage of labor, they only report one accuracy value. Reported accuracy values were higher for NI-fECG compared to DU (see appendix B).[22-24]

Reinhard et al. chose the correlation coefficient to express accuracy for NI-fECG with DU as reference. They found a Spearman's rank correlation coefficient of 0.94 (range -0.11 to 0.99) for the first stage of labor and 0.85 (range -0.73 to 0.99) for the second stage of labor, suggesting a good statistical agreement between both methods.[25]

Frank et al. describe five cases of laboring women monitored by NI-fECG and FSE. Their definition of accuracy was the absolute difference in the R-R interval. They reported that 92.6% of the total time of each NI-fECG measurement lays within 1 bpm difference of the FSE measurement.[26]

Reliability

Reliability is defined as the percentage of time that the investigational product (NI-fECG or DU) generates a FHR output within 10% of the FHR output of the product used as reference (FSE), expressed as positive percent agreement (PPA). Both Cohen et al. and Euliano et al. compared NI-fECG with FSE. They found similar results for overall PPA for NI-fECG (81.7% (± 20.5) in Cohen et al. and 83.4% (± 15.4) in Euliano et al.). For DU, Cohen et al. reported an overall PPA of 73.0% (± 24.6) and Euliano et al. an overall PPA of 62.4% (± 26.5), both significantly lower than NI-fECG.

When the first stage of labor was considered separately, Cohen et al. found a PPA of 84.9% (± 21.5) for NI-fECG and 74.7% (± 28.2) for DU (<0.001). Euliano et al. found a PPA in the first stage of labor of 86.3% (± 14.7) for NI-fECG and 61.3% (± 29.6) for DU (<0.0001). Both Cohen et al. and Euliano et al. describe a drop in reliability percentages for NI-fECG and DU during the second stage of labor (71.9% (± 20.4) and 77.5% (± 15.1) for NI-fECG in Cohen et al. and Euliano et al., respectively, and 61.7% (± 24.8) and 64.8% (± 18.5) for DU). Overall, the reliability of NI-fECG is significantly higher than DU.[22,23] Ashwal et al. also used FSE as golden standard, but found a much higher PPA of 99% (± 1.72) for NI-fECG and 96.6% (± 4.6) for DU. They showed a decrease of 0.5% for NI-fECG and 1.7% for DU during the second stage of labor.[24]

Success rate

Success rate is defined as the percentage of time that NI-fECG or DU provide any output. Stampalija et al. reported an overall success rate of 88.5% (± 16.7) for NI-fECG and 89.4% (± 7.6) for DU (p = 0.77).[27] Cohen et al. found an overall success rate of 83.4% (± 20.1) for NI-fECG and 82.5% (± 21.1) (p = 0.38) for DU.[22] Stampalija et al. found a success rate of 89.8% (± 16.1) in the first stage of labor for NI-fECG and 89.9% (± 7.9) for DU (p = 0.98). In the second stage of labor a success rate of 66.5% (± 21.3) for NI-fECG and 83.7% (± 7.4) for DU (p = 0.001) was found.[27] Cohen et al. reported a success rate of 86.4% (± 20.1) for NI-fECG in the first stage of labor and 82.6% (± 24.4) for DU. In the second stage of labor this was 75.2% (± 19.2) and 77.8% (± 21.1) (p = 0.25), respectively.[22] Reinhard et al. also reported on the success rate of NI-fECG and DU. In the first stage of labor they found a success rate of 97.7% (7.8–100) for NI-fECG and 85.5% (35.1–99.8) for DU. In the second stage of labor this rate dropped to 85.5% (13.4–100) for NI-fECG, but rose to 92.3% (22.5–99.8) for DU.[25] In 2013 Reinhard et al. published another report with results on reliability using the abovementioned definition for success rate. The reliability reported in this paper for NI-fECG was 87.1% (± 19.10) for first stage and 70.5% (± 27.90) for second stage of labor.[28]

Signal loss

Breuker et al. reported on quality defined as signal loss, the percentage of time the NI-fECG did not provide an output. The quality of the NI-fECG was assessed by placing recordings in different categories: excellent (<5% signal loss), good (>5 - <10 % signal loss), satisfactory (>10 - <20% signal loss), sufficient (>20 - <35% signal loss), deficient (>35 - <50% signal loss), not interpretable (> 50% signal loss). Overall, 17.3% of the cases were classified as excellent, 23.1% as good, 26.6% as satisfactory, 17.9% as sufficient and 15.0% as deficient. In the first stage of labor, no cases had more than 50% signal loss whereas in second stage of labor this was 30%.[29]

Confusion rate

Stampalija et al., Reinhard et al. and Cohen et al. reported on the percentage of time the investigational product confused maternal heart rate (MHR) for fetal heart rate (FHR).[22,27,28] Stampalija et al. and Cohen et al. used the term confusion rate (CR) in their paper, whereas Reinhard et al. used the term MHR/FHR ambiguity. Stampalija et al. and Reinhard et al. used the NI-fECG as the reference method for MHR. Cohen et al. used pulse oximetry as the reference method for MHR.[22,27,28]

Cohen et al. defined confusion rate as the percentage of FHR determinations for which each external device (DU and NI-fECG) calculated a FHR value that was both more than 5% different from that of the FSE and within 5% of the MHR.[22] Stampalija et al. defined confusion rate as a FHR within 5 bpm of MHR.[27] Reinhard et al. used the same definition but called it MHR/FHR ambiguity.[28]

All three studies found a lower CR for the NI-fECG compared to DU. Stampalija et al. found a CR in the first stage of labor for DU and NI-fECG of 3.9% (± 4.6) and 1.0% (± 1.9), respectively. For the second stage this was 11.3% (± 8.2) and 4.6% (± 5.0) respectively.[27] Cohen et al. found a CR of 9.5% (± 17.8) in the first stage of labor for DU and 11.0% (± 15.4) in second stage of labor, whereas this was 0.3% (± 0.6) and 0.7% (± 0.8) for the NI-fECG, respectively.[22] Reinhard et al. showed an ambiguity of DU in the first stage of labor of 1.22% (± 1.9) and for NI-fECG of 0.70% (± 1.2). For the second stage of labor ambiguity was 6.20% (± 9.0) for DU and 3.30% (± 4.4) for NI-fECG.[28]

DISCUSSION

The most common method of monitoring fetal wellbeing during labor is by monitoring the FHR in relation to uterine contractions. Unfortunately, FSE, considered the gold standard for FHR monitoring, is invasive and carries risks for infection and trauma. Furthermore, FSE can be applied only when sufficient dilation of the cervix is achieved and membranes have ruptured. DU is a non-invasive method, but shows high percentages of signal loss, especially in obese women, and it is often is experienced as uncomfortable by the patient.[7] NI-fECG is a relatively new method based on electrophysiologic monitoring performed non-invasively using electrodes on the abdomen of the mother. Recent developments in signal processing techniques and improvements of algorithms make it possible to simultaneously monitor FHR, MHR and uterine contractions with one device in a non-invasive manner. Intrapartum monitoring by NI-fECG may therefore be an alternative for monitoring by FSE and DU. This review evaluates the performance of the NI-fECG technique during the last decade.

Performance measures of the NI-fECG

The earliest studies describing the use of NI-fECG during labor date back to the 20th century and therefore describe the performance of NI-fECG devices that are outdated.[26,29] However, such studies substantiate the potential added value of NI-fECG during labor, even when development of the technique was in a premature stage. Breuker et al. found that only 15% of the recordings were

of deficient quality and in the 5 cases described by Frank et al. 92.6% of the FHR output of the NI-fECG was within 1bpm of the FHR measured by FSE.[26,29]

Accuracy

All studies found a higher accuracy for the NI-fECG technique compared to DU, when using FSE as reference.[22-24] Both Cohen et al. and Euliano et al. report an accuracy of about 5 bpm, which is noticeably higher than their reported values for DU. However, there is a risk of selection bias in these studies since they only include women who received FSE for fetal monitoring due to insufficient quality of DU. Therefore, results of the performance measures of the DU may be negatively influenced. The insufficient quality of the registration by DU may be partially explained by the high median BMI of both study populations, since it is known that DU performance worsens with increasing maternal BMI.[30,31]

Ashwal et al. found a high accuracy for NI-fECG. Their reported accuracy for DU was also high compared to the literature. As they used random segments from the total recording, they may not be representative of the total measurement.[24]

Reinhard et al. used the correlation coefficient as an outcome measure to reflect the accuracy of their device, using the DU method as reference. They report a good statistical agreement between NI-fECG and DU (Spearman's rank correlation coefficient of 0.94 for the first stage of labor and 0.85 for the second stage of labor).[25] A correlation coefficient close to 1 means that there is a high level of agreement between the output of both devices. However, this is an inappropriate method for measuring accuracy, as the correlation coefficient only measures the strength of the linear association between variables.[32] In addition, since Reinhard et al. used the DU method, which has poor performance measures compared to FSE, as reference method, this high level of agreement has no clinical importance.

Reliability

A high reliability is an important property for a medical device to be of value in clinical practice. Cohen et al. and Euliano et al. found similar results for overall reliability (81.7 and 83.4 respectively) for NI-fECG monitoring. Overall reliability for DU reported by Cohen et al. and Euliano et al. is lower than NI-fECG (73.0 and 62.4). Reliability percentages decrease during the second stage of labor in both studies, for the NI-fECG as well as the DU technique.[22,23] This decrease in performance is a known disadvantage of the DU method, probably due to maternal movement and increased intra-abdominal pressure during the active pushing phase. Both Euliano et al. and Cohen et al. found higher reliability percentages for NI-fECG compared to the DU technique, also during the second stage of labor.[22,23] Reliability values reported by Ashwal et al. are nearly 100%, for both the NI-fECG and the DU method. As previously described, in this study random segments from the total measurement were used to analyze reliability.[24] The fact that their reported reliability value for the DU technique is 96.6% whereas other literature shows much lower reliability percentages for DU, further supports our explanation that these random segments are not representative for the entire measurement.[22,23]

Success rate

Only three articles reported on the success rate.[22,25,27] Since success rate is defined as the percentage of time the device provides output, it resembles the percentage of signal loss, without providing information on the quality of the registered information. A similar overall success rate for the NI-fECG and DU technique was reported by Cohen et al. and Stampalija et al.[22,27]

In all three articles a decrease in success rate of NI-fECG was noticed as labor progressed. This is also a known pitfall of the DU technique.[2] Cohen et al. found similar success rates between NI-fECG and DU (83.4% and 82.5% respectively).[22] Stampalija et al. found a significantly higher success rate for DU in the second stage of labor as compared to NI-fECG, which was also described by Reinhard et al.[25,27] They also report a rise in success rate between the first and second stage of labor for DU.[25] These results may demonstrate the limitation of success rate as an outcome measure if other outcome measures are not taken into consideration.

Reinhard et al. used a different definition for reliability. They defined reliability as the percentage of available FHR in the recorded time period. According to this definition, they found a significant difference in reliability between NI-fECG and DU during the first stage of labor (87.09% vs. 85.21%) but not during the second stage of labor (70.51%vs 76.46%).[28] Since no reference method was used to compare the FHR output from DU and NI-fECG interpretation of these results is difficult. In this setting, their definition for reliability better reflects the definition of success rate; the time the investigational device provides an output.

Confusion rate

From the articles that reported on MHR/FHR confusion only Cohen et al. used a validated method for MHR monitoring, which is pulse oximetry.[22] Reinhard et al. and Stampalija et al. used the NI-fECG device as a reference method for the performance measures being researched in their study.[27,28] Theoretically, by using NI-fECG, confusion between MHR and FHR is unlikely since electrophysiological signals from the mother are relatively strong compared to those of the fetus. Since NI-fECG is measuring both MHR and FHR by a single device, these signals can be separated very well. All three studies demonstrated that confusion of MHR and FHR is significantly lower with NI-fECG as compared to DU.[22,27,28] This is an important characteristic, since confusion of MHR and FHR can lead to unnecessary interventions or failure to intervene where intervention was needed, sometimes leading to a seriously compromised fetus.

General remarks

Overall, this review demonstrates that there is limited research regarding monitoring by NI-fECG during labor. Studies have small sample sizes and comparing them is difficult due to heterogeneity. Furthermore, three studies did not use the FSE as reference.[25,27,28] Therefore, interpretation and clinical validity of their results regarding accuracy, reliability and confusion rate is difficult.

Despite differences in methodology and type of NI-fECG devices, all included studies in this review demonstrate that it is possible to apply NI-fECG during labor. Compared to the currently used standard method for non-invasive fetal monitoring, which is DU, NI-fECG performs equally well, or better in most studies. Even during the second stage of labor, when a decrease in performance is noticed in most reports, it is shown that NI-fECG still performs equally or better compared to DU.[2] Studies that compare NI-fECG and DU with FSE showed that DU and NI-fECG have comparable success rates. However, compared to DU, accuracy and reliability of NI-fECG is higher and confusion rate is lower.

In two studies, the success rate for NI-fECG in the second stage of labor was lower compared to DU.[25,27] These success rates are insufficient according to the FIGO criteria for accepted percentages of signal loss of ≤20%.[33] One of these studies also showed a higher FHR/MHR confusion rate for DU, especially during the second stage of labor.[27] Even though DU may have a higher success rate, the output that is generated may not always be as reliable as NI-fECG. Although in fetal monitoring it is generally desirable to have a good signal quality at all times, it is most important to have a good balance between signal quality and the reliability of the generated output. This review therefore shows NI-fECG to be a more accurate alternative to DU.

In addition to improved test characteristics, patient satisfaction with this type of non-invasive monitoring is also better with NI-fECG, as compared to conventional non-invasive monitoring by DU.[7] Moreover, non-invasive monitoring by NI-fECG also yields several diagnostic opportunities. It may provide information on a preterm fetus, when invasive monitoring is not an option or discouraged due to contraindications. The NI-fECG provides beat-to-beat fetal heart rate, which enables the use of spectral analysis.[34] Spectral analysis can monitor the modulation of the autonomic nervous system by evaluating oscillations in beat-to-beat fetal heart rate and can differentiate between an asphyxiated and healthy fetus during labor.[35-39] Furthermore, the NI-fECG may provide information on the actual fetal ECG waveform complex, identifying other abnormalities that may indicate fetal distress. This has previously been attempted by combining FSE with ST waveform analysis (STAN).[13-16] Since the NI-fECG uses multiple leads, one of the limitations of STAN, which only uses a single lead scalp electrode, is avoided.[17-19]

To conclude, NI-fECG for FHR monitoring is a promising technique that is non-invasive, patient-friendly and provides accurate information. Future studies should focus on evaluating and improving signal quality of the NI-fECG, especially during the second stage of labor. Prospective studies on several diagnostic opportunities of this technique may help implementing NI-fECG in daily clinical practice.

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Appendix A. Search strategy: Medline (Pubmed, 1966 – present)

1. "Fetus"[Mesh] OR fetus[tiab] OR fetus*[tiab] OR fetal[tiab] OR fetal*[tiab]*
2. "Electrocardiography"[Mesh] OR electrocardiogram[tiab] OR ECG[tiab]*
3. "Cardiotocography"[Mesh] OR cardiotocogram[tiab] OR CTG[tiab]*
4. #2 OR #3
5. #1 AND #4
6. "Fetal Monitoring"[Mesh]
7. (fetal[tiab] OR fetal[tiab] OR fetus[tiab] OR fetus*[tiab]) AND monitor*[tiab]*
8. #6 OR #7
9. #5 OR #8
10. abdominal[tiab] OR noninvasive[tiab] OR external[tiab]
11. #9 AND #10
12. "Labor, Obstetric"[Mesh] OR labor[tiab] OR labor[tiab] OR intrapartum[tiab]
13. #11 AND #12

Appendix B. Summary of the eight included articles.

Author, year	Participants	NI-fECG method	Reference method	Outcome measures	Results during labor	Comments
Breuker 1976	**Inclusion criteria:** during pregnancy and labor	Prototype Hewlett & Packard, model nr. 15174 A.	FSE	**Quality:** percentage of signal loss	N=173. **Results:** Excellent: N=30 17,3% Good: N=40 23,1% Satisfactory: N=46 26,6% Sufficient: N=31 17,9% Deficient: N=26 15,0% 2nd stage: No clinical evaluation possible: N=34, 30.3%	· Used self-defined outcome measure.
Frank 1992	**Inclusion criteria:** term uncomplicated singleton pregnancy	Prototype Perinatronics Prototype FHR monitor.	FSE	**Accuracy:** Differences in R-R interval	N=5. **Results**: Mean difference R-R interval 0.0056 bpm Accuracy: - Within 1 bpm 92,6% - Within 2 bpm 98,2%	· Different definition of accuracy compared to other studies.

Appendix B. Summary of the eight included articles.

Author, year	Participants	NI-fECG method	Reference method	Outcome measures	Results during labor	Comments
Stampalija 2012	**Inclusion criteria:** uneventful term singleton pregnancy **Exclusion criteria:** multiple pregnancies, fetal abnormalities, presence of maternal pathologies	Monica AN24 [Monica Healthcare, Nottingham, UK]	DU telemetry	**(Overall) success rate of FHR monitoring:** Percentage of the 0.25 seconds epochs where a FHR was produced. **Maternal-fetal heart rate confusion (CR):** FHR within 5bpm from MHR.	N=41. N=21 1st and 2nd stage. N=18 1st stage only. **Results** Success rate: Overall DU 89.4% (±7.6), NI-fECG 88.5% (±16.7) (p0.77). 1st stage DU 89.9% (±7.9), NI-fECG 89.8% (±16.1) (p0.98) 2nd stage DU 83.7% (±7.4), NI-fECG 66.5% (±21.3) (p<0.001). Confusion rate: Overall DU 4.5% (±4.5), NI-fECG 1.3% (±1.9) p<0.001). 1st stage DU 3.9% (±4.6), NI-fECG 1.0 (±1.9) (p<0.001). 2nd stage DU 11.3% (±8.2), NI-fECG 4.6% (±5.0) (p=0.002).	· No gold standard as reference · 2 cases excluded: no FHR in fECG measurements due to high electrical noise · No gold standard used for MHR. MHR derived from Monica AN24

Appendix B. Summary of the eight included articles.

Author, year	Participants	NI-fECG method	Reference method	Outcome measures	Results during labor	Comments
Reinhard 2012	**Inclusion criteria:** Singleton pregnancy, admitted to Marien Hospital Witten for delivery.	Monica AN24 [Monica Healthcare, Nottingham, UK]	DU	**FHR Success rate**: Percentage of time a FHR value was reported divided by total time. **Percentage of patients with FHR signal loss <20% or <15%.** **Correlation:** Correlation between FHR success rate and BMI/stage of labor/birth weight/epidural	N=144. 1st stage N=138, 2nd stage N=98 **Results** Success rate: 1st stage. DU 85,5% (35.1-99.8%) NI-fECG 97.7% (7.8-100%) (p<0.001) 2nd stage: DU 92.3% (22.5-99.8%), NI-fECG 85.5% (13.4-100%), (p>0.05) Signal loss <20%: 1st stage: DU 89.6%, fECG 81.5% 2nd stage: DU 76.5%, fECG 54.1% Signal loss <15%: 1st stage: DU 80.7%, fECG 77.8% 2nd stage: DU 64.3% fECG 48%	· No gold standard as reference · Intermittent DU · For different baseline characteristics a mean and median is given · Data was excluded if: simultaneous DU and fECG <20min during 1st stage or <5 min during 2nd stage

Appendix B. Summary of the eight included articles.

Author, year	Participants	NI-fECG method	Reference method	Outcome measures	Results during labor	Comments
					Correlation: *1st stage fECG FHR success rate correlation with:* - 2nd stage fECG FHR 0.68 - Birth weight 0.22 - 1st stage CTG FHR 0.34 - 2nd stage CTG 0.15 - EDA 0.10 - BMI 0.00 *2nd stage fECG FHR success rate correlation with:* - DU 1st stage 0.15 - DU 2nd stage 0.41 - BMI -0.14 - Birth weight 0.19 - EDA -0.03	· Outlier removal: data outside a 60–200 bpm, FHR data within 5bpm from MHR, isolated FHR datapoints (FHR <10 s in duration with absolute FHR difference from the baseline of >15 bpm)

Appendix B. Summary of the eight included articles.

Author, year	Participants	NI-fECG method	Reference method	Outcome measures	Results during labor	Comments
Cohen 2012	**Inclusion criteria**: singleton term pregnancy, arrived at the hospital early in or prior to labor. **Exclusion criteria**: known major fetal anomaly, fetal malpresentation, maternal abdominal skin rash or history of adhesive sensitivity, patients only monitored with the two external monitors	Monica AN24 [Monica Healthcare, Nottingham, UK])	FHR: FSE MHR: Pulse oximetry	**Accuracy:** Comparison of FHR output from DU and NI-fECG with the average of FHR of the FSE. **Reliability:** output within 10% of the standard (FSE) **Success rate:** proportion of recording DU and NI-fECG had a non-zero output for FHR **Confusion rate (CR):** percentage of FHR of DU and NI-fECG that was both more than 5% different from that of the FSE and within 5% of the MHR.	N=138. N=75 complete for analysis. **Results** Overall reliability: Overall DU 73% (±24.6), NI-fECG 81,7% (±20.5) (p<0.01) 1st stage DU 74.7%(±28.2), NI-fECG 84.9% (±21.5) (p<0.01) 2nd stage DU 61.7% (±24.8), NI-fECG 71.9% (±20.4) (p<0.01) Accuracy: DU 10.6 bpm, NI-fECG 5.2 bpm (p<0.0001) 1st stage DU 8.7 bpm (±5.7), NI-fECG 4.5 (±2.4) (p<0.0001) 2nd stage DU 16.1 bpm (±7.6), NI-fECG 7.9 (±4.2) (p<0.0001)	· FSE was only applied when CTG was abnormal to substitute DU · 63 excluded participants · High mean BMI 32.6 kg/m2

Appendix B. Summary of the eight included articles.

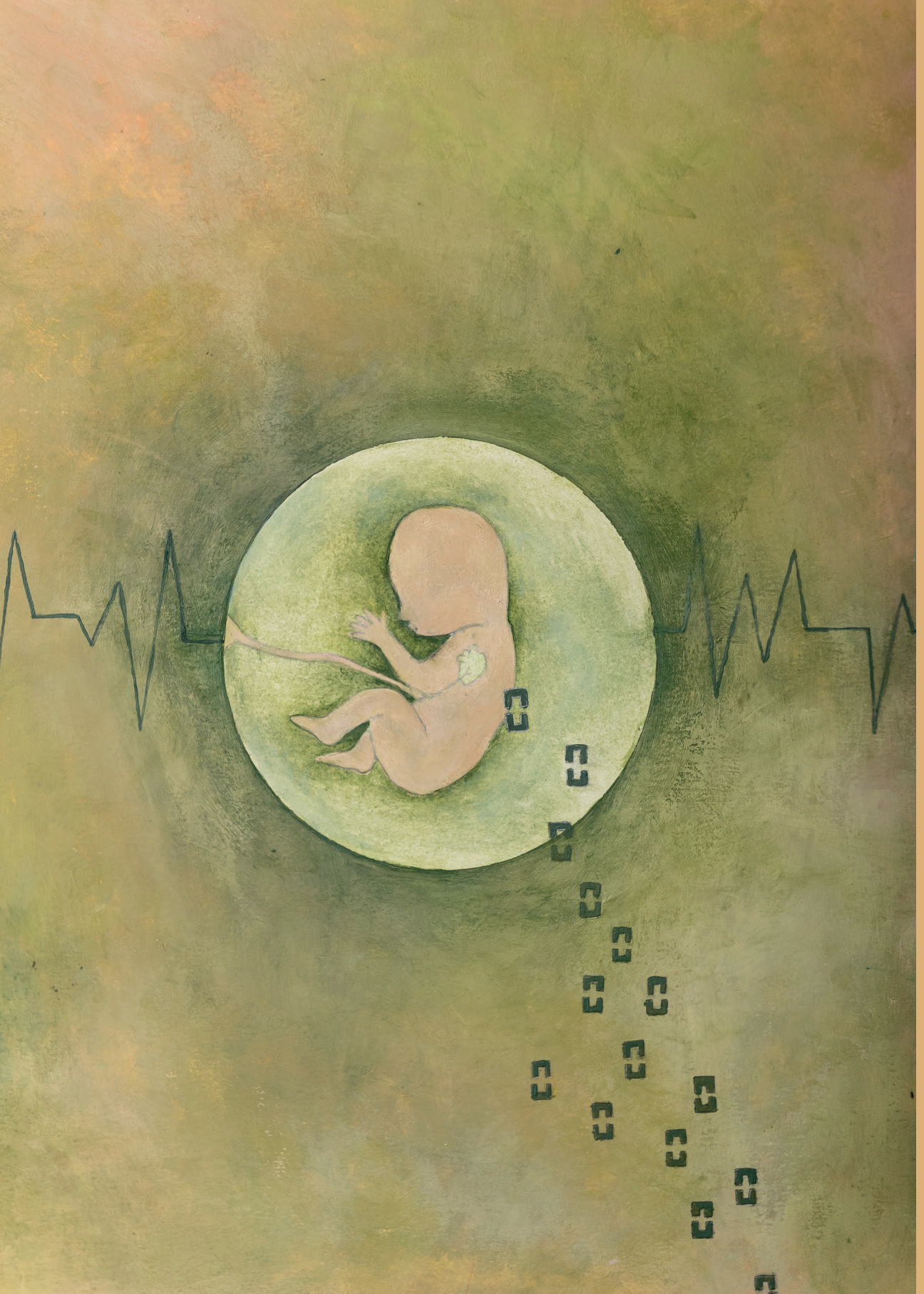
Author, year	Participants	NI-fECG method	Reference method	Outcome measures	Results during labor	Comments
					Success rate: DU 82.5% (±21.1), NI-fECG 83.4% (±20.1) (p=0.38) 1st stage DU 82.6% (±24.4), NI-fECG 86.4% (±21.1) (p=0.12) 2nd stage DU 77.8% (±21.1), NI-fECG 75.2% (±19.2) (p=0.25) Confusion rate (n=47): Overall DU 8.9% (±15.2), NI-fECG 0.4% (±0.6) (p0.0002). 1st stage DU 9.5% (±17.8), NI-fECG 0.3% (±0.6) (p0.0007) 2nd stage DU 11.0% (±15.4), NI-fECG 0.7% (±0.8) (p0.0007)	

Appendix B. Summary of the eight included articles.

Author, year	Participants	NI-fECG method	Reference method	Outcome measures	Results during labor	Comments
Reinhard 2013	**Inclusion criteria:** singleton pregnancy, admitted to Marien Hospital Witten for delivery.	Monica AN24 [Monica Healthcare, Nottingham, UK]	DU	**Percentage FHR and MHR ambiguity over total recording time:** FHR within 5bpm of MHR. **Reliability:** percentage of success rate of recording FHR data.	N=144. 1st stage N=135, 2nd stage N=98. **Results** Ambiguity 1st stage DU 1.22%, NI-fECG 0,70%(p<0.001) 2nd stage DU 6.20%, NI-fECG 3,30% (p<0.001) Reliability: 1st stage DU 85,2%, NI-fECG 87,1% (p<0.001) 2nd stage DU 76,5%, NI-fECG 70,5% (p>0.05)	· No gold standard as reference for FHR · No gold standard for MHR. MHR derived from Monica AN24 · Did not use the right definition for reliability. · For multiple characteristics a median and mean is given

Appendix B. Summary of the eight included articles.

Author, year	Participants	NI-fECG method	Reference method	Outcome measures	Results during labor	Comments
Ashwal 2017	**Inclusion criteria:** ≥18 years, singleton term pregnancy, no known fetal anomalies or chromosomal defects, spontaneous rupture of membranes during latent phase of labor. **Exclusion criteria:** signs suggestive for chorioamnionitis, implanted electronic device, maternal allergy to silver, irritated skin or open abdominal wounds	EUM100Pro [OB tools, Nesher, Israel]	FSE	**Correlation:** between DU and FSE, NI-fECG and FSE FHR traces. **Accuracy:** difference in FHR output of DU and NI-fECG compared to FSE	N=33. **Results** Correlation: DU/FSE and NI-fECG/FSE both r^2=0.98 (p<0.001). Reliability: Overall DU 96.0%, EUM 98.5%, (p<0,001). 1st stage DU 97.1%, NI-fECG 99.0% 2nd stage DU 94.9%, NI-fECG 98.5% Accuracy: DU 5.39 bpm, EUM 1.47bpm	· Only random non-continuous 30 minutes of the recording time was used for analysis from each phase (latent, 1st stage and 2nd stage) of labor. · Mean and median are given for correlation



Chapter 5

Intrapartum non-invasive electrophysiological monitoring: a prospective observational study

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ABSTRACT

Introduction: Doppler ultrasound (DU) cardiotocography (CTG) is a non-invasive alternative which despite its poor specificity is often first choice for intrapartum monitoring. DU suffers from signal loss due to fetal movements and is negatively correlated with maternal BMI. Reported accuracy of fetal heart rate (FHR) monitoring by DU varies between 10.6 and 14.3 beats per minute (bpm) and reliability between 62.4% and 73%. The fetal scalp electrode (FSE) is considered gold standard for fetal monitoring but can only be applied after membranes have ruptured with sufficient cervical dilatation and is sometimes contra-indicated. A non-invasive alternative which overcomes the shortcomings of DU, providing reliable information on FHR could be the answer. Non-invasive fetal electrocardiography (NI-fECG) uses a wireless electrode patch on the maternal abdomen to obtain both fetal and maternal heart rate signals as well as an electrohysterogram. We aimed to validate a wireless NI-fECG device for intrapartum monitoring in term singleton pregnancies, by comparison to the FSE.

Material and methods: We performed a multicenter cross-sectional observational study at labor wards of six hospitals located in the Netherlands, Belgium and Spain. Laboring women with a healthy singleton fetus in cephalic presentation and gestational age between 36 and 42 weeks were included. Participants received an abdominal electrode patch and FSE after written informed consent. Accuracy, reliability and success rate of fetal heart rate were determined, using FSE as reference standard. Analysis was done for the total population and measurement period as well as separated by labor stage and BMI class (≤ 30 and > 30 kg/m^2).

Results: We included a total of 125 women. Simultaneous registrations with NI-fECG and FSE were available in 103 women. Overall accuracy is -1.46 bpm and overall reliability 86.84%. Overall success rate of the NI-fECG is around 90% for the total population as well as for both BMI subgroups. Success rate dropped to 63% during second stage of labor, similar results are found when looking at the separate BMI groups.

Conclusion: Performance measures of the NI-fECG device are good in the overall group and the separate BMI groups. Compared to DU performance measures from the literature, NI-fECG is a more accurate alternative. Especially, when patients have a higher BMI, NI-fECG performs well, resembling FSE performance measures.

INTRODUCTION

External monitoring of the fetal heart rate (FHR) and uterine activity by means of Doppler ultrasound (DU) and tocodynamometry (TOCO) is often first choice for intrapartum monitoring. Monitoring by means of fetal scalp electrode (FSE) and intra-uterine pressure catheter (IUPC) remain the gold standard, but healthcare providers are cautious in applying these invasive methods due to risk of injury and infection.[1] Compared to the FSE, performance measures for DU are poor. Previous studies found an accuracy varying between 10.6 and 14.3 beats per minute (bpm) and reliability varying between 62.4% and 73%.[2,3] Furthermore, the performance of both DU and TOCO deteriorates with increasing maternal BMI and are susceptible to signal loss due to fetal and maternal movements.[4,5]

Development of additional technologies to improve the poor specificity of the CTG did not significantly improve perinatal outcome (e.g. ST waveform analysis, fetal blood sampling).[6,7] A reliable non-invasive fetal monitoring method which overcomes the shortcomings of DU and TOCO, with the possibility of obtaining additional information regarding fetal wellbeing could be the answer.

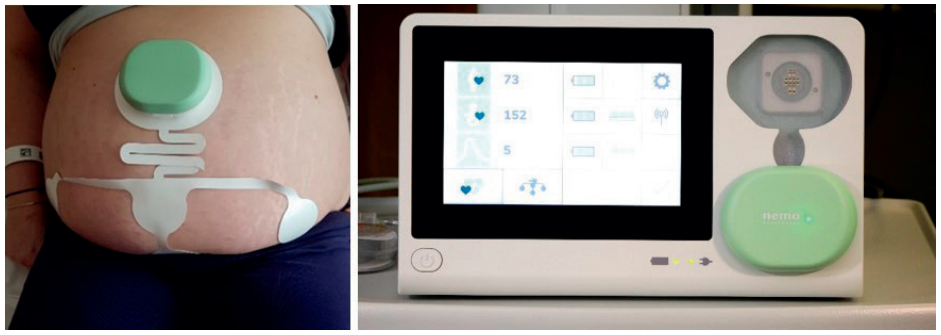
Non-invasive fetal electrocardiography (NI-fECG) is a relatively new technology that uses an electrode patch on the maternal abdomen to monitor both fetal and maternal heart rate (MHR) as well as uterine activity. The NI-fECG technology relies on electrophysiological signals to deliver beat-to-beat information on the FHR, by detecting a real-time ECG. Uterine activity can also be monitored using electrophysiology, by means of electrohysterography (EHG). Previous studies have shown that EHG has a higher sensitivity in detecting uterine contractions during labor, especially in obese women.[8,9] In this study, we aimed to validate a wireless NI-fECG device as a non-inferior method to DU for intrapartum fetomaternal monitoring in term singleton pregnancies, by comparison to the FSE. Furthermore, we compared our results with the performance measures of DU from existing literature.[2,3]

MATERIALS AND METHODS

We conducted an international multicenter cross-sectional observational study from February 2018 until July 2018. Women in established labor, carrying a healthy singleton fetus in cephalic presentation, with a gestational age between 36 and 42 weeks were eligible to participate. Exclusion criteria were multiple pregnancy, contra-indications for FSE, dermatologic diseases of the abdomen and signs

of fetal distress at the moment of inclusion. After written informed consent, participants received an electrode patch (Nemo Healthcare BV, Veldhoven, the Netherlands) consisting of 6 electrodes (Figure 1). First, to improve signal quality, the skin was washed with water and soap and prepared using medical abrasive paper (Red Dot™ Trace Prep, 3M Health Care, Ontario, Canada). Second, the electrode patch was applied and a wireless amplifier (link) was placed on top of the patch (Figure 1). Skin impedance was automatically checked and skin preparation was repeated if necessary.

Figure 1. NI-fECG electrode patch and device.



The left picture shows the electrode patch with a green amplifier (Link). On the right, a pre-production version of the NI-fECG base station is shown, with two charging positions for individual Links.

Patients were simultaneously monitored according to standard clinical protocol with DU (Philips Avalon FM30 CTG, Philips Healthcare, Eindhoven, the Netherlands) in the period before rupture of membranes. DU was replaced by our standard reference (FSE) once membranes had ruptured as part of standard clinical practice, which was connected to the CTG monitor (Philips Avalon FM30 or STAN® S31 monitor, Neoventa Medical AB, Mölndal, Sweden). Both the NI-fECG device (Nemo healthcare BV, Veldhoven the Netherlands, not commercially available) and the CTG monitor were connected to an external datalogger (CMS series 50) to ensure parallel data storage from both devices. NI-fECG measurement ended once the woman gave birth, when cesarean delivery was needed, when the woman ended participation or when she wanted to take a bath or shower.

Data acquisition and signal processing

Signals recorded by each of the electrodes were digitized and pre-processed by the link and transmitted wirelessly to the base station. Further signal processing was performed via proprietary algorithms and comprised checking the validity of the received data, suppression of maternal ECG and other interferences (e.g. from abdominal muscles and mains powerline), and subsequent calculation of FHR, MHR, and uterine activity.

The FHR, MHR, and uterine activity values were calculated at 0.25s intervals (4 Hz) and via serial port communicated to aforementioned data logger and central monitoring system. To enable retrospective analysis, calculated FHR, MHR, and uterine activity values, as well as raw data, are also locally stored on the base station.

Statistical analysis

Power calculations

Sample size calculation was performed based on paired data from our pilot study (data not published) in 50 term singleton deliveries at the Máxima Medical Center. A sample size of 100 patients enables the estimation of the standard deviation (SD) with a precision of 0.34*SD. This sample size together with the SD from the pilot study of 8.6 bpm will enable with 80% power for the estimate of the accuracy to lie within 95% confidence within 3.5 bpm. This margin for accuracy was considered to be clinically significant by several obstetric clinicians. Taking into account a missing data rate of 20%, we aimed to include 120 participants.

Analyses were done for the total population and measurement period as well as separated by labor stage (first and second stage)[10] and BMI class based on the preconceptional weight (≤ 30 and > 30 kg/m^2).

Fetal heart rate

The FSE was used as reference standard to determine the performance measures of FHR. We then later compared our results descriptively with DU performance measures as described in the literature.

Accuracy (bpm) was calculated as the difference between NI-fECG and FSE value. To account for multiple observations on the same subject, accuracy was determined following the method of Bland & Altman. The 95% confidence interval (CI) was first determined by averaging accuracies per subject and subsequent calculating mean and SD of these averages. This 95% CI was compared with the aimed accuracy of 3.5 bpm. Limits of agreement (LoA) were determined using the approach for precision of estimated LoA.[11] In addition, FHR values of NI-fECG and FSE were compared through bootstrapping.[12] Each

bootstrap sample was generated by drawing a random data-point (1 paired value for NI-fECG and FSE for each patient included in the analysis). Mean difference, SD and LoA were determined for the bootstrap sample. This process was then frequently repeated, leading to large distributions for the mean difference and lower and upper LoA. The average accuracy and 95% CI were then determined by taking the mean of the distribution of mean differences, with associated bootstrap 95% CI as determined by 2.5% and 97.5% percentile of the distribution of 10,000 mean differences from the bootstrap samples. From the 10,000 bootstrap samples also the mean S (SD of the bootstrap sample) was derived. LoA were then defined as mean accuracy +/- 2*mean(S).

Reliability is defined as the percentage of time in which the NI-fECG device delivers a FHR value within 10 bpm of the FSE value, during the period when both devices deliver output. Reliability was determined for each subject. Mean, SD and 95% CI of the mean reliability were calculated.

Success rate is defined as the percentage of time in which the NI-fECG device delivers a FHR value. Success rate was determined following the same steps as described for reliability. In addition, success rate of the three modalities were compared using a non-parametric test on ranks, adjusted for multiple comparison using Tukey-Kramer.

Maternal heart rate

Accuracy and reliability of MHR monitored by NI-fECG was compared to MHR monitoring by standard of care such as Doppler pulse measurements provided by abdominal pulse oximetry, incorporated in the TOCO button (Philips Avalon FM30 CTG, Philips Healthcare, Eindhoven, the Netherlands) or finger pulse oximetry (LNCS DC-I® Adult digit sensor, Masimo, Neuchatel, Switzerland), depending on local protocol. Accuracy and reliability were determined as described under FHR. The clinically relevant boundaries were set at +/-10 bpm. Both upper and lower LoA should lie within these boundaries.

Uterine activity

We aimed to include 10 women who received an IUPC for contraction monitoring during labor. Due to the rarely reported risks of the IUPC, it is not routinely applied during labor and in some hospitals only used on indication.[13,14] Since the EHG algorithm incorporated in this NI-fECG device is an improved version of a previously validated technology[15], we believed that this limited number of IUPC registrations would be sufficient for validation of contraction monitoring.

Ethical approval

The study protocol was approved by the institutional review board of the Máxima Medical Center on the 22nd of December 2017 (NL63732.015.17), University Hospital Antwerp on the 7th of May 2018 (B300201836393), La Paz Hospital Madrid on the 25th of March 2018 (PI-3140) and by local feasibility advisory committees in the remaining Dutch participating centers. The trial was registered in the Dutch trial register (www.trialregister.nl, NTR7064).

RESULTS

From 125 laboring women informed consent was obtained. Figure 2 shows the flow diagram of patient inclusion. Baseline characteristics of 121 participants of which data was available are shown in table 1. These were similar to the baseline characteristics of the subgroup of 103 participants of whom combined registration by FSE and NI-fECG was available for analysis of our main outcome parameters.

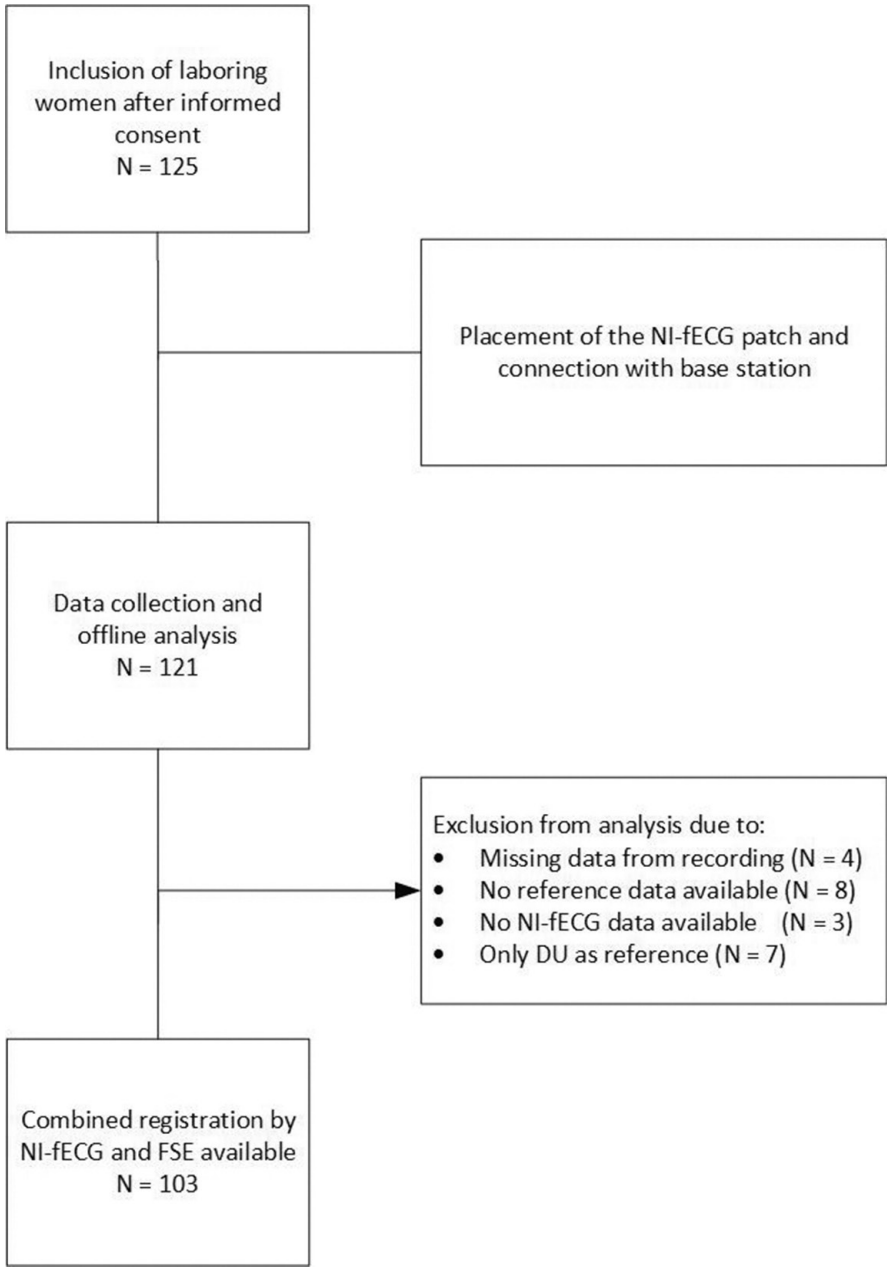
Average duration of combined monitoring by NI-fECG and FSE for all participants was 223.6 minutes.

Table 1. Baseline Characteristics.

Characteristics	N	
No. patients	121	
Age (years)	121	30.8 ± 4.6
Gestational age (wks)	121	39.5 ± 1.5
Ethnicity (%)		
Caucasian		83.5
Other		16.5
BMI (kg/m²)		
BMI category (%)		28.1 ± 5.9
≤ 30 kg/m²	82	67.8
> 30 kg/m²	38	31.4
Missing	1	0.8
Parity (%)		
Nullipara	61	50.4
Multipara	60	49.6
EDA (%)		
Yes	73	60.3
No	48	39.7

Data provided are percentages (%) or means ± SD.
Abbreviations: BMI = body mass index, EDA = epidural analgesia.

Figure 2. Flow diagram of patient inclusion.



Fetal heart rate

Overall accuracy of NI-fECG device is -1.46 bpm (SD 4.22, 95% CI [-3.4, 0.48]) compared to FSE. The results were similar in both first and second stage, the latter having a larger SD leading to a wider 95% CI (table 2). Separate analysis based on BMI showed a slightly better accuracy in the higher BMI class with a more narrow LoA (table 2).

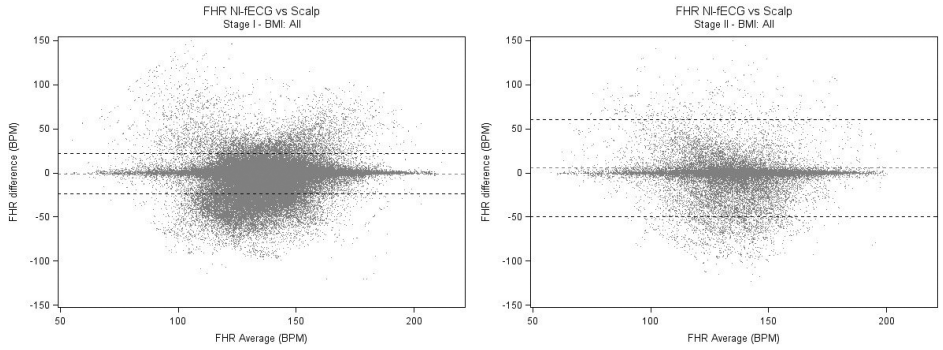
Table 2. Accuracy of FHR measurements by NI-fECG as compared to FSE.

						Limits of agreement	
	Accuracy	**SD**	**95% CI**	**Min**	**Max**	**Lower**	**Upper**
All patients							
Overall (N = 103)	-1.5	4.2	-3.4; 0.5	-29.6	7.5	-29.2	26.3
Stage 1 (N = 102)	-1.4	3.7	-3.2; 0.4	-19.0	8.9	-27.2	24.4
Stage 2 (N = 56)	-1.7	8.2	-5.4; 2.0	-38.8	77.8	-42.4	39.0
BMI ≤ 30 kg/m²							
Overall (N = 68)	-1.7	4.7	-4.2; 0.8	-29.6	5.7	-31.4	28.0
Stage 1 (N = 67)	-1.7	4.0	-4.0; 0.7	-19.0	4.7	-29.5	26.2
Stage 2 (N = 39)	-1.8	9.2	-6.4; 2.7	-38.8	72.6	-45.2	41.5
BMI > 30 kg/m²							
Overall (N = 34)	-1.0	3.0	-4.2; 2.1	-13.2	2.4	-29.3	27.2
Stage 1 (N = 34)	-1.0	2.6	-3.8; 1.9	-12.6	2.1	-26.8	24.9
Stage 2 (N = 16)	-1.6	6.0	-8.5; 5.3	-17.4	77.8	-47.4	44.1

Accuracy is presented as beats per minute (bpm). Stage refers to stage of labor.
Abbreviations: BMI = body mass index, CI = confidence interval, SD = standard deviation, min = minimum, max = maximum.

Sensitivity analysis using bootstrapping to illustrate the relative accuracy showed similar results (data not shown separately). Figure 3 shows bland-Altman plots for this analysis for both first and second stage of labor.

Figure 3. Bland-Altman plot including limits of agreement (LoA) of FHR difference between NI-fECG and FSE for all subjects for stage 1 of labor (left) and for stage 2 of labor (right), using bootstrapping.



Overall reliability (N = 103) of the NI-fECG device compared to the FSE is 86.8% ± 16.3%, 95% CI [84.17, 89.50]. For the first stage of labor only (N = 102), reliability is slightly higher (88.4% ± 14.6%, 95% CI [86.04, 90.83]). Reliability in the second stage of labor (N = 56) was 68.5% ± 24.5%, 95% CI [62.93, 74.08].

When the different BMI classes were analyzed separately, we found a slightly higher reliability for the higher BMI group (table 3).

Table 3. Reliability of FHR measurements by NI-fECG, according to BMI.

	Mean (± SD)	95% CI
BMI ≤ 30 kg/m²		
Overall (N = 68)	85.9 ± 17.7	82.33, 89.5
Stage 1 (N = 67)	87.8 ± 15.5	84.67, 91.0
Stage 2 (N=38)	68.7 ± 25.7	61.70, 75.8
BMI > 30 kg/m²		
Overall (N = 34)	89.1 ± 13.0	85.3, 92.9
Stage 1 (N = 34)	90.1 ± 12.7	86.4, 93.7
Stage 2 (N = 15)	67.8 ± 22.8	57.4, 78.2

Reliability is presented as percentages. Data provided are means ± standard deviation (SD). Stage refers to stage of labor.
Abbreviations: BMI = body mass index, CI = confidence interval.

Table 4 shows success rate of all three monitoring techniques used in our study. FSE had the highest success rate (97.7%). NI-fECG had a higher overall success rate compared to DU. When first and second stage of labor were analyzed separately, the success rate of NI-fECG in the first stage of labor was higher than DU, whereas the success rates during the second stage of labor were similar. In the higher BMI class (>30 kg/m²) success rates of NI-fECG were higher compared to DU (table 4).

Table 4. Success rates of all three monitoring modalities.

	NI-fECG	FSE	DU
All patients			
Overall			
No. patients	118	105	48
Mean (±SD)	89.5[ab] (± 10.8)	97.8 (± 3.3)	82.8[c] (± 23.1)
[95% CI]	[87.9, 91.1]	[97.2, 98.3]	[77.3, 88.4]
Stage 1			
No. patients	118	104	39
Mean (±SD)	91.3[a] (± 9.9)	98.6 (± 3.2)	88.1[c] (± 16.2)
[95% CI]	[89.8, 92.8]	[98.1, 99.1]	[83.7, 92.4]
Stage 2			
No. patients	63	65	12
Mean (±SD)	63.3[a] (± 21.7)	89.3 (± 17.6)	64.6[c] (± 32.2)
[95% CI]	[58.7, 67.8]	[85.7, 93.0]	[47.9, 81.3]
BMI ≤ 30 kg/m²			
Overall			
No. patients	80	70	32
Mean (±SD)	88.9[ab] (± 11.4)	97.9 (± 2.9)	84.1[c] (± 23.9)
[95% CI]	[86.8, 91.1]	[97.3, 98.5]	[77.90 91.3]
Stage 1			
No. patients	80	69	26
Mean (±SD)	90.7[a] (± 10.7)	98.6 (± 2.4)	89.0[c] (± 18.2)
[95% CI]	[88.7, 92.7]	[98.2, 99.1]	[82.9, 95.1]
Stage 2			
No. patients	44	46	9

Table 4. Continued.

	NI-fECG	FSE	DU
Mean (±SD)	62.2[a] (± 21.8)	91.7 (± 13.0)	67.9[c] (± 31.1)
[95% CI]	[56.6, 67.7]	[88.5, 94.9]	[48.6, 87.2]
BMI > 30 kg/m²			
Overall			
No. patients	37	34	15
Mean (±SD)	91.0[a] (± 9.5)	97.7 (± 3.6)	79.2[c] (± 22.3)
[95% CI]	[88.3, 93.6]	[96.7, 98.8]	[69.1, 89.4]
Stage 1			
No. patients	37	34	12
Mean (±SD)	92.6[a] (± 8.1)	99.2 (± 1.3)	85.3[c] (± 11.7)
[95% CI]	[90.4, 94.9]	[98.8, 99.6]	[79.3, 91.4]
Stage 2			
No. patients	18	18	3
Mean (±SD)	66.4[a] (± 22.4)	82.7 (± 25.4)	54.8 (± 40.2)
[95% CI]	[57.2, 75.6]	[72.2, 93.1]	[-13.1, 122.6]

Success rate is presented as percentages. Data provided are means ± standard deviation (SD).
Stage refers to stage of labor.
To test for significant differences between the monitoring modalities, post-hoc non-parametric test on ranks was performed with adjustment for multiple comparison using Tukey-Kramer.
[a] $p<0.05$, NI-fECG vs FSE, [b] $p<0.05$ NI-fECG vs Doppler, [c] $p<0.05$ Doppler vs FSE.
Abbreviations: NI-fECG = non-invasive fetal electrocardiography, FSE = fetal scalp electrode, DU = doppler ultrasound, BMI = body mass index, CI = confidence interval.

Maternal heart rate

For MHR monitoring 118 patients were monitored using NI-fECG, with an average monitoring duration of 258.8 minutes. For 83 patients paired data of NI-fECG and conventional MHR monitoring were available, with an average paired monitoring duration of 227.8 minutes.

Overall accuracy of NI-fECG for MHR is 0.54 bpm (SD 1.30, 95% CI [-0.67; 6.50]) compared to conventional MHR monitoring. Separate analysis based on separate labor stages and BMI classes showed similar results.

Overall reliability (N= 80) of the NI-fECG as compared to conventional monitoring was 95.33% ± 10.09%, 95% CI [93.45, 97.21]. For the first stage of labor alone (N = 79), reliability remained equal (95.76% ± 10.32%, 95% CI [93.82, 97.69]). For the 35 patients from whom results from second stage of labor were available, reliability was 89.87% ± 10.55%, 95% CI [86.86, 92.89].

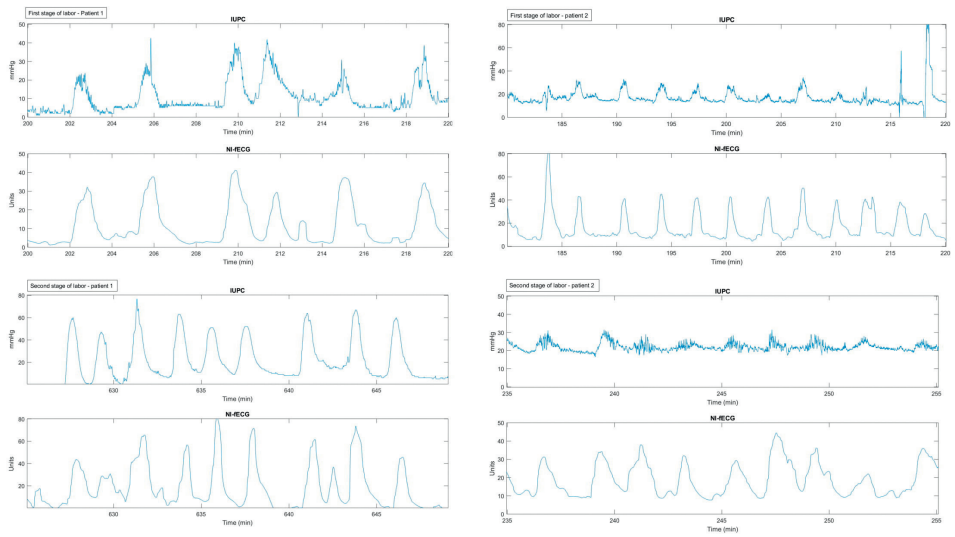
When the different BMI classes were analyzed, we found similar results for reliability percentages in both groups (data not shown).

Overall success rate for MHR monitoring by NI-fECG was higher than conventional monitoring techniques, approaching 100% for all stages of labor as well as for analysis according to BMI class.

Uterine activity

We included 10 women who received an IUPC during labor. Unfortunately, skin impedance was too high in 8 of these measurements, making it impossible to extract EHG signals. In the remaining 2 inclusions, EHG registration was sufficient for comparison with the IUPC. In both patients, the recording from both the EHG and the IUPC agreed well (Figure 4).

Figure 4. Simultaneously registered contractions with both the intra-uterine pressure catheter (IUPC) and electrohysterogram (EHG) during first (top figure) and second stage (bottom figure) of labor of both patients.



DISCUSSION

Main Findings

To validate this technology for intrapartum fetomaternal monitoring, we compared its performance measures to both the gold standard (FSE) and DU performance measures from the literature.[2,3] This study shows that NI-fECG has generally more accurate and reliable FHR tracings compared to DU. Furthermore, performance measures of NI-fECG are not influenced by maternal BMI.

Interpretation of the results in light of other evidence

We found a higher accuracy for NI-fECG (1.46 bpm) compared to that of DU as reported in literature (10.6 bpm – 14.3 bpm) and therefore NI-fECG provided more correct FHR information for all stages of labor.[2,3] Moreover, our overall accuracy lay within our prespecified limit of 3.5 bpm since the 95% CI did not exceed this limit. Furthermore, NI-fECG appears to be a more reliable technology (88.4% ± 14.6%) than DU (62.4% – 73.0%) during first stage of labor.[2,3] However, during second stage reliability of NI-fECG decreased to 68.74%, but remains higher compared to values previously reported for DU (61.7% and 64.5%).[2,3] An explanation for the decrease in reliability may be that the two outer electrodes are pinched during the pushing phase of the delivery, when women draw their legs toward their chest, causing disturbances in the electrophysiological signals. Placing those two electrodes higher and closer to the midline of the abdomen may reduce these disturbances.

When comparing different modalities for FHR detection, taking into account that each method averages FHR output throughout different heartbeats, occurrence of measurement errors is inevitable. For this reason, we allowed an error width of 10 bpm from the FSE value with minimal clinical relevance. Other studies used less strict error widths of 10%, therefore allowing a larger absolute margin since basal FHR ranges from 110 to 160 bpm.[16] Overall success rate of the NI-fECG (89.49% ± 10.80%) was also higher than that of DU (82.84% ± 23.09%) in our study. Since the risk of fetal hypoxia is highest during second stage of labor, minimizing signal loss is even more important during this phase. Unfortunately, we found similar success rates for both NI-fECG and DU during second stage. Further identification of the causes of signal loss during second stage and optimization of the NI-fECG technology could aid in raising success rates.

We performed a separate analysis for BMI subgroups, since the decrease in performance in obese patients is one of the major limitations of DU technology with the worldwide increasing incidence of obesity.[4,17] Since the risk of unfavorable perinatal outcomes is higher in obese women, adequate fetomaternal surveillance is even more important.[18–22] Previous studies have shown that in obese women monitoring of uterine activity by EHG is more reliable than by TOCO.[5,8,23] In this study we show that in women with a BMI above 30 also monitoring of FHR by NI-fECG is as accurate and even more reliable when compared to DU.[24] We therefore conclude that the NI-fECG technology is not affected by maternal BMI and could be superior to DU for FHR and uterine activity monitoring in this high-risk population.

Intrapartum monitoring using DU is also susceptible to maternal-fetal HR confusion.[25,26] When left undetected, deterioration of the fetal status can occur and lead to adverse fetal outcome. Simultaneous registration of both the FHR and MHR by one device allows for early detection of maternal-fetal HR confusion. ECG is the gold standard for MHR registration, but requires placement of maternal chest ECG electrodes and equipment, which is undesirable during labor. Finger pulse oximetry is the most common method and easy to use. New CTG monitors also have pulse oximetry technology incorporated in the tocodynamometer, allowing continuous MHR registration without the need for additional equipment. The NI-fECG technology also continuously records MHR. Since detection and subtraction of the maternal ECG is a key element in the NI-fECG algorithm for FHR detection, the NI-fECG provides a simultaneous MHR trace nearly in 100% of cases. Our results show that this built-in MHR recording of the NI-fECG is both accurate and reliable, which is an asset for this wireless method.

Since NI-fECG can be used before membranes have ruptured and without the necessity for cervical dilatation, it may also have applications in antepartum as well as preterm monitoring. Another intrapartum application may be the analysis of fetal ECG waveform changes or fetal heart rate variability, to obtain more specific information on fetal well-being.[27,28] Further research should focus on the applicability of this technology in the abovementioned setting.

Strengths and Limitations

The main strength of our study is that it comprises an international multicenter trial which enlarges the generalizability of our results. Furthermore, we used the

gold standard (FSE) for intrapartum monitoring rather than DU as reference method.

A potential weakness of this study relates to the low number of recordings during second stage of labor (n=56). This was caused by patient withdrawal (main reason was showering for pain relief) or secondary cesarean deliveries. Since the duration of this stage was also shorter, this lower number of observations during this critical part of labor makes our results more sensitive to potential outliers. This could have influenced the interpretation of our results in a negative manner.

Another limitation relates to the use of the DU performance measures from the literature as comparison which prevented statistical comparison of all three monitoring modalities. Before conducting this study, a pilot study was performed to assess technical and practical difficulties (data not published). This pilot taught us that the fixating band of the DU button negatively affects the performance of the wireless patch used in the current study. Moreover, application of both technologies causes discomfort for the patient. Since two recent studies reported on the performance measures of DU, using a study design similar to ours, we decided to restrict our study design to comparison of the NI-fECG with the FSE.[2,3]

Finally, 80% of our EHG registrations with simultaneous IUPC were not usable for validating the EHG algorithm in the current study due to high skin impedances following incorrect skin preparation. However, visual assessment of the remaining two registrations showed high agreement, both in first and second stage of labor. Previous research has shown that the EHG technology performs better than TOCO during the first stage of labor in non-obese and obese women.[15] Furthermore, the technology is preferred by patients compared to conventional technologies for uterine activity monitoring.[29]

CONCLUSION

This study shows that monitoring by NI-fECG is not inferior to DU performance measures, when validating this technology to the FSE. We found a higher overall accuracy and higher reliability in the first stage of labor and similar success rates during second stage. Performance measures of the NI-fECG are not influenced by maternal BMI.

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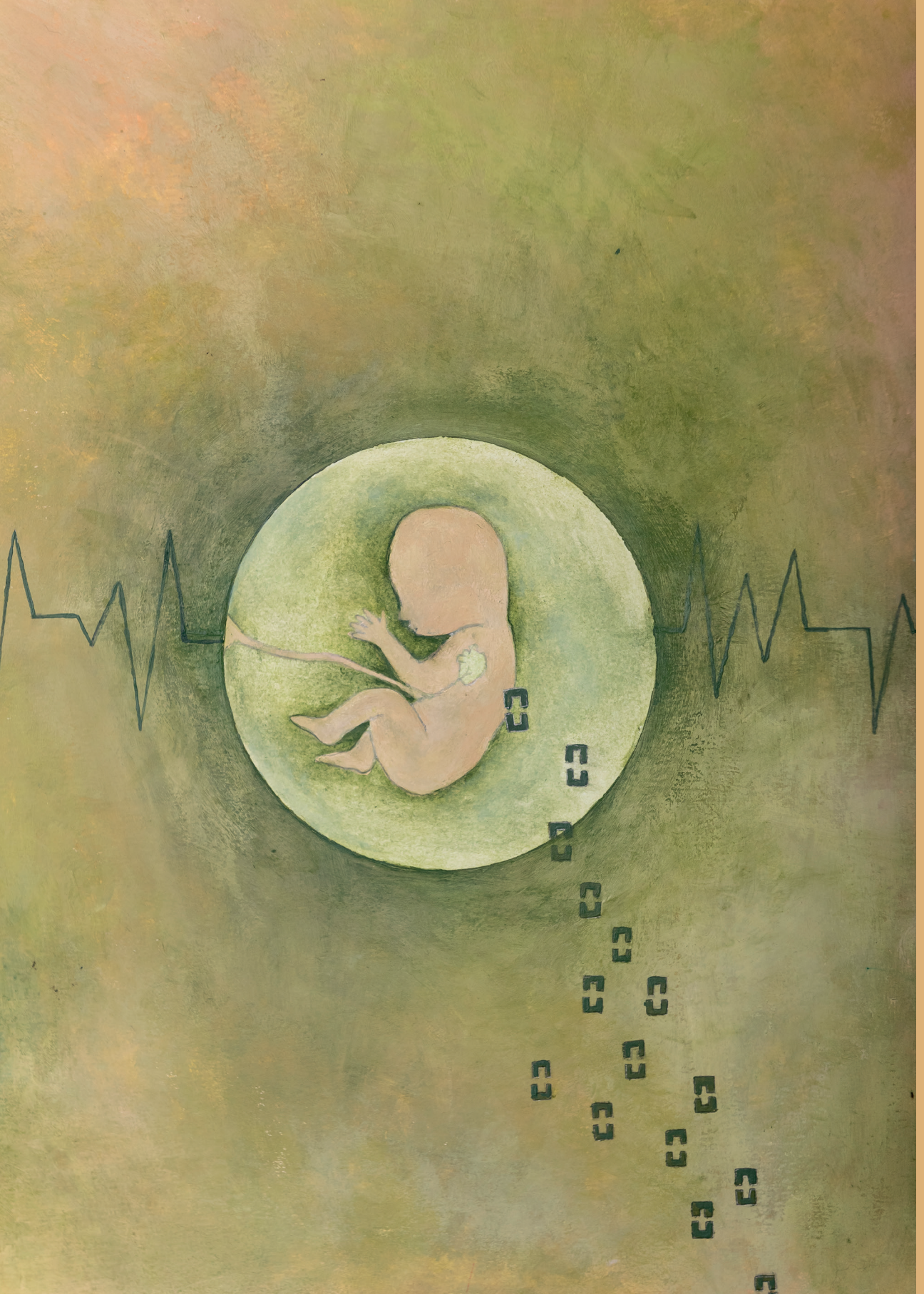

Chapter 6

The fetal electrocardiogram to detect the effects of betamethasone on fetal heart rate variability

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ABSTRACT

Background: Betamethasone is widely used to enhance fetal lung maturation in threatened preterm birth. Antenatal corticosteroids are known to reduce fetal heart rate variability (FHRV) in the days following administration. Since decreased FHRV is a marker for fetal distress, this transient decrease of FHRV can cause unnecessary medical intervention.

Aim: To describe the effect of betamethasone on FHRV, by applying spectral analysis on non-invasive fetal electrocardiogram (fECG) recordings.

Study design: Secondary analysis of a prospective cohort study.

Subjects: Women with a singleton pregnancy, at risk for preterm delivery and receiving betamethasone, admitted to the obstetric high care unit in the period from March 2013 until July 2016.

Outcome Measures: The primary outcome measure was FHRV in both time- and frequency-domain. Secondary outcome measures included basal fetal heart rate (FHR) and FHR variance. FHRV parameters were then calculated separately for the quiet and active state.

Results: Following 68 inclusions, 22 patients remained with complete series of measurements and sufficient data quality. FHRV parameters and FHR showed a decrease on day 2 compared to day 1, significant for short-term variability and high-frequency power. Similar results were found when analyzing for separate behavioral states. The number of segments in quiet state increased during day 1 and 2. Normalized values showed no difference for all behavioral states.

Conclusion: FHRV decreased on day 2 after betamethasone administration, while periods of fetal quiescence increased. No changes were found in the normalized values, indicating that the influence of autonomic modulation is minor.

INTRODUCTION

Corticosteroids significantly reduce neonatal morbidity and mortality and are widely used in cases of impending premature delivery.[1] Betamethasone is the most frequently used corticosteroid, and is administered between 24 and 34 weeks of gestation. The effects of betamethasone on fetal heart rate variability (FHRV) have been thoroughly researched during the last two decades. A transient decrease in FHRV, most pronounced on day two after administration, has been repeatedly reported.[2-6] This effect is of clinical significance since FHRV is an important parameter of fetal wellbeing.[7] Decreased variability can be misinterpreted as fetal distress, causing unnecessary iatrogenic preterm birth. Therefore, thorough knowledge of these effects is warranted.

Fetal heart rate (FHR) and thus FHRV are regulated by a complex interplay between the sympathetic and parasympathetic nervous system. This autonomic regulation of FHRV can be estimated by means of spectral analysis.[8] Fetal electrocardiography (fECG) can be measured non-invasively from the maternal abdomen.[9] It provides beat-to-beat information on the FHR, making analysis of FHR variability through spectral analysis possible.

The currently used method for fetal monitoring, the cardiotocogram (CTG) is highly dependent on visual assessment by the physician. Therefore, agreement between observers (inter-observer reliability) and even within the same observer (intra-observer reliability) is poor.[10] This technique measures FHR by means of doppler-ultrasound, averaging the FHR over several heartbeats. Beat-to-beat information on the FHR, necessary to perform spectral analysis, is lacking.

Verdurmen et al. previously reported on the effect of betamethasone administration on spectral values of FHRV.[11] At that time, only 42.8% of the collected data was of sufficient quality for analysis. Due to an improvement of the data processing algorithm, we were able to increase the amount of data of sufficient quality to 70.9%. In this paper we re-evaluated the effect of betamethasone on overall FHRV values. In addition, we evaluated the effect of fetal behavioral states on FHRV.

MATERIALS AND METHODS

The results presented in this paper are derived from the previously published study by Verdurmen et al.[11] A detailed description of the study methods can be

found in their paper. A prospective longitudinal cohort study was performed at the Máxima Medical Center Veldhoven, The Netherlands. This is a tertiary care hospital for obstetrics. The local Medical Ethical Committee approved the study protocol. Participants were included after written informed consent.

Study population

Women with a singleton pregnancy, receiving betamethasone (Celestone Chrondose®, Schering AG, Berlin, Germany; 2 doses of 12mg intramuscularly, 24 hours apart) as part of standard clinical management were eligible to participate. Concomitant use of other medication was allowed. Exclusion criteria were maternal age under 18 years, multiple pregnancy, fetuses with a known congenital malformation, signs of intra-uterine infection of fetal growth restriction (i.e. estimated weight of the fetus below the 5th percentile for gestational age).

Outcome measures

The primary outcome was FHRV, which is a function of the fluctuation of the R-R interval (length between two successive R waves). We quantified FHRV using both time-domain features (short-term variability [STV] and long-term variability [LTV]) and frequency-domain features (low-frequency (LF-) and high-frequency (HF-) power).[12-14] STV is sensitive to changes in successive heartbeats and is calculated based on the difference between successive inter-beat intervals.[15,16] LTV gives a measure for the overall variability in the heart rate, and is calculated as the difference between the maximum and minimum inter-beat interval within a one-minute period.[16] LF- and HF-power reflect the energy in specific frequency components. HF-power is associated with respiratory activity and regulated by the parasympathetic nervous system. LF-power is mediated by both the sympathetic and the parasympathetic branches of the autonomic nervous system and reflects the baroreceptor reflex.[8,17]

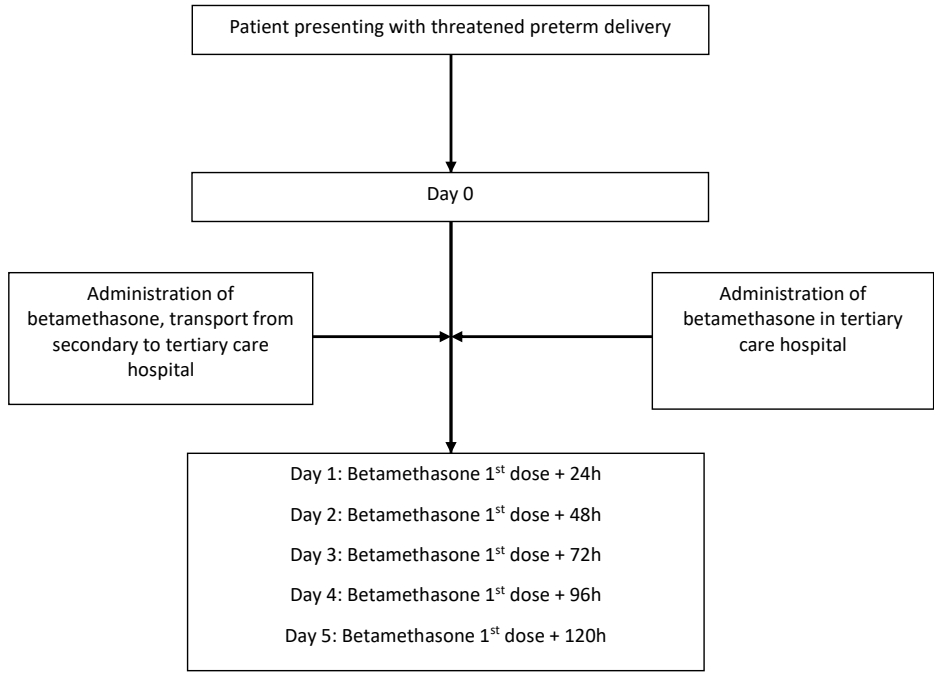
As secondary outcomes, we calculated the FHR (in beats per minute, bpm). In addition, we calculated FHR variance. FHR variance is calculated as the square of the standard deviation of the FHR and reflects the variation around the mean heart rate for each 60 second segment (in bpm). Based on the FHR variance, segments can be classified into periods of quiet state (FHR variance <15 bpm^2) and periods of active state (FHR variance >30 bpm^2).[12,14,18]

FHRV parameters were first calculated for the overall measurement and then separately for both quiet and active state.

Measurements

We performed a series of fetal electrocardiographic (fECG) measurements as visualized in Figure 1. Each measurement lasted approximately 30 minutes. No CTG measurements were performed during the fECG measurement, and the output of the fECG measurements was not available for healthcare givers. Complete series were defined as series including a reference measurement, and measurements during at least days 1, 2, and 3. When one or more of these measurements was missing, the patient was excluded. A baseline measurement was performed before the administration of betamethasone (day 0, 0-measurement). When betamethasone treatment was started in secondary care hospitals prior to transport to our center, no baseline measurement was available. Literature shows that FHR and FHRV values return to baseline on day 4 (96 hours after the first dose of betamethasone).[19] Therefore, we used the median value of the measurements during day 0, and/or day 4, and/or day 5 as the "reference measurement".

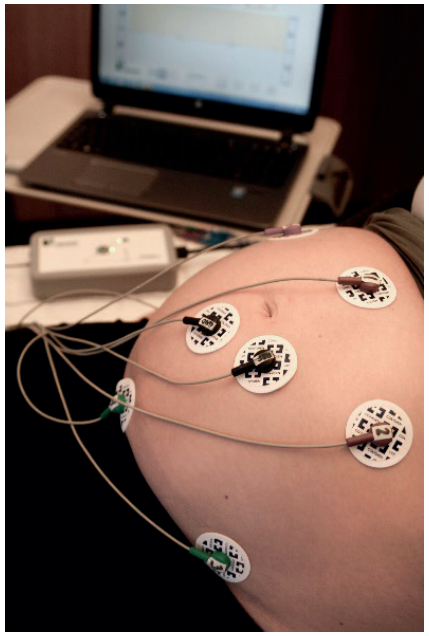
Figure 1. Flowchart of patient inclusion and timing of measurements.



Data acquisition and signal processing

We used two non-invasive electrophysiological monitoring devices: a prototype version of the Nemo fetal monitoring system (Nemo Healthcare BV, Eindhoven, the Netherlands) and the Porti system (TMSi, Enschede, the Netherlands). Approval of the Medical Technical Service Department of the Máxima Medical Center was obtained. Eight electrodes were placed on the maternal abdomen in a fixed configuration (Figure 2), including one ground and one reference electrode.

Figure 2. The fetal electrocardiogram.



The recordings from the previously published study were re-analyzed offline.[11] Recordings were first pre-processed to suppress the maternal ECG using a dynamic template subtraction technique.[20] The signals remaining after maternal ECG suppression were spatially combined to enhance the signal-to-noise ratio of the fetal ECG with respect to remaining electrophysiological interferences (e.g. muscle activity). Finally, fetal R peak detection was performed using an adaptive ECG model to obtain a beat-to-beat FHR.[21]

Prior to FHRV analysis, the obtained heart rates were automatically analyzed for incorrect R-R intervals. R-R intervals shorter than 0.3 seconds or longer than 1.2 seconds (<50 or >200 bpm) were assumed to be incorrect.[22] Furthermore, if an R-R interval deviated more than 12% from a running average R-R interval, it was also assumed to be incorrect.[23] The incorrect R-R intervals were replaced by linear interpolation. To ensure reliable spectral analysis, only heart rate segments of 60 seconds were included with less than 20% interpolation and less than five seconds of consecutive interpolation.[23] We only included measurements with at least three segments that met the quality criteria.

Heart rate variability analysis

Spectral analysis was performed using a continuous wavelet transform. Since spectral analysis required signals that were equidistantly distributed in time, the obtained heart rates were resampled at 4 Hz by linear interpolation. Spectral power bands were defined based on previous studies: total frequency 0.04 - 1.5 Hz, LF 0.04 - 0.15 Hz and HF 0.4 - 1.5 Hz.[8,14,24-27] LF- and HF-power was expressed in absolute units (ms^2) and normalized units. Normalized values were calculated by dividing LF and HF power by total power (LFn = LF-power/total power, HFn = HF-power/total power). Due to this normalization, relative changes in LF- and HF-power were not affected by changes in total power.

To compare our results to prior research performed with CTG measurements, STV and LTV were calculated in addition to spectral analysis. LTV was calculated as the difference between the maximum and minimum R-R interval in every 60 seconds segment.[28,29] STV was calculated as the mean of absolute differences between consecutive R-R intervals in every 60 seconds segment.[28] Note that STV in Doppler monitoring was defined based on epochs (e.g. 1/16th of a minute) because beat-to-beat FHR was not possible with this technique. However, since the gold standard for STV is beat-to-beat variation, we used the aforementioned ECG-based STV calculation.

Statistical analysis

A Wilcoxon-signed rank test was used to study significant changes between the measurement days for each HRV parameter. We compared the median value of each parameter on each measurement day to the reference measurement as well as the remaining days. We used the Bonferroni correction to correct for multiple testing. Thus, a probability value of 0.0083 was calculated as the significance level (p=0.05/6). We calculated a Spearman's rho coefficient to test whether the FHRV parameters on day 2 were influenced by the time of day at which the measurement had been performed.

RESULTS

Initially, 68 women were included in this study. Three patients requested withdrawal from the study, one because of poor prognosis for an extremely premature child, one because of technical problems with the measuring equipment and one because of the inconvenient timing of the measurements for the patient. In one patient an unexpected intra-uterine death occurred during the study period. Extensive evaluation revealed no evident cause. In 33 patients the measurement series was not completed due to discharge from the hospital or delivery (n=17), the presence of a congenital heart disease (n=1) or arrythmia (n=1), intra-uterine growth retardation (n=1), interrupted measurement sequence (n=2) or clinical evaluation revealed corticosteroid administration was no longer necessary after the reference measurement on day 0 had already taken place (n=6). Of the remaining 31 complete series, 8 were excluded due to insufficient data quality. One patient was excluded later on due to loss to follow-up. 22 patients with a complete set of sufficient data quality were included for analysis. Table 1 shows the baseline characteristics of this group.

Table 1. Baseline characteristics.

No. Patients	22
Maternal characteristics	
GA (wk) on admittance	28.4 ± 3.1
Gravidity	2 (1-3)
Parity	1 (0-1)
BMI	25.4 ± 5.6
Smoking (%)	4.5
Medication (%)	
Nifedipine	63.3
Indomethacin	4.5
Atosiban	4.5
Indication CCS (%)	
TPL	36.4
VBL	31.8
PPROM	22.7
PE	4.5
PPROM + VBL	4.5

Table 1. Continued.

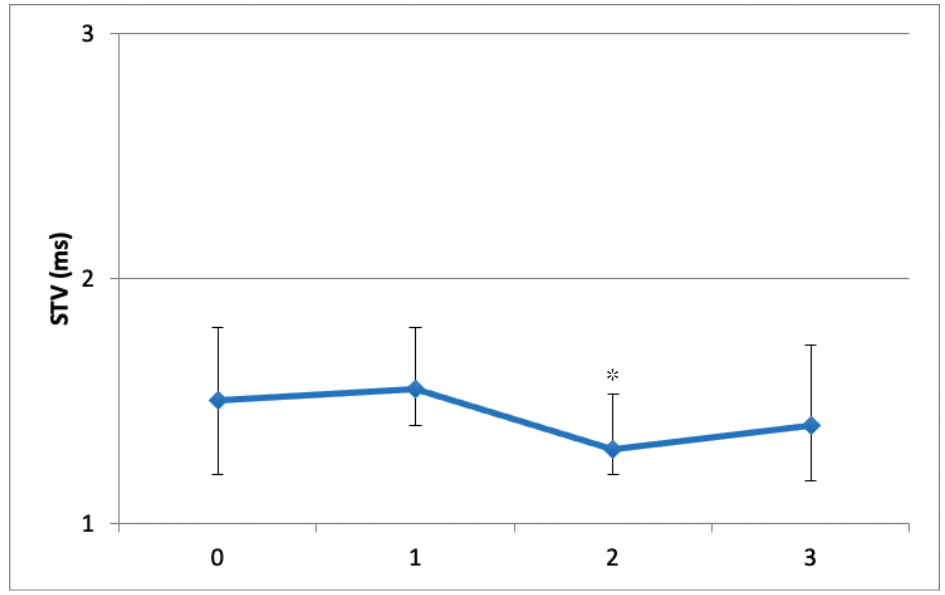
No. Patients	22
Neonatal characteristics	
GA (wk) at birth	34.7 ± 4.7
Birthweight (in grams)	2487.7 ± 991.9
Apgar 1 min (*N = 19*)	9 (7-9)
Apgar 5 min (*N = 21*)	10 (9-10)
NICU admittance (%)	22.7

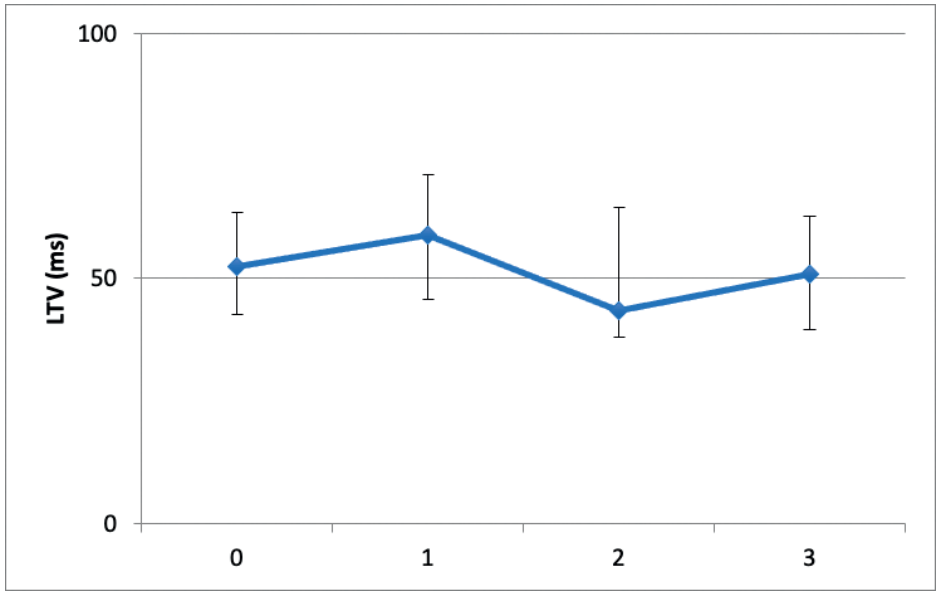
Data provided are percentages or means ± SD. Median (interquartile range) are provided for variables that are not normally distributed.
Abbreviations: GA = gestational age, BMI = body mass index, CCS = corticosteroids, TPL = threatened preterm labor, VBL = vaginal blood loss, PPROM = premature preterm rupture of membranes, PE = pre-eclampsia, NICU = neonatal intensive care unit.

Primary outcome

Our primary outcome was changes in HRV during corticosteroid treatment. Figure 3 shows the changes of the different FHRV parameters over the study period.

Figure 3. Changes in the fetal heart rate variability parameters during the study period.




100
50
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LTV (ms)
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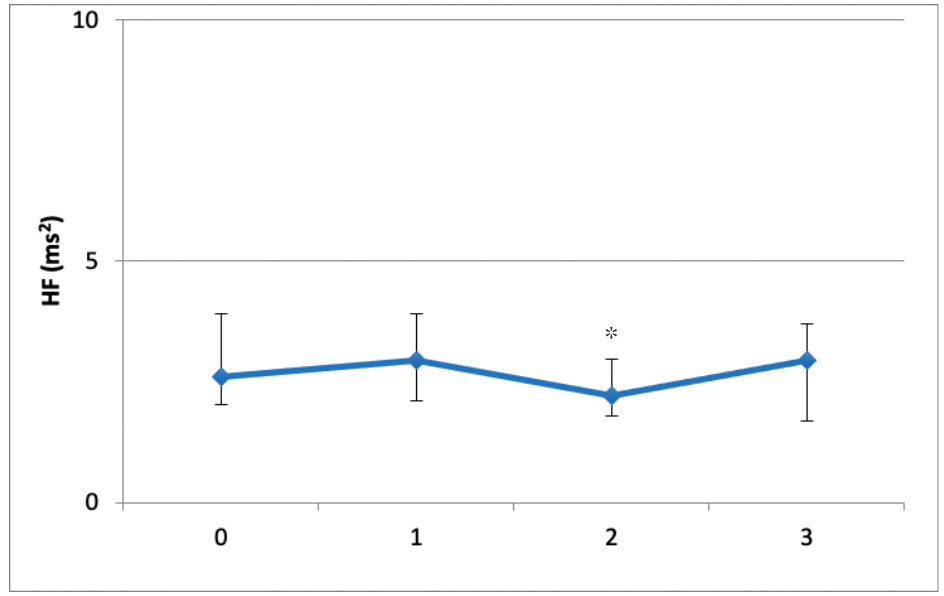
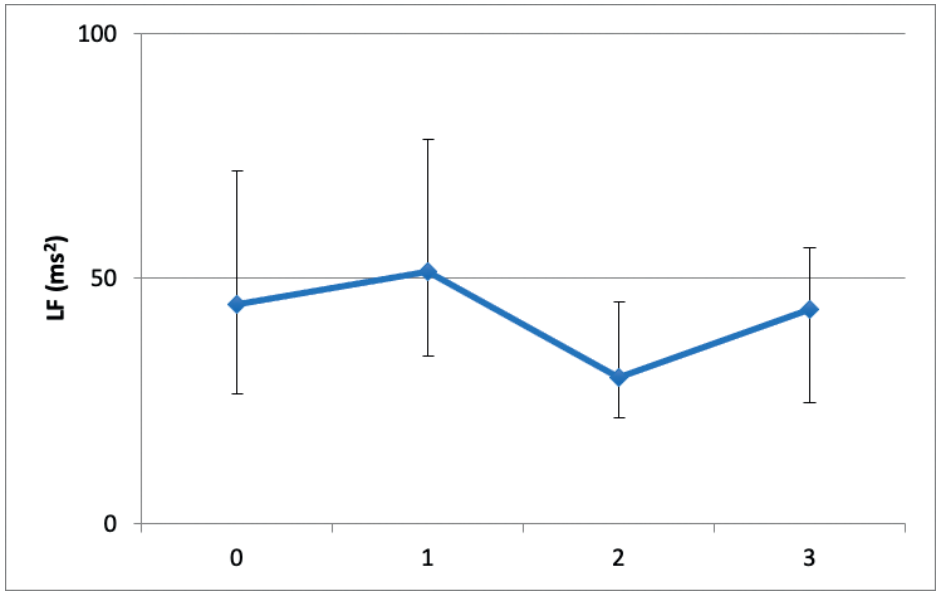
3


10
5
0
HF (ms²)
*
0
1
2
3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50
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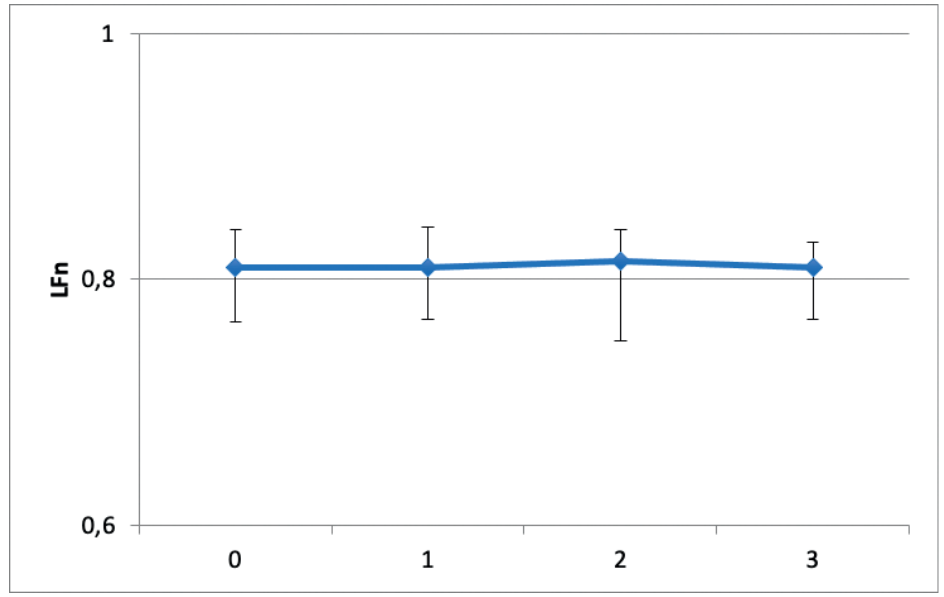
LF (ms²)
0
1
2
3


1
0,8
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LFn
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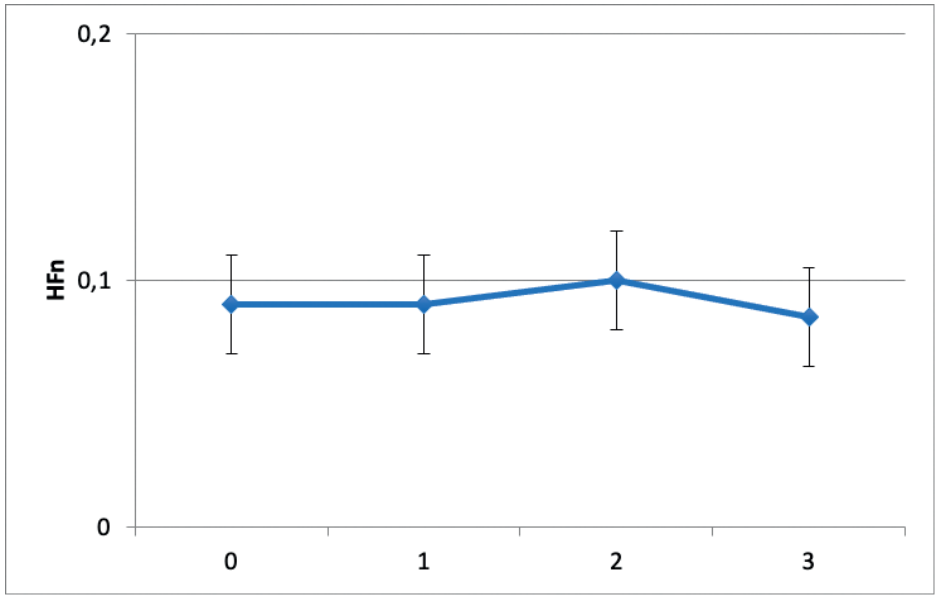
1
2
3

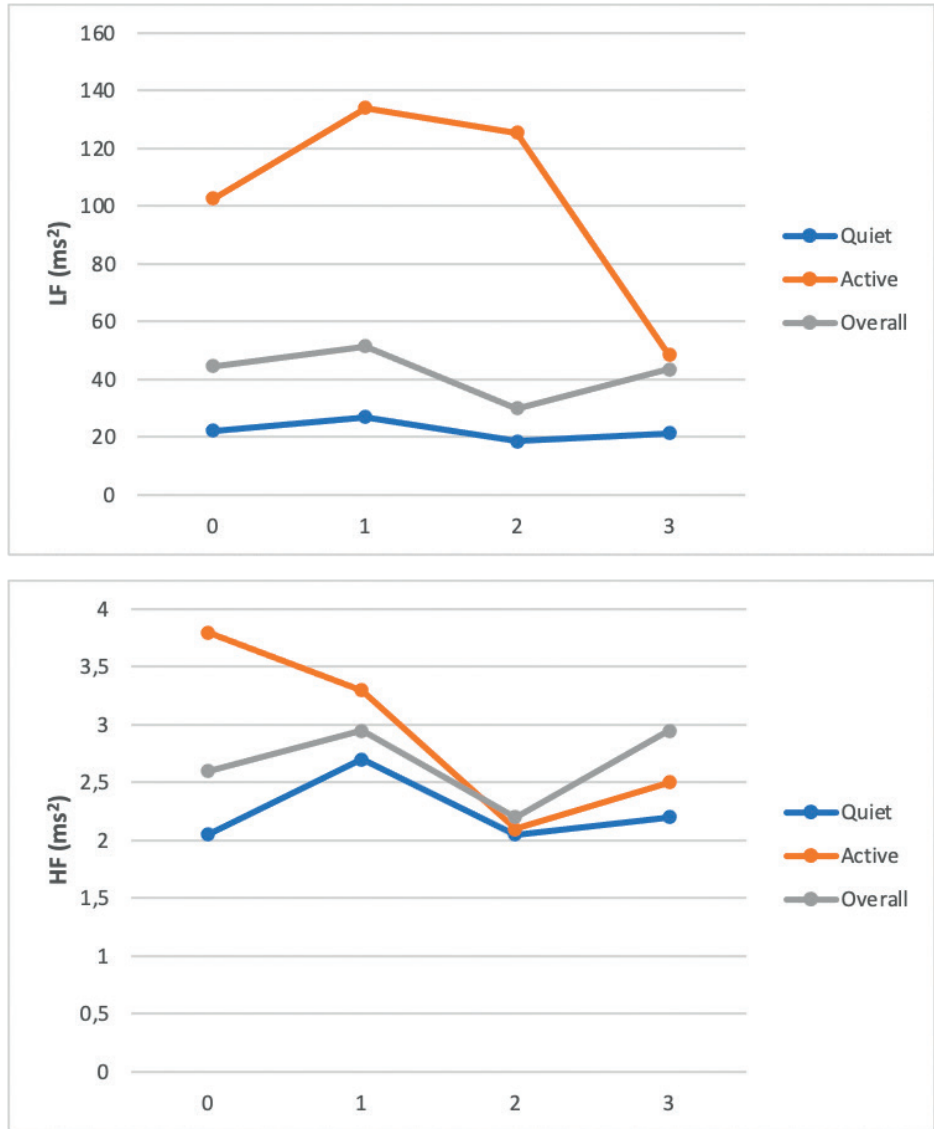


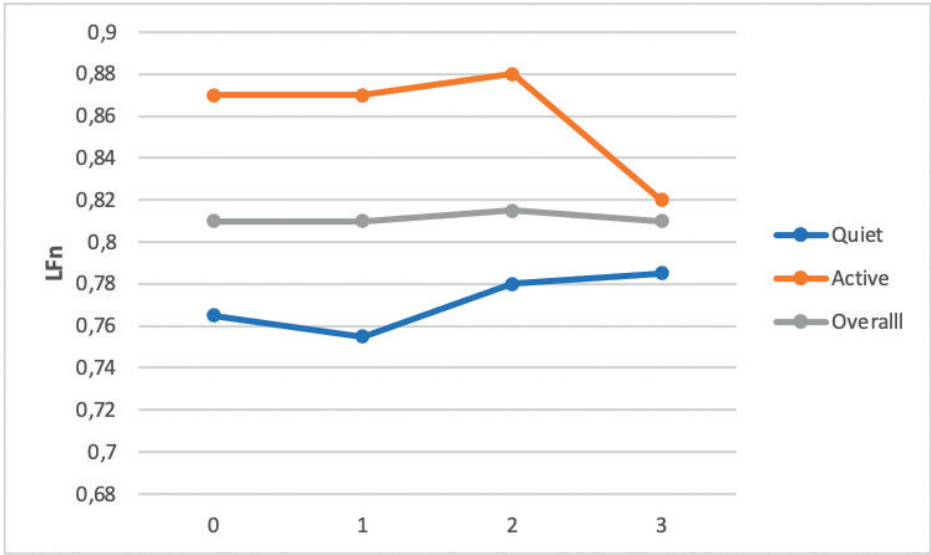
Median values with interquartile ranges are shown for the reference day and day 1, 2 and 3 after the first betamethasone administration (x-axis). Day 0 is the median value of the measurements during day 0, and/or day 4, and/or day 5.
* = statistically significant difference relative to day 1.
Abbreviations: STV = short-term variability, LTV = long-term variability, LF = low-frequency power, HF = high-frequency power, LFn = normalized low-frequency power, HFn = normalized high-frequency power.

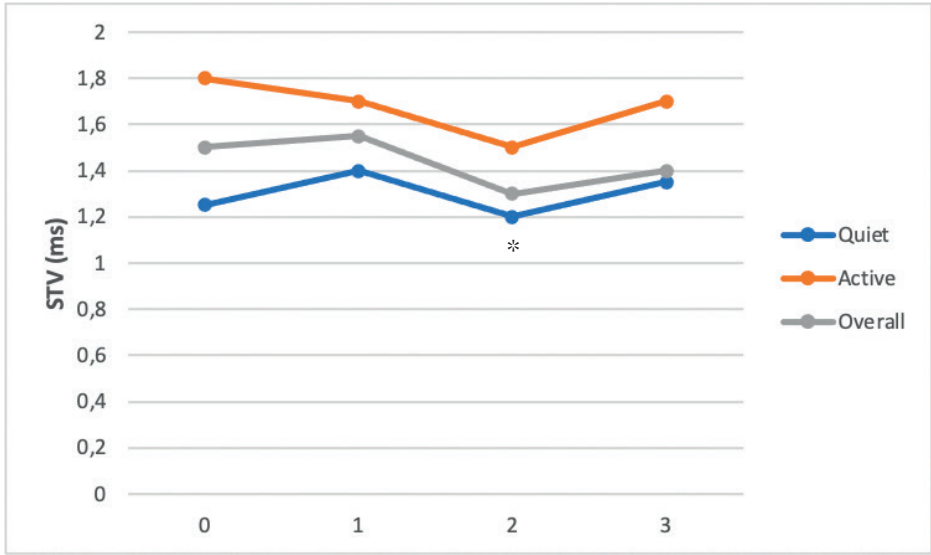
We found an increasing trend of both STV and LTV on day 1, and a decreasing trend on day 2 compared to the reference measurement, which is comparable to the previously published results by Verdurmen et al.[11] Due to the small amount of complete data sets available, they only performed descriptive statistics. We found a significant decrease in STV on day 2 compared to day 1 in our enlarged dataset (p=0.002). Absolute spectral values showed the same trend. We found a significant decrease in HF-power on day 2 compared to day 1 (p=0.002). Normalized LF and HF showed little changes during the study period.

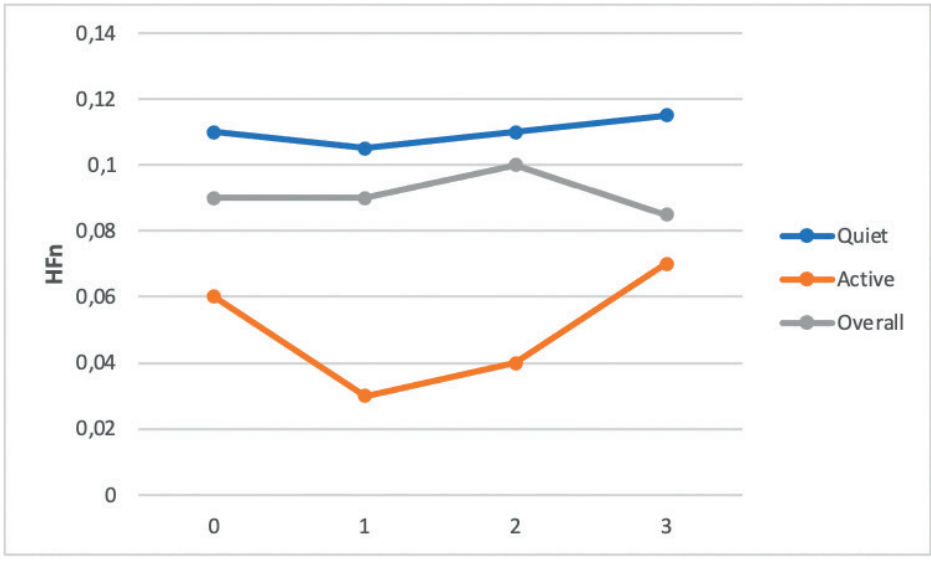
Fetal HRV parameters were then calculated separately for recorded segments during quiet and active state (Figure 4). For the quiet state, sufficient data was available from 18 of the included patients. There was a similar increasing trend visible on day 1 for STV and LTV as well as LF- and HF-power. Furthermore, we found a significant decrease in STV on day 2 compared to day 1 (p=0.005) during the quiet state. For the active state only 7 complete datasets were available, and no significant results were observed.

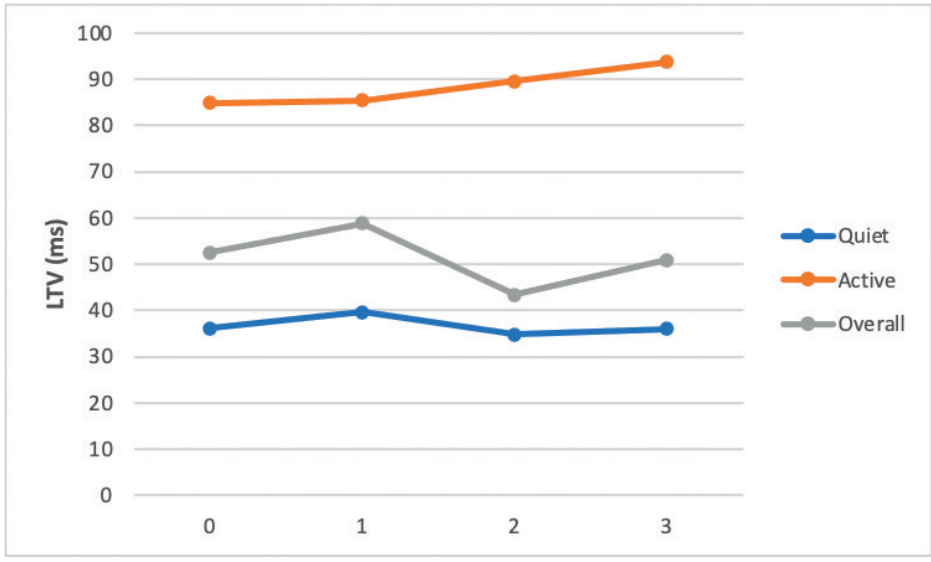
Figure 4. Changes in the fetal heart rate variability parameters during the study period for active and quiet state.









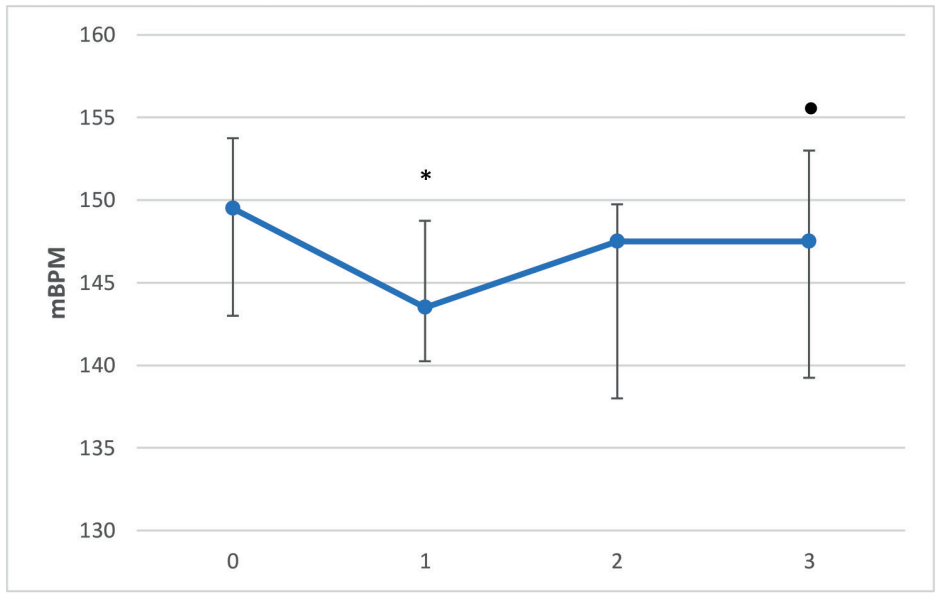


Median values are shown for the reference day and day 1, 2 and 3 after the first betamethasone administration (x-axis), for quiet and active state seperately as well as combined for all fetal behavioral states. Day 0 is the median value of the measurements during day 0, and/or day 4, and/or day 5.
* = statistically significant difference relative to day 1 for the quiet state.
Abbreviations: STV = short-term variability, LTV = long-term variability, LF = low-frequency power, HF = high-frequency power, LFn = normalized low-frequency power, HFn = normalized high-frequency power.

Secondary outcome

Figure 5 shows the changes seen in FHR during the study period. It shows a significant decrease on day 1 compared to the reference measurement (p=0.001) as well as a significant increase on day 3 compared to day 1 (p=0.006).

Figure 5. Changes in fetal heart rate during the study period.



Median values with interquartile ranges are shown for the reference day and day 1, 2 and 3 after the first betamethasone administration (x-axis). Day 0 is the median value of the measurements during day 0, and/or day 4, and/or day 5.
* = statistically significant difference relative to day 0 = statistically significant difference relative to day 1

Figure 6 shows the FHR variance over the study period. There was a clear decrease on day 2. The changes in periods in quiet (fetal heart rate variance < 15 bpm^2) and active (fetal heart rate variance >30 bpm^2) state are shown in Figure 7. The number of segments in quiet state increased on day 1 and 2, while the number of segments in active state decreased. On day 4 the number of segments in quiet and active state returned back to premedication values.

We found no correlation between the time of day of the measurements and the FHRV parameter values (Table 2).

Figure 6. Changes in heart rate (HR) variance.

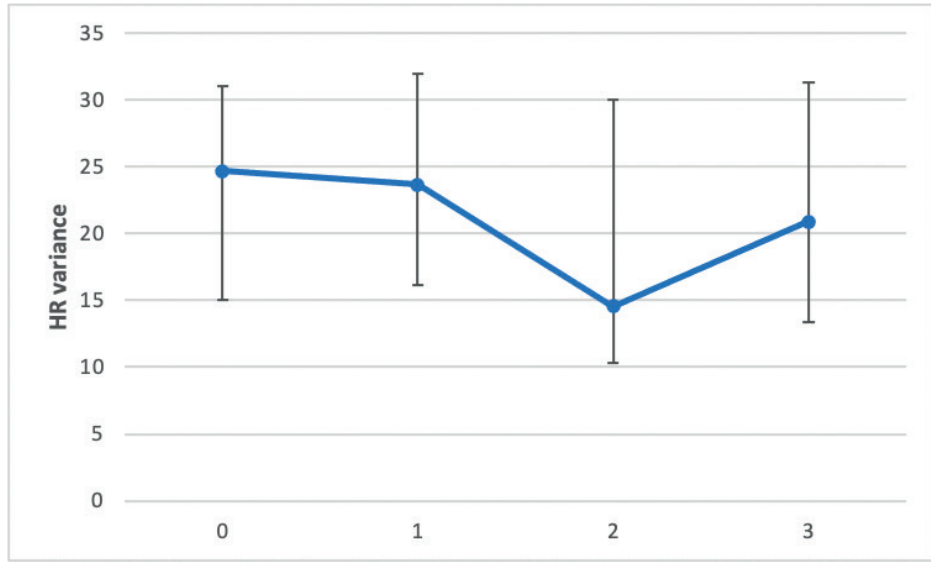


Figure 7. Changes in periods in quiet and active state.

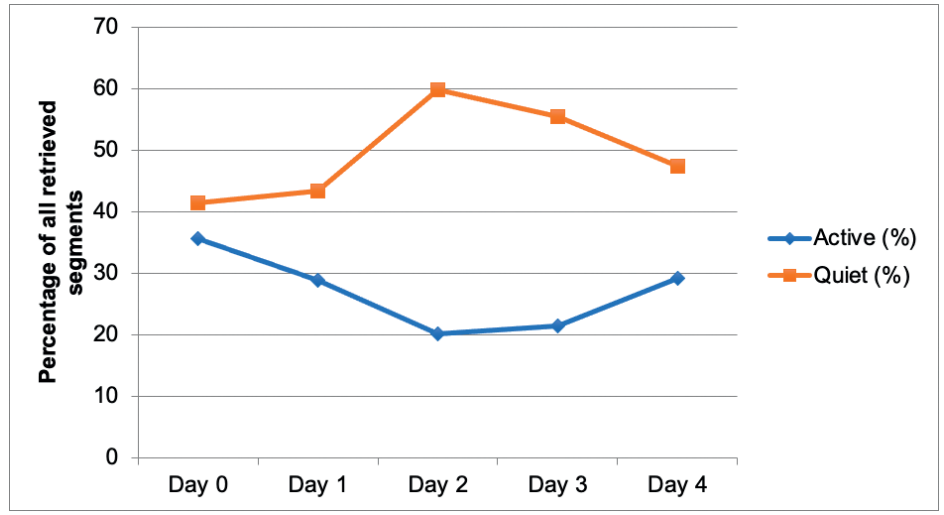


Table 2. Spearman's rank correlation between the time of day of the measurements and the fetal heart rate variability parameters.

	LF	HF	LFn	HFn	STV	LTV
Correlation coefficient	-0.01	-0.12	-0.04	-0.23	-0.03	-0.05
p-value	0.98	0.61	0.87	0.30	0.90	0.83

A probability value (p-value) of 0.05 is used as the cutoff for significance.
Abbreviations: LF = low-frequency, HF = high-frequency, LFn = normalized low-frequency, HFn = normalized high-frequency, STV = short-term variability, LTV = long-term variability.

Segments available for analysis

Table 3 shows the number of segments available for analysis. Due to algorithm improvements these percentages were considerably higher than before, except for day 0.[11]

Table 3. Number of segments available for analysis.

	Segments available for analysis/total recorded segments	Percentage of segments available for analysis	
		Current paper	*Verdurmen et al.*
Reference measurement			
Day 0[a]	174/249	70%	94%
Day 4	518/714	73%	66%
Day 5[b]	306/487	63%	58%
Day 1	571/674	85%	57%
Day 2	528/769	69%	53%
Day 3	528/751	70%	55%

[a]Day 0: measurements performed in 8 out of 22 patients.
[b]Day 5: measurements performed in 16 out of 22 patients.
On the remaining study days, measurements were performed in all 22 patients.

DISCUSSION

We found similar results compared to previous studies where FHRV was evaluated using CTG analysis.[19] STV and LTV values decreased 48 hours after the first betamethasone administration, before returning to baseline values on day 4.[2,3] By using non-invasive abdominal ECG recordings for fetal monitoring, we were able to obtain beat-to-beat information of the FHR. This enabled us to use spectral analysis for measuring HRV in the frequency domain. LF- and HF-power are absolute spectral estimates that related well to respectively LTV and STV. As expected, they showed a similar trend during our study period. In adults, the use of normalized values is recommended since they reflect relative changes.[30] Both our LFn and HFn values showed little changes during the study period, indicating that the influence of autonomic modulation is minor.

Besides changes in variability parameters, we found a small but significant decrease in basal FHR on day 1, which has been previously described in other studies performed with CTG data.[2,3,5,31-33] Although significant, the clinical value of this small difference (149 bpm on the reference day compared to 143 bpm on day 1) can be disputed. Furthermore, it is known that FHRV and FHR are inversely correlated.[4,31,33,34] Although an increasing trend on day 1 could be noticed in our FHRV parameters, these results were not significant.

The subsequent increase in basal FHR on day 2 and 3, described by Mulder et al. could not be confirmed by our results.[2,33] This might be due to the low number of series included, or by the fact that CTG uses averaging over several heartbeats, which could influence the results.

Due to an improvement of the algorithm, ten additional complete series could be included in our analysis. This increased the total amount of data available for analysis from 18% to 32%. This is still a relatively small proportion due to loss-to-follow up (56%) and insufficient data quality (12%). We applied a high standard for good signal quality; only measurements containing at least three segments with good signal quality per measurement were selected. When looking at the number of complete measurement series, 71% was of sufficient quality for analysis, compared to only 43% in the previously published paper. Due to this increase we found it relevant to re-analyze our data.

Our results confirm the decrease in overall FHRV parameters following betamethasone administration as previously described by Verdurmen et al.[11] Due to the larger dataset available for analysis, the decrease of STV and HF on day 2 compared to the reference measurement became significant (Figure 3).[11]

In current daily clinical practice, FHRV (assessed by CTG interpretation) and fetal body movements are important parameters for evaluating fetal wellbeing. The decrease in FHRV, maximal on day 2 of betamethasone treatment, was substantiated by a decrease in fetal body movements reported by mothers and confirmed with ultrasound measurements in previous studies.[2,3,35] Like

Verdurmen et al., we confirmed this decrease in FHRV parameters (in time and frequency domain) on day 2.[11] We also found an increase in number of segments retrieved during periods of quiet state on day 2 (Figure 7).

This transient decrease in FHRV parameters following betamethasone administration can be misinterpreted as fetal distress, resulting in unwarranted iatrogenic delivery. To prevent unnecessary preterm delivery, thorough knowledge about this effect of betamethasone on FHRV is crucial. Previous studies on the presence of other indices for fetal distress found no increase of FHR decelerations or changes in Doppler flow indices of various blood vessels after betamethasone administration.[36,37] Shenhav et al. also demonstrated there was no relationship between fetal acid-base balance and reduced FHRV in fetuses that were born less than 48 hours after betamethasone administration.[38] Therefore, the observed transient changes in FHRV parameters are unlikely to be due to fetal distress.

As spectral power estimates are known to reflect the autonomic modulation after birth, we aimed to gain more insight into the role of the fetal autonomic nervous system in FHRV changes following betamethasone administration. Fetal autonomic fluctuations, and thus FHRV, are known to be influenced by fetal behavioral states.[9] Van Laar et al. previously found a decrease in FHRV in the frequency domain during quiet state compared to active state.[9] We calculated the FHRV parameters separately for both the active and the quiet state to gain more insight in the suppressive effect of betamethasone. The FHRV values in the quiet state showed little variation over the study period. Therefore, it seems likely that the observed changes in FHRV parameters found were due to decreased fetal movements. This hypothesis is also supported by the fact that betamethasone crosses the placenta and is believed to bind to glucocorticosteroid receptors in the fetal brain.[19] These receptors show a high affinity to synthetic glucocorticosteroids and suppress neuronal activity when occupied, leading to increased fetal quiescence.[2]

The number of available complete datasets was considerably lower during the active state. This could be due to a low signal-to-noise ratio caused by fetal movement or merely because, due to betamethasone treatment, the fetus spends less time in the active state, leading to a decreased number of segments for this state. Figure 7 pleads for the latter, showing a decrease in percentage of retrieved segments during the active state on day 2. Since not all segments of the separate behavioral states were available for analysis, no hard conclusions can be drawn from these results. However, we believe that together with previously reported literature these results support the evidence that the decrease in FHRV values on day 2 is caused by a decrease in fetal activity following betamethasone administration.

Two additional factors known to influence FHRV are gestational age and diurnal rhythms. In healthy fetuses, LTV and STV increase with increasing gestational age, whereas basal FHR decreases.[34] LF- and HF-power significantly increase during pregnancy.[9] All fetuses included in our study had a gestational age between 24^{+4} and 33^{+4} weeks. We measured each fetus on successive days and looked at relative changes in FHRV parameters. Therefore, the influence of this gradual increase in FHRV parameters during gestation was likely to be minor.

Fetal diurnal states have been described starting from 22 weeks of gestation.[39,40] Normal fetal diurnal rhythm shows an increase in FHRV in the afternoon and evening compared to the morning. Previous research found this increase in FHRV during the course of the day to be absent on day 2 after betamethasone administration. [36,41] A correlation between the time of day of the measurement and the FHRV values on day 2 was also absent in our results. To reduce the influence of diurnal variation within our study, we fixed the timing of measurements within a series between 20 and 28 hours after the previous measurement.

During our study period, participants received pregnancy-related drugs other than betamethasone. Since in daily clinical practice betamethasone, for threatened preterm delivery, is rarely administered without tocolytics, studying the effects of corticosteroids in patients without co-medication is not feasible. Verdurmen et al. previously reviewed the literature concerning the effects of tocolytic drugs on HRV.[42] They found that nifedipine and atosiban had no significant effect on FHRV. There is no literature available on the effect of indomethacin on FHRV, but an effect on FHRV parameters is unlikely given its mechanism of action. This is also the case for the remaining concomitant medication such as antibiotics, progesterone, insulin and anticoagulants.

CONCLUSION

Fetal HRV parameters showed a decreasing trend on day 2 after betamethasone administration, both in the time- and frequency-domain. This decrease was significant for STV and HF-power. The reported changes in FHRV parameters

were likely due to a drug-induced decrease in fetal activity, rather than a sign of fetal distress. All FHRV parameters returned to baseline values on day 4 after betamethasone treatment was started.

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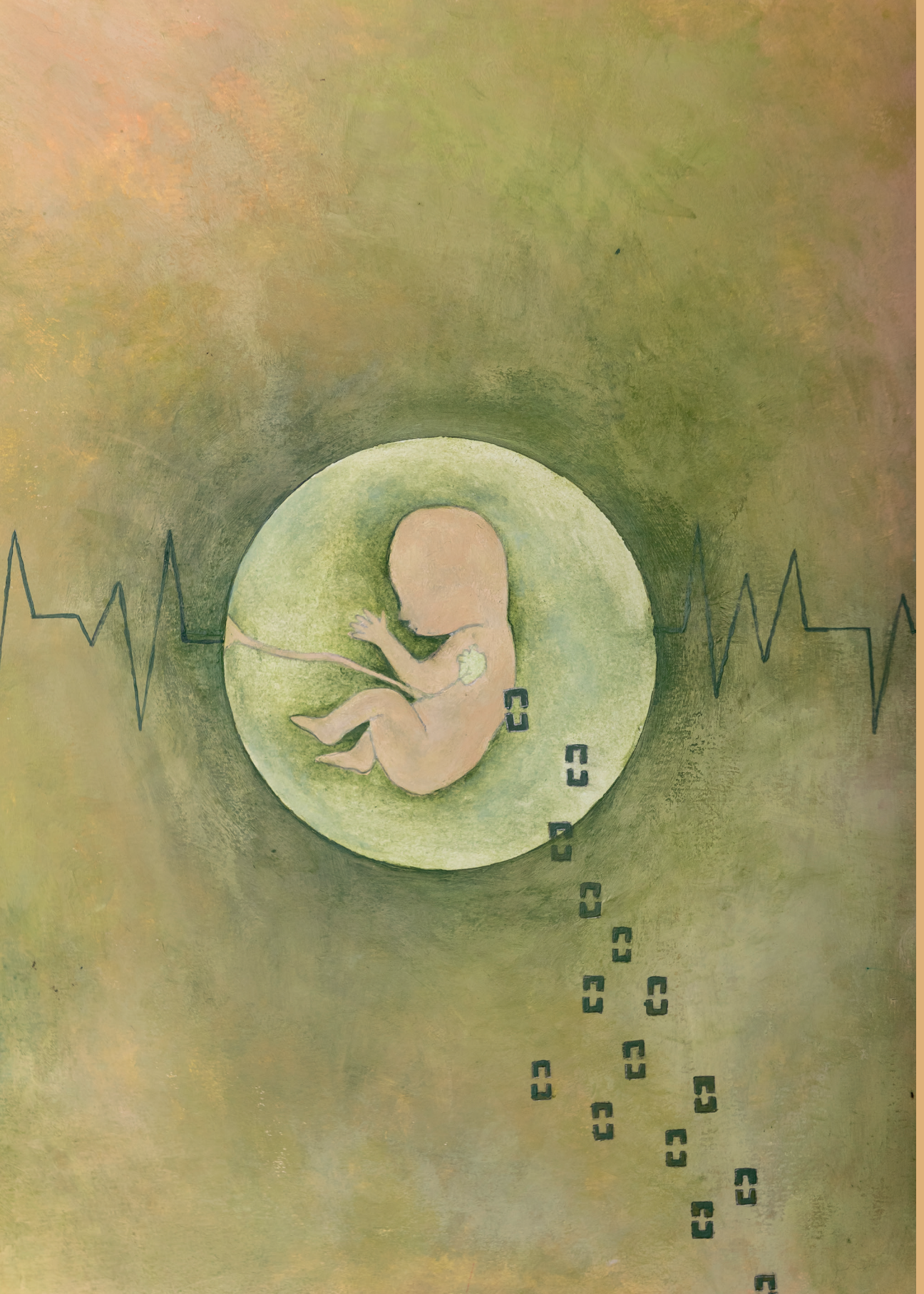

Chapter 7

Feasibility of non-invasive fetal electrocardiography in a twin pregnancy

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ABSTRACT

Background: Twin pregnancy is associated with increased perinatal mortality. Close fetal monitoring is therefore warranted. Doppler Ultrasound cardiotocography is currently the only available method to monitor both individual fetuses. Unfortunately, the performance measures of this method are poor and erroneous monitoring of the same twin with both transducers may occur, leaving the second twin unmonitored. In this study we aimed to determine the feasibility of monitoring both fetuses simultaneously in twin gestation by means of non-invasive fetal electrocardiography (NI-fECG), using an electrode patch on the maternal abdomen.

Methods: A NI-fECG recording was performed at 25+3 weeks of gestation on a multiparous woman pregnant with dichorionic diamniotic twins. An electrode patch consisting of eight adhesive electrodes was applied on the maternal abdomen, yielding six channels of bipolar electrophysiological measurements. The output was digitized and stored for offline processing. The recorded signals were preprocessed by suppression of high-frequency noise, baseline wander, and powerline interference. Secondly, the maternal ECG was subtracted and segmentation into individual ECG complexes was performed. Finally, ensemble averaging of these individual ECG complexes was performed to suppress interferences.

Results: Six different recordings were obtained from each of the six recording channels. Depending on the orientation and distance of the fetal heart with respect to each electrode, a distinction could be made between each fetus based on the morphology of the signals. Yielding of the fetal ECGs was performed manually based on the QRS complexes of each fetus.

Conclusion: NI-fECG with multiple electrodes allows for monitoring of the fetal heart rate and ECG of both individual fetuses in twin pregnancies.

BACKGROUND

Multiple gestation is the most common high-risk condition in obstetric medicine, with a varying incidence from 6.7 per 1000 births in Japan to 40 per 1000 births in Nigeria.[1] In the Netherlands, 1.6% of all deliveries after 22 weeks of gestation in 2017 were twins.[2] Twin pregnancies are associated with increased perinatal morbidity and mortality rates.[3] They have a higher risk of fetal growth restriction and preterm birth compared to singleton pregnancies.[4] In monochorionic twin pregnancies, both twin-twin transfusion syndrome (TTTS) and twin anemia polycythemia sequence (TAPS) are complications which can result in fetal death when left untreated.[5] Hence, close fetal surveillance is imperative for early identification of complications and intervention. As in singleton pregnancies, fetal monitoring in twin pregnancies is done by means of the cardiotocogram (CTG). The non-invasive version of this method consists of a tocodynamometer (TOCO) which registers uterine activity and a Doppler ultrasound (DU) transducer to obtain the fetal heart rate (FHR). In multiple pregnancies, each fetus requires its own DU transducer. Erroneous monitoring of the same twin with both transducers may occur. The observation of identical tracings can avoid fatal consequences in this situation, such as fetal demise due to undiagnosed chronic hypoxia. Unfortunately, DU CTG has a poor specificity and high inter- and intra-observer variability, since it is dependent on visual assessment by a physician.[6] Furthermore, DU CTG is highly sensitive to signal loss due to fetal and maternal movement and its performance is negatively correlated with the maternal BMI.[7] The fixating elastic bands may cause discomfort for the pregnant woman while the need for multiple DU transducers in multiple gestation often requires more elastic bands. The CTG can also be obtained via invasive means: the fetal scalp electrode (FSE) is the gold standard for fetal monitoring. However, this invasive method can only be applied once membranes have ruptured and with sufficient cervical dilatation. Therefore, this method is only suitable during labor and not for antepartum monitoring. Furthermore, invasive CTG has a higher risk of injury and infection and only registers the FHR of the leading twin. Monitoring of the FHR with a DU transducer is still required for the second twin.

For evaluation of the FHR pattern, simultaneous registration of uterine activity is required. The intra-uterine pressure catheter (IUPC) is an invasive technique which is considered the gold standard for contraction monitoring. Due to the reported risks of placental and uterine perforation, TOCO is the current method

of choice.[8,9] However its performance is negatively influenced by maternal BMI and often needs to be relocated due to maternal movements.[10]

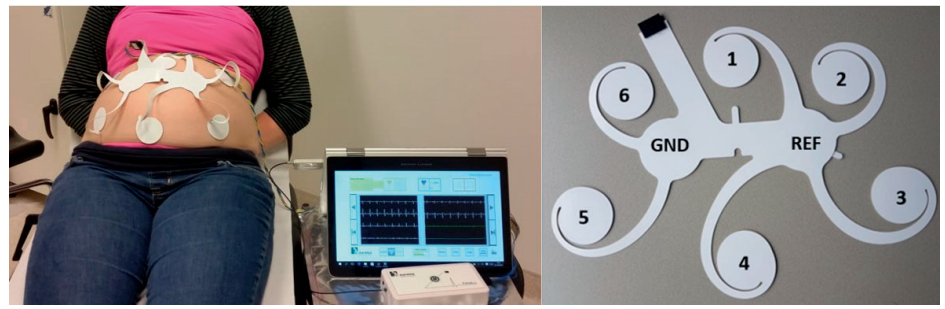
Non-invasive fetal electrocardiography (NI-fECG) uses multiple electrodes, possibly combined in a single patch, on the maternal abdomen to monitor both fetal and maternal heart rate as well as uterine contractions by means of the electrohysterogram (EHG). This method was first described as early as 1906.[11] Due to the technical struggle of isolating the low voltage fetal signal from the relatively large maternal signal, development of the technology lagged behind the development of DU and FSE technology. Recent advances in signal processing techniques made it possible to separate the FHR from the interfering signals. Taylor et al. previously described the use of NI-fECG technology to separate both individual fetal signals in twin pregnancies, using twelve lead electrodes.[12]

In this paper we present a case of a twin pregnancy in which successful separation and differentiation of both fetal signals was achieved, measured with one single electrode patch consisting of only 6 electrodes on the maternal abdomen. Based on the ECG of each individual fetus, a continuous FHR trace can be monitored and plotted.

METHODS

A 33-year old gravida 2, para 1 with dichorionic diamniotic twins received a one-time fetal ECG recording at 25+3 weeks of gestation in a research context after written informed consent was obtained. We received a statement of the Institutional Review Board of the Máxima Medical Centre stating that no ethical approval was required (N18.074). She previously delivered a healthy female neonate at term gestation, weighing 3460 grams. Fetal anomaly screening at 20 weeks of gestation showed no abnormalities in both fetuses. The fetal ECG was recorded with six channels, using a prototype of the Nemo non-invasive electrophysiological monitoring device (Nemo Healthcare BV, Veldhoven, the Netherlands). An electrode patch was placed on the maternal abdomen consisting of 8 electrodes, including one ground and one reference electrode (Figure 1), yielding six channels of bipolar electrophysiological measurements. Before applying the patch, the skin was washed with water and soap and prepared using medical abrasive paper (Red DotTM Trace Prep, 3M Health Care, Canada). The recording lasted for 28 minutes, during which the pregnant woman was lying in a semi-recumbent position to prevent aorta-caval compression.

Figure 1. Illustration of the non-invasive fetal electrocardiography (NI-fECG) device and electrode patch.



The left picture shows the electrode patch applied on the maternal abdomen and attached to the amplifier and a computer. The right picture shows the electrode patch with the numbered electrode channels and the ground (GND) and reference (REF) electrode.

The recording was digitized at 500Hz and stored for offline processing. Offline data analysis was performed using MATLAB® (The MathWorks, Inc., MA, USA). The recorded signals were first pre-processed by suppression of high-frequency noise, baseline wander, and powerline interference. Then, the maternal ECG was suppressed using a dynamic template subtraction technique.[13] Two linear combinations of the six recorded signals were generated to separate the fetal ECG signals. Each combination enhanced the fetal ECG signal for one twin, while suppressing the ECG for another. The enhanced fetal ECG signals were used to detect the location of fetal QRS complexes. These locations served as reference to perform segmentation of individual ECG complexes for each of the six recorded signals of each fetus. Subsequently, ensemble averaging (i.e. averaging the ECG complexes over all heartbeats) of these individual ECG complexes was performed to further suppress interferences. It should be noted here that ensemble averaging for one twin means suppressing the ECG of the other fetus. The result of these signal processing steps is an average fetal ECG complex for each of the six recorded channels for each of the fetus. Finally, knowledge on the locations of the recording electrodes was used to calculate a fetal vectorcardiogram for each twin.[14]

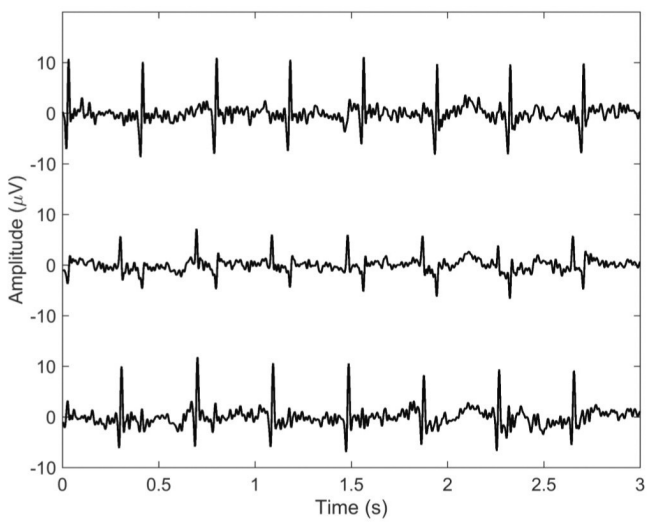
The shape of the calculated fetal vectorcardiogram depends on the orientation of the fetus within the uterus. A fetus in cephalic orientation should have a vectorcardiogram that is rotated by 180 degrees compared to a fetus in breech presentation. Assuming both twins to have a normal vectorcardiogram with normal electrical heart axis the orientation of the fetus within the uterus can

be estimated.[14,15] This estimation was blinded from the orientations that were determined by ultrasonic examination during the measurement.

RESULTS

Figure 2 shows the fetal signals obtained after suppression of the maternal ECG from the bottom three electrodes. Based on these ECGs it was possible to differentiate both fetuses with respect to each electrode. The top graph (Figure 2) comprises the ECG derived from electrode number 3 (Figure 1). This ECG shows mainly QRS complexes of the fetus positioned on the right side of the uterus, in proximity to this electrode. The bottom graph (Figure 2) comprises the ECG of the fetus located on the left, derived from electrode number 5 which was positioned on the left side of the maternal abdomen (Figure 1). Electrode number 4 picked up signals from both fetuses, since this electrode was located around the midline in between both fetuses (Figure 1). The middle graph therefore contains QRS complexes of both fetuses, one with clearly positive QRS deflections, and one with negative deflections.

Figure 2. Fetal signals obtained from electrode number 3 (top graph), electrode number 4 (middle graph) and electrode number 5 (bottom graph) as numbered in Figure 1.



The top graph comprises the electrocardiogram (ECG) of the fetus located in utero on the right, beneath electrode number 3. The bottom graph comprises the ECG of the fetus located in utero in the left, beneath electrode number 5. The middle graph contains the ECGs of both fetuses, derived from electrode number 4, which was situated in the midline.

After differentiating the fetal ECG signals from both fetuses, the beat-to-beat fetal heart rate could be calculated based on the detected fetal QRS-complexes and plotted as a continuous FHR trace for clinical practice (Figure 3). Moreover, an average fetal ECG complex per fetus was yielded by means of ensemble averaging based on the QRS locations of each fetus (Figure 4).

Figure 3. Continuous tracing of beat-to-beat fetal heart rate of both individual fetuses, based on the QRS-complexes of the fetal ECG, which resembles the display of a FHR tracing monitored with the widely used Doppler ultrasound cardiotocography.

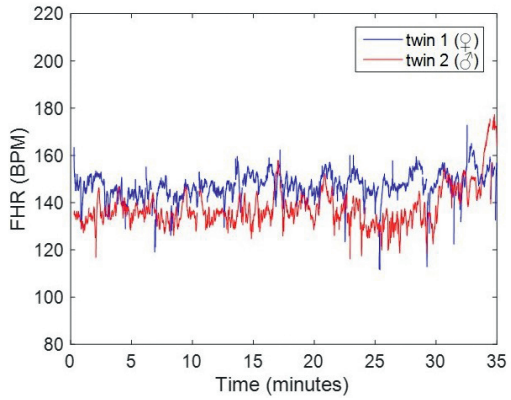
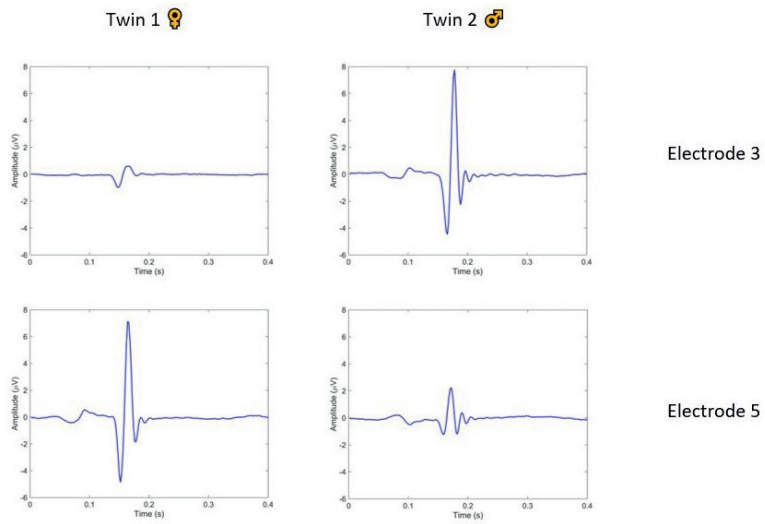
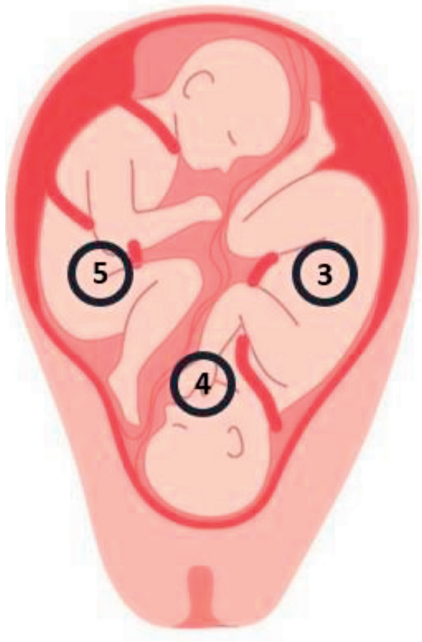


Figure 4. Average fetal ECG complex for both fetuses derived from the two outer electrodes, by means of ensemble averaging based on the QRS locations of each fetus.



Finally, a fetal vectorcardiogram was calculated for each fetus of which the orientation of both fetuses was estimated (Figure 5). These orientations were confirmed by ultrasonic examination during the measurement.

Figure 5. Representation of the position of both fetuses in utero during the measurement, estimated based on both vectorcardiograms.



The female fetus is positioned on the left side of the image in breech presentation (Twin 1). The male fetus is positioned on the right side of the image in cephalic presentation (Twin 2).

DISCUSSION

We have demonstrated that non-invasive fetal electrocardiography is feasible for simultaneous FHR monitoring of both fetuses in twin pregnancies. Taylor et al. first described successful separation of individual fetuses in multiple gestation using the NI-fECG.[12] They used 16 electrodes to obtain five-minute recordings from both twin and triplet gestations. In 42 of 58 (72%) twin gestations, separation of both fetuses was possible.[12]

In our case, separation of the fetal ECG signals from both twins was done manually. According to the ECG principle as in adults, electrical activity towards the electrode causes a positive deflection.[16] While in adults the electrodes are placed in a fixed configuration relative to the cardiac mass, the fetus can move around freely in the uterus. In twin pregnancies, the positions, orientations and distance from each fetal heart relative to each electrode varied. This led to the different waveform amplitudes and morphology of both fetal ECGs derived from the different electrodes. Based on how the patterns of both fetal ECGs varied across the different electrodes, a vectorcardiogram could be calculated for each fetus. The vectorcardiogram is a three-dimensional representation of the electrical activity during one cardiac cycle from which the fetal orientation could be estimated, under the assumption of a healthy, normal heart.[17]

The use of NI-fECG for fetal monitoring offers many diagnostic opportunities. Since it delivers beat-to-beat information on the FHR, based on the QRS-complexes of the fetal ECG, fetal heart rate variability of both fetuses can be analyzed through spectral analysis.[18-20] This could aid in the diagnosis and surveillance of TTTS in monochorionic twin pregnancies, but also pre-eclampsia and fetal growth restriction, which are more common in multiple gestation.[21] Furthermore, the possibility of obtaining an (averaged) fetal ECG complex facilitates the detection of changes in ECG waveform, which could provide valuable information about the fetal condition in the antenatal period as well as during labor. Velayo et al. previously described the use of fetal ECG parameters to differentiate the donor and recipient fetus in monochorionic pregnancies complicated with severe TTTS from non-TTTS monochorionic or singleton pregnancies.[22] Their findings reflected cardiac dysfunction in the recipient twin due to the increased cardiac output.

Moreover, changes in the ST-segment of the fetal ECG are related to metabolic acidosis of the fetus.[23] Consequently ST-segment analysis (STAN, Neoventa Medical AB, Mölndal, Sweden) was introduced at the end of the 20th century as a promising tool to detect impending metabolic acidosis during labor.[23] Unfortunately, the initial beneficial effect of STAN on perinatal outcome could not be confirmed in subsequent studies.[24,25] Previous research has shown that variation in the orientation of the electrical heart axis between fetuses causes different T/QRS baseline values. Fetuses with a higher T/QRS baseline value were shown to be more prone to false positive ST events.[26,27] Multi-lead NI-fECG recordings can deliver a 12-lead fetal ECG, taking information on the orientation of the electrical heart axis, derived from ultrasound evaluation, into account. This is in contrast to STAN, in which the signals are obtained during labor from a single-lead (FSE) and therefore can only be applied to the leading twin.

Although separation of the fetal ECGs of the twins was performed manually in this case, we expect that computerized separation of both twins is feasible, for instance using (blind) source separation techniques.[28] This would allow for real-time monitoring of the FHR in twin gestations, delivering a continuous heart rate tracing similar to that of the currently used Doppler ultrasound (Figure 3) but without the risk of confusion of both fetal heart rates. Since the electrode patch also registers the maternal heart rate as well as uterine activity, it is a beneficial method for fetal monitoring in twin gestation, where there is a 12-fold higher rate of preterm birth.[29] Further research towards incorporating computerized separation techniques and using multiple twin pregnancies to test the reproducibility is needed before this technology can be implemented in clinical practice.

CONCLUSION

Our research shows that in a twin pregnancy non-invasive electrophysiological fetal ECG recording with multiple electrodes allows for monitoring of the FHR and ECG of both individual fetuses. This technology may introduce an alternative method for non-invasive fetal monitoring in twin pregnancies, after further enhancement of the signal separation techniques.

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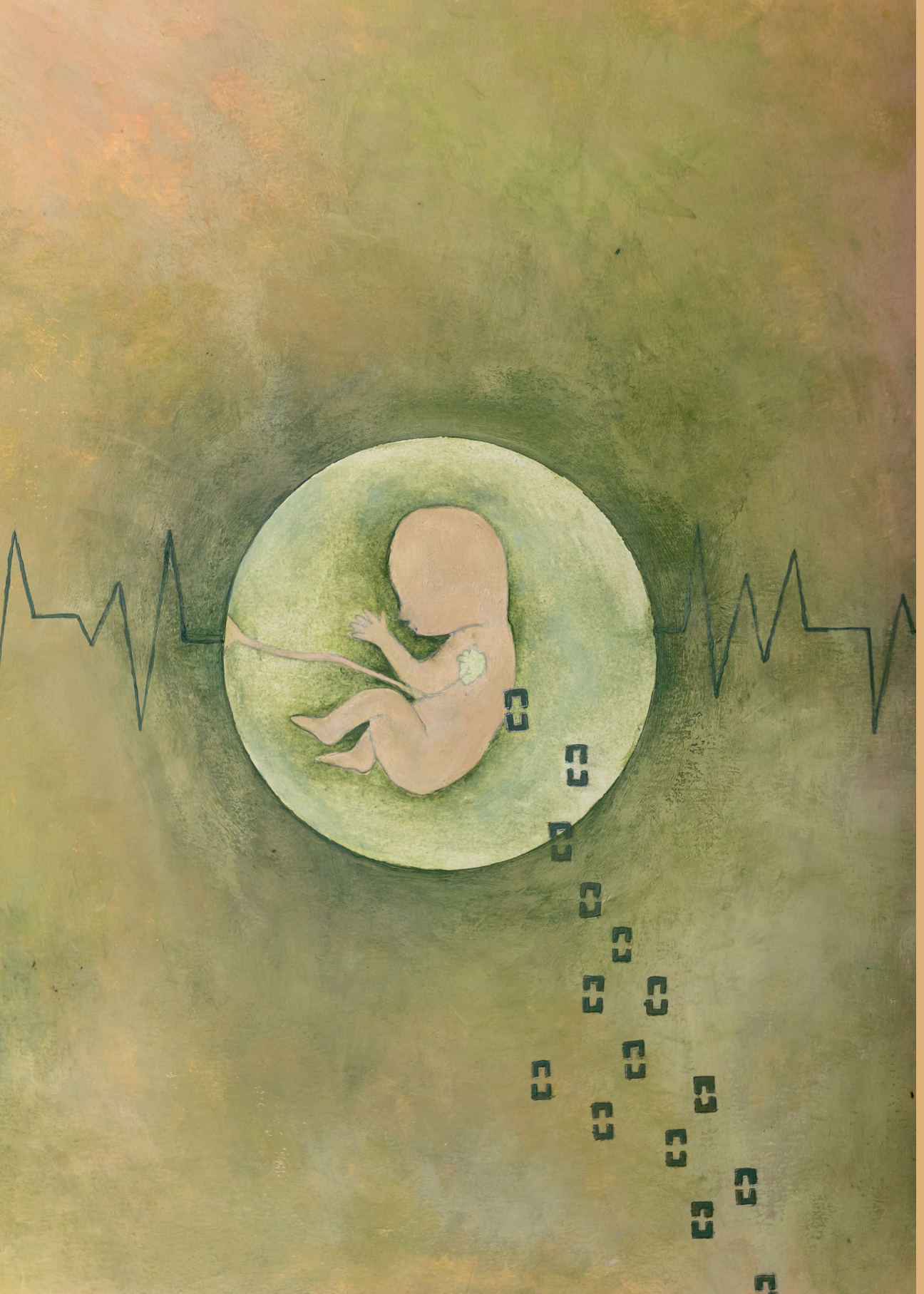

Chapter 8

Deformation measurements and spectral estimates for antenatal assessment of the premature growth-restricted fetus

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Submitted

ABSTRACT

Introduction: Growth restricted fetuses are at risk for an adverse perinatal outcome. Antenatal management of fetal growth restriction (FGR) remains challenging. Two-dimensional speckle tracking echocardiography (2D-STE) and fetal electrocardiography (fECG) are relatively new techniques that might improve FGR management. Our aim was to compare fetal cardiac deformation values and spectral estimates of fetal heart rate variability (FHRV) between FGR and appropriate for gestational age (AGA) fetuses.

Methods and outcome measures: FGR cases were prospectively included and compared with AGA fetuses. 2D-STE was used to measure global longitudinal strain (GLS) and global longitudinal strain rate (GLSR) in the left ventricle (LV) and right ventricle (RV). Beat-to-beat fetal heart rate was calculated from the fECG and used to quantify FHRV in the frequency domain by means of spectral analysis. The percentage of segments in resting and active states were compared.

Results: 14 FGR and 21 AGA cases were analyzed with a gestational age from 24 to 36 weeks. LV- and RV-GLS values were both significantly increased in FGR compared to AGA fetuses (LV-GLS: -15.4% vs -21.7%, p=0.02; RV-GLS: -15.7% vs -18.6%, p=0.049). The LV-GLSR value was also significantly increased in FGR compared to AGA fetuses (-1.4 1/s vs -1.7 1/s, p=0.002). Spectral estimates were comparable. FGR fetuses spent significantly more time in resting state compared to AGA fetuses (segments in resting-state 67% vs 33%, p=0.001).

Conclusion: Altered cardiac deformation and decreased fetal activity were seen without changes in FHRV or Doppler parameters, and their detection may facilitate earlier identification of FGR.

INTRODUCTION

Fetal growth restriction (FGR) is a condition in which the fetus fails to reach its full growth potential and is generally defined as an estimated fetal weight (EFW) <10th percentile.[1] The major cause of FGR is considered to be placental dysfunction, leading to a state of fetal hypoxia and malnutrition, ultimately interfering with the growth of the fetus.[2] FGR is associated with stillbirth, increased perinatal morbidity, mortality and long-term severe neurodevelopmental and cardiovascular diseases.[3,4] In clinical practice, FGR poses several challenges. First, the growth-restricted fetus needs to be identified by the obstetrician. Second, if identified, fetal compromise needs to be recognized and the most optimal timing for the delivery of the baby needs to be decided by weighing the risks of prolonged hypoxia against the risks associated with iatrogenic premature birth. However, despite careful antenatal examinations using Doppler sonography (including umbilical artery (UA) and middle cerebral artery (MCA) Dopplers), biophysical profile scoring (BPS), and cardiotocography (CTG), fetal well-being and optimal timing for delivery remain difficult to quantify.[5-8] Therefore, more accurate tools to assess fetal well-being in FGR are needed to improve perinatal outcomes.

FGR is a state of chronic undersupply of oxygen and nutrients where uteroplacental insufficiency results in an increased cardiac afterload. Several adaptative mechanisms occur in an attempt to reduce oxygen consumption and increase cardiac output. Ultimately, with ongoing hypoxia, these adaptions fail and the fetus may die. Clinically observed features include hemodynamic redistribution, a reduction of fetal movements and a reduction in fetal heart rate variability (FHRV). The fetal heart rate (FHR) increases, the myocardium becomes hypertrophic, and the heart assumes a more globular form.[9-11] Changes in fetal myocardial deformation have been observed.[12-18] Global longitudinal strain (GLS), the fractional percentage of the cardiac wall change, and global longitudinal strain rate (GLSR), the velocity of strain, are suggested to be the most realistic deformation parameters representing the myocardial function.[19,20]

Two-dimensional speckle tracking echocardiography (2D-STE) is a relatively new, feasible method of assessing early and mild fetal myocardial deformation.[20-22] 2D-STE uses pattern matching technology to analyze the movement of the entire myocardium. The obtained 2D cine data is frame-by-frame post-processed and analyzed. Doppler information is not used in 2D-STE and it is thus less angle dependent than Doppler techniques, making it attractive to use in the

moving fetus.[23] A few studies have measured GLS and GLSR using 2D-STE in FGR. Although limited by small study cohorts with heterogeneous gestational ages, and UA and MCA Doppler profiles, these studies suggest a possible role for 2D-STE in the detection of changing deformation values in FGR.[18,24]

Power spectral analysis (PSA) is a non-invasive method to quantify FHRV in the frequency domain.[25] Dividing the heart rate tracing into its component frequency bands provides more insight into the autonomic control of FHR fluctuations.[26,27] Fetal behavioral states are strongly correlated with the autonomic nervous system (ANS) activity. Therefore, accounting for it is imperative in evaluating FHRV.[28] In human fetuses, two frequency bands can be mainly distinguished; low- and high-frequency power. Low-frequency (LF-) power reflects baroreceptor reflex activity which is mediated by both the sympathetic and parasympathetic branches of the ANS. High-frequency (HF-) power is solely parasympathetically modulated and associated with the respiratory activity.[29,30] Normalizing spectral estimates, by dividing values by total power, can highlight relative changes in ANS modulation and therefore seem more suitable for fetal monitoring.[31]

PSA requires beat-to-beat heart rate information. This cannot be obtained from conventional CTG tracings, but it can be obtained from fetal electrocardiography (fECG), where the FHR is calculated directly from the R-R interval.[32] Studies performing PSA on fECG measurements in FGR have not been performed to date.

We hypothesize that fetal cardiac deformation values and FHRV change in FGR due to increased fetal cardiac afterload and ANS dysregulation resulting from chronic hypoxia caused by placental insufficiency.

Our study aimed to compare cardiac deformation values (measured by 2D-STE) and spectral estimates of FHRV in FGR compared to appropriate for gestational age (AGA) fetuses.

MATERIALS AND METHODS

This prospective study was performed between May 2018 and July 2019 at the Máxima Medical Center Veldhoven (the Netherlands), a tertiary care teaching hospital. The study protocol was approved by the institutional review board (NL164999.015.18). All participants were included after oral and written informed consent.

Study population

Women expecting a non-anomalous singleton baby were eligible for inclusion in the study from 24 weeks gestational age (GA) onwards. The GA had to have been confirmed with first-trimester ultrasound. Exclusion criteria were maternal age under 18 years, multiple pregnancies, and pre-existing maternal disease. Participants eligible for the FGR group included all women with a suspected growth-restricted fetus, defined as an EFW below the 10th percentile and/or fetal abdominal circumference below the 10th percentile. Inclusion was independent of UA and MCA Doppler measurements. Abnormal Doppler measurements were defined as an umbilical artery pulsatility index (UA-PI) >95th percentile and/or a cerebroplacental ratio (CPR) <5th percentile.[1] After enrollment of a FGR case, an eligible participant for the AGA group was recruited at the outpatient antenatal clinic, matched for GA to minimize the influence of physiological ANS maturation. Postnatally, birth weight was checked to confirm the diagnosis of FGR, according to local reference curves.[33] Birth weight was corrected for fetal sex and GA at birth. If the birth weight of a FGR case turned out to be normal (above or equal to the 10th percentile), the case was reallocated to the AGA group and vice versa.

The following maternal and fetal characteristics were obtained prospectively: maternal age, length, weight, body mass index (BMI, kg/m2), parity and obstetric history, smoking, and medication use during pregnancy, the occurrence of pregnancy complications, mode of delivery, and fetal growth and UA and MCA Doppler measurements. The collected neonatal characteristics obtained were GA at birth, gender, birth weight and corresponding percentile, and Apgar scores at 5 and 10 minutes.

Data collection

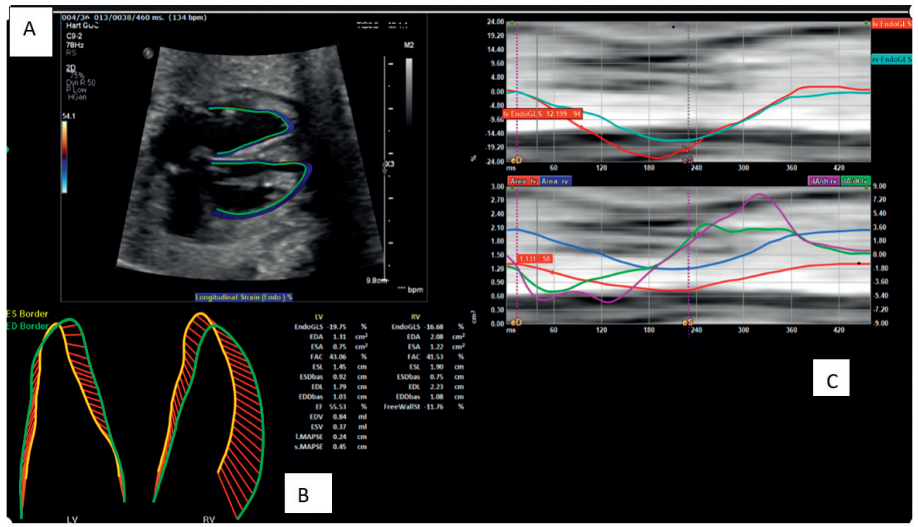
At the moment of inclusion, an ultrasound of the fetal heart four-chamber view was recorded, followed by a 40-minute fECG measurement.

2D-STE

Fetal heart four-chamber view ultrasounds were performed by an experienced fetal heart ultrasonographer (NvO). Digital four-chamber loops of the heart were acquired using an Epiq W7 ultrasound system (Philips, Eindhoven, the Netherlands) with a 9-MHz linear transducer, and stored as DICOM clips. B-mode image depth was reduced and the sector width was narrowed to achieve frame rates >90 frames/minute. DICOM clips were analyzed using an offline fetal cardiac software program (2D Cardiac Performance 1.2) developed

by TomTec Imaging Systems GmbH (Munich, Germany). A line was drawn across the left ventricle (LV) wall through the ventricle and the septum. A corresponding M-Mode appeared. The R wave in the M-Mode corresponded to the opening and closure of the mitral valve and was used to identify one heart cycle. Thereafter, the left and right ventricular myocardial regions of interest were manually marked in one frame of the DICOM, and the software automatically tracked the myocardium and its displacement in every frame included in the clip. The primary outcomes GLS and GLSR in the LV and right ventricle (RV) were then automatically measured (Figure 1).

Figure 1 STE-analysis.

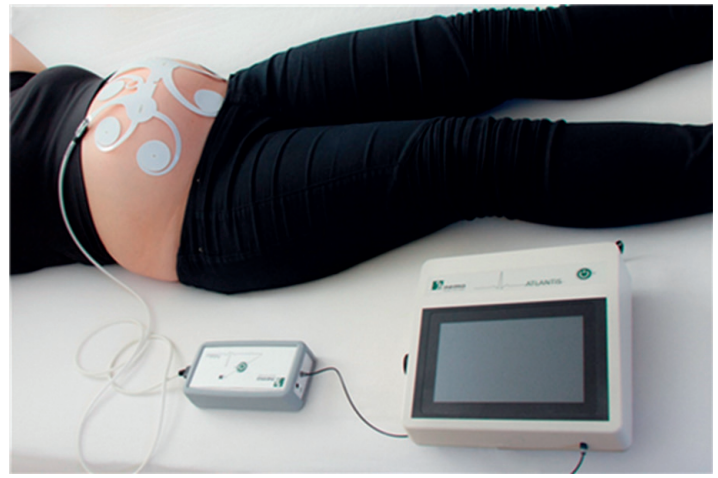


A; Marked myocardial region of interest in the left ventricle (LV) and right ventricle (RV), B; Deformation vectors in the LV and RV, C; Left and right ventricular global longitudinal strain (GLS) analysis. Figure adapted from van Oostrum et al.[18]

FHRV

FECG measurements were performed using an abdominal patch (Nemo Healthcare BV, Veldhoven, the Netherlands) consisting of 8 adhesive electrodes, including one ground and one reference electrode (Figure 2). To lower skin impedance and improve signal quality, the skin was washed with water and soap and prepared using medical abrasive paper (Red DotTM Trace Prep, 3M Health Care, Ontario, Canada). Each measurement lasted approximately 40 minutes. The recordings were digitized at 500Hz and stored for offline processing. Signal processing took place as described in more detail in previous papers.[34,35] Beat-to-beat FHR was obtained first. These FHR data were subsequently used to quantify FHRV in the frequency domain by using a continuous wavelet transform.[36]

Figure 2. Non-invasive fetal electrocardiogram.



Both LF-power (0.04–0.15 Hz) and HF-power (0.4–1.5 Hz) were calculated in normalized units (LFn and HFn) by dividing them by total power (0.04-1.5 Hz; LFn = LF/total power, HFn = HF/total power) and for each 60s segment of the fECG measurement, providing one LFn and one HFn value per segment.[37] This 60s time window was determined based on the largest wavelet of the LF band required to reliably calculate LF-power.[38] For each fECG measurement, all available 60s segments were used for the spectral analysis.

Segments were classified, based on FHR variance, into resting state (defined as an FHR variance < 15 bpm^2) and active state (defined as an FHR variance > 30 bpm^2).[28,31,39]

Basal FHR, LFn- and HFn-power of FHRV for the total duration of the measurement including all available segments as well as separately in resting and active state, and the percentage of 60s segments in rest and active state were compared between the groups.

Statistical analysis

Statistical analysis was performed using SPSS 25 (SPSS Inc., Chicago, IL, USA) or, where specified, SAS (version 9.4, SAS Institute Inc., NC, USA). Baseline characteristics were compared using Mann-Whitney U or Chi-square test, as

appropriate. The significance level for all tests was set at $p<0.05$. Basal FHR was calculated using the median of all available 60s segments for each measurement. Myocardial deformation parameters and basal FHR of both groups were compared using a Mann-Whitney U test. Spectral estimates were compared between groups using a linear mixed model with a random intercept to account for repeated measurements and between-subject variability since the number of 60s segments available for analysis varied between the different fetuses. This analysis was conducted using the MIXED procedure in SAS.[40] The percentage of 60s segments which the fetus spent in rest and activity was calculated for each individual and then compared between the groups using Mann-Whitney U in SPSS.

RESULTS

Figure 3 shows the flowchart of the included participants. Initially, 35 women were included in our study: 16 in the FGR group and 19 in the AGA group. The gestational age varied from 24 to 36 weeks. Postnatally, 2 cases in the FGR group turned out to have a birth weight above the 10th percentile and were therefore transferred from the FGR to the AGA group, resulting in 14 FGR and 21 AGA fetuses for further analysis.

Of the 14 FGR fetuses, data from 12 fetuses were available for GLS and GLSR assessment and 11 were available for PSA. One fetus was excluded due to poor ultrasound image quality, resulting in the inability to assess GLS and GLSR. One participant had an emergency cesarean section before the ultrasound could be performed. Three cases had no consecutive 60s fetal heart rate data segment available for PSA and were therefore excluded from the analysis. GLS and GLSR analysis of both ventricles as well as PSA data were available in nine FGR fetuses,

Of the 21 AGA fetuses, data from 20 fetuses were available for left ventricular GLS and GLSR analysis, 19 for right ventricular GLS and GLSR analysis, and 16 for PSA. One fetus was excluded for GLS and GLSR analysis for both ventricles due to poor ultrasound image quality. Another fetus was excluded for the analysis of GLS and GLSR of the RV due to poor right ventricular ultrasound imaging. Five fetuses were excluded from PSA because no consecutive 60-second heart rate segment was available. GLS and GLSR analysis of both ventricles as well as PSA data were available in 13 AGA fetuses.

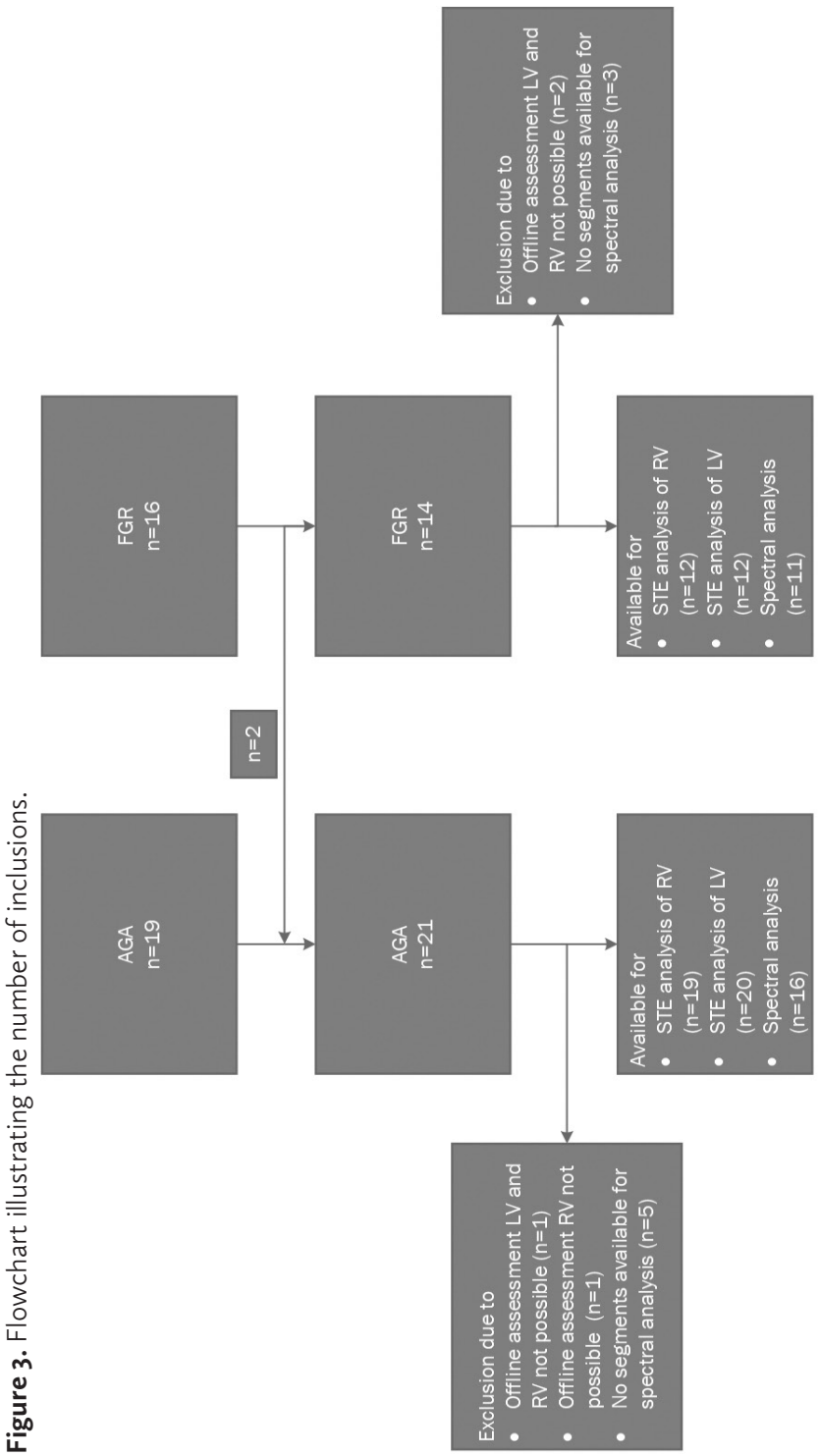


Figure 3. Flowchart illustrating the number of inclusions.

Abbreviations: AGA=appropriate for gestational age, FGR=fetal growth restriction, LV=left ventricle, RV=right ventricle, STE=2-dimensional speckle tracking echocardiography

Baseline characteristics of both groups are shown in table 1. Women with fetuses in the FGR group had a significantly lower BMI (p=0.048) and a significantly higher percentage of cesarean deliveries (p<0.001) compared to the AGA group. As to be expected, the percentage of corticosteroid administration for antenatal fetal lung maturation was significantly higher in the FGR group (p<0.001) and GA at birth and birth weight were significantly lower in the FGR group compared to the AGA group (p=0.001 and p<0.001, respectively). In the FGR group, three women were using a selective serotonin reuptake inhibitor (SSRI) compared to none in the AGA group. In five fetuses of the FGR group, UA and MCA Doppler abnormalities were seen. One had an UA-PI >p95 and a CPR <p5, two had an absent end-diastolic flow in the UA, and two had reversed flow in the UA. None of the newborns was diagnosed with chromosomal or genetic abnormalities.

Table 1. Baseline characteristics.

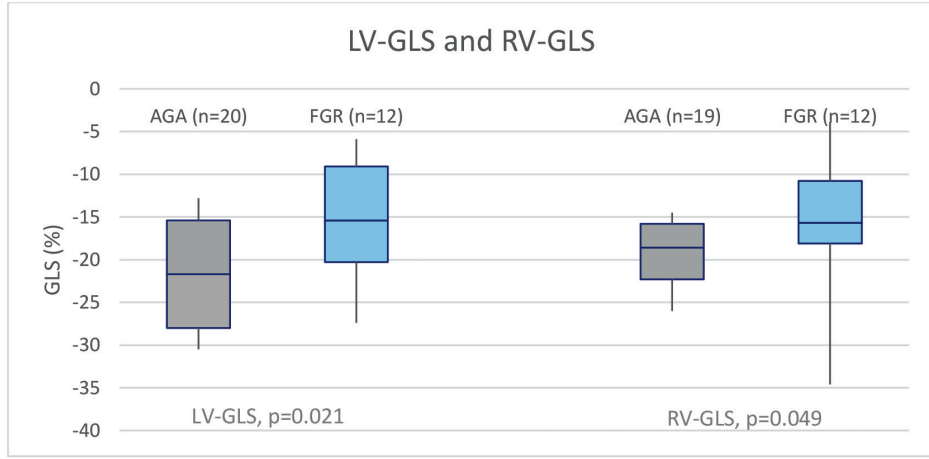
	AGA (n=21)	FGR (n=14)	p-value
Maternal characteristics			
Age at inclusion (years)	32.2 (28.5-34.6)	32.4 (29.6-34.1)	*0.93*
BMI at inclusion (kg/m²)	23.2 (21.1-27.2)	20.7 (18.9-24.4)	**0.048**
Primipara	7 (33.3%)	6 (42.9%)	*0.57*
Smokers at inclusion	1 (4.8%)	2 (14.3%)	*0.35*
GA at ultrasound (days)	215 (193-223)	213 (193-242)	*0.56*
Doppler abnormalities at inclusion†	Not performed	5 (35.7%)	
Corticosteroids during pregnancy	0 (0.0%)	9 (64.3%)	**<0.001**
Mode of delivery			**<0.001**
Vaginal birth	18 (85.7%)	5 (35.7%)	
Planned CD	1 (4.8%)	9 (64.3%)	
Secondary CD	2 (9.5%)	0 (0.0%)	
Neonatal characteristics			
GA at birth (days)	278 (269-282)	221 (215-273)	**0.001**
Birth weight (grams)	3455 (2955-3738)	1410 (1003-2623)	**<0.001**

Abbreviations: AGA=appropriate for gestational age, BMI=body mass index, CD=cesarean delivery, FGR=fetal growth restriction, GA=gestational age
† defined as: umbilical artery pulsatility index (UA-PI) >95th percentile and/or cerebroplacental ratio (CPR) <5th percentile
Significant results are shown in bold.

Fetal myocardial deformation

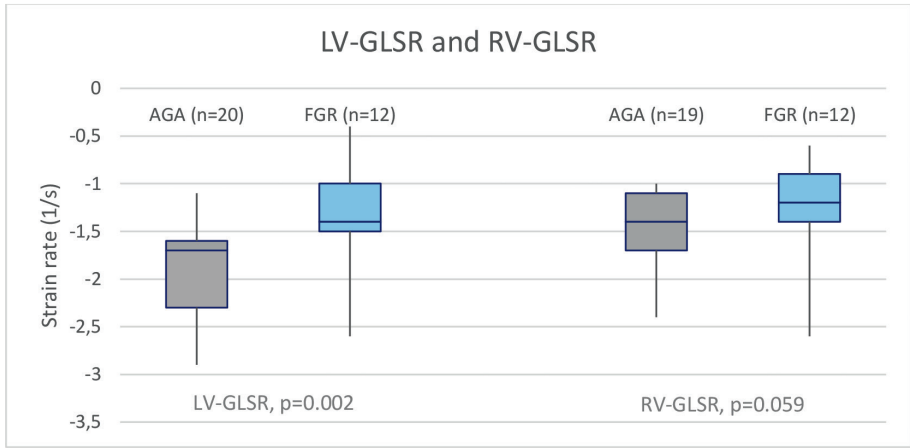
The medians with interquartile range of the GLS of both ventricles are shown in figure 4. Left ventricular global longitudinal strain (LV-GLS) and right ventricular global longitudinal strain (RV-GLS) values were significantly increased in the FGR group compared to the AGA group: LV-GLS -15,4% (-9.1% to -20.3%) versus -21.7% (-14.4% to -28.0%); p=0.021, RV-GLS -15.7% (-10.8% to -18.1%) versus -18.6% (-15.8% to -22.3%); p=0.049. The medians with interquartile ranges of the GLSR in both ventricles are shown in figure 5. The LV-GLSR value was significantly increased in the FGR compared to the AGA group; LV-GLSR -1.4 1/sec (-1.0 to -1.5 1/sec) versus -1.7 1/sec (-1.6 to -2.3 1/sec); p=0.002. The RV-GLSR showed a trend to larger values in the FGR group; -1.2 1/sec (- 0.9 to -1.4 1/sec) versus -1.4 1/sec (-1.1 to -1.7 1/sec); p=0.059.

Figure 4. Left and right ventricular global longitudinal strain.



Abbreviations: AGA=appropriate for gestational age, FGR=fetal growth restriction, GLS=global longitudinal strain, LV=left ventricular, RV=right ventricular.

Figure 5. Left and right ventricular global longitudinal strain rate.



Abbreviations: AGA=appropriate for gestational age, FGR=fetal growth restriction, GLSR=global longitudinal strain rate, LV=left ventricular, RV=right ventricular

We also performed a subgroup analysis comparing the seven FGR fetuses without UA or MCA Doppler abnormalities with the AGA fetuses. Significantly increased values for GLS and GLSR for both ventricles were found as shown in table 2.

Table 2. GLS and GLSR in AGA fetuses and FGR fetuses with normal Dopplers.

	AGA (n=20)	FGR [normal Dopplers] (n=7)	p-value
LV-GLS (%)	21.7 (15.4 - 28.0)	15.4 (8.2 - 15.8)	**0.0004**
LV-GLSR (1/s)	1.7 (1.6 - 2.3)	1.3 (1 - 1.5)	**0.002**
RV-GLS	18.6 (15.8 - 22.3)	13.8 (5.3 - 17.8)	**0.004**
RV-GLSR (1/s)	1.4 (1.1 - 1.7)	1.1 (0.7 - 1.3)	**0.007**

Abbreviations: AGA=appropriate for gestational age, FGR=fetal growth restriction, GLS=global longitudinal strain, GLSR=global longitudinal strain rate, IQR=interquartile range, LV=left ventricular, RV=right ventricular.
Significant results are shown in bold.

Fetal heart rate

The median FHR during the fECG measurements was comparable between the FGR and AGA group; 139.8 bpm (129.3 to 146.8 bpm) versus 141.6 bpm (135.3 to 146.8 bpm); p=0.40.

Fetal heart rate variability

In total 254 segments were available in the FGR group and 177 segments in the AGA group. The results of the linear mixed model for repeated measures of LFn- and HFn-power for the overall measurement as well as in rest and active state are shown in table 3. No significant differences in spectral estimates of FHRV were found.

Table 3. Linear mixed models of normalized LF- and HF-power for FGR (1) and AGA (0).

	Effect	FGR (1) AGA (0)	Estimated coefficient (SE)	95% CI	p-value
LFn (overall)	Intercept		0.64 (0.05)	0.54 – 0.74	
		0	0.07 (0.06)	-0.06 – 0.20	0.27
		1	—		
LFn (rest)	Intercept		0.61 (0.06)	0.49 – 0.73	
		0	0.03 (0.08)	-0.13 – 0.20	0.67
		1	—		
LFn (active)	Intercept		0.75 (0.04)	0.67 – 0.84	
		0	0.02 (0.05)	-0.08 – 0.12	0.63
		1	—		
HFn (overall)	Intercept		0.23 (0.04)	0.15 – 0.32	
		0	-0.06 (0.05)	-0.17 – 0.05	0.25
		1	—		
HFn (rest)	Intercept		0.26 (0.05)	0.16 – 0.37	
		0	-0.03 (0.07)	-0.17 – 0.12	0.71
		1	—		
HFn (active)	Intercept		0.13 (0.03)	0.06 – 0.19	
		0	-0.01 (0.04)	-0.09 – 0.06	0.69
		1	—		

Abbreviations: AGA=appropriate for gestational age, FGR=fetal growth restriction, HFn=normalized high-frequency power, IQR=interquartile range, LFn=normalized low-frequency.

Fetal rest and activity state

The proportion of segments in rest and activity are shown in table 4. In the FGR group, the proportion of segments in rest was significantly higher compared to the AGA group; 66.7% (51.9 to 85.0%) versus 33.2% (9.5 to 53.8%); p=0.001. Also, the proportion of activity was significantly lower in the FGR compared to the AGA group; 6.3% (0.0 to 21.1%) versus 34.9% (16.6 to 63.2%); p=0.008.

Table 4. Median [IQR] of individual percentages of segments in rest and activity.

	AGA		FGR		
	N	**Median [IQR]**	**N**	**Median [IQR]**	**p-value**
Rest	16	33.2 [9.5-53.8]	11	66.7 [51.9-85.0]	**0.001**
Activity	16	34.85 [16.6-63.2]	11	6.3 [0.0-21.1]	**0.008**

Abbreviations: AGA=appropriate for gestational age, FGR= fetal growth restriction, IQR = interquartile range.
Significant results are shown in bold.

In addition, we performed a subgroup analysis comparing FGR fetuses without UA and MCA Doppler abnormalities with the AGA fetuses and found significantly reduced activity in these FGR fetuses as well (table 5).

Table 5. Median [IQR] of individual percentages of segments in rest and activity between AGA fetuses and FGR fetuses with normal Dopplers.

	AGA		FGR [normal Dopplers]		
	N	**Median [IQR]**	**N**	**Median [IQR]**	**p-value**
Rest	16	33.2 [9.5-53.8]	8	61.3 [50.4-70.2]	**0.009**
Activity	16	34.9 [16.6-63.2]	8	15.3 [1.6-26.7]	**0.045**

Abbreviations: AGA= appropriate for gestational age, FGR= fetal growth restriction, IQR=interquartile range.
Significant results are shown in bold.

DISCUSSION

Our study demonstrated that the fetal heart deformation in FGR fetuses differs from that in AGA fetuses. LV-GLS, LV-GLSR and RV-GLS values were significantly increased in FGR compared to AGA fetuses. Growth-restricted fetuses spent more time in resting state than the AGA fetuses, yet power spectral estimates of FHRV, as well as basal FHR, were comparable between the FGR and AGA fetuses

Our findings of significantly increased values of LV-GLS, LV-GLSR and RV-GLS in FGR are in line with the first fetal heart response to prolonged hypoxia suggested in previous studies.[9] Studies using Tissue Doppler Imaging to assess myocardial function showed changed deformation values in FGR fetuses, regardless of the UA and MCA Doppler findings.[41-44] Although limited by heterogeneity and small study cohorts, recent studies using 2D-STE to evaluate deformation in FGR compared to AGA fetuses, also showed increased or comparable GLS and GLSR in FGR.[18,22,24,45,46] Abnormal strain values (defined as >95th centile of their Z-score) measured by 2D-STE have also been reported in FGR, irrespective of UA and MCA Doppler findings.[47] In our subgroup analysis comparing the seven FGR fetuses without UA or MCA Doppler abnormalities with the AGA fetuses, significantly increased values for GLS and GLSR for both ventricles were found. In a recent study performed by our group, abnormal RV-GLS was shown in the FGR fetuses even before the growth restriction was clinically evident. Interestingly these fetuses could still maintain the right ventricular cardiac output by increasing their heart rate.[18] These findings suggest that changes in the fetal heart occur early in the continuum of fetal distress due to prolonged hypoxia in FGR, i.e. even before UA Doppler abnormalities are present.[18] The detection of deformation abnormalities could thus facilitate the detection of at-risk growth-restricted fetuses earlier.

Due to chronic hypoxia and undernutrition, growth-restricted fetuses will tend to move less to limit the energy and oxygen consumption through movement. In this way vital organs are protected from hypoxic injury.[15,16] In the current study, we observed a reduced time spent in the active state in the FGR fetuses compared to the AGA fetuses. This is in line with earlier studies concerning fetal activity in FGR.[15,16] However, previous studies using BPS to quantify fetal activity showed decreased fetal movements in FGR to occur only late in the process of fetal deterioration, after redistribution of cardiac output and declined amniotic fluid were shown.[16,17,48,49] In the current study, including FGR with and without UA and MCA Doppler abnormalities, we quantified fetal activity states based on FHR variance measured with fECG. Using this method, significantly reduced fetal activity was shown (Table 4). Our subgroup analysis comparing FGR fetuses without UA and MCA Doppler abnormalities with the AGA fetuses showed significantly reduced activity in these FGR fetuses as well. This suggests that, like the remodeling of the heart, reduced fetal activity appears to occur early in the process of fetal adaptation to a hypoxic state, even before the appearance of UA and MCA Doppler abnormalities. Our FHRV estimates were comparable between FGR and AGA fetuses, independent of the fetal activity state. This is in contrast to Breborowicz et al. and Vinkesteijn et al., who found a significant decrease in spectral estimates in FGR compared to AGA fetuses.[50,51] However, Breborowicz et al. used conventional CTG tracings in which beat-to-beat information of the FHR is lacking, making it less reliable for PSA.[50] Vinkesteijn et al. included FGR fetuses with an EFW below the fifth percentile and median

values of the UA-PI were high in their FGR group suggesting they included fetuses with more severely growth-restriction.[51]

Sequential changes in clinical features in pregnancies complicated with uteroplacental dysfunction may explain why we did not detect significant differences in FHRV values between the study groups, irrespective of fetal movements, in our study. Earlier studies have described reduced FHRV late in the deterioration process, and only when the hypoxia has become chronic.[12,16,49,52] Only five growth-restricted fetuses with UA and MCA Doppler abnormalities were included in our study. Changes in UA and MCA Dopplers appear when the FGR is established, suggesting that a reduction in FHRV probably occurs late in the process of fetal deterioration during chronic hypoxia as well.

Strengths and limitations

The strengths of our study include the prospective design and the unique combination of two relatively new, different techniques that have the potential to be used for the assessment of fetal well-being in FGR. To our knowledge, this is the first study on FHRV in FGR fetuses using fECG measurements which allows for reliable spectral analysis, in contrast to conventional CTG tracings.[26]

Our study has several limitations. First, the generalizability of our results as well as the power for detecting differences in FHRV between both groups is limited by the small sample size. Second, fetuses with an EFW under the 10th percentile were considered eligible for the FGR group, while the group was heterogeneous concerning UA and MCA Doppler abnormalities, representing FGR fetuses at different stages in the process of placental dysfunction. However, even though only five out of 14 growth-restricted fetuses had UA or MCA Doppler abnormalities, a significant increase in fetal deformation values and decreased fetal activity in FGR was shown.

An effect of usage of pregnancy-related drugs, on the FHRV results in our study is unlikely but cannot be completely excluded. In the FGR group, nine out of 14 women received corticosteroids and three received SSRIs during pregnancy. No medication was used in the control group. While corticosteroids are known to decrease FHRV in general, they do not influence normalized power spectral estimates.[34,35] It is therefore unlikely that corticosteroid use in the FGR group influenced our results.

There is no literature concerning the influence of SSRIs on FHRV. A previous study described an increase in fetal activity in women using SSRIs.[53] We found a decrease in fetal activity in the FGR group, SSRI use in the FGR group might have led to an underestimation of our results.

Recommendations

Future research should focus on a prospective longitudinal study regarding cardiac deformation values and power spectral estimates in AGA and FGR with increasing gestational age, and with various stages of placental function deterioration in the FGR fetuses.

CONCLUSION

Growth-restricted fetuses have increased values of GLS and GLSR in both ventricles compared to AGA fetuses. Growth-restricted fetuses spend more time in rest than AGA fetuses. No statistically significant difference could be shown in FHRV between AGA and FGR fetuses even after correcting for rest and activity state. Our results suggest that cardiac remodeling and decreased fetal activity appear earlier in the process of fetal adaptation to placental dysfunction compared to changes in FHRV, and probably even before UA and MCA Doppler abnormalities are present.

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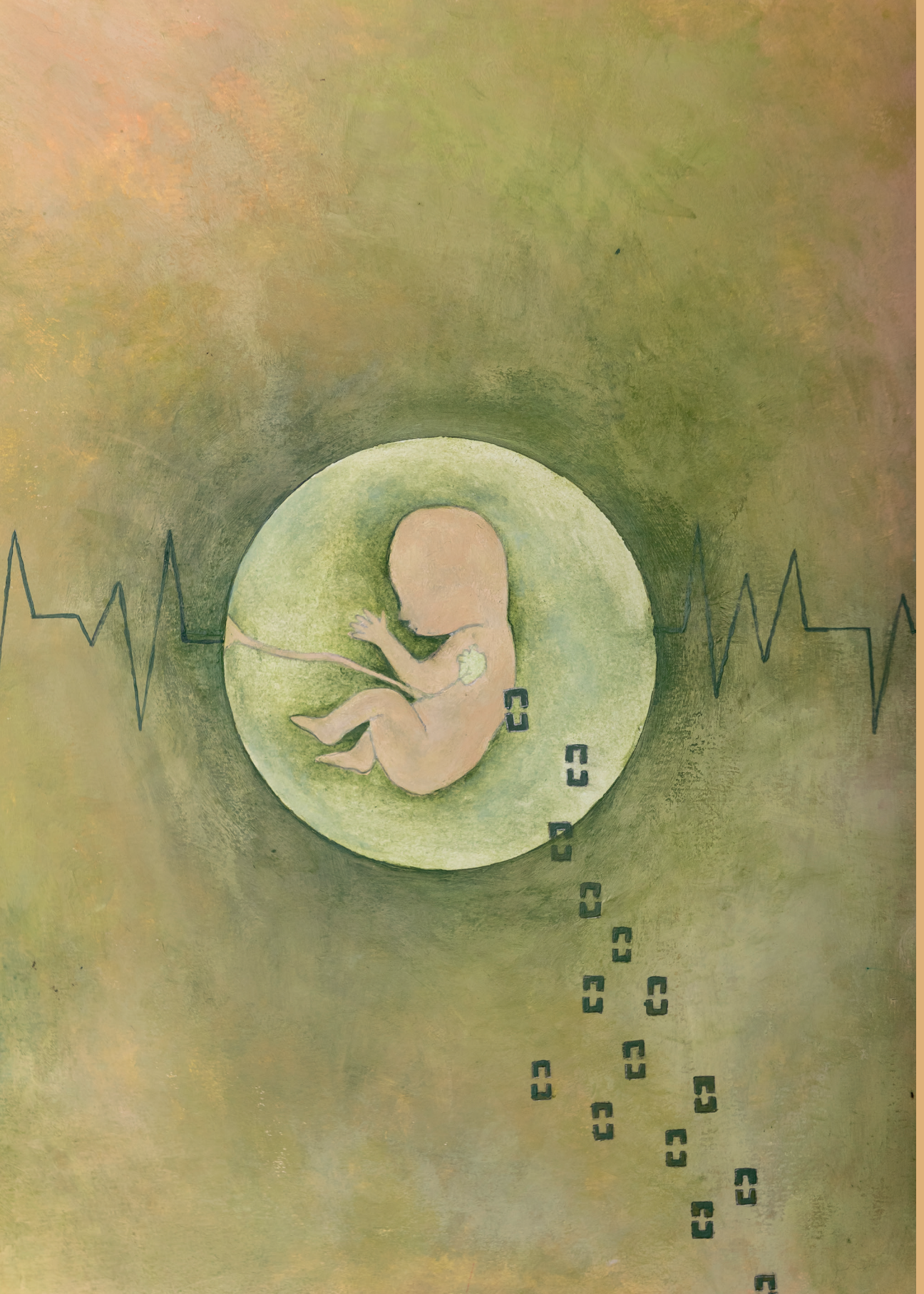
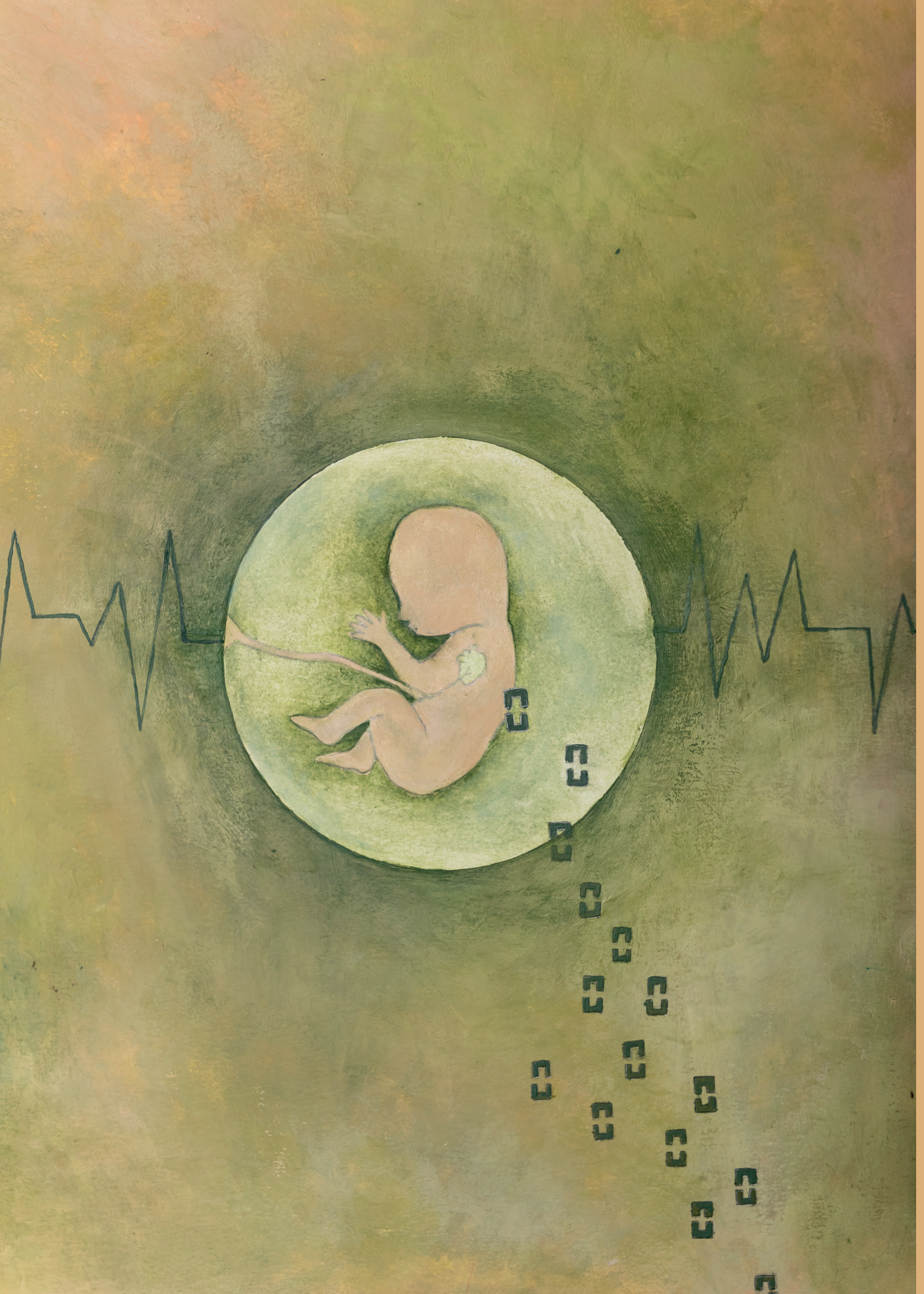


Part II

Fetal ECG for diagnostic purposes



Chapter 9

The electrical heart axis of the fetus in mid-pregnancy: a cohort study

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Submitted

ABSTRACT

Introduction: A fetal anomaly scan in mid-pregnancy is performed, to check for the presence of congenital anomalies, including congenital heart disease (CHD). Unfortunately, 40% of CHD is still missed. The combined use of ultrasound and electrocardiography might boost detection rates. The electrical heart axis is one of the characteristics which can be deduced from an electrocardiogram (ECG). The aim of this study was to determine reference values for the electrical heart axis in healthy fetuses around 20 weeks of gestation.

Material and methods: Non-invasive fetal electrocardiography was performed subsequent to the fetal anomaly scan in pregnant women carrying a healthy singleton fetus between 18 and 24 weeks of gestation. Eight adhesive electrodes were applied on the maternal abdomen including one ground and one reference electrode, yielding six channels of bipolar electrophysiological measurements. After removal of interferences, a fetal vectorcardiogram was calculated and then corrected for fetal orientation. The orientation of the electrical heart axis was determined from this normalized fetal vectorcardiogram. Descriptive statistics were used on normalized cartesian coordinates to determine the average electrical heart axis in the frontal plane. Furthermore, 90% prediction intervals (PI) for abnormality were calculated.

Results: Of the 328 fetal ECGs performed, 281 were included in the analysis. The average electrical heart axis in the frontal plane was determined at 122.7° (90% PI: -25.6°; 270.9°).

Conclusion: The average electrical heart axis of healthy fetuses around mid-gestation is oriented to the right, which is, due to the unique fetal circulation, in line with muscle distribution in the fetal heart. However, the electrical heart axis alone is not suitable for screening for CHD, due to the wide prediction interval.

INTRODUCTION

In developed countries, a fetal anomaly scan in mid-pregnancy is performed, to check for the presence of congenital anomalies, including congenital heart disease (CHD). The importance of prenatal detection of CHD is shown in previous research that found an reduction in neonatal morbidity and mortality when CHD was prenatally diagnosed.[1,2] The introduction of a standardized screening program for the fetal anomaly scan in mid-pregnancy has led to an increase in prenatal detection rates of CHD in the Netherlands up to 40-60%. However, 40% of CHD is still missed.[3] Ultrasound detection of CHD is difficult due to fetal body movements, the small size and rhythmic movements of the fetal heart. Furthermore, detection rates depend on the experience of the sonographer, fetal position and BMI of the mother.[4–13] To further increase prenatal detection of CHD, new diagnostic tools are needed.

This tool might be the non-invasive fetal electrocardiogram (NI-fECG). NI-fECG enables the production of a 12-lead electrocardiogram by means of a standardized method. ST-segment elevations are seen in ischemia and deviation of the electrical heart axis occurs in some cardiac malformations (e.g. hypoplastic right heart syndrome, atrioventricular septal defect).[14–16] The electrical heart axis is one of the characteristics which can be deduced from an ECG. It represents the median vector of the electrical activity through the heart during one cardiac cycle and provides information about the muscle distribution of the heart. Previous studies show a relationship between a deviation in the electrical heart axis and the presence of certain types of CHD.

Verdurmen et al. found a right-oriented electrical heart axis in healthy fetuses.[17] This has also been described in term fetuses during labor and neonates. [18,19] The right-oriented electrical heart axis in healthy fetuses can be explained by the fetal circulation that has a unique physiology with multiple shunts to bypass the lungs, so that the right ventricle pumps 60% of the cardiac output, leading to a right ventricular dominance. After birth the pulmonary vascular resistance drops and the venous return to the left atrium increases leading to an increase in the cardiac output of the left ventricle. The left ventricle pumps against the high resistance systemic system once the placental circulation is eliminated.[20] With time the left ventricular muscle mass gradually increases and a leftwards shift of the electrical heart axis occurs. We hypothesize that the presence of certain CHD can already cause a deviated electrical heart axis in utero.

The aim of this paper is to determine reference values for the electrical heart axis in mid-term healthy fetuses.

MATERIAL AND METHODS

The study protocol was previously published by Verdurmen et al.[21] Ethical approval by the institutional review board of the Máxima Medical Center was obtained before enrolment (NL48535.015.14). Fetal ECG measurements were performed from May 2014 until September 2018 at the Máxima Medical Centre Veldhoven, The Netherlands, a tertiary care referral center for obstetrics and at 'Diagnostiek voor U' diagnostic center, Eindhoven, The Netherlands.

Study population

Pregnant women carrying a singleton fetus without known congenital anomalies and a gestational age between 18 and 24 weeks of gestation were included. All patients were older than 18 years and gave written informed consent prior to the fetal ECG measurement.

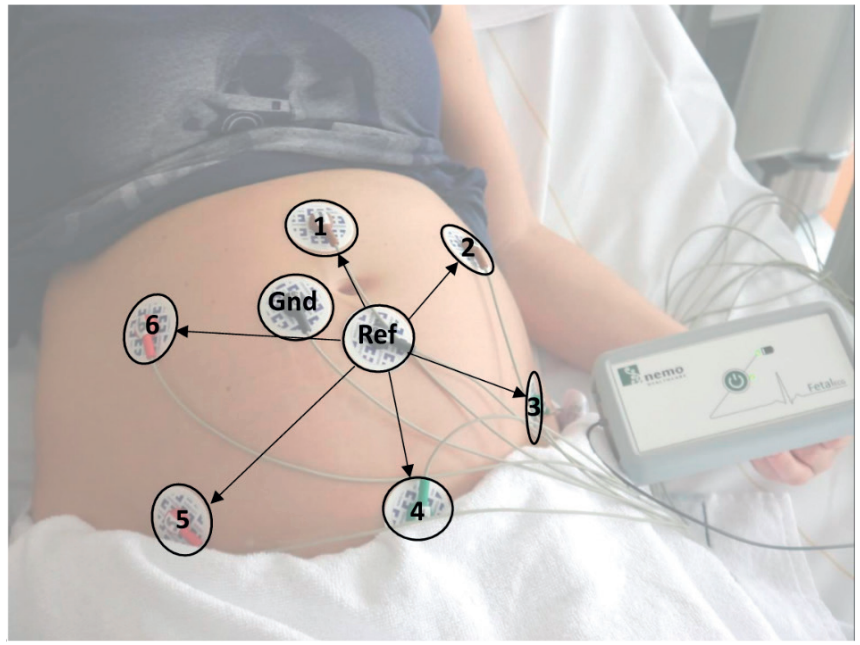
Patients who did not understand the Dutch language well and/or had multiple pregnancies were excluded. If CHD was found later in pregnancy or after birth, the measurement was excluded from analysis.

The following data was gained prospectively: maternal gravidity and parity, as well as obstetric and general medical history. Parents received a questionnaire three months after birth to confirm that the child was healthy and did not have any congenital diseases. We chose this three-month cut-off point as at this age, all children in the Netherlands have had their second medical check-up by a doctor, who, among other things, evaluated cardiac health.

fECG Measurements and signal processing

Singular fetal ECG measurements were performed subsequent to the fetal anomaly scan. Women lay in a semi-recumbent position to prevent aortocaval compression. To yield six channels of bipolar electrophysiological measurements, eight electrodes were placed on the maternal abdomen in a fixed configuration. Two electrodes served as common reference and ground electrodes respectively (Figure 1).[22] Before application of the electrodes, the skin was washed with water and soap after which skin preparation was performed with medical abrasive paper (Red DotTM Trace Prep, 3M Health Care, Ontario, Canada) to optimize skin impedance. Each measurement lasted around 30 minutes during which fetal orientation was ultrasonographically checked following a protocol at four fixed time intervals. After a short training by an experienced researcher, gynecologist or sonographer the researcher (most often a medical student) was able to determine the fetal orientation. The protocol describes how the ultrasound should be made and in which anatomical plane. The researcher than depicted those planes on a form. Furthermore, the ultrasound pictures with the position of the probe were printed so they could later be checked by a fellow researcher or gynecologist.

Figure 1. Measurement set-up of the non-invasive fetal electrocardiogram.[22]



Eight electrodes were placed on the maternal abdomen in a fixed configuration. Two electrodes served as common reference (Ref) and ground (Gnd). The cartesian coordinate system as used in our analyses is displayed in the bottom right corner.

Fetal ECG measurements were performed with a 6-channel electrophysiological amplifier (Nemo Healthcare BV, The Netherlands) using adhesive Ag/AgCl electrodes (Red DotTM, 3M Health Care, Ontario, Canada) on the maternal abdomen. The measured electrophysiological signals were digitized at 500 Hz sampling frequency and stored on a computer for offline analysis.

This offline analysis consisted of a series of signal processing steps, aimed to suppress interferences and standardize the fetal ECG signals for fetal orientation,

so that the fetal electrical heart axis could be measured. These signal processing steps have been described in more detail in Lempersz et al. 2020.[22] In the first step of signal processing, interferences from the maternal ECG, abdominal muscles, and extracorporeal sources were suppressed by an adaptive template-based method [23]. As a result, for each of the six recorded signals a fetal ECG signal was obtained, yet at relatively low signal-to-noise ratio. Because each fetus could have a different orientation with respect to the maternal abdomen and the recording electrodes placed on this abdomen, the fetal ECG signals not only changed between participants, but also within participants due to fetal movement.

The second step in the signal processing aimed to standardize for fetal orientation. To allow for such standardization, a fetal vectorcardiogram was calculated for every heartbeat first, combining the information from the six abdominal signals into a 3-dimensional fetal ECG complex.[24] This vectorcardiogram could subsequently be tracked over time, detecting fetal movements and correcting for them by rotating the fetal vectorcardiogram in 3-dimensional space. Finally, another rotation in 3-dimensional space was applied that corrected for the fetal orientation, which was assessed from intermittent ultrasound scans. For instance, if the ultrasound indicated that the fetus was in a cephalic position, the recorded fetal vectorcardiogram was rotated by 180 degrees to represent the fetal vectorcardiogram as if the fetus was in a breech position, similar to the position used when making adult ECGs. Similarly, a fetal back to the front was rotated along the longitudinal axis as if the fetal back was to the back. The parts of the measurements of sufficient signal quality, closest to the performance of the ultrasound determining fetal orientation, were used to create the vectorcardiogram.

Finally, to enhance the signal-to-noise ratio, orientation-standardized fetal vectorcardiograms were averaged over multiple heartbeats to yield one fetal vectorcardiogram per measurement.

The orientation of the electrical heart axis was defined as the direction in which the vectorcardiogram had its maximum amplitude.[14] The latter direction was estimated as the average direction of the dominant vectors in the QRS complex, defined as the vectors from the point that the R-wave exceeded 70% of its maximum value until the point that it fell below 70% of the maximum value. The orientation of the fetal heart axis was expressed in degrees ranging from minus 180° to plus 180° and calculated in the frontal plane, where minus 90° is located superiorly.

Statistical analysis

The observed frontal angle was determined in the (x,y)-plane. The normalized coordinates $(\tilde{x}, \tilde{y})$ were calculated as the division of the originate coordinates (x, y) by their Euclidean norm $\sqrt{x^2 + y^2}$.

We calculated descriptive statistics (median with interquartile range (IQR)) on the normalized $(\tilde{x}, \tilde{y})$ Cartesian coordinates. We also reported the average frontal axis with 90% prediction intervals that would function as reference values. Prediction intervals are chosen because they account for the uncertainty in estimating the population mean and the random variation of the individual values.[25] The prediction intervals were calculated, using the lower and upper quantiles of the Von Mises distribution with the estimated parameters.

Statistical analysis was conducted with SAS (version 9.4, SAS Institute Inc., NC, USA) and R (version 3.5.3, R Foundation, Vienna, Austria). Descriptive statistics (median with interquartile ranges) were used to describe baseline characteristics, using IBM SPSS statistics version 25.0 (SPSS Inc., Chicago, Ill., USA).

RESULTS

A total of 328 patients were included. From these, 15 measurements were excluded due to missing or incomplete questionnaires and 23 measurements were excluded due to missing information on the fetal orientation. CHD was found in one neonate and a chromosomal disorder was present in three neonates as reported in the postpartum questionnaire, necessitating their exclusion. Of the remaining 286 inclusions (87.2% of the original 328 included patients), five measurements had to be excluded due to poor quality NI-fECG recordings. A total of 281/286 measurements were available for further analysis giving a success rate of 98%. Table 1 shows the characteristics of the study population. Figure 2 shows a flowchart of the included measurements.

Table 1. Baseline characteristics of participants (N=281).

	Mean (± SD)
Age (years)	31.3 (± 4.0)
GA (weeks)	20.2 (± 1.3)
Nulliparous (%)	52.3
BMI (kg/m²)	24.4 (± 5.4)

Abbreviations: BMI = body mass index, GA = gestational age.

Figure 2. Flowchart of the included measurements.

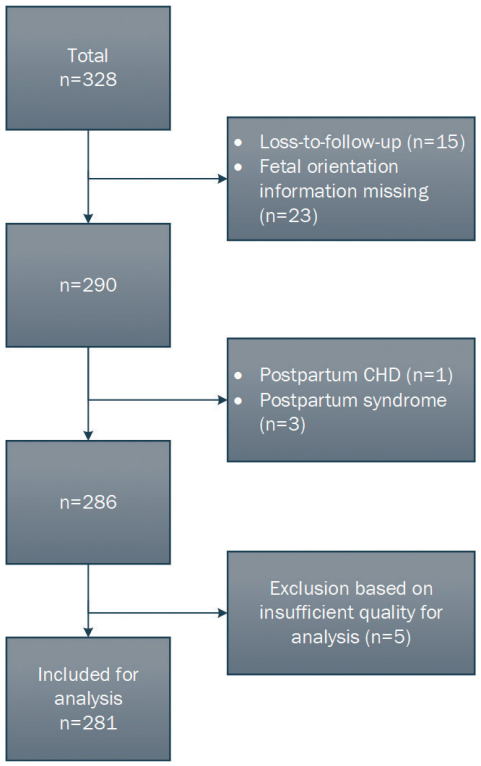
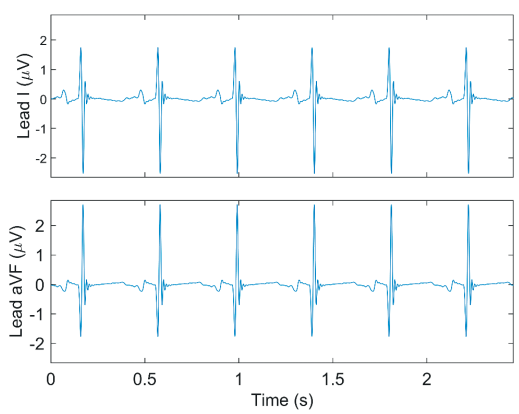


Figure 3. is an example of a fetal electrocardiogram, here one can see a clear QRS-complex.

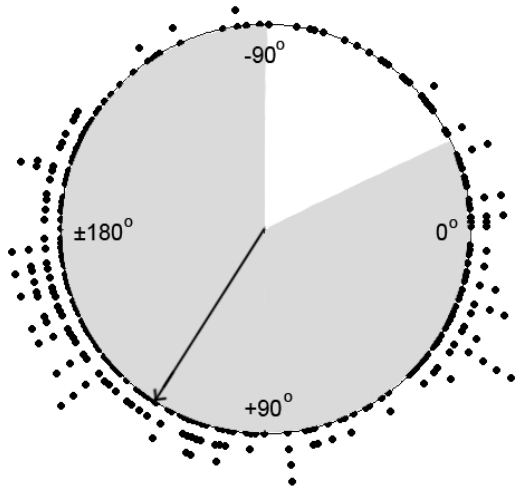
Figure 3. Example of a fetal electrocardiogram. Lead I and aVF.



x-axis is time in seconds (s), y-axis is electric potential in microvolt (μV)

The median and interquartile range (IQR) of the $\tilde{x}$ coordinate was 0.347 (1.660) and that of the $\tilde{y}$ coordinate was 0.327 (0.956). Based on these normalized coordinates, the average frontal angle was determined at 122.68° (90% PI: -25.6°; 270.9°). Figure 4 shows the distribution of the orientation of the electrical heart axis of each fetus. The arrow shows the mean electrical heart axis with, in grey, corresponding 90% PI in the frontal plane.

Figure 4. Distribution of the orientation of the electrical heart axis plotted in a circle diagram. Each dot represents one fetus. The arrow represents the mean electrical heart axis with corresponding 90% PI in the frontal plane in grey.



DISCUSSION

Main Findings

In this paper we present reference values for the electrical heart axis calculated from our cohort of 281 healthy fetuses at mid-gestation. We found that the mean electrical heart axis of the healthy fetus is orientated to the right (122.68°), which is in line with the distribution of fetal cardiac muscle mass due to the unique anatomy of the fetal circulatory system and findings from previous studies.[16-19,26] We found that the prediction intervals based on our cohort are wide, indicating a broad range wherein future observations will fall.

Strengths and Limitations

The main strength of this study is the large group of participants and the low number of recordings excluded due to insufficient data quality. The latter shows

that this technology has improved significantly compared to earlier reported research.[27–29] This high success rate is an indispensable characteristic for any technology to be implemented in daily practice. However, the time needed to process the recordings is at this moment the limiting factor for the NI-fECG technology, which currently still takes place offline. Therefore, results are not yet readily available during the measurement. This can be solved by automatization of the signal processing algorithms in the future which can then be incorporated in the measurement hardware. Furthermore, correction for fetal orientation by ultrasound could give minor inaccuracies. To minimize potential inaccuracies, the data recorded closest to the time of fetal orientation determination with ultrasound were used to create a vectorcardiogram.

Interpretation

To our knowledge, this is the first study that determines reference values for the electrical heart axis in healthy midterm fetuses. Recent advances in the signal processing algorithms have made it possible to acquire information on the fetal ECG in the antenatal period in a non-invasive manner. This makes it possible to identify reference values of the electrical heart axis in healthy fetuses in mid-pregnancy.

The electrical heart axis reflects the distribution of muscle mass in the fetal heart. In the fetal circulation with its three obligatory shunts and the high resistance pulmonary and low resistance systemic circulations, the right ventricle is dominant and pumps about 60% of the cardiac output. As a consequence, the muscle mass of the right ventricle is greater than that of the left ventricle and this results in greater amplitude of depolarization together with decreased speed of depolarization on the right side.[30] Our results confirm this right oriented electrical heart axis in healthy fetuses. The next step towards determining the use of this parameter for screening purposes is to define the electrical heart axis in fetuses with CHD.

Studies in neonates with CHD have already shown changes in the electrical heart axis in certain types of CHD.[14–16] For instance, a deviation of the electrical heart axis to the left is seen in neonates with an atrioventricular septal defect (AVSD). This altered electrical activation is associated with anatomic displacement of the left ventricular (LV) papillary muscles (PM). The fascicles of the left bundle branch end at the insertion places of the PM on the ventricular wall and therefore function as the most lateral starting points of LV activation. In the case of an AVSD, the anterior PM is positioned relatively closer to the septum than the posterior PM which causes a delay of activation of the anterior LV free wall and therefore left axis deviation in the frontal plane.[31]

In other CHD, the structural defect directly influences cardiac hemodynamics and the hereby altered distribution of the cardiac musculature might cause deviation of the electrical heart axis. For example, in hypoplastic right heart disease the electrical heart axis is expected to be deviated to the left due under development of the right-sided cardiac structures. In the same way, fetuses with hypoplastic left heart syndrome would be expected to have a right oriented electrical heart axis. In these fetuses, the electrical heart axis alone will not add in differentiating these CHD from the healthy fetal heart. Here, other morphologic changes in the fetal ECG need to be explored in order to optimize the detection rates of these defects. The same applies to conotruncal CHD, which would be expected to have a right-oriented electrical heart axis.[14,32]

Fetal electrocardiography is an easy to use, non-invasive, safe technology with a minimal burden for the pregnant women. Further research towards the electrical heart axis in fetuses with different types of CHD is necessary to determine which defects are associated with a deviated fetal electrical heart axis. Then the NI-fECG could be performed in addition to the fetal anomaly scan around the 20th week of gestation as part of prenatal screening after automatization of the signal processing of the recording. A point of attention is the broad distribution of the electrical heart axis found in our cohort of healthy fetuses in mid-pregnancy. This resulted in wide predictions intervals [-25.6°; 270.9°] making the use of the electrical heart axis alone as a parameter for the screening of CHD less suitable. Future research towards ECG waveform and ECG intervals may add to the development of additional ECG parameters which could further enhance the prenatal detection of CHD.

The use of the electrical heart axis as screening parameter on its own may not be of great value, however the electrical heart axis may be of value in fetuses with critical aortic or pulmonary stenosis where there may be a change in the electrical heart axis overtime (i.e. more leftward in critical pulmonary stenosis and more rightward in critical aortic stenosis) should growth of the relevant ventricle fall behind. Here, the electrical heart axis may be used to observe the consequences of the cardiac defect in utero when pregnancy continues. For this purpose normal serial fetal ECG reference ranges are needed. The use of the electrical heart axis in fetuses with a known CHD could be a subject for future research.

CONCLUSION

Our results confirm that the mean electrical heart axis of healthy fetuses around mid-gestation is oriented to the right. The wide prediction interval for the frontal heart axis found in our cohort, is unfavorable for future implementation of this method for screening purposes. Further research towards the electrical heart axis in fetuses with CHD as well as additional ECG waveform and intervals may elucidate the role of fetal ECG as a screening parameter for the detection of CHD.

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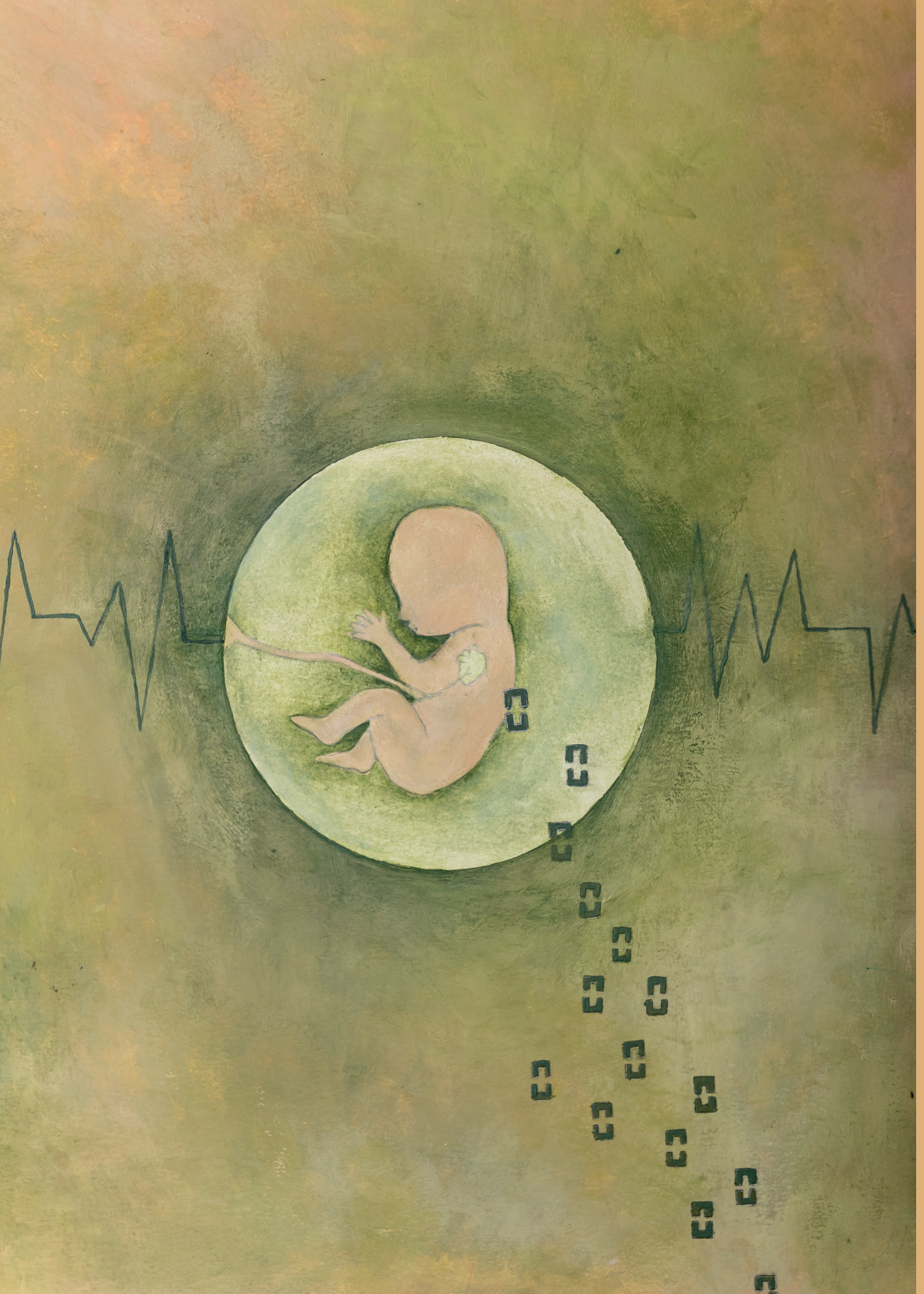

Chapter 10

The electrical heart axis in fetuses with congenital heart disease, measured with non-invasive fetal electrocardiography

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In preparation

ABSTRACT

Objectives: To determine if the electrical heart axis in different types of congenital heart defects (CHD) differs from the electrical heart axis as determined in our healthy cohort at mid-gestation.

Methods: Non-invasive fetal electrocardiography (NI-fECG) was performed in women carrying a singleton fetus with a suspected CHD between 16 and 30 weeks of gestation. The mean electrical heart axis (MEHA) was determined from the fetal vectorcardiogram after correction for fetal orientation. Descriptive statistics were used to determine the MEHA with corresponding 95% confidence intervals (CI) in the frontal plane of all fetuses with CHD and the following subgroups: conotruncal anomalies (CTA), atrioventricular septal defects (AVSD) and hypoplastic right heart syndrome (HRHS). The MEHA of the CHD fetuses was compared to the previously published healthy control group. A spherically projected multivariate linear regression analysis was used to determine differences in the frontal axis between healthy controls and the CHD subgroups. Discriminant analysis was applied to calculate the sensitivity and specificity of the electrical heart axis for CHD detection.

Results: The MEHA was determined in 127 fetuses. The MEHA was 83.0° (95% CI: 6.7°; 159.3°) in the total CHD group, and not significantly different from the control group (122.7° (95% CI: 101.7°; 143.6°). The MEHA was 105.6° (95% CI: 46.8°; 164.4°) in the CTA group (n=54), -27.4° (95% CI: -118.6°; 63.9°) in the AVSD group (n=9) and 26.0° (95% CI: -34.1°; 86.1°) in the HRHS group (n=5). The MEHA of the AVSD and the HRHS subgroups were significantly different from the control group (resp. p=0.04 and p=0.02).

The sensitivity and specificity of the MEHA for the diagnosis of CHD was 50.6% (95% CI 47.5% - 53.7%) and 60.1% (95% CI 57.1% - 63.1%) respectively.

Conclusion: The MEHA alone does not discriminate between healthy fetuses and fetuses with CHD. However, the left-oriented electrical heart axis in fetuses with AVSD and HRHS was significantly different from the control group suggesting that cardiac conduction is influenced by the structural defect. More research is required to assess if the fetal ECG performed in addition to the fetal anomaly scan can increase prenatal detection rates of CHD.

INTRODUCTION

Congenital heart disease (CHD) is the most common congenital anomaly, with a reported prevalence of 8 per 1000 live births.[1–3] It is a major cause of neonatal morbidity and mortality.[1–10] Prenatal detection of CHD allows for deliberate management to optimize the preoperative neonatal condition and therefore improve neonatal outcome. Furthermore, it keeps the option of pregnancy termination open if the diagnosis is made before the legal limit for pregnancy termination in the said country.[11–16]

Screening for CHD is currently performed by means of the second-trimester anomaly scan around 20 weeks of gestation.[17] Since the introduction of national screening programs, the overall detection rate for CHD in low-risk populations increased up to 50-60% in Europe.[6,8,18–21] The detection rate is strongly correlated with the severity of the CHD.[22] The highest detection rates are those of univentricular defects such as hypoplastic left heart syndrome and heterotaxy, reaching up to 90%.[18,22] The lowest detection rates are seen in CHD involving the outflow tracts, which are not visible on the four chamber view.[22] Recent evaluation showed that adding the three vessel view as part of the screening program significantly increased detection rates of both tetralogy of Fallot (TOF) and transposition of the great arteries (TGA).[23] In specialized tertiary care centers with experienced sonographers, the general detection rate of CHD rose up to 89%.[24] However, only 10% of the infants born with CHD are born to mothers with known risk factors, and therefore end up in tertiary care.[25]

We hypothesized that non-invasive fetal electrocardiography (NI-fECG) could play a role in raising detection rates for CHD, primarily in the low-risk population. We previously showed a right-oriented electrical heart axis in healthy fetuses, due to fetal right ventricular dominance as a result of the unique fetal circulation and differential ventricular cardiac output favoring the right ventricle.[26] Structural anomalies in fetuses with CHD may be associated with an abnormal electrical heart axis as is seen postnatally. The objective of this study was to investigate the possibility to detect CHD based on a deviated electrical heart axis.

MATERIALS AND METHODS

We conducted a multicenter case-cohort study from May 2014 until September 2018 at the following tertiary care hospitals in the Netherlands: Máxima Medical Center Veldhoven, Amsterdam University Medical Center, Radboud University

Medical Center Nijmegen, Leiden University Medical Center and Maastricht University Medical Center. The study protocol was approved by the institutional review board of the Máxima Medical Center, Veldhoven, the Netherlands (NL48535.015.14). Written informed consent was obtained prior to enrolment.

Study population

Women pregnant with a fetus with suspected CHD, based on advanced ultrasound evaluation, were asked to participate in this prospective cohort study. Women 18 years or older and pregnant of a singleton between 16 and 30 weeks of gestation were included. In addition, measurements of fetuses who were included in our healthy cohort as described in chapter 9 and diagnosed with CHD postpartum were transferred to the CHD cohort.[27]

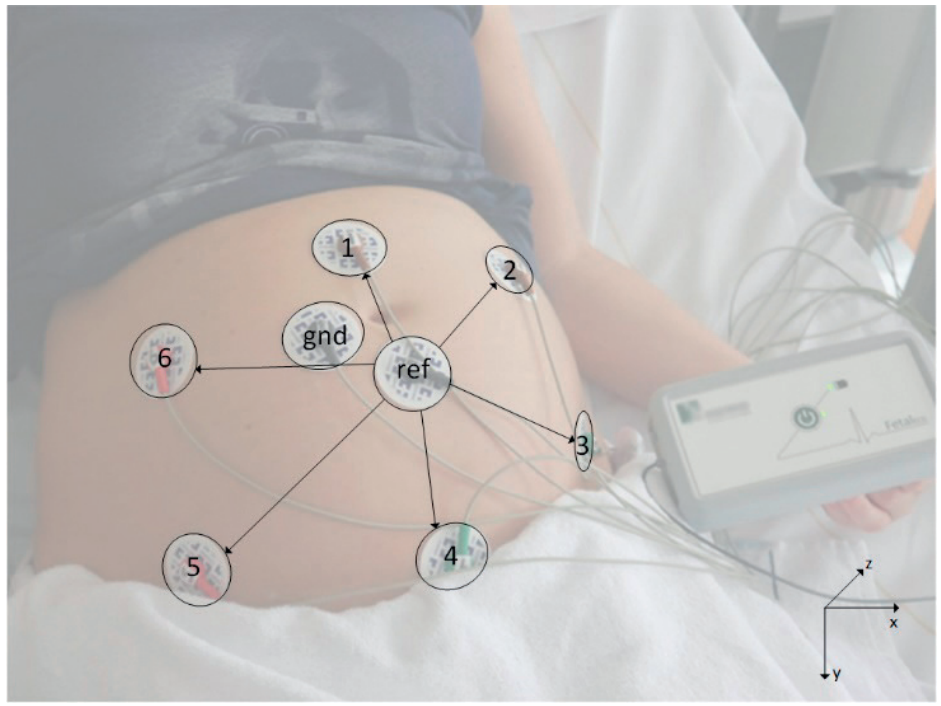
Exclusion criteria were a fetal cardiac arrhythmia and insufficient understanding of the Dutch language.

The following data were gained prospectively: general medical history, maternal gravidity and parity, obstetrical history, gestational age at inclusion, suspected CHD based on fetal echocardiography. Postpartum, neonatal charts were checked for confirmation of the CHD through echocardiography by a pediatric cardiologist. If the pregnancy was terminated immaturely, post mortem examination reports were consulted if available.

Measurements

Fetal ECG measurements were performed using a prototype fetal ECG system (Nemo Healthcare BV, the Netherlands) after a fetal echocardiographic examination in a tertiary care center. Pregnant women were positioned in a semi-recumbent position to prevent aortocaval compression. Eight adhesive Ag/AgCl electrodes (Red DotTM, 3M Health Care, Ontario, Canada) were placed on the abdomen in a fixed configuration in order to yield six channels of bipolar electrophysiological measurements. Two electrodes functioned as common ground and reference electrode respectively (Figure 1). Before applying the electrodes, the abdominal skin was washed with water and soap and then scrubbed using medical abrasive paper (Red DotTM Trace Prep, 3M Health Care, Ontario, Canada) to optimize skin impedance. Each measurement lasted around 40 minutes. The position of the fetus was determined by ultrasonography at four fixed time intervals during the measurement.

Figure 1. Measurement set-up of the non-invasive fetal electrocardiogram.[28]



Eight electrodes were placed on the maternal abdomen in a fixed configuration. Two electrodes served as common reference (Ref) and ground (Gnd). The cartesian coordinate system as used in our analyses is displayed in the bottom right corner.

The recordings were digitized at 500Hz sampling frequency and stored on a computer for offline analysis. This offline analysis consisted of a series of signal processing steps, designed to suppress interferences and standardize the fetal ECG signals for fetal orientation, so that the fetal electrical heart axis could be measured. These signal processing steps have been described in more detail in Lempersz et al.[28] In the first step of signal processing, interferences from maternal ECG, abdominal muscles, and extracorporal sources were suppressed by an adaptive template-based method.[29] As a result, for each of the six recorded signals a fetal ECG signal is obtained, yet at relatively low signal-to-noise ratio. Because each fetus could have a different orientation with respect to the maternal abdomen and the recording electrodes placed on the abdomen, the fetal ECG signals could be different between participants, but also within participants due to fetal movement.

The second step in the signal processing aimed to standardize for fetal orientation. To allow for such standardization, first for every heartbeat a fetal vectorcardiogram was calculated, combining the information from the six abdominal signals into a 3-dimensional fetal ECG complex.[30] This vectorcardiogram could subsequently be tracked over time, detecting fetal movements and correcting for them by rotating the fetal vectorcardiogram in 3-dimensional space. Finally, another rotation in 3-dimensional space was applied that corrected for the fetal orientation. For instance, if the ultrasound indicated that the fetus was in cephalic position, the recorded fetal vectorcardiogram was rotated by 180 degrees to represent the fetal vectorcardiogram as if the fetus was in breech position, mimicking the anatomical position. Similarly, a fetal back which was oriented to the maternal abdomen was rotated along the longitudinal axis as if the fetal back was oriented to the maternal spine. The parts of the measurements of sufficient signal quality, closest to the performance of the ultrasound determining fetal orientation, were used to create the vectorcardiogram.

Finally, to enhance the signal-to-noise ratio, orientation-standardized fetal vectorcardiograms were averaged over multiple heartbeats to yield one fetal vectorcardiogram per measurement.

The orientation of the electrical heart axis was defined as the direction in which the vectorcardiogram had its maximum amplitude.[31] The latter direction was estimated as the average direction of the dominant vectors in the QRS complex, defined as the vectors from the point that the R-wave exceeded 70% of its maximum value until the point that it fell below 70% of the maximum value. The orientation of the fetal heart axis was expressed in degrees ranging from minus 180° to plus 180° and calculated in the frontal plane, where minus 90° is located superiorly.

Classification of CHD

CHD were classified in subgroups based on the type of defect and its hemodynamic consequences. Table 1 shows an overview of all included CHD types and their corresponding subgroup. We included the following three CHD (subgroups) for statistical analysis: conotruncal anomalies (CTA), atrioventricular septal defects (AVSD) and hypoplastic right heart syndrome (HRHS). These were chosen for the following reasons. CTA make up an important part of all CHD and may be missed on the fetal anomaly scan, especially when the outflow tracts are difficult to image due to fetal position and the complex multiplanar

evaluation, since the four-chamber view may appear normal. Furthermore, some fetuses with undiagnosed CTA, such as transposition of the great arteries (TGA) with intact septum or pulmonary atresia with ventricular septal defect (extreme tetralogy of Fallot [TOF]), may develop acute hypoxia in the first few days postpartum when the arterial duct undergoes physiological closure. Without immediate intervention, i.e. administration of prostaglandins to keep the arterial duct open, this can be a life-threatening event. We expected the fetal ECG to show a right axis.

Both fetuses with AVSD and HRHS may be expected to have a left-oriented electrical heart axis. We chose to include these CHD where the most overt differences in electrical heart axis can be expected compared to the healthy control group, since literature on the electrical heart axis in fetuses with CHD is scarce.[16,32,33]

Statistical analysis

Results from our CHD cohort were compared using our cohort of healthy fetuses from chapter 9 as reference group.[27] Descriptive statistics were used to determine baseline characteristics of our overall CHD cohort. Differences in baseline characteristics between the overall CHD group and the healthy control group were tested using the Mann-Whitney U test for not normally distributed data and an independent T-test for normally distributed data.

Spherical statistics were applied to compare the two-dimensional mean electrical heart axis (MEHA) in the frontal plane between the groups, which required using the individual Cartesian coordinates. The observed frontal angle was determined in the (x,y)-plane, where x represented the left-right horizontal axis and y represented the craniocaudal axis. Since the length of the vector of the electrical heart axis in the frontal plane is influenced by electrical propagation in all directions, the vector of each fetus was normalized to create unit vectors i.e. with equal length. The normalized coordinates $(\tilde{x}, \tilde{y})$ of these unit vectors were calculated as the division of the originate coordinates (x, y) by their Euclidean norm $\sqrt{x^2 + y^2}$.

Descriptive statistics (median with interquartile range (IQR)) were calculated based on the normalized $(\tilde{x}, \tilde{y})$. Cartesian coordinates for the overall CHD group as well as for each of the three selected CHD subgroups. Differences between the overall CHD group as well as each CHD subgroup and the control group were tested using the Kolmogorov-Smirnov test.

The mean frontal angle with 95% confidence intervals (CI) were calculated for both the overall CHD group and each CHD subgroup.[34]

A likelihood ratio test (LRT) was used to determine differences in frontal angles between the previously published control group and the overall CHD group assuming equal concentration parameters (i.e. similar to equal variances in 2-sample t-tests).[35] This assumption was verified with a circular concentration test.[35] If the equal concentration assumption was violated, a sensitivity analysis using the non-equal concentration approach suggested by Mardia and Jupp (2000) was performed.[35]

Furthermore, a LRT was also performed to determine the overall difference in frontal angles of the CHD subgroups and the control group. In addition, a spherically projected multivariate linear (SPML) regression model with the frontal angle as the outcome and the subgroup as a categorical independent variable (control group was considered as the reference level) was fitted to the data, under the assumption that the data follows a von Mises-Fisher distribution (analogous to the normal distribution in linear regression).[36,37]

Circular discriminant analysis was performed on the unit vectors between the healthy control group and the overall CHD group.[38] Sensitivity and specificity were calculated based on 1000 Monte Carlo cross validation samples (20% of the original sample was randomly selected as the testing sample and the rest used as training sample).

Descriptive statistics were used to describe baseline characteristics, using IBM SPSS statistics version 25.0 (SPSS Inc., Chicago, Ill., USA). Statistical analysis was conducted with SAS (version 9.4, SAS Institute Inc., NC, USA) and R (version 3.5.3, R Foundation, Vienna, Austria). Significance level for all tests was set at 0.05.

RESULTS

A total of 148 women were included carrying a fetus with suspected CHD after fetal echocardiography. The inclusion process is depicted in Figure 2. The electrical heart axis was determined in 127 fetuses with CHD. Within the overall CHD group, 54 fetuses were allocated to the CTA group, 9 to the AVSD group and 5 to the HRHS group. Table 1 shows an overview of all included CHD types and their corresponding subgroup. Baseline characteristics are shown in Table 2.

The CHD group was not different to the normal control group for maternal age, parity or maternal BMI. The gestational age during the NI-fECG measurement for the control group was on average three weeks earlier than for the CHD group (p=0.00).

Table 1. Distribution of the different types of CHD included in the study population.

CHD group	n	CHD type		n	GA at measurement[$]	% of study population
Overall	*127*	*All*			*23.2 ± 3.2*	*100*
Septal defects	25				23.28 ± 3.2	19.7
		VSD		16	23.4 ± 3.5	12.6
		AVSD		9	23.1 ± 2.7	7.1
Conotruncal anomalies	54				23.2 ± 3.6	42.5
		TGA (IVS and VSD)		27	23.6 ± 3.2	21.3
			TGA + IVS	19	24.1 ± 3.2	15.0
			TGA + VSD	8	21.7 [20.2 - 23.5]	6.3
		TOF		16	23.2 ± 2.9	12.6
		VSD + pulmonary atresia		2	20.7; 23.1	1.6
		DORV + pulmonary stenosis		2	19.4; 21.3	1.6
		TGA + VSD + pulmonary stenosis		2	19.9; 24.3	1.6
		Truncus arteriosus		1	22.1	1.0
		ccTGA		2	26.0; 28.3	1.6
		DORV, no PS		2	20.4; 20.6	1.6
Single ventricle	10				20.6 [20.0 – 24.0]	
		Hypoplastic right heart syndrome		5	20.4 [19.9 – 21.9]	3.9
		Hypoplastic left heart syndrome		5	23.1 ± 4.8	3.9
Complex	15				20.9 [20.1 – 21.7]	
		AVSD combined with other cardiac anomalies		3	20.8 ± 4.0	2.4

Table 1. Continued.

CHD group	n	CHD type	n	GA at measurement[$]	% of study population
		DILV	4	20.5 ± 0.6	3.1
		Ebstein anomaly	5	20.7 [20.4 - 27.0]	3.9
		Other	3	21.0; 21.1; 23.7	2.4
Miscellaneous	5			25.8 ± 2.4	3.9
R/L disproportion	9			26.2 ± 2.9	
		Aortic coarctation	8	25.9 ± 3.0	6.3
		No aortic coarctation	1	28.3	1.0
Vascular ring	6			21.9 ± 1.5	4.7
Chromosomal aberration		Noonan syndrome	3	19.4; 21.0; 28.0	2.4

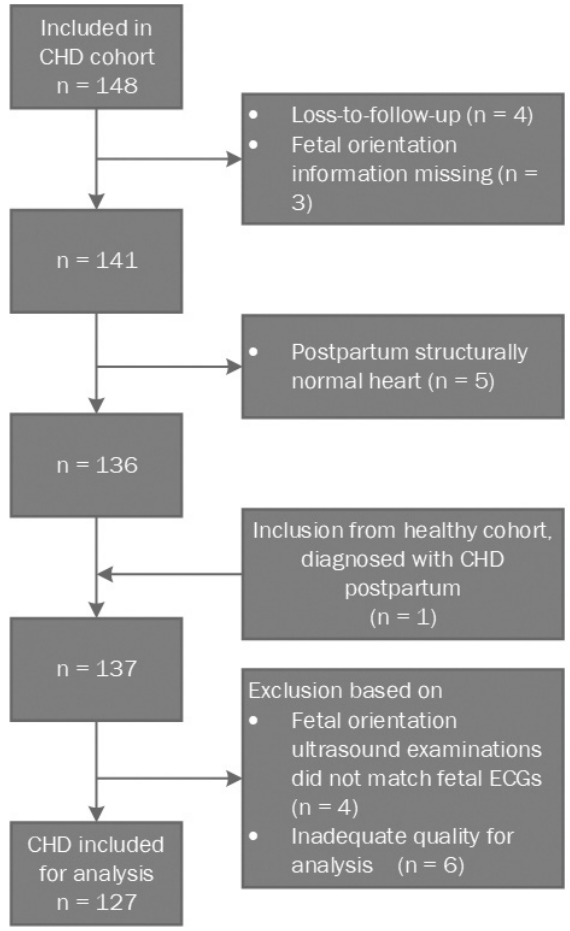
[$] Data provided are percentages or mean ± SD. Median [interquartile range] are provided for variables that are not normally distributed.
Abbreviations: AVSD = atrioventricular septal defect, ccTGA = congenitally corrected transposition of the great arteries (double discordance), CHD = congenital heart disease, DILV = double inlet left ventricle, DORV = double outlet right ventricle, IVS = intact ventricular septum, TGA = transposition of the great arteries, TOF = tetralogy of Fallot, VSD = ventricular septal defect.

Table 2. Baseline characteristics of participants.

	CHD		Healthy cohort		p-value
		n		n	
Maternal Age (years)	30.5 ± 4.6	127	31.0 [26.0 – 36.0]	281	0.09[a]
GA (weeks) at time of measurement	23.2 ± 3.2	127	20.2 ± 1.3	281	0.00[b]
CTA	23.2 ± 3.6	54			
AVSD	23.1 ± 2.7	9			
HRHS	20.8 ± 1.3	5			
Nulliparous (%)	44.1	127	52.0	281	0.14[c]
BMI (kg/m²)	23.8 [18.4 – 29.2]	125	22.8 [16.7 – 28.9]	280	0.07[a]

Data provided are means ± SD. Median [interquartile range] are provided for variables that are not normally distributed. Differences in baseline characteristics between the CHD group and the healthy cohort were tested using the [a] Mann-Whitney U test, [b] Independent T-test and [c] Chi square test.
Abbreviations: AVSD = atrioventricular septal defect, BMI = body mass index, CHD = congenital heart disease, CTA = conotruncal anomaly, GA = gestational age, HRHS = hypoplastic right heart syndrome, kg = kilograms, m = meter.

Figure 2. Flow diagram of patient inclusion.



No significant difference in distribution of the normalized $\tilde{x}$ and $\tilde{y}$ coordinates were found between the overall CHD group and the control group and between each CHD subgroup and the control group (Table 3).

Table 3. Summary statistics (median [IQR]) on the two dimensions for the overall CHD group and each subgroup compared to the healthy control group.

	Groups								
	Healthy control group n=281	Overall CHD n=127		CHD subgroups CTA n=54		AVSD n=9		HRHS n=5	
	Median (IQR)	Median (IQR)	p-value	Median (IQR)	p-value	Median (IQR)	p-value	Median (IQR)	p-value
$\tilde{x}$	-0.35 (1.66)	-0.01 (1.75)	0.22	-0.18 (1.72)	0.78	0.88 (1.49)	0.13	0.63 (0.60)	0.08
$\tilde{y}$	-0.33 (0.96)	-0.24 (0.90)	0.17	-0.33 (1.12)	0.90	0.12 (1.11)	0.10	-0.31 (0.58)	0.90

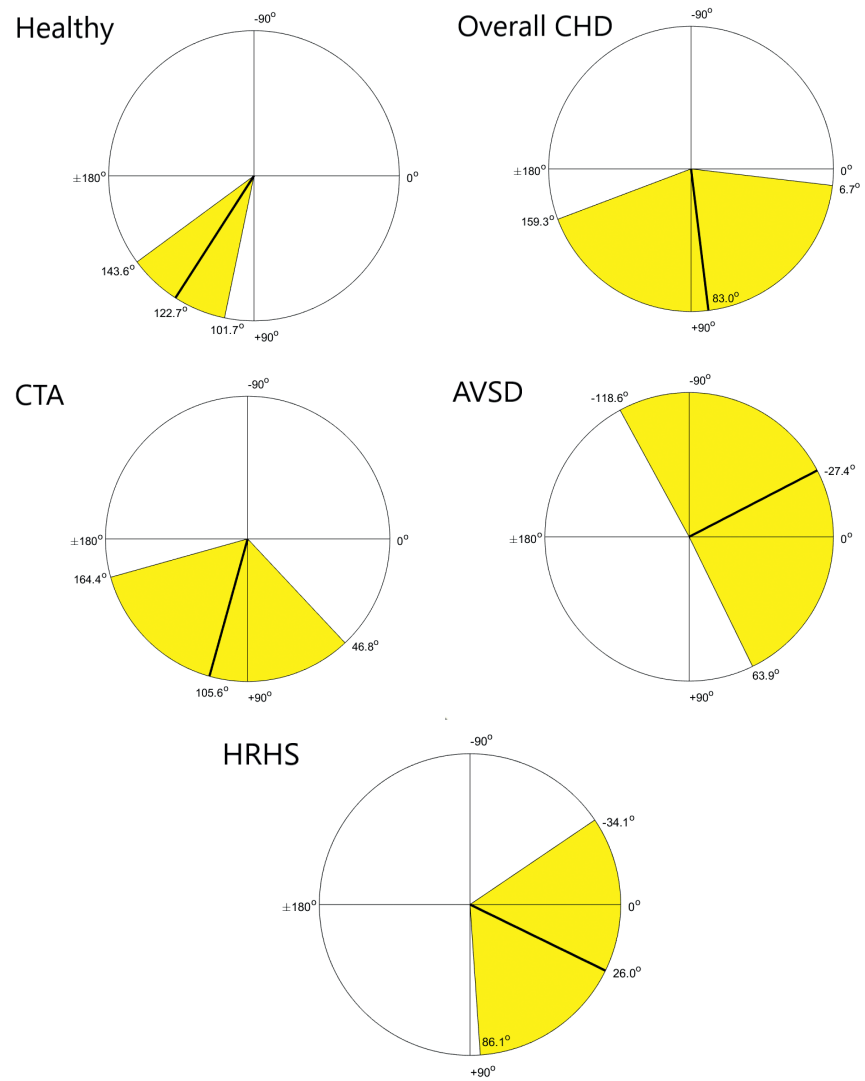
P-values calculated by means of a Kolmogorov-Smirnov test showed no significant difference in distribution between the overall CHD group as well as each CHD subgroup with respect to the control group on both normalized coordinates.
Abbreviations: AVSD = atrioventricular septal defect, CTA = conotruncal anomaly, HRHS = hypoplastic right heart syndrome, IQR = interquartile range.

We described reference ranges using 90% prediction intervals for the electrical heart axis in healthy fetuses in chapter 9, based on data from 281 fetuses between 18 and 24 weeks of gestation. The mean frontal angle for this control group was determined at 122.7° (95% CI: 101.7°; 143.6°).

In our overall CHD group, the mean frontal angle was determined at 83.0° (95% CI: 6.7°; 159.3°). For the three CHD subgroups, the mean frontal angles were estimated at 105.6° (95% CI: 46.8°; 164.4°) for the CTA, -27.4° (95% CI: -118.6°; 63.9°) for the AVSD, and 26.0° (95% CI: -34.1°; 86.1°) for the HRHS group. Figure 3 shows the mean frontal angle with corresponding 95% CI of these groups on a circle diagram.

We found no significant difference in electrical heart axis between the overall CHD group and the healthy control group (test statistic=2.17, p=0.14). Since the test for equality of concentration between both groups was significant (test statistic=3.99, p=0.046), we conducted a sensitivity analysis which confirmed that there was no difference in electrical heart axis between both groups (test statistic=1.22, p=0.27).

Figure 3. Mean electrical heart axis (MEHA) with corresponding 95% CI in the frontal plane plotted in a circle diagram for each group.



Abbreviations: AVSD = atrioventricular septal defect, CHD = congenital heart disease, CTA = conotruncal anomalies, HRHS = hypoplastic right heart syndrome.

Discriminant analysis between the healthy control group and the overall CHD showed a sensitivity of 50.6% (95% CI 47.5% - 53.7%) and a specificity of 60.1% (95% CI 57.1% - 63.1%) for the detection of CHD.

We found a significant difference in electrical heart axis when comparing the healthy control group with all three CHD subgroups (test statistic=8.35, p=0.04) with equal concentration across the groups (equal concentration test statistic=0.62, p=0.89), indicating a difference in electrical heart axis between these groups. To gain more insight in the difference between each CHD subgroup and the healthy control group, a SPML regression analysis was performed and the results are displayed in Table 4. We found a significant difference in frontal angle between the healthy control group and both the AVSD subgroup (p=0.04) and the HRHS subgroup (p=0.02).

Table 4. Difference in normalized $(\tilde{x}, \tilde{y})$ coordinates between the healthy control group and each CHD subgroup.

	$\tilde{x}$		$\tilde{y}$	
	Estimate (S.E)	p-value	Estimate (S.E)	p-value
Intercept	-0.28 (0.07)	<0.001	-0.36 (0.07)	<0.001
CTA vs healthy	0.17 (0.17)	0.32	0.03 (0.16)	0.86
AVSD vs healthy	0.84 (0.41)	**0.04**	0.53 (0.37)	0.15
HRHS vs healthy	1.29 (0.54)	**0.02**	-0.19 (0.52)	0.72

P-values are obtained by means of a spherically projected multivariate linear (SPML) regression analysis with the frontal angle as the outcome and the subgroup as a categorical independent variable. The healthy control group was considered as reference level. Significant results are shown in bold.
Abbreviations: AVSD = atrioventricular septal defect, CTA = conotruncal anomaly, HRHS = hypoplastic right heart syndrome, S.E. = standard error.

DISCUSSION

Main findings

To our knowledge this is the first study of NI-fECG in a large cohort of fetuses with CHD, looking at the MEHA in the frontal plane. We found no significant difference in MEHA between the healthy control group and the overall CHD group, which resulted in low sensitivity and specificity of the electrical heart axis for the detection of CHD. The MEHA of the AVSD and HRHS subgroups were left-oriented and statistically significant from the healthy control group which may be helpful in the prenatal detection of these types of CHD.

Interpretation of findings and comparison with existing literature

We described a right-oriented MEHA in healthy fetuses around mid-gestation in chapter 9. This right-oriented axis is still present after birth, but gradually deviates towards the left during the first year of life.[39] These changes reflect the developmental changes from fetus to child where the right ventricle is dominant prenatally pumping a higher cardiac output against high resistance in the fetus, and the dominant left ventricle pumping against high resistance in the child and adult. As the pulmonary vascular resistance declines postnatally the workload of the right ventricle is reduced relative to the left ventricle with an associated change in relative ventricular muscle mass.[26,40]

We found a MEHA in our overall CHD group which is oriented slightly to the left and not significantly different from that of our healthy control group (X^2(df=1)=2.17, p=0.14). Since we included all types of CHD, it comprised a heterogenous group. As this heterogeneity may have confounded our results, we also looked at three clinically relevant subgroups and compared them with the healthy control group as well.

First, we chose the CTA subgroup which makes up a large part of all CHD. The prevalence of CTA varies between prenatal (2.5-21%) and postnatal (10-12%) series [4,41–43] and is influenced by differing prenatal CHD detection rates between countries.[44–49] CTA comprised 42.5% of all CHD included in our study. As the four-chamber view of the heart in many cases of CTA such as TOF and TGA may be normal, detection rates can be improved by using the outflow tract and three vessel views as part of the fetal anomaly scan for CHD screening.[8,23,50] We found a right-oriented MEHA in our CTA subgroup, which was not significantly different from the healthy control group. This was in line with our expectations, since this subgroup comprises mainly fetuses with TOF and TGA, and a right axis deviation is seen postnatally in these defects due to right ventricular hypertrophy and strain analogous to the fetal situation.

Second, we compared the AVSD group with our healthy control group. Only 2 cases describing the electrical heart axis in AVSD fetuses are available in the literature, with inconsistent results.[32,33] We expected to find a distinctly left-orientated MEHA in these fetuses, as is seen in neonates postpartum with these defects. Left ventricular hypertrophy may contribute to the deviated electrical heart axis in AVSD [51], but anatomic displacement of the left ventricular (LV) papillary muscles (PM) is more important in the altered electrical activation in this condition.[52] The insertion place of the PM on the ventricular wall

coincides with the end of the left bundle branch fascicles. In AVSD, the anterior PM is positioned relatively closer to the septum than the posterior PM which produces a delay in activation of the anterior LV free wall, causing a left anterior hemiblock. Our data confirm a left-oriented MEHA in our AVSD subgroup, which was significantly different from the healthy control group (test statistic=0.84, p=0.04). Third, we included fetuses with HRHS. In HRHS there is underdevelopment of the right-sided cardiac structures and thus a relative dominance of the left-sided cardiac musculature, and an expectation of a left-oriented electrical heart axis. Our findings confirm this left-oriented MEHA our HRHS subgroup, which is significantly different from the healthy control group. (test statistic=1.29, p=0.02).

Strengths and limitations

A major strength of our study is the large cohort of healthy fetuses (n=281) and fetuses with CHD (n=127). As the cohort of CHD was heterogenous, the numbers per individual CHD type were small precluding individual analysis per diagnosis. We thus chose for three groups which are prenatally relevant, either due to prevalence or expected abnormal heart axis.

The number of excluded recordings due to inadequate data quality was low (n=6). However, the NI-fECG technology is currently limited by the lack of real-time results. Offline analysis of the recordings is still required. Automatization of the signal processing steps is ongoing for future implementation in the measurement hardware to address this problem.

The gestational age at time of measurement was three weeks later in the CHD group compared to the healthy control group. As there is limited data available on the course of the electrical heart axis in fetuses during pregnancy, this may have influenced our results. The MEHA of term babies is 110°, ranging from 30° to 180°.[53] This suggests a minimal shift of the electrical heart axis to the left between mid-gestation and term. Therefore, we do not expect this difference in gestational age to have significantly influenced our results.

Clinical and research implications

NI-fECG is a patient-friendly method which requires minimum training for healthcare personnel to apply. With further development of the technology, it could be a non-expensive diagnostic test. Our data show that the electrical heart axis in the frontal plane as a single parameter, measured with NI-fECG, does not discriminate between healthy fetuses and fetuses with CHD. However, the left-oriented MEHA in fetuses with AVSD and HRHS differs significantly from the healthy control group. This supports the idea that electrical conduction may be influenced by the cardiac anatomy. Other ECG characteristics such as ECG morphology and cardiac time intervals may unveil information necessary to distinguish fetuses with CHD. More research is needed to evaluate if the addition of a fetal ECG to current prenatal screening increases CHD detection rates.

CONCLUSION

The MEHA in our CHD cohort was oriented slightly to the left and not significantly different from that of our healthy control group. Consequently, sensitivity and specificity of the electrical heart axis in the detection of CHD was low. The MEHA in the AVSD and HRHS subgroups was oriented to the left and significantly different from our healthy control group. More research is needed to see if other ECG characteristics can play a role in the detection of CHD in the future.

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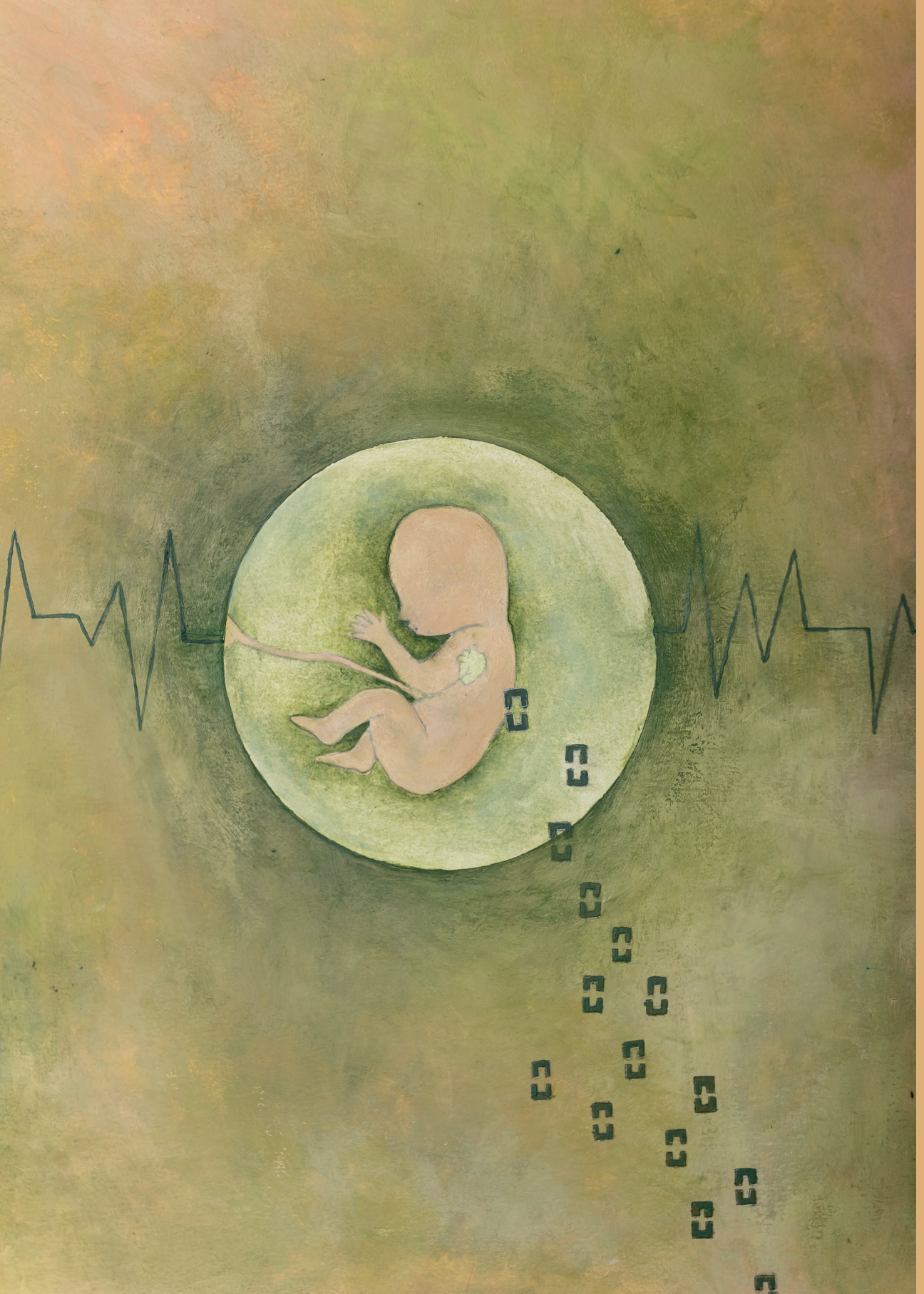

Chapter 11

Prenatal diagnosis of a bundle branch block based on the fetal ECG

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SUMMARY

A non-invasive fetal electrocardiogram was performed on a 36-year-old pregnant women at 24+6 weeks of gestation as part of ongoing clinical research. A pediatric cardiologist suspected an incomplete bundle branch block based on the averaged electrocardiograms (ECGs) from the recording. The characteristic terminal R'-wave was present in multiple leads of the fetal ECGs. A fetal anomaly scan had been performed at 20 weeks of gestation and showed no abnormalities. An incomplete right bundle branch block was confirmed on an ECG recorded at the age of 2 years. This case shows the possibility of novel non-invasive fetal ECG technology as an adjunct to the diagnosis of fetal cardiac anomalies in the future.

BACKGROUND

Congenital heart disease (CHD) is the most common major congenital anomaly worldwide, with an estimated prevalence of 8 per 1000 live births.[1-3] About 20-30% of all CHD are severe, in that they require early surgery or catheter intervention.[4-6] Despite the decrease in mortality rates over the last decade due to improved diagnostics and treatment techniques, CHD remains the leading cause of infant mortality in developed countries.[7,8] Timely detection of CHD has important advantages: it allows for close monitoring during pregnancy, planning the delivery in a center with the required treatment facilities and it keeps the option of pregnancy termination open for the parents if the diagnosis is made before 24 weeks gestation. Prenatal diagnosis of CHD has shown to increase survival prior to planned cardiac surgery and decreases pre-operative morbidity, especially in the case of ductal dependent lesions.[9,10]

Screening for CHD is performed through ultrasound examination by means of the second-trimester anomaly scan around 20 weeks of gestation. Since the introduction of national screening programs around Europe, the detection rate for CHD in the low-risk population has increased up to 50-60%.[11-14] However, the detection rate is strongly correlated with the severity of the CHD and highly dependent on the sonographer's experience.[15] In some specialized tertiary care centers, the general detection rate has risen to 89%.[16] However, only 10% of infants born with CHD are born to mothers with known risk factors, and therefore end up in tertiary care.[17] Most CHD occur in the low-risk population, where at least 4 out of 10 cases of severe CHD are still missed.[11-14]

Non-invasive fetal electrocardiography (NI-fECG) in addition to ultrasound screening might raise the detection rate for CHD in low-risk populations, by providing a multi-lead fetal ECG. To date the diagnosis of significant ECG abnormalities has been difficult prenatally. We report a case where a bundle branch block was diagnosed on a NI-fECG measurement performed at 24 weeks of gestation, as part of ongoing clinical research.[18]

CASE PRESENTATION

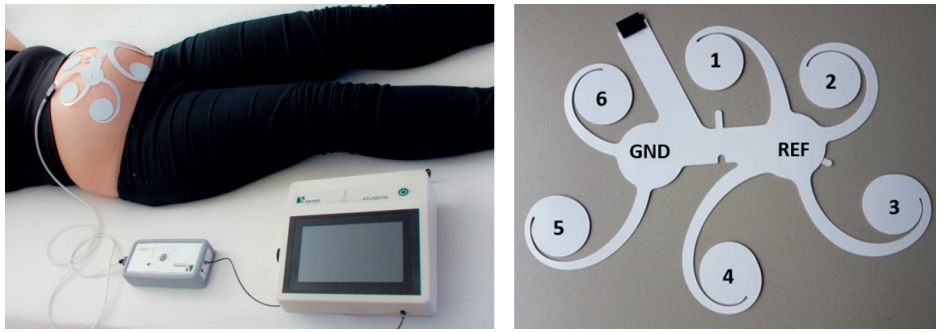
A 36-year-old gravida 2 para 1 had a fetal anomaly scan as part of prenatal screening at 20 weeks of gestation. No abnormalities were seen at this time. As part of ongoing clinical research, she received a single fetal electrocardiographic measurement of 17 minutes at 24+6 weeks of gestation. There was no family history of (congenital) cardiac pathology.

INVESTIGATIONS

Non-invasive fetal electrocardiography

The recording was performed with a prototype fetal ECG system (Nemo Healthcare BV, the Netherlands). An electrode patch consisting of eight adhesive electrodes was placed on the maternal abdomen, including one ground and one reference electrode (Figure 1). An averaged fetal ECG was calculated for each of the six recording electrodes through a series of signal processing techniques. First, the maternal signal was suppressed using a dynamic template subtraction technique.[19] The signal-to-noise ratio was then enhanced by spatially combining the remaining signals to filter out electrophysiological interferences from i.e. muscle activity.[20] In this enhanced signal, fetal QRS complexes were detected using a low-complexity R-peak detection method.[21] Because fetal QRS complexes occur in each of the six recorded channels at the same time, the QRS complexes that were detected in the spatially combined signal, were used for each of the six individual channels to segment the recording in individual ECG complexes. These ECG complexes were subsequently averaged across multiple heartbeats, where the number of heartbeats was dynamically varied by an adaptive Kalman filter, depending on the quality and stationarity of the ECG signal, to produce a further enhanced fetal ECG (Figure 2).[22]

Figure 1. The non-invasive fetal electrocardiogram.



The left picture shows the electrode patch attached to the maternal abdomen, which is connected through a single wire to an amplifier and the base station. The right picture shows the electrode patch with the six recording electrodes (numbered), the ground electrode (GND) and the reference electrode (REF).

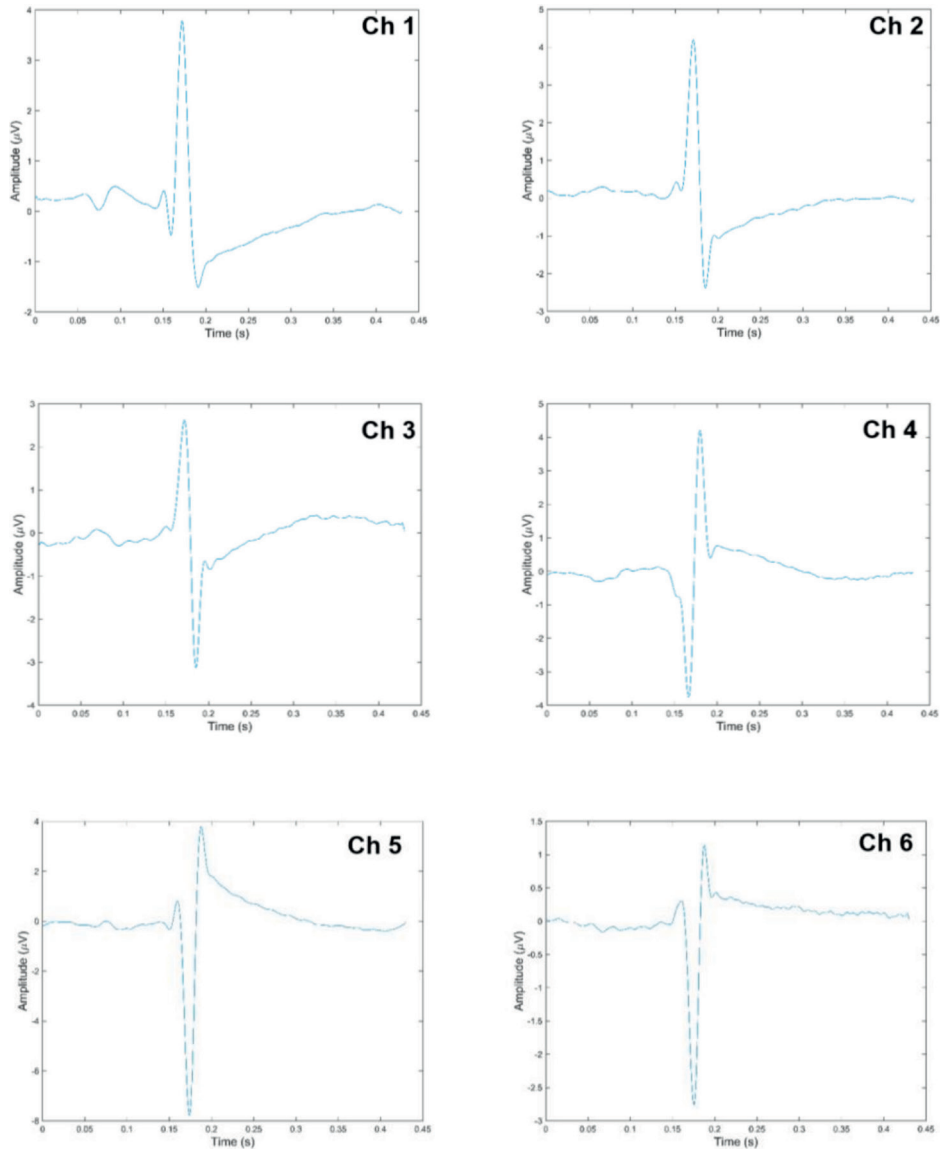
DIFFERENTIAL DIAGNOSIS

The six averaged ECGs were presented to a pediatric cardiologist (Figure 2). Based on the morphology of the QRS complex, incomplete bundle branch block was suspected. In the absence of information on the fetal orientation, the location of the bundle branch block could not be determined.

OUTCOME AND FOLLOW-UP

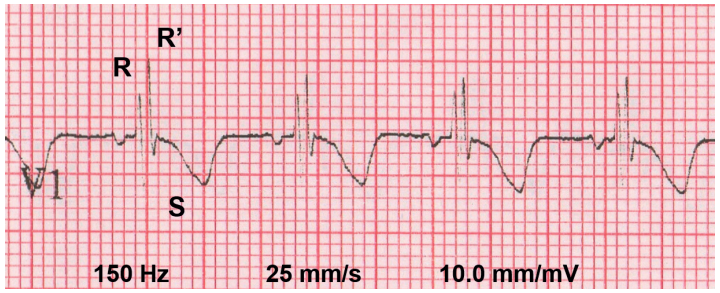
At 40+2 weeks of gestation, a spontaneous vaginal delivery took place. A male neonate was born weighing 3510 grams and with an Apgar score of 8 and 9 at 1 and 5 minutes respectively. He showed no clinical signs of cardiac pathology. A cardiac ultrasound and ECG were performed at the age of 2 years after a cardiac murmur was heard. The presence of an incomplete right bundle branch block was confirmed. The ECG showed the characteristic late R' wave in the right precordial lead V1 (Figure 3). Duration of the QRS-complex (78 ms) lies within the normal ranges described in the literature for this age group.[23,24] The child is alive and well and has no cardiac symptoms.

Figure 2. Averaged fetal electrocardiogram for each electrode.



Averaged fetal electrocardiogram for each of the six recording electrodes. Channel numbers match those of the corresponding electrodes as displayed in figure 1. Terminal R'-wave is visible in channel 4 - 6. Ch = channel.

Figure 3. Right precordial lead V1 from the electrocardiogram recorded at 2 years of age.



The QRS-complex shows the characteristic pattern of an incomplete RBBB with an additional terminal R-peak, reflecting the delayed activation of the right ventricle. The QRS-complex is not widened (78ms).

DISCUSSION

A complete right bundle branch block (RBBB) is an abnormality of cardiac ventricular conduction. Due to a conduction delay in the peripheral conduction system on the right side, activation and subsequent contraction of both ventricles are no longer synchronized. This causes a characteristic pattern of the QRS-complex on the ECG which reflects the delayed depolarization of the right ventricle as an additional R' wave in the right precordial leads.[25] In an incomplete RBBB, the QRS complex is widened, but no more than 120 ms. It is a common finding in pediatric ECGs,[26-31] and in the absence of an underlying cardiac condition, is usually a benign finding without clinical consequences.[31]

To our knowledge, we report the first case where an incomplete RBBB was detected prenatally on a fetal ECG. NI-fECG uses electrodes placed on the maternal abdomen (Figure 1). This non-invasive technique has first been described as early as 1906 by Cremer, but development has lagged behind due to technical challenges.[32] The maternal electrophysiological signal dominates that of the fetus, making it extremely challenging to extract the fetal ECG with sufficient quality to enable use in diagnostics.[33] Other factors, such as the amniotic fluid, the vernix caseosa and fetal movements also affect the quality of the fetal signal.[34,35] With improvement of technology, it is now possible to effectively suppress the maternal signal. Since this is relatively new technology, little is known about the normal ECG morphology in the fetus. The fetal circulatory system has a unique shunting system, bypassing the lungs, resulting in a higher cardiac output of the right ventricle than left ventricle, compared to postnatal life. Also, the right ventricle pumps against higher resistance prenatally resulting in a larger mass compared to the left ventricle. These hemodynamic differences can influence fetal ECG morphology. Previous research has shown that the electrical heart axis of the fetus points toward the right.[36] Until now, only a few studies have been published studying fetal ECG waveform characteristics.[37-44] Differences in study design (antepartum versus intrapartum), NI-fECG systems used to acquire the signals, and signal processing techniques have led to large heterogeneity in the studies which complicates combined interpretation of the results. A large variation in gestational age at time of fetal ECG registration is seen between the studies. As the fetal cardiac mass grows with increasing gestational age, cardiac time intervals can be expected to change accordingly.[38,45] Standardizing groups based on gestational age is indispensable when trying to define normal ranges for the population. Knowledge of normal ECG morphology in the fetus is essential before this technology can be clinically implemented for the detection of abnormal ECG variations.

Typically, converting the fetal ECG to a twelve-lead ECG aids the interpretation for trained clinicians, since this is the standard format used for postnatal ECGs. Such conversion to a twelve-lead fetal ECG has been described in Vullings 2010, but is not yet available for clinical practice.[46] Moreover, this conversion requires information on the fetal orientation, which was absent in this case. Due to the missing fetal orientation, it was unknown which vector with respect to the heart each of the electrodes comprised and thus the location of the conduction delay (i.e. right or left) could not be determined.

Although the incomplete bundle branch block was benign in our patient, this is the first case describing its detection on a fetal ECG and serves as a proof of principle that ECG abnormalities can be detected prenatally using NI-fECG recordings. The NI-fECG can be used as an additional screening tool for CHD. In line with the current prenatal screening process, a NI-fECG measurement could be carried out along with the fetal anomaly scan around 20 weeks of gestation. When combining the NI-fECG technology with the fetal anomaly scan, fetal orientation is available and a twelve-lead fetal ECG can become available for interpretation. Abnormalities seen on the NI-fECG should encourage additional awareness for the cardiac anatomy during the anomaly scan. Only when the ultrasound confirms the abnormality or, at the least, cannot refute the abnormality, should the patient be referred for advanced ultrasound examination by an experienced gynecologist and/or pediatric cardiologist. As this follow-up ultrasound usually takes place within a few days after referral,

the expecting parents are left in uncertainty only for a limited amount of time. Since the detection of CHD in advanced ultrasound examination is high (i.e. 89%), NI-fECG may play a role in increasing prenatal detection of various cardiac anomalies.[16] Moreover, cardiac conduction disorders without overt anatomic anomalies which are easily missed with ultrasound may become visible on the fetal ECG.

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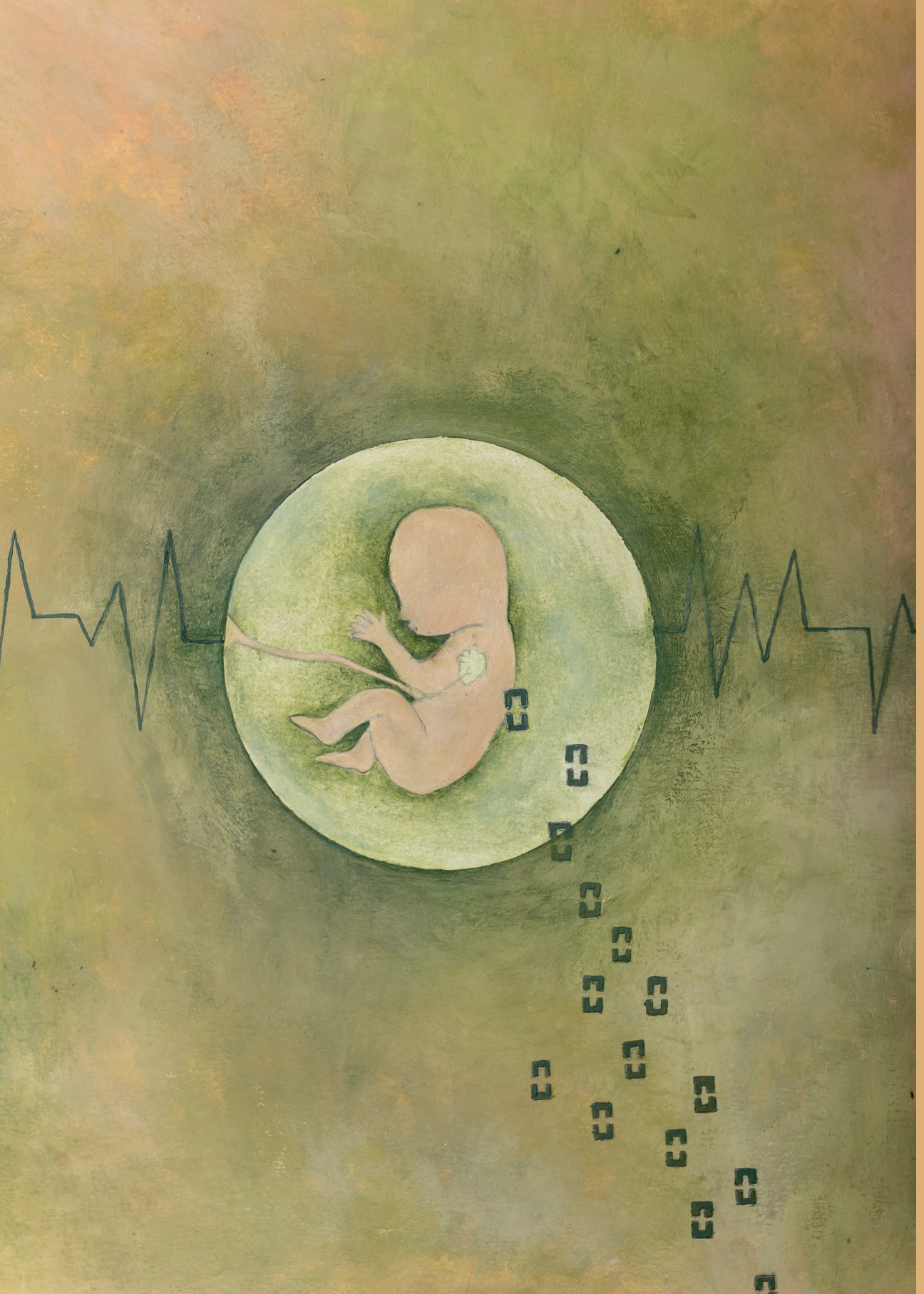

Chapter 12

General discussion

GENERAL DISCUSSION

The primary goal of obstetric care is to deliver a healthy neonate. However, adequate prediction of the fetal condition remains challenging. Current fetal monitoring methods available in clinical practice have limited diagnostic value in the identification of fetal compromise.

Since the fetus is inaccessible for direct measurements during pregnancy, fetal heart rate (FHR) monitoring is one of the few physiological parameters which can be measured during the antenatal period. FHR monitoring by means of Doppler ultrasound (DU) cardiotocography (CTG) is currently used in daily clinical practice. However, specificity and positive predictive value of the CTG are poor. During labor, other methods such as fetal scalp blood sampling and direct monitoring by means of the fetal scalp electrode (FSE) are available. Yet, these methods have an invasive character and cannot be applied in the preterm period. Hence, there is an urgent need for a more reliable non-invasive method which can be applied during both pregnancy and labor to predict the fetal status.

As 85% of cases of perinatal mortality are associated with at least one of the "Big Four" conditions, i.e. birth asphyxia, preterm birth, fetal growth restriction and congenital anomalies; we used these as a thread throughout this thesis.[1] Application of non-invasive fetal electrocardiography (NI-fECG) during pregnancy and labor in each of the "Big Four" conditions is explored in the different chapters. This thesis complements the work of Lempersz C. causing a few chapters to overlap (i.e. chapter 4, 5 and 9).[2] In the current chapter, the following research questions as mentioned in **chapter 1** are discussed taking the studies in this thesis and the most recent literature into account.

Part I: fetal ECG for fetal monitoring

1. Is the non-invasive fetal electrocardiogram a valid technology for intrapartum feto-maternal monitoring in daily clinical practice?

2. Is the non-invasive fetal electrocardiogram able to monitor two individual fetuses by means of one abdominal electrode patch in twin gestation?

3. Are the changes in fetal heart rate variability following betamethasone administration as measured with time-domain indices comparable to those measured with frequency-domain indices?

4. Are there differences in cardiac deformation values and power spectral estimates of fetal heart rate variability between appropriate for gestational age fetuses and growth-restricted fetuses?

Part II: fetal ECG for diagnostic purposes

5. Can we determine reference values for the electrical heart axis in healthy fetuses between 18 and 24 weeks of gestation?

6. Do fetuses with a congenital heart defect have a deviated electrical heart axis?

Part I: fetal ECG for fetal monitoring

Is the non-invasive fetal electrocardiogram a valid technology for intrapartum feto-maternal monitoring in daily clinical practice?

Cremer et al. first described non-invasive fetal electrocardiography at the beginning of the 20th century.[3] Due to the technical challenge of a low signal-to-noise ratio (SNR), further development of this technology for clinical use ceased. In the meantime, continuous fetal monitoring by means of DU CTG was introduced over 50 years ago and is nowadays applied at every labor ward around the globe. In **chapter 4** we reviewed the available literature to date on the performance of the NI-fECG for fetal monitoring during labor.[4] Eight articles met our inclusion criteria. Due to large heterogeneity between the studies, pooled analysis was not possible. Despite differences in methodology, all included studies demonstrated that FHR monitoring during labor by means of NI-fECG is feasible. Overall, accuracy and reliability of NI-fECG was higher than those of DU, even in the second stage of labor. Publication dates of the included studies were in line with the fast-evolving computer technology over the last decades. Six out of the eight included articles were published within the last ten years.[5–10] Advances in computer software and signal processing techniques have gradually led to the development of specific algorithms to surpass the obstacle of low SNR. The biggest limitation in the available research concerning NI-fECG monitoring during labor is non-uniformity of the outcome measures used in the different studies. Also, not all studies used the gold standard for FHR monitoring,

the FSE, as a reference method. The use of DU as the reference method, with a high rate of signal loss especially in the second stage of labor, leads to incorrect results. Further research should apply uniform outcome measures to study the performance of NI-fECG such as accuracy, reliability and success rate.

In **chapter 5** we validated a new NI-fECG device for intrapartum feto-maternal monitoring taking into account the knowledge derived from our literature review in **chapter 4**.[11] We used the FSE as reference and compared our results to those of DU as reported in the literature.[7,10] The accuracy of NI-fECG (1.46 bpm) was much higher compared to DU (10.6 – 14.3 bpm). Furthermore, NI-fECG appeared to be a more reliable technology (88.4% ± 14.6%) than DU (62.4% - 73.0%) during the first stage of labor.[10–12] Reliability decreased during the second stage of labor to 68.74% but remained higher compared with values previously reported for DU (61.7% - 64.5%). The overall success rate of the NI-fECG (89.49% ± 10.80%) was also higher than that of DU (82.84% ± 23.09%). The performance of the NI-fECG was not affected by maternal BMI. Our study showed that the NI-fECG is a good alternative to DU for intrapartum FHR monitoring. Another advantage of the NI-fECG technology was the simultaneous recording of the maternal heart rate, limiting the risk of maternal/fetal heart rate confusion, and uterine activity by means of the electrohysterogram.

A limitation of our trial could be the low number of recordings during the second stage of labor (n = 56) available for analysis, which made the results more sensitive to potential outliers. This could have influenced the interpretation of our results in a negative manner. Since the second stage of labor comprises the most critical part of labor for the fetus, which is often subject to reduced oxygenation, accurate fetal monitoring during this stage is even more important. Future research should focus on improving performance measures of the NI-fECG especially during the second stage of labor, so that it resembles those of the FSE.

Are the changes in fetal heart rate variability following betamethasone administration as measured with time-domain indices comparable to those measured with frequency-domain indices?

In cases with a threatened preterm birth between 24 and 34 weeks of gestation, corticosteroids are administered to enhance fetal lung maturation. Betamethasone is the most frequently used corticosteroid and is administered as two separate doses with a 24-hour interval. It is known to cause a transient decrease in fetal heart rate variability (FHRV), which is most pronounced on day two after administration.[13–17] Since a decrease in FHRV can be misinterpreted as fetal distress, it is important to thoroughly understand the underlying mechanisms to prevent unnecessary iatrogenic preterm birth. Previous studies concerning the effect of betamethasone on FHRV were all performed using conventional CTG. The FHR provided by DU CTG is averaged over a few cardiac cycles which affects spectral information in the high-frequency domain. Spectral estimates calculated from conventional CTG tracings are therefore only reliable in the low-frequency domain.[18]

In **chapter 6** we describe a secondary analysis of a prospective cohort study in which we performed NI-fECG recordings in patients receiving antenatal corticosteroids. Prior to, and during the four successive days after the betamethasone injections, NI-fECG measurements were performed to evaluate the successive changes in FHRV. A decrease in FHRV was seen on day 2 compared to day 1. The changes in FHRV as reported by the literature based on conventional CTG measurements were similar to those calculated with spectral analysis of NI-fECG measurements. Normalized spectral values showed small changes, indicating a minor influence of autonomic modulation. Furthermore, we found an increase in time spent in resting state on day 2 parallel to the decrease in FHRV. The latter substantiated our conclusion that the decrease in FHRV was likely due to a drug-induced decrease in fetal activity.

Is the non-invasive fetal electrocardiogram able to monitor two individual fetuses by means of one abdominal electrode patch in twin gestation?

Twin pregnancies are associated with an increased risk of pregnancy complications such as preterm birth and fetal growth restriction.[19] They are therefore classified as high-risk pregnancies requiring close fetal monitoring during pregnancy and labor. FHR monitoring in twin pregnancies currently occurs by means of DU due to a lack of better monitoring technologies, where each twin requires their own DU transducer. Erroneous monitoring of the same twin with both transducers may occur with possible fatal consequences. During labor, a FSE can be applied only to the leading twin. Monitoring of the FHR with a DU transducer is still required for the second twin. In **chapter 7** we describe a case of a twin pregnancy in which successful separation and differentiation of both fetal signals was achieved, measured with the NI-fECG.[20] Separation of the fetal ECG signals from both twins was done manually. Based on the detected fetal QRS-complexes, a continuous FHR trace could be plotted. This allowed simultaneous monitoring of both individual fetuses in clinical practice, once computerized separation of both twins was achieved.

Are there differences in cardiac deformation values and power spectral estimates of fetal heart rate variability between appropriate for gestational age fetuses and growth-restricted fetuses?

Fetal growth restriction (FGR) is associated with increased perinatal mortality and morbidity.[21,22] The major cause of FGR is placental dysfunction leading to chronic hypoxia and malnutrition.[23] Despite current available methods, i.e. CTG and umbilical artery Doppler measurements, timely diagnosis of FGR and planning the correct timing for delivery remains difficult. Several adaptative mechanisms in fetuses with FGR occur in an attempt to reduce oxygen consumption and increase cardiac output. Fetal cardiac deformation and a reduction in FHRV have been observed.[24–28]

In **chapter 8** we describe the results of a prospective study. We compared cardiac deformation values measured with 2D speckle tracking echocardiography (2D-STE) and spectral estimates of FHRV measured with NI-fECG in FGR fetuses, to those in appropriate for gestational age (AGA) fetuses. Cardiac deformation values were significantly increased in FGR compared to AGA fetuses. This was also the case in the subgroup without umbilical artery Doppler abnormalities suggesting that changes in the fetal heart occur early in the continuum of fetal distress due to prolonged hypoxia in FGR. This indicated that detection of deformation abnormalities could facilitate the detection of at-risk growth-restricted fetuses earlier. Spectral estimates were comparable between both groups, independent of the fetal activity state. Earlier studies have described reduced short-term variability on computerized analysis of FHRV late in the deterioration process, and only when the hypoxia has become chronic. Since doppler abnormalities of the umbilical artery appear early in the process of fetal adaptation to chronic stress, the low number of included fetuses with Doppler abnormalities in our study could explain the lack of significant results.[29] Finally, FGR fetuses spent significantly more time in resting state compared to AGA fetuses (segments in rest 67% vs 33%, p=0.001). This reduction in fetal activity was also seen in the subgroup of growth-restricted fetuses without Doppler abnormalities.

From a physiological point of view differences in spectral estimates which reflect autonomic modulation would be expected in the case of chronic hypoxia. Our study comprised a small sample size as it was the first time spectral analysis had been performed on NI-fECG measurements. This small sample size combined with heterogeneity of the umbilical artery Doppler abnormalities probably contributed to the lack of significant differences in FHRV values in our study. Further research including a larger study population is needed to further explore how chronic hypoxia in growth-restricted fetuses is reflected by spectral estimates of FHRV.

Part II: fetal ECG for diagnostic purposes

Congenital heart disease (CHD) is the most common congenital anomaly and a major cause of neonatal morbidity and mortality.[30–38] Currently, screening for CHD is performed by means of the second-trimester anomaly scan. Despite the introduction of national screening programs, 4 out of 10 severe CHD are still missed in low-risk populations, where most CHDs occur.[35,36,39,40] Prenatal diagnosis of CHD is important since it allows for an adequate treatment plan which improves neonatal outcome.

Can we determine reference values for the electrical heart axis in healthy fetuses between 18 and 24 weeks of gestation?

Electrocardiography gives information about the electrophysiological properties of the heart. It provides global and regional information on the heart rate, rhythm and electrical conduction. In pediatric and adult ECGs, it is already known that characteristic ECG patterns are associated with structural heart defects.[41] Therefore, the NI-fECG could be a promising tool to complement ultrasonography in the detection of CHD. Since the signal processing steps to acquire a fetal ECG still require averaging of fetal ECG complexes over multiple heartbeats to enhance SNR, we are not yet able to determine ECG intervals. One of the ECG characteristics available from the fECG recordings, despite averaging, is the electrical heart axis. The electrical heart axis is the mean direction of the overall electrical activity of the heart. It can be calculated from the vectorcardiogram, which is a 3-dimensional representation of cardiac electrical activity during one heart cycle, after correction for fetal orientation. The electrical heart axis is defined as the direction in which the vectorcardiogram has its maximum amplitude.

In healthy adults the electrical heart axis is oriented to the left. A right-oriented electrical heart axis has been described in term fetuses and neonates.[41,42] Verdurmen et al. also found a right-oriented electrical heart axis in 25 healthy fetuses.[43] In **chapter 9** we performed a prospective cohort study in women pregnant with a singleton fetus without known congenital anomalies. NI-fECG measurements were performed at a gestational age between 18 and 24 weeks. We determined reference ranges based on prediction intervals of the electrical heart axis in 281 healthy fetuses. The average electrical heart axis in the frontal

plane was oriented to the right (122.7°). However, prediction intervals of our cohort were wide (90% PI: -25.6°; 270.9°), indicating a broad range wherein future observations will fall. Based on these results, the electrical heart axis alone seems less suitable as a parameter for antenatal CHD screening.

Do fetuses with a congenital heart defect have a deviated electrical heart axis?

In **chapter 10** we performed a case-cohort study where we included fetuses with a suspected CHD based on advanced ultrasound evaluation. The electrical heart axis was 83.0° (95% CI: 6.7°; 159.3°), determined in 127 fetuses with various types of CHD. It was not significantly different from the electrical heart axis as determined in healthy fetuses previously described in **chapter 9,** which functioned as the control group. This can be explained by the heterogeneity of the CHD group, which also resulted in poor sensitivity (50.6%, 95% CI 47.5% - 53.7%) and specificity (60.1%, 95% CI 57.1% - 63.1%) of the electrical heart axis for the detection of CHD. Therefore, we chose three clinically relevant CHD subgroups which we separately compared to the healthy control group from **chapter 9**. In fetuses with atrioventricular septal defects or hypoplastic right heart syndrome the electrical heart axis was deviated to the left and significantly different from the healthy control group. The electrical heart axis of fetuses with conotruncal anomalies was oriented to the right. These findings are in line with the anatomical and physiological characteristics of the chosen CHD. The results of this study confirm our previous statement that the electrical heart axis alone is insufficient for the detection of CHD. Other aspects of the fetal ECG such as ECG morphology and cardiac time intervals may provide other features which reflect the altered cardiac anatomy in the different types of CHD. Lempersz et al. presented in her thesis that the multilead approach of obtaining the NI-fECG, with correction for fetal orientation, allows for the production of a standardized 12-lead fetal ECG as used in pediatric and adult cardiology.[2,44]

Finally, we concluded this thesis with **chapter 11** presenting a case where a bundle branch block was diagnosed on a NI-fECG measurement performed at 20 weeks of gestation.[45] Here, the averaged ECG from each of the six fECG leads was presented to a pediatric cardiologist. Based on the morphology of the QRS complex an incomplete bundle branch block was suspected. A bundle branch block is an abnormality of cardiac ventricular conduction which causes characteristic changes in the QRS complex of the ECG. This case substantiates our confidence that NI-fECG measurements contain valuable information about the structure and functioning of the fetal heart.

Future perspectives

Overall, this thesis provides an overview of multiple promising prospects of the NI-fECG during pregnancy and labor. Development of this innovative technology initially stagnated after it was first reported, back in 1906 by Cremer et al.[3] With the arrival of modern computer technology to improve SNR, signal quality increased reviving scientific interest in the NI-fECG. The fECG harbors a variety of information which could aid in assessing the fetal status. As early as 1942 it was already implied that the effects of drugs, hypoxia and labor could be studied by the fetal ECG.[46] Part of the possible applications of this technology are probably yet to be discovered.

The use of real-time spectral analysis could be a useful tool in diagnosing fetal distress during pregnancy and labor. Spectral analysis provides a tool to quantify FHRV and detect small changes which remain undetected by visual interpretation of FHR tracings.[47] Van Laar et al. previously studied the effect of severe acidemia during labor on FHRV indices, using the FSE. They found a significant increase in normalized low-frequency (LFn-) and decrease in normalized high-frequency (HFn-) power during the last 30 minutes of labor in acidemic fetuses compared to non-acidemic fetuses. These findings are in line with the autonomic response to stress in adults.[48] Furthermore, a negative association was reported between LFn-power and fetal scalp blood pH.[49] Although both studies comprised a small study population, these results are promising for the use of spectral analysis to predict fetal hypoxia during labor. A large prospective study is necessary to verify these results. However, due to the low incidence of asphyxia, i.e. 2 per 1000 births in developed countries, an extensive study population is needed to be able to demonstrate significant results.[50] After CE marking following our validation trial as reported in **chapter 5**, the NI-fECG device is now available for clinical use.[11] This facilitates utilization of the NI-fECG for clinical trials to obtain large datasets. Currently, ethical approval has been obtained for a pilot trial in Máxima Medical Center which will commence shortly.[51] When more insight is gained into the response of spectral estimates on fetal distress, this could aid in the development of intrapartum threshold values for spectral estimates to timely detect fetal asphyxia.

FGR is a severe pregnancy complication caused by uteroplacental dysfunction and is associated with perinatal mortality and morbidity. FGR infants are susceptible to adverse long-term consequences following the substandard conditions in utero caused by chronic hypoxia, according to the "Barker hypothesis".[52] Previous studies in human fetuses have implied that a reduction

in overall FHRV in FGR fetuses is caused by a reduction in the sympathetic contribution to autonomic cardiovascular control without a change in the parasympathetic contribution.[23,53] However, one study used conventional CTG measurements which are not suited for spectral analysis since no beat-to-beat FHR can be obtained.[23] The other study used fetal magnetocardiography (fMCG) which is a correct method to obtain beat-to-beat FHR data for spectral analysis of FHRV, although fMCG is an expensive modality and only available in some centers.[53] Shaw et al. studied the effect of chronic hypoxia in fetal sheep.[24] They confirmed the aforementioned hypothesis with the occurrence of sympathetic suppression after inducing chronic hypoxia, while parasympathetic tone remained unchanged. The exact mechanism of this dysregulation of sympathetic control is yet to be explored. Spectral analysis can contribute to further understanding the mechanisms causing decreased FHRV in uteroplacental dysfunction. The latter is indispensable to develop the use of spectral estimates for the detection and monitoring of FGR fetuses in utero. In **chapter 8** we performed an initial study regarding spectral estimates of FHRV in FGR fetuses compared to AGA fetuses, based on beat-to-beat FHR derived from NI-fECG measurements. No significant differences in spectral estimates could be found, possibly due to the limited sample size of our study. A large prospective study in human fetuses is needed to gain further insight into the effect of FGR on FHRV. Here, various stadia of FGR should be included based on umbilical artery Doppler measurements to monitor changes in FHRV over the course of deterioration in FGR.

The NI-fECG provides the opportunity to study fetal ECG waveform characteristics. Cardiac time intervals (CTI) are useful in the evaluation of cardiovascular function and can provide important information about the fetal status. Clear P-wave, QRS-complex and T-wave morphologies were first demonstrated by Davis and Meares et al. back in 1954.[54] Since the fetal cardiovascular system is physiologically different from its adult counterpart, the morphology of the fetal electrocardiogram differs from that of an adult. To be able to distinguish ECG abnormalities, first knowledge of the normal morphology of the fetal ECG is required. The number of studies describing fetal ECG waveform characteristics is limited. Several observational studies have attempted to provide normal ranges for fetal CTI.[55–61] A review by Smith et al. combined the results of these studies, although meta-analysis was not possible due to large heterogeneity between these studies in terms of number of abdominal recording electrodes used and signal processing methods.[62] Several factors should be taken into account when trying to establish reference ranges for fetal CTI. First, the duration of CTI increase with gestational age as the

cardiac mass increases in the growing fetus.[63] Second, further enhancement of the fECG signal for waveform detection requires averaging the fECG over several beats. Although the signal becomes cleaner when more beats are used, the P-, QRS- and T-wave will widen providing inaccurate CTI results. The length of the time window varies between studies and there is no standard. Third, research has shown that comorbidities such as diabetes also influence CTI, since the myocardial mass increases more quickly in fetuses of diabetic mothers than in normal fetuses irrespective of fetal size.[64] Large scale prospective studies with consistent methodology and use of similar signal processing techniques are necessary to further define reference values for CTI in healthy fetuses across various gestations. Preferably, no averaging of the fECG should be performed to acquire reliable results. Pending signal processing techniques which enable this, predefined time windows over which averaging occurs is necessary to decrease heterogeneity between studies. Time windows of less than 5 seconds are preferred due to high variability of the FHR.[62]

Both animal and human studies have shown that T-wave changes are associated with fetal hypoxia and acidosis.[65–68] This led to the development of ST analysis of the fetal ECG (STAN) during labor.[69] NI-fECG provides the opportunity to acquire a multi-lead fECG providing more information on the fetal status. Furthermore, due to the non-invasiveness of this technology ST waveform changes can be studied antenatally in high-risk pregnancies, e.g. fetal growth restriction, where chronic hypoxia occurs. However, T-wave detection in fECG is currently limited by its small amplitude and sensitivity to low frequency background noise.

NI-fECG could play a role in raising antenatal detection rates of CHD in the future since secondary effects of CHD can be reflected by the fECG, e.g. hypoplasia or hypertrophy and conduction abnormalities. In **chapter 10** of this thesis we showed that the electrical heart axis is one of the characteristics derived from the fECG which could aid in the detection of CHD. The electrical heart axis is not influenced by the signal-averaging method and can therefore be calculated reliably pending the development of new signal processing methods which do not require signal-averaging. Although first a normal fECG needs to be established before fECG waveform abnormalities can be distinguished, few studies have reported on fECG waveform changes in fetuses with CHD or cardiac arrythmias to date.[70–72] Their results substantiate the hypothesis that CHD cause significant alterations in cardiac anatomy and electrical conduction which are reflected in the fECG. However, interpretation of the reported CTI requires caution due to the previously reported signal-averaging method used to

create a fECG waveform leading to incorrect calculations of CTI. Furthermore, signal-averaging prevents the detection of cardiac arrythmias for which beat-to-beat information is needed.

Recent advances in the field of computer-processing have led to the ongoing growth of computational power, increasing the possibilities of developing applications of artificial intelligence (AI) in different areas of today's society. A recent paper describing an AI model for R-peak detection and subsequent detection of the R-R interval in fECG measurements showed promising results. The AI model significantly increased performance measures in the second stage of labor, when active pushing of the mother causes increased electrical interference.[73,74] Since this AI model enables retaining the individual variation of the R-R interval, it can also be beneficial in the detection of cardiac arrhythmias. Furthermore, it can attribute to the detection of fECG features which are not visible to the human eye. For example, the low amplitude of the T-wave prohibits clear demarcation of the start and end of the T-wave, which AI probably can detect after training on similar data. AI might also discover fECG properties which are not yet known. However, AI is no panacea and thorough understanding of the pathophysiology is needed for accurate interpretation of the fECG signal properties.

A big advantage of the NI-fECG technology is its non-invasiveness, making it applicable throughout gestation. It is safe and easy to apply. However, despite all efforts to improve signal processing methods, there is still a long way to go before the full potential of this innovative technology is reached. Currently, only beat-to-beat FHR based on the R-R interval is available for real-time monitoring. Real-time spectral information on FHRV can be obtained, however, more knowledge needs to be obtained first on how to interpret these results before implementation in clinical practice can occur. In the studies presented in this thesis data processing as well as signal separation of twin recordings and calculation of the fetal electrical heart axis was performed offline. This limits the clinical applicability of the NI-fECG technology. Research should continue to focus on making the suggested applications from this thesis available simultaneous with the NI-fECG measurement, without the need for offline-analysis.

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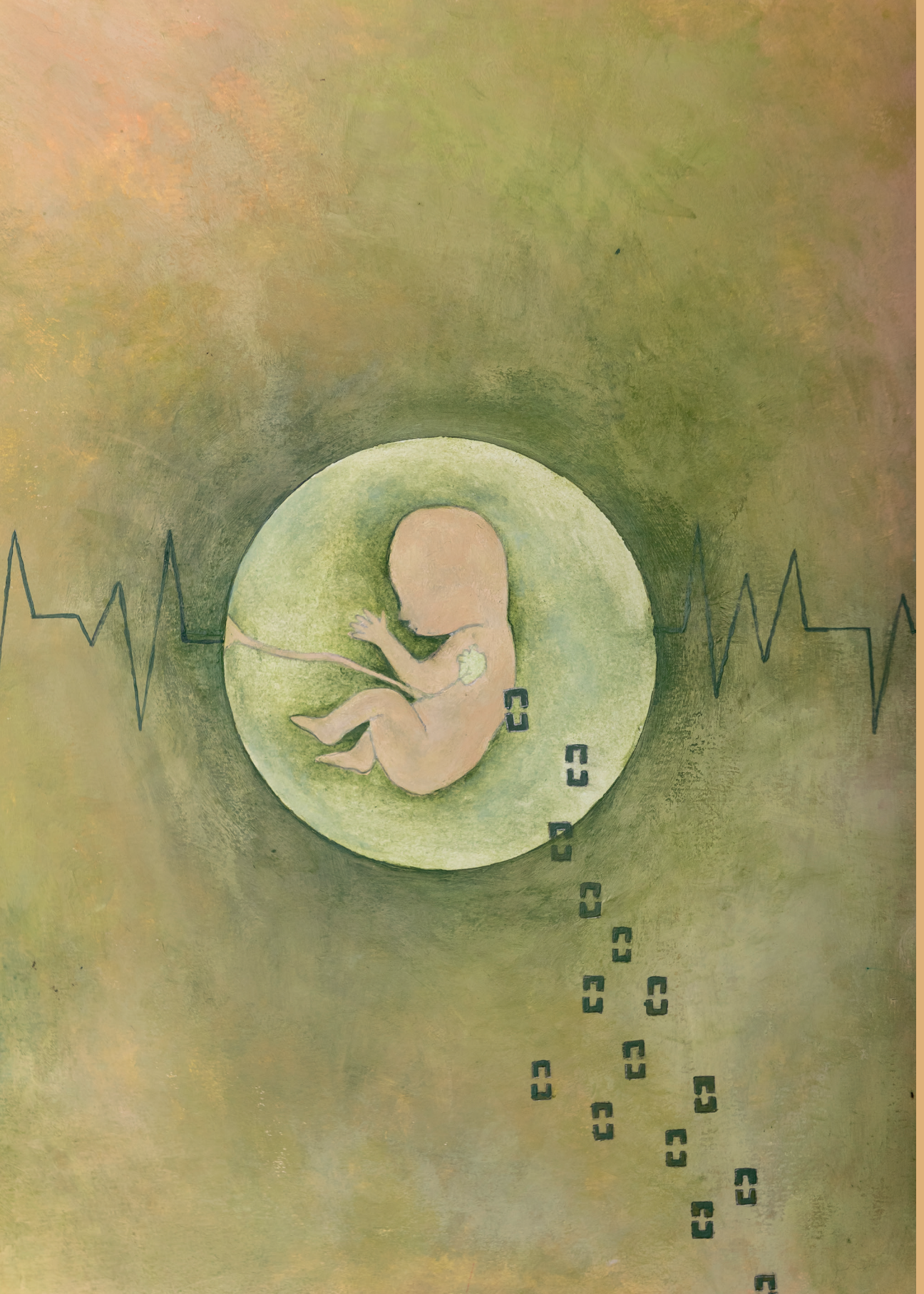

Appendices

SUMMARY

The goal of obstetric care is to deliver a healthy neonate, while preserving the health of the mother. Close fetal monitoring during pregnancy and labor is therefore warranted. Conventional CTG is currently used in clinical practice around the globe. However, it is known to have a poor specificity and high rate of false positive tests. During pregnancy, external monitoring by means of Doppler ultrasound (DU) is the only available method for fetal monitoring during pregnancy in clinical practice. During labor, when fetal membranes have ruptured, a fetal scalp electrode (FSE) can be placed which is considered the gold standard with high performance measures. However, this is an invasive method with increased risk of injury as well as intra-uterine infection.

Non-invasive fetal electrocardiography (NI-fECG) is an innovative and patient-friendly method for external feto-maternal monitoring. FHR as well as maternal heart rate and uterine activity can be monitored through an electrode patch placed on the maternal abdomen. In contrast to the fetal scalp electrode, a fetal electrocardiogram can be obtained non-invasively making this method applicable throughout pregnancy.

In this thesis we explore the clinical implications for transabdominal fetal electrocardiography related to the "Big Four" conditions associated with perinatal mortality: birth asphyxia, preterm birth, fetal growth restriction and/or congenital anomalies.

In **Part I** of this thesis we describe the role of NI-fECG for fetal monitoring during pregnancy and labor.

Birth asphyxia

Birth asphyxia is caused by oxygen deprivation to the fetus during labor, when placental gas exchange is compromised. This can cause irreversible damage to the vital organs and cause serious long-term effects such as hypoxic-ischemic encephalopathy. The goal of fetal monitoring during labor is timely detection of hypoxia so that action can be taken to prevent progression towards asphyxia. In this thesis we first explored if NI-fECG was feasible for intrapartum FHR monitoring. To obtain insight into the available literature on this topic, we performed a review as described in **chapter 4**. Only eight studies were available with large heterogeneity, reflecting the technical challenges of this technology which delayed its development for several decades. Still, all studies demonstrated that it is possible to apply NI-fECG during labor. Overall, NI-fECG performs equally well or better in most studies compared to DU, even in the second stage of labor. However, further research should apply uniform outcome measures to enable direct comparison of the results. We then validated a new NI-fECG device for intrapartum feto-maternal monitoring in **chapter 5**. We used the FSE as reference and compared our results to those of DU as reported in the literature. NI-fECG was a more accurate and reliable alternative compared to DU, especially in women with a higher BMI. Reliability decreased in the second stage of labor, but remained higher than that of DU.

Preterm birth

In cases of threatened preterm birth between 24 and 34 weeks of gestation, corticosteroids are administered to enhance fetal lung maturation. Betamethasone, the most frequently used corticosteroid, is known to transiently decrease fetal heart rate variability (FHRV) on day two after administration. This transient decrease in FHRV can be misinterpreted as fetal distress. In **chapter 7** we confirmed this transient decrease in FHRV using spectral analysis, with a minor influence of autonomic modulation. In addition, we found a decrease in fetal activity on day 2. This indicated that the reduced FHRV was drug-induced rather than a sign of fetal distress.

Multiple pregnancies are associated with an increased risk of pregnancy complications such as preterm birth, but also fetal growth restriction. These high-risk pregnancies therefore require close fetal monitoring during pregnancy and labor. In **chapter 6** we describe a case of a twin pregnancy in which NI-fECG allowed for monitoring of the FHR and ECG of both individual fetuses. Separation of the fetal ECG signals from both twins was done manually, but we are confident that computerized separation is feasible in the future. Based on the detected fetal QRS-complexes, a continuous FHR trace could be plotted. This would allow for simultaneous monitoring of both individual fetuses in clinical practice, once computerized separation of both twins has been achieved.

Fetal growth restriction

Fetal growth restriction (FGR) is caused by placental dysfunction leading to a state of chronic hypoxia. We hypothesized that this chronic hypoxia is reflected by spectral estimates of FHRV in growth-restricted fetuses. In **chapter 8** we describe the results of a prospective study in which we compared spectral estimates of FHRV in FGR fetuses and appropriate for gestational age (AGA) fetuses. Although no differences were found in spectral estimates between

both groups, FGR fetuses spent more time in resting state compared to AGA fetuses. This reduction in fetal activity was also seen in the subgroup of growth-restricted fetuses without Doppler abnormalities. We attributed our lack of significant differences in spectral estimates between both groups to the small sample size of our study. More research is necessary towards this subject using a larger sample size.

In **Part II** of this thesis we discuss the opportunities of the NI-fECG in the diagnosis of congenital heart disease (CHD).

Congenital heart disease

CHD is the most common congenital anomaly and a major cause of neonatal morbidity and mortality. The NI-fECG provides information on the electrophysiological properties of the heart and can therefore play an important role in diagnosing CHD in the future. Determining fetal ECG intervals is currently still prevented by the necessity to average fetal ECG complexes to enhance the signal-to-noise ratio. The electrical heart axis can however be determined despite averaging. A right-oriented electrical heart axis has been described in term fetuses and neonates. In **chapter 9** we determined reference values of the electrical heart axis in healthy midterm fetuses. Our results confirmed a right-oriented fetal electrical heart axis. However, due to the wide prediction intervals of our cohort, the electrical heart axis alone seems less suitable as a parameter for antenatal CHD screening. In **chapter 10** we describe the results of a case-cohort study including fetuses with a suspected CHD. Sensitivity and specificity of the electrical heart axis to detect CHD was low due to the large heterogeneity of the group. Depending on the type of CHD, the cardiac anatomical defect can be reflected by a change in the electrical heart axis. Therefore, we chose three clinically relevant CHD subgroups which we separately compared to the healthy control group from chapter 9. We found a significant difference in electrical heart axis between fetuses with atrioventricular septal defects and fetuses with hypoplastic right heart syndrome compared to the healthy control group.

Finally, we concluded this thesis in **chapter 11** with a case where a prolonged intraventricular conduction was diagnosed based on the fetal ECG. An averaged fetal ECG from a fetus around 20 weeks of gestation was presented to a pediatric cardiologist. The diagnosis of an incomplete bundle branch block was made based on this ECG and postnatally confirmed.

The results described in part II of this thesis substantiate our confidence that NI-fECG measurements contain valuable information about the structure and functioning of the fetal heart. Further research towards obtaining a non-averaged fetal ECG complex to determine cardiac time intervals is ongoing.

Overall, this thesis describes multiple promising prospects of transabdominal electrocardiography. It allows for more insight into the physiological background of several frequently occurring obstetric complications. This could aid in the diagnosis and follow-up of fetal compromise and hopefully improve neonatal outcome in the future.

NEDERLANDSE SAMENVATTING

Obstetrische zorg heeft als doel een gezonde baby geboren te laten worden en daarbij ook de gezondheid van moeder te bewaken. Het nauwlettend monitoren van de foetus tijdens de zwangerschap en de bevalling is daarom van groot belang.

Het conventionele CTG wordt momenteel wereldwijd standaard gebruikt voor foetale bewaking. Deze methode heeft echter een lage specificiteit en geeft een hoog aantal vals positieve testen. De uitwendige methode door middel van echo-doppler om de foetale hartslag te monitoren is de enige beschikbare methode voor foetale bewaking tijdens de zwangerschap. Tijdens de bevalling, nadat de vliezen zijn gebroken, kan een foetale schedelelektrode (FSE) worden bevestigd. De FSE is de gouden standaard voor foetale bewaking tijdens de bevalling. Het is echter een invasieve methode met een verhoogd risico op letsel en intra-uteriene infectie.

Niet-invasieve foetale elektrocardiografie is een innovatieve en patiëntvriendelijke methode voor uitwendige foetomaternale monitoring. De foetale hartslag kan samen met de maternale hartslag en de activiteit van de baarmoeder worden gemonitord door middel van een elektrodepleister welke op de buik van de moeder wordt geplaatst. In tegenstelling tot de FSE heeft het foetale elektrocardiogram een niet-invasief karakter. Hierdoor is het toepasbaar gedurende de gehele zwangerschap.

In dit proefschrift verkennen we de mogelijkheden van transabdominale foetale elektrocardiografie in de kliniek in relatie tot de 'Big Four' aandoeningen die geassocieerd zijn met perinatale mortaliteit: perinatale asfyxie, vroeggeboorte, foetale groeirestrictie en/of aangeboren afwijkingen.

In **deel I** van dit proefschrift beschrijven we de rol van het NI-fECG voor foetale monitoring tijdens de zwangerschap en de bevalling.

Perinatale asfyxie

Perinatale asfyxie wordt veroorzaakt door zuurstoftekort bij de foetus tijdens de bevalling doordat de uitwisseling van zuurstof en koolstofdioxide in de placenta wordt verstoord. Dit kan voor onherstelbare schade aan vitale organen zorgen en leiden tot ernstige lange termijn gevolgen zoals hypoxisch-ischemische encefalopathie. Het doel van foetale bewaking tijdens de bevalling is het tijdig herkennen van zuurstofgebrek zodat er kan worden ingegrepen om verdere ontwikkeling richting onherstelbare schade te voorkomen. In dit proefschrift hebben we eerst gekeken of het mogelijk was om de foetale hartslag te monitoren tijdens de bevalling door middel van het NI-fECG. Om inzicht te verkrijgen in de beschikbare literatuur omtrent dit onderwerp hebben we een literatuurstudie gedaan, welke beschreven staat in **hoofdstuk 4**. Er waren slechts acht studies beschikbaar met grote heterogeniteit tussen de studies. Dit weerspiegelt de technische uitdagingen van deze technologie welke ervoor gezorgd hebben dat de ontwikkeling ervan werd vertraagd. Alle geïncludeerde studies laten echter zien dat het mogelijk is om het NI-fECG toe te passen in het kader van foetale bewaking tijdens de bevalling. Het NI-fECG presteert in het algemeen even goed of zelfs beter dan echo-doppler in de meeste studies, zelfs in het tweede stadium van de bevalling welke het meest cruciale moment betreft voor de foetus. Verder onderzoek naar dit onderwerp dient zich te focussen op het hanteren van meer uniforme uitkomstmaten zodat de resultaten van de onderzoeken direct met elkaar vergeleken worden.

Vervolgens hebben we een nieuw NI-fECG apparaat voor foetomaternale monitoring tijdens de bevalling gevalideerd in **hoofdstuk 5**. We hebben de FSE als referentiemethode gebruikt en onze resultaten vergeleken met die van echo-doppler uit de beschikbare literatuur. Hieruit bleek dat NI-fECG een meer nauwkeurig en betrouwbaar alternatief is voor echo-doppler, voornamelijk bij vrouwen met een hoog BMI. De betrouwbaarheid nam af in het tweede stadium van de bevalling maar bleef hoger dan dat van echo-doppler.

Vroeggeboorte

In het geval van een dreigende vroeggeboorte tussen 24 en 34 weken zwangerschap worden corticosteroïden toegediend om de foetale longrijping te bevorderen. Betamethason is het meest gebruikte corticosteroïd. Het is reeds bekend dat betamethason de foetale hartritmevariabiliteit kortdurend doet afnemen op dag twee na toediening. Deze kortdurende afname in hartritmevariabiliteit bij de foetus kan verkeerd geïnterpreteerd worden als foetale nood. In **hoofdstuk 6** hebben we bevestigd dat deze afname in foetale hartritmevariabiliteit van voorbijgaande aard is door middel van spectraal analyse en dat de invloed vanuit het autonome zenuwstelsel klein is. Verder zagen we dat er ook een afname is van de foetale activiteit op dag twee. Dit alles wijst erop dat de afname in foetale hartritmevariabiliteit geen gevolg is van foetale nood maar een bijwerking van de medicatie.

Meerlingzwangerschappen zijn geassocieerd met een verhoogd risico op zwangerschapscomplicaties waaronder vroeggeboorte en foetale groeirestrictie. Deze hoog-risico zwangerschappen vereisen daarom nauwlettende monitoring van de foetus tijdens de zwangerschap en de bevalling. In **hoofdstuk 7** beschrijven we een casus van een tweelingzwangerschap waarbij het NI-fECG in staat was de foetale hartslag en het individuele ECG van beide foetussen te registreren. Het onderscheiden van de foetale ECG signalen van de individuele foetussen is in deze casus handmatig gedaan. We zijn echter overtuigd dat geautomatiseerd onderscheid maken mogelijk is in de toekomst. Op basis van de foetale QRS-complexen kon tevens een continu hartritme worden weergegeven. Dit zou het tegelijkertijd monitoren van de individuele foetussen mogelijk kunnen maken in de toekomst, nadat het automatiseren is bereikt.

Foetale groeirestrictie

Foetale groeirestrictie wordt veroorzaakt door een verminderde placentafunctie hetgeen kan leiden tot een chronisch zuurstoftekort. Wij veronderstelden dat dit chronisch zuurstoftekort ook terug te zien is in spectraalwaarden van de foetale hartritmevariabiliteit. In **hoofdstuk 8** beschrijven we de resultaten van een prospectieve studie waarin we de spectraal waarden in groeibeperkte foetussen vergeleken hebben met die in normaal gegroeide foetussen. We vonden geen verschillen. Wel zagen we dat de groeibeperkte foetussen meer tijd doorbrachten in rust vergeleken met de normaal gegroeide foetussen. Deze afname in foetale activiteit werd ook gezien in de subgroep van groeibeperkte foetussen met een afwijkende dopplermeting in de slagader van de navelstreng. Het gebrek aan significante verschillen in spectraal waarden tussen beide groepen is waarschijnlijk te wijten aan de kleine groepsomvang in onze studie. Meer onderzoek naar dit onderwerp is nodig met een grotere studiegroep.

In **deel 2** van dit proefschrift beschrijven we de mogelijkheden van het NI-fECG in het diagnosticeren van congenitale hartafwijkingen.

Aangeboren hartafwijkingen

Aangeboren hartafwijkingen zijn de meest voorkomende aangeboren afwijking en een belangrijke oorzaak voor neonatale morbiditeit en mortaliteit. Het NI-fECG levert informatie over de elektrofysiologische eigenschappen van het hart en kan daarom een belangrijke rol spelen in het diagnosticeren van aangeboren hartafwijkingen in de toekomst. Het bepalen van de duur van de foetale ECG intervallen is op dit moment nog niet mogelijk vanwege het middelen van de foetale ECG complexen. Dit laatste is nodig om de signaal-ruisverhouding

te verbeteren. De elektrische hartas kan wel worden berekend ondanks het middelen. Een naar rechts georiënteerde elektrische hartas is reeds beschreven in à terme foetussen en neonaten als gevolg van het unieke shunting systeem van de foetale circulatie. In **hoofdstuk 9** hebben we referentiewaarden bepaald van de elektrische hartas in gezonde foetussen rondom de twintigste week zwangerschapsduur. Onze resultaten bevestigden de eerder beschreven rechtsgeoriënteerde hartas. Door de wijde spreiding van het voorspellingsinterval lijkt de elektrische hartas op zichzelf geen geschikte parameter voor antenatale screening van aangeboren hartafwijkingen. In **hoofdstuk 10** beschrijven we de resultaten van een cohortstudie waarin we foetussen hebben geïncludeerd met een verdenking op een aangeboren hartafwijking. De sensitiviteit en de specificiteit van de elektrische hartas waren laag door de heterogeniteit van de groep. Het anatomische defect kan een verandering in de elektrische hartas veroorzaken, afhankelijk van het type hartafwijkingen. We hebben daarom drie typen aangeboren hartafwijkingen gekozen voor onze subgroep analyse welke relevant zijn voor de kliniek. Deze hebben we vergeleken met de gezonde controlegroep zoals beschreven in hoofdstuk 9. We vonden een significant verschil in elektrische hartas in foetussen met een atrioventriculair septum defect en foetussen met een hypoplastisch rechterhart syndroom, vergeleken met de gezonde controlegroep.

Tot slot hebben we in **hoofdstuk 11** een casus beschreven waarin een cardiale geleidingsstoornis was gediagnosticeerd op basis van het foetale ECG. Een gemiddeld foetaal ECG complex van een foetus rond twintig weken zwangerschapsduur werd voorgelegd aan een kindercardioloog die een incompleet bundeltakblok diagnosticeerde. Deze diagnose werd na de geboorte bevestigd.

De resultaten beschreven in deel II van dit proefschrift ondersteunen onze overtuiging dat NI-fECG metingen belangrijke informatie bevatten over de anatomie en de functie van het foetale hart. Verder onderzoek naar het verkrijgen van een foetaal ECG zonder middeling van de ECG complexen loopt.

Dit proefschrift beschrijft verschillende veelbelovende mogelijkheden van transabdominale elektrocardiografie. Hierdoor kan meer inzicht verkregen worden in de fysiologische achtergrond van de verschillende veel voorkomende obstetrische complicaties. Het NI-fECG kan hiermee bijdragen aan het diagnosticeren en monitoren van de foetale conditie en hopelijk de neonatale uitkomsten verbeteren in de toekomst.

LIST OF ABBREVIATIONS

AGA	Appropriate for gestational age
ANS	Autonomic nervous system
AV	atrioventricular
AVSD	Atrioventricular septal defect
BMI	Body mass index
Bpm	Beats per minute
BPS	Biophysical profile scoring
CCS	Corticosteroids
ccTGA	Congenitally corrected transposition of the great arteries
CD	Cesarean delivery
CHD	Congenital heart disease
CI	Confidence interval
CPR	Cerebroplacental ratio
CR	Confusion rate
CTA	Conotruncal anomalies
CTG	Cardiotocography
CWT	Continuous wavelet transform
DILV	Double inlet left ventricle
DORV	Double outlet right ventricle
DU	Doppler Ultrasound
ECG	electrocardiography
EDA	Epidural analgesia
EFW	Estimated fetal weight
EHG	Electrohysterography
fECG	Fetal electrocardiogram
FBS	Fetal blood sampling
FGR	Fetal growth restriction
FSE	Fetal scalp electrode
FHR	Fetal heart rate
FHRV	Fetal heart rate variability
fMCG	Fetal magnetocardiography
GA	Gestational age
GND	Ground
GLS	Global longitudinal strain
GLSR	Global longitudinal strain rate
HF	High-frequency
HFn	Normalized high-frequency
HRHS	Hypoplastic right heart syndrome
IUPC	Intra-uterine pressure catheter
IVS	Intact ventricular septum
IQR	Interquartile range
LF	Low-frequency
LFn	Normalized low-frequency
LoA	Limits of agreement
LRT	Likelihood ratio test
LTV	Long-term variability
LV	Left ventricle
MEHA	Mean electrical heart axis
MCA	Middle cerebral artery
MHR	Maternal heart rate
MMC	Máxima Medical Center
NICU	Neonatal intensive care unit
NI-fECG	Non-invasive fetal electrocardiography
PE	Pre-eclampsia
PI	Prediction interval
PM	Papillary muscles
PPROM	Preterm premature rupture of membranes
PPA	Positive power agreement
PRN	Perinatal Registry of the Netherlands
PSA	Power spectral analysis
RBBB	Right bundle branch block
REF	Reference
RV	Right ventricle
SA	Sinoatrial
SD	Standard deviation
SE	Standard error
SNR	Signal-to-noise ratio
SPML	Spherically projected multivariate linear
SSRI	Serotonin reuptake inhibitor
STAN	ST waveform analysis

STV	Short-term variability
TAPS	Twin anemia polycythemia sequence
TGA	Transposition of the great arteries
TOCO	Tocodynamometer
TOF	Tetralogy of Fallot
TPL	Threatened preterm labor
TTTS	Twin-to-twin transfusion syndrome
TU/e	Eindhoven university of Technology
UA	Umbilical artery
UA-PI	Umbilical artery pulsatility index
VBL	Vaginal blood loss
VCG	Vectorcardiogram
VSD	Ventricular septal defect
2D-STE	Two-dimensional speckle-tracking echocardiography

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CURRICULUM VITAE

Lore Noben werd op 11 januari 1994 geboren in Bilzen, België. In 2011 behaalde zij haar ASO-diploma (equivalent VWO) aan het Heilig-Grafinstituut te Bilzen waarna ze geneeskunde ging studeren aan de Universiteit Maastricht. Tijdens haar master volgde zij een keuzecoschap gynaecologie in het Zuyderland ziekenhuis te Heerlen. Het laatste jaar van haar opleiding was zij semi-arts op de afdeling gynaecologie en obstetrie in het Máxima Medisch Centrum. Tijdens het wetenschappelijke deel van deze stage raakte ze betrokken bij de onderzoeksgroep fundamentele perinatologie. Ze werkte mee binnen de onderzoekslijn elektrofysiologische monitoring onder begeleiding van dr. Judith van Laar en prof. dr. Guid Oei, waar de basis werd gelegd voor dit proefschrift. In 2017 ging Lore na haar afstuderen aan het werk als arts-onderzoeker om dit onderzoek verder te zetten in het kader van een promotietraject. In januari 2020 zette ze de stap naar de kliniek en ging aan de slag als arts-assistent niet in opleiding bij de afdeling gynaecologie en obstetrie in het Máxima Medisch Centrum. Tijdens deze periode rondde zij haar proefschrift af.

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