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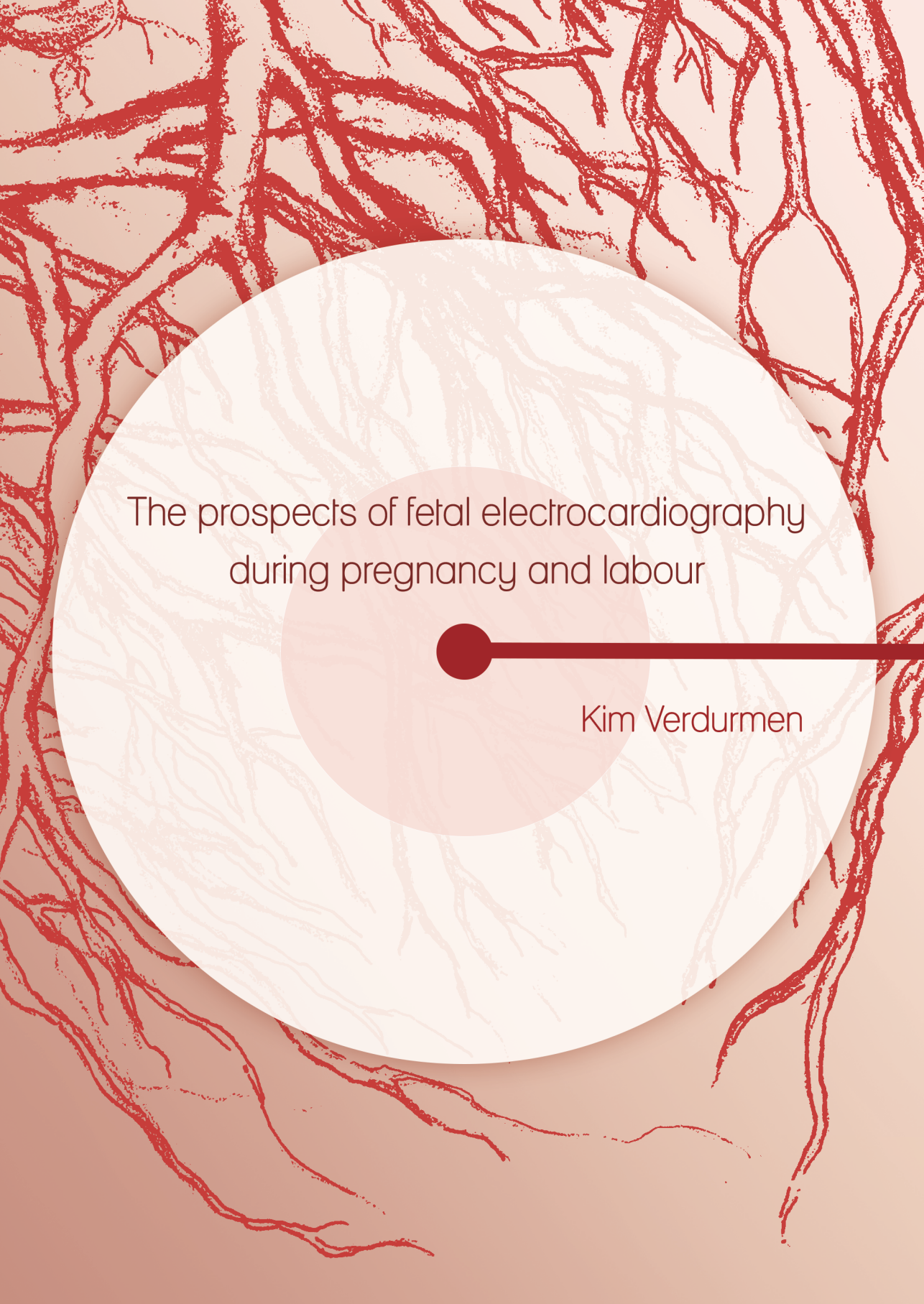

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A part of the research described in this thesis is performed within the IMPULS perinatology framework.

The prospects of fetal electrocardiography during pregnancy and labour

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Technische Universiteit Eindhoven, op gezag van de rector magnificus prof. dr. ir. F.P.T. Baaijens, voor een commissie aangewezen door het College voor Promoties, in het openbaar te verdedigen op woensdag 5 juli 2017 om 16:00 uur

door

Kim Margriet Johannes Verdurmen

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Het onderzoek dat in dit proefschrift wordt beschreven is uitgevoerd in overeenstemming met de TU/e Gedragscode Wetenschapsbeoefening.

Summary

The prospects of fetal electrocardiography during pregnancy and labour

Fetal electrocardiography (ECG) is a relatively new and still evolving technique in fetal monitoring. During pregnancy it can be registered non-invasively via electrodes on the maternal abdomen and during labour it can be obtained via a fetal scalp electrode. In this thesis, several prospects of fetal ECG are described.

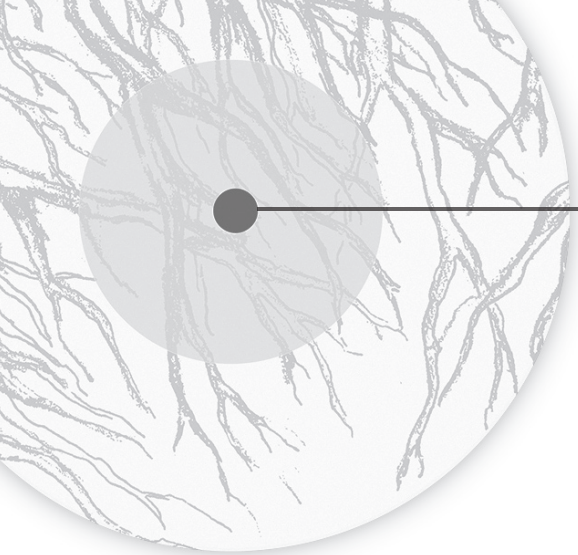
In Part I of this thesis we describe that fetal ECG could be valuable in diagnosing congenital heart disease (CHD) in fetuses. Since CHD is the most common severe congenital anomaly worldwide, an adequate and timely diagnosis is important. Nowadays, screening for CHD is performed during the fetal anomaly scan around 20 weeks of gestation. This ultrasound has a detection rate of approximately 65-80%. The fetal ECG can be obtained non-invasively from 18 weeks of gestation onwards. It reflects the intimate relation between the conduction system and the structural morphology of the heart, and it is particularly helpful in detecting the electrophysiological effects of cardiac anatomical defects (e.g. hypotrophy, hypertrophy and conduction interruption). Therefore, it seems to be a promising diagnostic tool to complement ultrasonography in the screening for CHD. However, the normal values and ranges of amplitudes and segment intervals of the fetal ECG in a healthy fetus should be established first, before we are able to detect CHD. In this thesis, the study design for a prospective cohort study that will provide these normal values and ranges is described.

In Part II of this thesis we study the effect of drugs that are administered during threatened preterm birth on heart rate frequency and variability. Corticosteroids are administered in order to expedite fetal lung maturation, and are known to decrease neonatal morbidity and mortality. Tocolytics are administered to attenuate uterine contractions, and therefore postpone preterm delivery. Since heart rate variability is one of the most important features when assessing fetal wellbeing, it is important to bear in mind the “side-effects” of administered drugs on heart rate variability. As corticosteroids and some tocolytic drugs can cause a decrease in fetal heart rate variability and in fetal movements, clinicians need to be aware

of the risk of iatrogenic preterm birth when patients receive these drugs. By analysing the fetal ECG, we found that the influence of the autonomic nervous system is minor following administration of betamethasone (a corticosteroid). This indicates that the reduced fetal heart rate variability is not a sign of fetal distress, but rather a consequence of a reduction in fetal movements in the first days following corticosteroid administration.

In Part III of this thesis we focus on ST monitoring during labour. In ST monitoring, the fetal ECG is obtained invasively via a fetal scalp electrode. The T/QRS baseline is measured early during delivery and serves as a benchmark for successive T/QRS ratios. The amplitude of the T wave, and therefore the T/QRS ratio, is influenced by hypoxia in the fetal myocard. T/QRS ratios that exceed the baseline value can cause an ST alarm, hence warning for possible fetal hypoxia. However, in current ST monitoring false alarms are encountered frequently. We hypothesised that this might be due to variation in orientation of the fetal electrical heart axis. We demonstrated that there is major variation in orientation of the electrical heart axis between fetuses. This variation in orientation yields variation in shape and amplitude of the ECG, and therefore in height of the T/QRS ratio. We further hypothesised that the orientation of the electrical heart axis is related to the occurrence of ST alarms. In a retrospective study we confirmed our hypothesis and found that there was a significant increment in ST alarms with increasing height of the T/QRS baseline, irrespective of the fetal condition at birth. As a solution for these false alarms we studied "relative" ST analysis, which analyses the T/QRS rise as a percentage from baseline. In a small retrospective case-control study we found the same sensitivity of conventional and relative ST analysis, and a significant increase in specificity of relative ST analysis. This first explorative study therefore shows that relative ST analysis is a promising alternative for detecting imminent fetal distress.

The results of the fundamental research reported in this thesis show that fetal ECG has multiple promising prospects, both during pregnancy and labour. Fetal ECG measurements can provide additional and objective information, amongst others in detecting congenital heart disease, measuring fetal heart rate variability, describing autonomic modulation and detecting fetal distress. Further improvement of the technologies described in this thesis will aid clinicians in more accurate diagnosis of the fetal condition, and will therefore improve perinatal outcome in the future.



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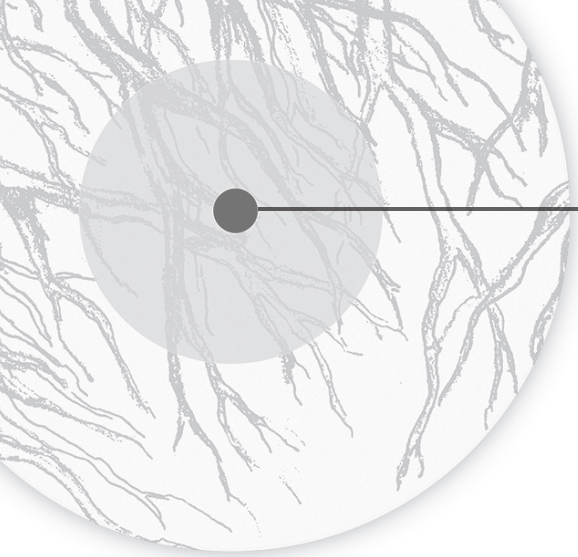


Chapter 1

1

General introduction

Introduction

Pregnancy and delivery are life changing events, and it is the task of obstetric caregivers to make sure both are completed as safely as possible. The World Health Organisation reports that of the 130 million babies born worldwide every year, there are over 6.3 million perinatal deaths[1]. The description "perinatal mortality" includes deaths that might be related to obstetric events, such as stillbirths and neonatal deaths in the first week of life. Perinatal mortality is six times more common in low-income countries, in comparison to high-income countries[1]. Despite the relatively low occurrence of perinatal mortality in high-income countries, the major part of these deaths is preventable. If all high-income countries achieved stillbirth rates equal to the best performing countries, almost 20.000 stillbirths beyond 28 weeks of gestation could have been avoided in 2015[2]. In the Netherlands, the perinatal mortality rates are relatively high compared to other European countries[3]. In 85% of the cases, perinatal mortality is preceded by at least one of the "Big Four"[4]:

- Congenital anomalies
- Preterm labour
- Birth asphyxia
- Fetal growth restriction

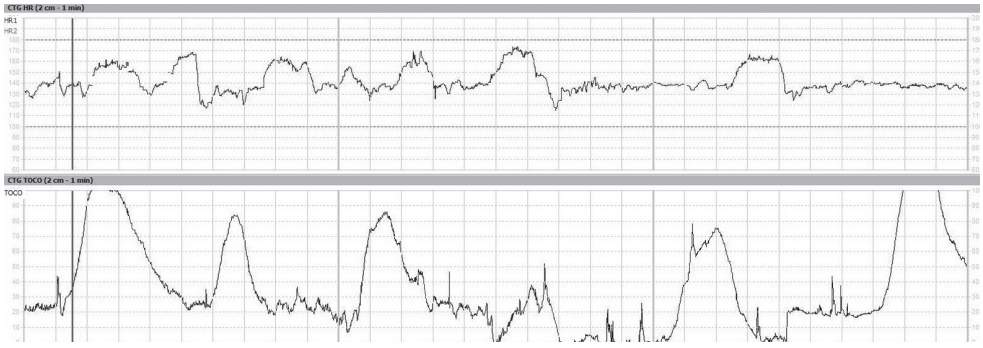
In addition to perinatal mortality, it is also important to take perinatal morbidity into account. The "Big Four" mentioned above can also lead to perinatal morbidity, possibly resulting in major impact on, for instance, neurological and cognitive development. Moreover, there are associations with chronic diseases such as diabetes, cardiovascular disease and chronic lung disease[5]. Therefore, it is important that obstetricians keep seeking for new methods that can aid in identifying possible threats in pregnancy or during labour.

This thesis is subdivided into three parts, that apply to the first three items of the "Big Four". In Part I, we focus on identifying congenital heart disease (CHD) early in gestation. CHD is the most common congenital anomaly worldwide. Next, in Part II we describe the effects of medication commonly used in threatened preterm labour on fetal heart rate parameters. By knowing the exact effect of these drugs, misinterpretation of fetal heart rate tracings and consequent unnecessary iatrogenic preterm delivery can be prevented. Finally, in Part III we focus on false alarms in fetal monitoring during labour; a method introduced to warn in case of fetal hypoxia. We explain and investigate our hypothesis regarding the orientation of the fetal electrical heart axis and these false alarms. Fetal electrocardiography (ECG) is a promising and still evolving technique that can be used for multiple purposes during pregnancy and labour. All studies described in this thesis use fetal ECG to detect possible threats during pregnancy and labour.

Fetal ECG; why do we need it?

During pregnancy and labour, we want to have an accurate monitor for fetal wellbeing. Nowadays, we can use ultrasonography for a biophysical profile and cardiotocography (CTG) for fetal heart rate recording. CTG is the simultaneous registration of the fetal heart rate and the uterine activity, and is used worldwide for fetal surveillance. In Figure 1, an example of a CTG tracing is shown. During pregnancy, it can be obtained by using an external non-invasive Doppler-ultrasound sensor and tocodynamometer. During labour, it can also be obtained via a scalp electrode on the fetal head and an intra-uterine pressure catheter. While the sensitivity of CTG is good, the specificity and positive predictive value of CTG are rather poor[6]. When using CTG during labour, the rate of neonatal seizures halves but there is no decrease in perinatal death or cerebral palsy, while the chances of an instrumental vaginal delivery or caesarean section are elevated[7]. In addition, CTG interpretation is based on visual pattern recognition by the physician. It has been known for a long time that this is characterised by a high inter- and intra-observer variability, especially in tracings that are not reactive[7,8]. Up to date, there is no satisfying solution for this and it is still a topic of debate and concern[9].

Figure 1. Example of a cardiotocogram.



Upper line: fetal heart rate. Lower line: uterine activity. Paper speed: 2cm/min.

During pregnancy, there are no complementary diagnostics like ST analysis or fetal scalp blood sampling that can be used to objectify fetal wellbeing[10]. Moreover, these complementary diagnostics are not applicable in case of prematurity. Therefore, there is need for a non-invasive method that provides more reliable information concerning the fetal condition than CTG alone can provide.

The fetal electrocardiogram (ECG) can be measured by direct registration via a scalp electrode on the fetal head during labour, or antepartum via indirect measurements with skin electrodes on the maternal abdomen. Fetal ECG recordings obtain beat-to-beat heart rate information and spectral analysis can be performed on these recordings. This gives detailed information regarding heart rate variability, which is a reliable marker for fetal wellbeing[11,12]. Spectral analysis can quantify rather small changes in fetal heart rate variability, that can remain undetected with visual interpretation of the fetal heart rate tracing[13]. In addition, the shape and amplitude of the fetal ECG can be assessed. More details concerning fetal ECG measurements and spectral analysis can be found in chapter 3 – technical background.

Part I: fetal ECG and congenital heart disease

CHD is the most common severe congenital anomaly worldwide[14]. It is estimated that CHD has an incidence of 6-12 per 1000 live births[15], of which 4 per 1000 are major forms of CHD that are lethal or require intervention[16]. CHD is a major health problem, being six times more common than chromosomal anomalies and four times more common than neural tube defects[16,17].

CHD is classically diagnosed by echocardiography, which is part of the congenital anomaly scan offered to all pregnant women around 20 weeks of gestation. However, the detection rate of CHD with this ultrasound is rather low and varies from 65-81%[16,18-20]. Specific echocardiography has a higher detection rate, with a sensitivity of 90% and a specificity of 98%[21]. This specific ultrasound is only performed in fetuses with a risk factor for CHD; amongst others family history, maternal diabetes, exposure to teratogens and infections, abnormal nuchal translucency, aneuploidies and other known congenital anomalies. However, up to 90% of all CHD occur in the low risk population[17]. About 25% of the neonates with major CHD is described to be discharged from the hospital undiagnosed[22].

It is important to diagnose CHD early in pregnancy for multiple reasons. First, it enables the identification of associated extracardiac and chromosomal anomalies, that occur in respectively 29% and 26% of the fetus with CHD[23]. Both influence the fetal and postnatal prognosis, and should be included in prenatal and genetic counselling that is offered to parents.

Hereafter, parents can decide to terminate or continue the pregnancy. The termination of pregnancy rate is higher if the prenatal diagnosis was made at an earlier gestational age (61% at 19 weeks of gestation, 44% at 24 weeks of gestation)[23,24]. When the pregnancy is continued, it is important to develop an adequate treatment plan including intra-uterine therapy, timing, mode and location of delivery and immediate treatment after birth. For ductus- and foramen ovale dependent CHDs, survival rates increase and long-term morbidity decreases if the CHD is diagnosed prenatally[24-27].

In neonates, it has already been described over 50 years ago that characteristic ECG patterns can be found which suggest the presence of a particular heart defect[28]. Therefore, the development of reliable non-invasive diagnostic methods that increase the predictive value for the diagnosis of CHD is of major importance. In Part I of this thesis, the opportunities of fetal ECG to aid in the diagnosis of CHD is elaborated.

Part II: fetal ECG in preterm labour

Preterm birth is defined as birth before 37 weeks of gestation, and is one of the "Big Four" as described earlier. The preterm delivery rate is approximately 5-9% in Europe, and even higher in the USA with rates near 12-13%[29]. It is described that preterm birth accounts for 75% of perinatal mortality and more than 50% of long-term morbidity such as neurodevelopmental impairments, respiratory and gastro-intestinal problems[29]. Preterm births occur spontaneously in 65-75% of the cases, due to contractions or preterm premature rupture of the membranes[29]. Approximately 25-35% of preterm births are iatrogenic, following both maternal and fetal indications (for instance severe pre-eclampsia or suspected fetal distress, respectively).

In case of threatened preterm labour between 24 and 34 weeks of gestation, both spontaneous or when iatrogenic preterm birth is expected, patients can be treated with corticosteroids and, if indicated, tocolytics. Antenatal administration of corticosteroids is known to enhance fetal lung maturation and is associated with an overall reduction in neonatal death, respiratory distress syndrome, cerebroventricular haemorrhage, necrotising enterocolitis, respiratory support, intensive care admissions and systemic infections in the first 48 hours of life[30]. There are no associated long-term negative effects reported after a single course of antenatal corticosteroids[30-33]. Betamethasone is the corticosteroid used most frequently, followed by dexamethasone[30]. Betamethasone is administered via two injections, 24 hours apart.

In spontaneous preterm labour, treatment with corticosteroids is often combined with short-term tocolytic therapy in an attempt to postpone delivery for at least 48 hours. This will yield time to transfer the patient to a centre with neonatal intensive care facilities and to

await maximal beneficial effect of corticosteroids. There are multiple tocolytic agents, and the tocolytic agent of first choice is still a topic of debate and varies considerably in different parts of the world[34]. The tocolytics most commonly used in clinical practice nowadays are nifedipine, magnesium sulphate, atosiban, indomethacin, fenoterol and ritodrine. Maintaining tocolytic therapy with nifedipine for more than 48 hours does not improve perinatal outcome, neither is it effective to prolong pregnancy[35,36].

Both corticosteroids and most tocolytics are known to have influence on fetal heart rate parameters. Since they are administered to a highly vulnerable population, fetuses at risk for preterm birth, it is of the utmost importance to know the exact effects of these drugs. Only then, iatrogenic preterm birth due to misinterpretation of fetal heart rate tracing, caused by therapeutic side-effects, can be avoided. In Part II of this thesis, the effects of corticosteroids and tocolytics on fetal heart rate tracings are studied.

Part III: fetal ECG to prevent asphyxia

The World Health Organisation estimated that 4 million neonatal deaths occur every year due to birth asphyxia, representing 38% of deaths of children under 5 years of age[37]. As described above, fetal monitoring with CTG alone has some shortcomings and additional information regarding the fetal condition is often desired during labour. Fetal blood sampling can offer information regarding the acid-base balance of the fetus. In some parts of the world it is used frequently in clinical practice, but it can only be performed during labour, when the membranes are ruptured and there is enough dilation. In addition, the relation between relative changes of acid-base balance in the various subcutaneous, cerebral and blood levels during fetal hypoxia are not yet fully understood[38]. The Cochrane review considering electronic fetal monitoring reported more instrumental deliveries, but less neonatal acidosis following fetal blood sampling ($p = 0.04$ for both) in a subgroup analysis[7]. However, the access to fetal blood sampling did not influence the difference in neonatal seizures or any other outcomes. Although the NICE guideline recommends fetal blood sampling as an additional test during labour[39], this received criticism since fetal blood sampling was never validated and the scientific evidence for its use is questionable[40]. It is important to realise that fetal blood sampling only gives information regarding the fetal condition at the time of blood collection and sometimes has to be repeated multiple times during labour. There are rare but serious complications such as leakage of cerebral spinal fluid, haemorrhage and sepsis reported following fetal blood sampling[41]. Therefore, advantages and disadvantages should be considered carefully before performing fetal blood sampling.

ST analysis is a second source for additional information regarding the fetal condition during labour. The ST segment of the fetal ECG is analysed, following registration via an invasive scalp electrode. More technical details considering ST analysis can be found in chapter 3 – technical background. In combination with CTG, ST analysis was reported to significantly lower the rates of metabolic acidosis[42] and operative delivery[42,43]. Subsequent multicentre trials were performed, including the most recent and largest randomised trial in the USA[44]. These trials could not reproduce the initial findings and showed no additional benefit for perinatal outcome, besides a reduction in the need for fetal blood sampling[44-47]. Conflicting results regarding the decrease in metabolic acidosis are reported in recent meta-analysis, indicating the need for more research[48-52]. In addition, ST analysis gives as many alarms in cases of proven uncompromised fetal condition as in cases of deteriorating fetal condition[53]. The guidelines that apply to ST analysis state that alarms must be ignored when CTG shows a reassuring pattern. However, taking the high inter-observer variability and low specificity of CTG into account, one can wonder if this is a proper solution for the false alarms encountered. Classifying between a reassuring or non-reassuring CTG determines whether or not to ignore an alarm, making the success of ST monitoring dependent on CTG assessment[54].

In term fetuses during labour, the orientation of the fetal electrical heart axis can vary between +90 and +180 degrees[55]. Similar inter-person variations in orientation of the electrical heart axis are present in neonates and adults[28,56-58]. This orientation of the electrical heart axis influences the shape and amplitude of the ECG. We hypothesise that the alignment between the scalp lead and the electrical heart axis, a normal variation in human physiology, can make the difference between ST alarms and no ST alarms. In current ST analysis, this is not taken into account properly.

In Part III of this thesis, we will discuss the orientation of the fetal electrical heart axis and its effect on false ST alarms.

Outline of the thesis

This thesis concerns fetal electrocardiography and its applicability. This thesis aims to answer the following questions:

1. Is fetal electrocardiography valuable in diagnosing congenital heart disease in fetuses?
2. What is the influence of corticosteroids and tocolytics on fetal heart rate variability?
3. Are the changes in fetal heart rate variability following corticosteroid administration in the time-domain (obtained by Doppler ultrasound cardiotocography) comparable to the changes in fetal heart rate variability in the frequency-domain (obtained by non-invasive fetal electrocardiography recordings)?
4. Is the variation in orientation of the fetal electrical heart axis in premature fetuses comparable to the variation seen in term fetuses?
5. Is variation in orientation of the electrical heart axis the cause of false ST events in ST analysis during labour?
6. Can we improve the method of ST analysis for fetal monitoring during labour?

To answer these questions we performed several literature and clinical studies, which are described below. The results of these studies are described in this thesis.

Chapter 2 provides physiological background information considering the fetal heart.

Chapter 3 provides technical background information considering CTG recordings, non-invasive transabdominal fetal ECG measurements, calculating fetal heart rate variability by means of spectral analysis and the reasoning and technology behind ST analysis.

Part I: fetal ECG and congenital heart disease

Chapter 4 reviews the possibilities of fetal ECG as a screening tool for the detection of CHD in fetuses.

Chapter 5 describes the study protocol of a prospective cohort study, in which the normal ranges for fetal ECG values for the healthy fetus of 18-24 weeks of gestation are established.

Part II: fetal ECG in preterm labour

Chapter 6 gives an overview of the literature regarding the influence of the corticosteroids betamethasone and dexamethasone on fetal heart rate parameters, in particular heart rate variability, and fetal behaviour.

Chapter 7 gives an overview of the literature regarding the influence of the tocolytics nifedipine, magnesium sulphate, atosiban, indomethacin, fenoterol and ritodrine on fetal heart rate parameters, in particular heart rate variability.

Chapter 8 presents the results of a prospective cohort study that describes the influence of betamethasone on fetal heart rate variability. Measurements were obtained by non-invasive fetal ECG recordings and spectral analysis was used to calculate fetal heart rate variability.

Part III: fetal ECG to prevent asphyxia

Chapter 9 describes the inter-fetal variation and the main orientation of the electrical heart axis in premature fetuses. These results are compared with what is known for term fetuses and adults.

Chapter 10 reveals the results from a post-hoc analysis following the Dutch multicentre randomised controlled ST analysis trial. This study describes the relation between the fetal electrical heart axis and the number of ST alarms that were encountered in fetal monitoring.

Chapter 11 presents the results of a case-control study, in which a new method for ST analysis is proposed; relative ST analysis is compared to regular "absolute" ST analysis in intrapartum fetal monitoring.

Chapter 12 provides a summary and general discussion considering the data presented in this thesis. In addition, suggestions for future research are included.

Chapters 4 to 11 are either published or submitted for publication. Therefore, these chapters are written to be self-contained which causes some overlap between these chapters.

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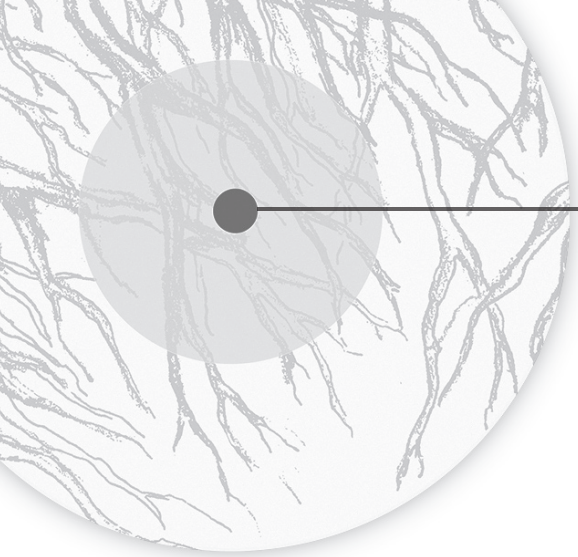


Chapter 2

2

Physiological background

The fetal heart

The fetal heart is a complex structure. There are shunts and metabolic adaptations present during intra-uterine life, while major changes occur in the postnatal period. Once one takes a closer look, the fetal heart is a very flexible, responsive and adaptive structure.

Embryology and circulation of the fetal heart

During the embryologic development, the fetal heart is the first functioning organ[1]. Initially, the embryologic body plan is symmetric. One of the first indications of left-right asymmetry is the rightward looping of the midline heart tube, at day 23 of the human embryology[2]. Simultaneously, the heart starts to beat from day 22 onwards and pumps blood by day 24-25[1]. The time line of the formation of the fetal heart is depicted in Figure 1. From day 28 onwards, the remainder of the development consists of remodelling of the chambers, development of the septa and valves, and formation of the epicardium, coronary vasculature and cardiac innervation and conduction system[1]. Once all the cardiac structures have been formed and organised, the fetal heart will continue to grow in an adaptive interplay with the changing demands[3].

The fetal myocardium can grow due to cell division. In addition, there is an increase in density of myofibrils. In the second half of pregnancy, there is also improvement in contractility of the myofibrils. In animal studies, the maximal systolic volume of a fetus is restricted by preload limitation through the extracardiac constraint (pericardium and chest wall-lung combination)[5]. Therefore, the myocardial contractile element is relatively poor during fetal life, which makes it difficult to change the stroke volume of the fetal heart[3,5]. As a consequence, regulation of the cardiac output is mainly dependent on alterations in fetal heart rate. In the fetus, the systemic circulation is fed from both the left and right ventricle in parallel, with equal intraventricular pressures[6]. The median biventricular output is estimated to be 425ml/min/kg, and is not associated with gestational age[7]. The cardiac outflow of the right ventricle is slightly larger (about 60% of total cardiac output) compared to the left ventricle (about 40% of total cardiac output)[3,7]. Approximately 55% of the left ventricular output is delivered directly to the brain via the carotid and vertebral arteries[8].

The heartbeat is initiated in the sino-atrial node, the pacemaker of the heart. Electrical depolarisation triggers the myocardium to contract, and the depolarisation spreads from cell to cell via conduction pathways. The timing of contraction of the various regions of the myocardium is thereby influenced, ensuring an efficient contraction in the correct sequence[1]. A secondary pacemaker, the atrioventricular node, is formed within the atrioventricular junction and regulates the conduction of depolarisation from the atria

to the ventricles. From there, the depolarisation is transmitted through both ventricles via the bundle of His. Following neural input of the sympathetic and parasympathetic branches of the autonomic nervous system, the heart rate can be modified.

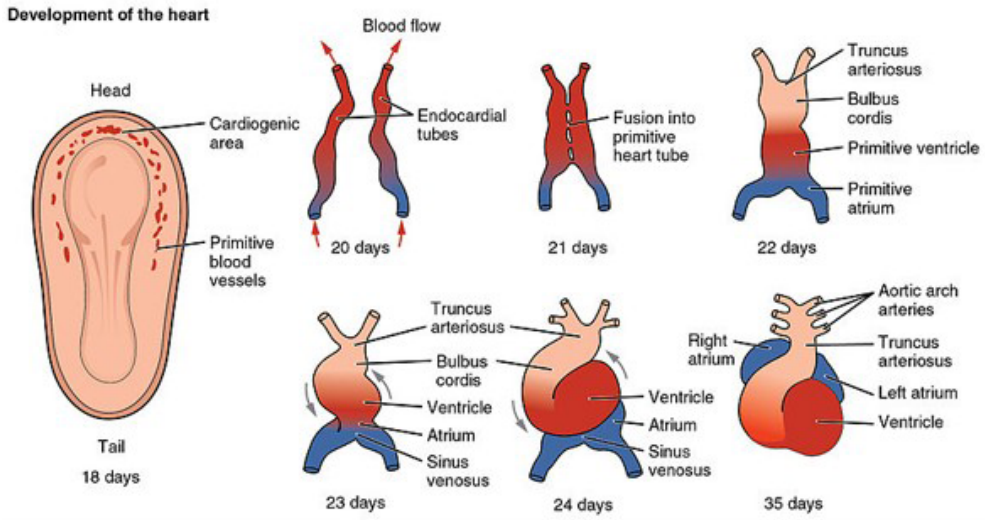
In Figure 2, an overview of the fetal blood flow is shown. During fetal life, oxygen-rich blood enters the fetal body via the umbilical vein. It mixes with a small amount of deoxygenated portal blood in the ductus venosus, and enters the inferior vena cava. From there, it is propelled into the right atrium. Due to hemodynamically distinct blood streams of the inferior vena cava (with oxygenated blood) and the superior vena cava (with deoxygenated blood), there is little mixture in the right atrium[1]. A part of the oxygenated blood originating from the inferior vena cava is moved via the foramen ovale to the left side of the heart, bypassing the fetal lungs. Since the vascular resistance of the collapsed fetal lungs is very high, there is only a limited amount of blood flow through the pulmonary circulation entering the left atrium that mixes with the oxygenated blood originating from the right atrium. Via the left ventricle, the blood is pushed into the aorta and the head, neck and arms are supplied with oxygenated blood. This blood is therefore slightly higher oxygenated than the blood in the descending aorta, where a mix with blood originating from the right side of the heart via the ductus arteriosus takes place. The amount of blood that is shunted increases exponentially during gestation[9]. About 46% of the combined cardiac output is propelled across the ductus arteriosus[9]. After distribution of blood to the trunk and lower limbs, the blood returns to the placenta for oxygenation via the umbilical arteries.

Postnatal adaptations

After birth, there is an abrupt dilation of the pulmonary vasculature and cessation of the umbilical flow. When the alveoli are filled with air, the pulmonary vessels open and pulmonary resistance drops. It is thought that this is a direct response to oxygen[1]. Simultaneously, due to spontaneous constriction or obstetrical clamping, the flow from the placenta is discontinued. Changes in flow and pressure occur as a consequence.

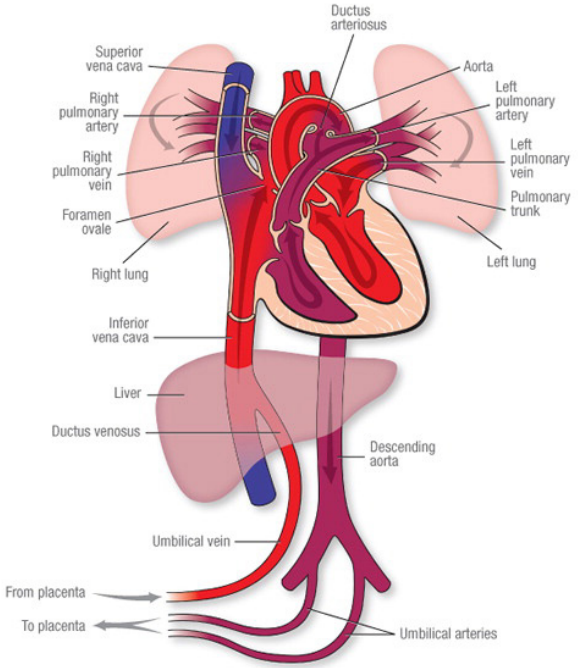
Due to opening of the pulmonary vasculature and cessation of the umbilical blood flow, the pressure in the right atrium decreases. The resultant sudden increase in pulmonary venous return causes a rise in pressure in the left atrium. The mechanical effect of the reversal in pressure between the left and right atrium causes the flexible and rigid part of the septum of the foramen ovale to be forced against one another, and thus to functionally close the foramen ovale. Normally, both parts of the septum are fused three months postpartum.

Figure 1. Time line of the formation of the fetal heart.



Adapted from: Anatomy & Physiology[4].

Figure 2. The fetal blood flow.



Adapted from: the American Heart Association.

The decrease in pressure in the pulmonary trunk resulting from opening of the pulmonary circulation, is thought to cause a slight reverse flow of oxygenated aortic blood through the ductus arteriosus[1]. It is thought that the oxygen tension might locally induce the vascular smooth muscle cells to contract and therefore restrict the blood flow. However, the exact mechanism for closure of the ductus arteriosus is not clear yet[1]. At term, constriction of the ductus arteriosus normally occurs within 72 hours after birth[10].

In addition, the ductus venosus closes soon after birth as no blood is flowing through the umbilical vein anymore[1]. Hereafter, the portal circulation replaces the hepatic blood flow from the placenta.

Hypoxia and the fetal heart

Hypoxemia is defined as an abnormally low level of oxygen in the arterial blood. In case of the human fetus, the natural environment is hypoxemic (but not pathologically hypoxic)[11]. The fetus can thrive under these conditions due to several adaptation mechanisms, amongst others fetal haemoglobin that has a high affinity for oxygen and allows easy diffusion from the maternal to the fetal circulation, the organisation of the fetal circulation as described above and the higher rate of tissue perfusion in the fetus compared to adults. These mechanisms compensate for the lower oxygen levels in the fetal blood, and make sure that oxygen supply is sufficient at tissue level.

In case of hypoxia, the oxygen supply at tissue level is inadequate and tissue damage can arise. Even so, the fetus can compensate through variabele mechanisms such as redistribution of blood flow and activation of the anaerobic metabolism. Progressive metabolic acidosis occurs following hypoxia if these mechanisms are not sufficient in compensating the oxygen shortage or in case of longlasting activation of the anaerobic metabolism. When there is acidosis in combination with organ damage, this is referred to as asphyxia.

In the late 1900s, multiple animal studies have been performed regarding the effect of hypoxia on the fetal heart. As summarised by Widmark et al.[12], these studies showed that when the maternal-placental blood flow is reduced, and therefore an acute hypoxic event is induced, both the chemo- and baroreceptor reflexes are activated. Initially, the chemoreceptor reflex increases both sympathetic and parasympathetic tone. In the fetal heart, parasympathetic influences predominate resulting in fetal heart rate bradycardia. During this reduced fetal heart rate the end-diastolic filling time is prolonged, which increases the end-diastolic volume. Therefore, cardiac output and perfusion pressure are both maintained despite fetal heart rate bradycardia[13]. Sympathetic activation causes

peripheral vasoconstriction, realising blood flow redistribution favouring the brain, heart and adrenals[13,14]. An increase in mean arterial blood pressure activates the baroreceptor reflex, and causes a secondary (inhibitory) effect on the fetal heart rate. Once initiated, the peripheral vasoconstriction is maintained by release of vasoactive agents[14]. These can be measured 15 minutes from the onset of acute hypoxia[13]. In addition, it is thought that impulse conduction through the atrioventricular node is directly inhibited (parasympathetic activation, baroreceptor reflexes) or directly facilitated (sympathetic activation)[12].

After reoxygenation, there is a baroreceptor reflex-enhanced parasympathetic tone that causes a negative chronotropic effect. This might exert a protective effect on the cardiovascular system, as this is still affected by an enhanced sympathetic tone due to circulating humoral agents[12]. Therefore, late decelerations may be interpreted as an adaptive mechanism to excessive sympathetic influence after a hypoxic event[12]. Because of the increased levels of catecholamines and other constrictor agents in the fetal circulation, the peripheral vasoconstrictor response and redistribution of blood flow is maintained longer[13].

A previous study by Amer-Wåhlin et al.[15] showed that cardiac effects following hypoxia (changes in the electrocardiogram) precede cerebral damage, and can therefore been seen as a marker for fetal distress. In the fetal heart, a high amount of glycogen is stored in case anaerobic metabolism needs to set in when oxygen supply is inadequate[16]. As described by Rosén and Isaksson[16], in the initial less severe states of hypoxia both liver and cerebral glycogen stores are well maintained and the fetus maintains a normal cardiac rhythm. When hypoxia becomes more severe, cerebral glycogen is still unaffected while there is depletion of liver glycogen stores. In 50% of these cases, fetal heart rate bradycardia was present. In case of severe hypoxia, both brain and liver glycogen stores were depleted and all cases showed fetal heart rate bradycardia. In addition, a correlation between changes in the ST segment of the electrocardiogram and depletion of glycogen in the fetal heart was found in animal experiments[16].

Fetal heart rate variability & the autonomic nervous system

Variability in the fetal heart rate is a resultant from the counteracting autonomic influences of the sympathetic and parasympathetic nervous system[17,18]. These systems do not simply interact as a “push-pull” system, but complex interactions exist between them[18]. Amongst others, intrinsic variability of the heart, the baroreceptor reflex, humoral agents (for instance circulating catecholamines), respiration and thermoregulation have their influence on heart rate variability[18,19].

When fetal heart rate variability is normal, this is a reliable indicator of fetal wellbeing, irrespective of the fetal heart rate pattern[20]. Decreased fetal heart rate variability is associated with fetal acidosis, low Apgar score and perinatal death[20]. Therefore, fetal heart rate variability is one of the most important factors to assess in fetal monitoring. Specific heart rate variability parameters that are mentioned below (for instance high-frequency (HF)-energy and low-frequency (LF)-energy) are described in detail in chapter 3 – technical background.

Multiple confounding factors can influence fetal heart rate variability. Several drugs that are commonly used in obstetric care may alter the fetal heart rate, heart rate variability, or the central nervous system. Two categories of these drugs will be described in this thesis in chapter 6 (betamethasone, a corticosteroid) and chapter 7 (various tocolytic drugs). Another confounder is birthweight; a study by Siira et al.[21] revealed that HF-power is negatively related to birthweight in case of fetal growth restriction. In addition, in cases where pregnancy is complicated by pregnancy induced hypertension or pre-eclampsia higher absolute LF- and HF-power was found in comparison to a control group, and greater instability of the fetal heart rate was seen in this group[22]. Changes in fetal behavioural states and diurnal rhythm can also influence fetal heart rate variability[23,24]. Below, the influences of gestational age and oxygen depletion on fetal heart rate variability are described in more detail.

When gestational age advances, there is evolution towards a more stable and mature autonomic nervous system[25]. By means of spectral analysis of fetal heart rate variability, the functional state of the autonomic nervous system can be assessed. This is described in more detail in chapter 3 – technical background. Prior research has shown there is an increase in absolute LF- and HF-power with increase in gestational age[26-28]. The sympathetic nervous system is effective from mid-gestation onwards, while the parasympathetic nervous system matures later[18,29]. The typical parasympathetic reflex responses are first seen during term gestation and reach adult levels after birth[29]. As gestational age progresses the parasympathetic modulation seems to increase, while the sympathetic modulation decreases[30].

As described previously in this chapter, the autonomic nervous system is activated in case of oxygen shortage. Subsequently, the beat-to-beat heart rate is modulated[17]. Initially, in case of mild fetal distress, there is a rise in fetal heart rate variability (total power, LF- and HF-power, LF/HF ratio)[21,31,32]. This is a reflection of increased sympathetic activity. Thereafter, in case of fetal hypoxia or acidemia, there is a decrease in fetal heart rate variability. More specifically, the absolute LF-power seems to be decreased[33]. In prior research, normalised LF-power was found to be negatively associated with fetal pH, while normalised HF-power was positively

associated with fetal pH[34,35]. This can be explained by increased sympathetic and decreased parasympathetic cardiac modulation, as the internal pH value decreases. This is in line with the increased LF/HF ratio that is found in acidotic fetuses, which indicates a shift towards sympathetic predominance[21]. It is suggested that both circulating catecholamines and sympathetic neural activity cause the decreased heart rate variability that is seen in case of severe fetal distress[35]. Eventually, in case of major fetal compromise, loss of central autonomic cardiovascular control and cardiovascular decompensation is likely[21,33].

In adult cardiology, heart rate variability already plays a role in determining prognosis and guiding therapy[36]. Almost 25 years ago, it was suggested that analysis of fetal heart rate variability might be able to improve the diagnosis of pathological conditions[25]. Since then, advances have been made regarding defining, monitoring and interpreting fetal heart rate variability.

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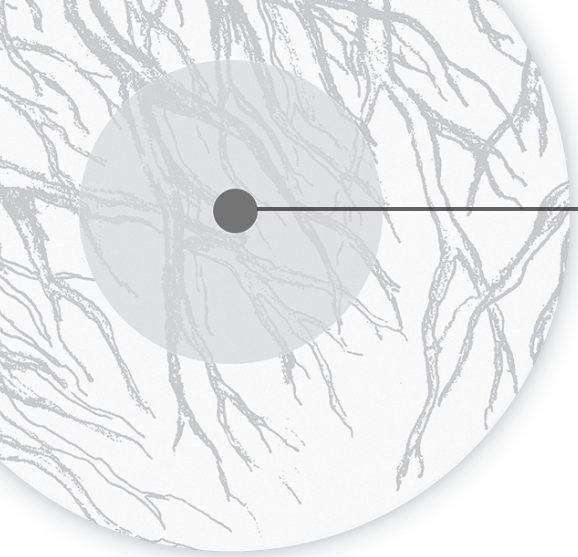


Chapter 3

3

Technical background

Introduction

In this thesis, various studies considering fetal monitoring are described in which multiple technologies were used. In this chapter, the technological background regarding these techniques will be explained. First, the cardiotocogram (CTG) will be discussed. This technique is mainly used in prior studies regarding fetal heart rate parameters, as described in chapters 6 and 7. The fetal electrocardiogram (ECG) is a technique that is still developing. In chapter 5 and chapter 9, fetal ECG measurements are used to establish the normal fetal ECG in mid-term pregnancy and to calculate the orientation of the electrical heart axis in premature fetuses. Once fetal ECG recordings have been performed, these can be used to apply spectral analysis and hence give more reliable estimates considering fetal heart rate variability, as described in chapter 8. During labour, fetal ECG measurements are required to be able to perform ST analysis. Chapters 10 and 11 relate to ST analysis.

The cardiotocogram

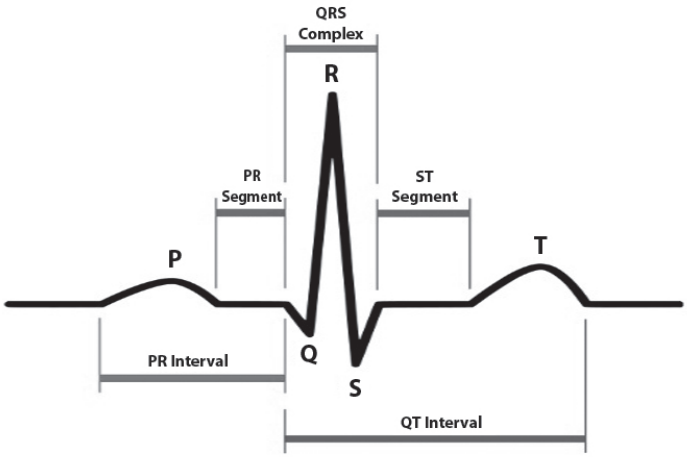
External cardiotocography (CTG) is a Doppler ultrasound-based system, detecting heartbeats as a reflection from all moving parts of the fetal heart. Simultaneously, uterine contractions are recorded by means of tocodynamometry. External registration of the fetal heart rate is prone to signal loss, inadvertent maternal heart rate monitoring, signal artefacts such as double-counting or half-counting and it might not record fetal arrhythmias accurately[1]. In addition, this technology is not able to provide beat-to-beat interval registration, since some of these irradiated ultrasound waves are reflected by the valves instead of the walls of the heart, causing inaccuracies. Moreover, the autocorrelation techniques used cause averaging of two to three subsequent cardiac cycles. Therefore, it cannot follow fast changes in fetal heart rate signal. This has a significant influence on the values of some variability indices; mainly on the indices that describe parasympathetic activity. As studied by Jezewski et al.[2], this introduces an average error in the RR-intervals of 0.42 ms, compared to the fetal ECG. For visual interpretation of fetal heart rate variability this has little influence, given the limited resolution of the human eye. However, in automated analysis this can have a significant effect on values of variability indices[2]. Therefore, CTG is an imprecise method for acquiring variability of the fetal heart rate. By means of fetal ECG measurements, QRS complex detection enables precise registration of fetal beat-to-beat heart rate variability. This technique considers the full shape of the analysed signal; an example is shown in Figure 1. Definitions for quantitative evaluation of fetal heart rate variability (long- and short-term variability) were originally proposed for the direct fetal ECG signal[2]. However, they have been applied for ultrasound-based registration without any adaptation.

Besides the shortcomings of CTG as listed above, the specificity and positive predictive value of CTG are rather poor as previously described in chapter 1 – introduction[1]. This indicates the need for a technology that enables more accurate and reliable monitoring of fetal wellbeing.

The fetal electrocardiogram

The fetal ECG during pregnancy can be obtained via non-invasive electrodes placed on the maternal abdomen. During labour, the fetal ECG can also be obtained via direct recordings through a scalp electrode on the fetal head.

Figure 1. Electrocardiography complex of one heartbeat.



The electrocardiography complex of one heartbeat, including the different segments and intervals referred to in this thesis.

Fetal ECG extraction through the maternal abdomen was first described by Cremer et al.[3] in 1906. In comparison to other fetal monitoring techniques, development of the fetal ECG lagged behind, because there were multiple technical challenges to overcome. At 20 weeks of gestation, the fetal heart is about 1/10th the size of an adult heart causing low voltage of the fetal ECG (1/50th of the maternal ECG)[4]. Therefore, there is a low signal-to-noise ratio when recording a fetal ECG. In addition, fetal signals are masked by the maternal ECG and high background noises caused by the abdominal and uterine electromyogram. Amniotic fluid and maternal tissues surrounding the fetus further enlarge the distance from the fetal heart to the electrodes on the maternal abdomen. Between 30 and 34 weeks of gestation, the fetus is surrounded by the vernix caseosa that results in an electrical isolation

which diminishes the signal amplitude further, and which is the main cause of the poor signal-to-noise ratio in this period[5,6]. Furthermore, the complex three-dimensional shape of the fetal ECG alters with changes in the fetal position with reference to the electrodes that are placed in a fixed configuration on the maternal abdomen. Despite these challenges, fetal ECG technique improved and it has previously been demonstrated that fetal heart rate recordings obtained by non-invasive fetal ECG measurements correlate very well with fetal ECG signals obtained directly via a scalp electrode[7].

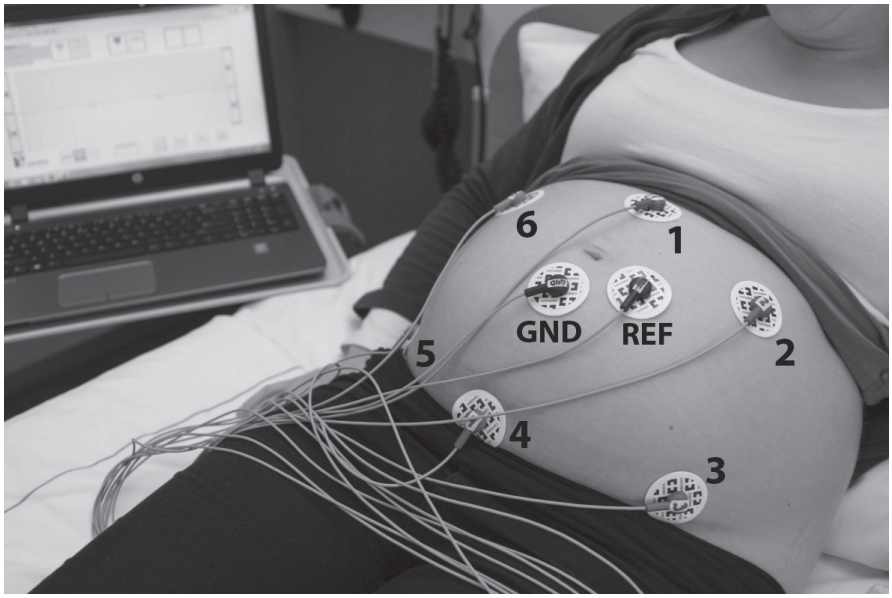
Apart from the technical difficulties encountered when performing a fetal ECG, the interpretation is also challenging. This is mainly caused by the marked differences in prenatal and postnatal circulation, which are elaborated in chapter 2 – physiological background.

In our studies, non-invasive fetal ECG recordings are performed using eight self-adhesive electrodes of which six are fetal ECG channel electrodes, one reference and one ground electrode. Other studies have used fewer electrodes[8] or more electrodes[9]. Before placing the electrodes, the maternal skin is prepared by gentle excoriation of surface skin cells and cleaning of the skin in order to reduce the electrode-skin impedance. The electrodes are placed in a fixed configuration on the maternal abdomen, as illustrated in Figure 2. For each of the six fetal ECG electrodes, the voltage difference between a recording electrode and the reference electrode is calculated. By using multi-lead recordings we can combine different leads in order to increase the signal quality and to allow recombination of leads to reconstruct the standard Einthoven leads. The chances of recording good quality fetal ECG signals in at least one of the electrodes is maximised by spreading the electrodes over the uterus. Electrode leads are shielded and a ground electrode is used to reduce the effect of power line interference.

For the measurements performed in the context of this thesis, two systems were used to obtain and store the fetal ECG recordings; the Porti amplifier system (Twente Medical Systems International B.V., Oldenzaal, the Netherlands) and the Nemo system (Nemo Healthcare, Veldhoven, the Netherlands). Both systems are approved by the Medical Technical Department of the Máxima Medical Centre.

In order to obtain fetal ECG recordings, several filters are applied to suppress high-frequency noise, baseline drift and power line interference. Thereafter, the maternal ECG is removed by weighted averaging of maternal ECG segments[10]. This is illustrated in Figure 3. By spatially combining the signals of the six fetal ECG channels, the signal-to-noise ratio is enhanced. Following detection of the R peaks in the fetal ECG, a beat-to-beat fetal heart rate signal is created.

Figure 2. Configuration of the electrodes on the maternal abdomen in order to acquire a non-invasive fetal electrocardiogram.



REF = reference electrode
GND = ground electrode

Fetal heart rate analysis

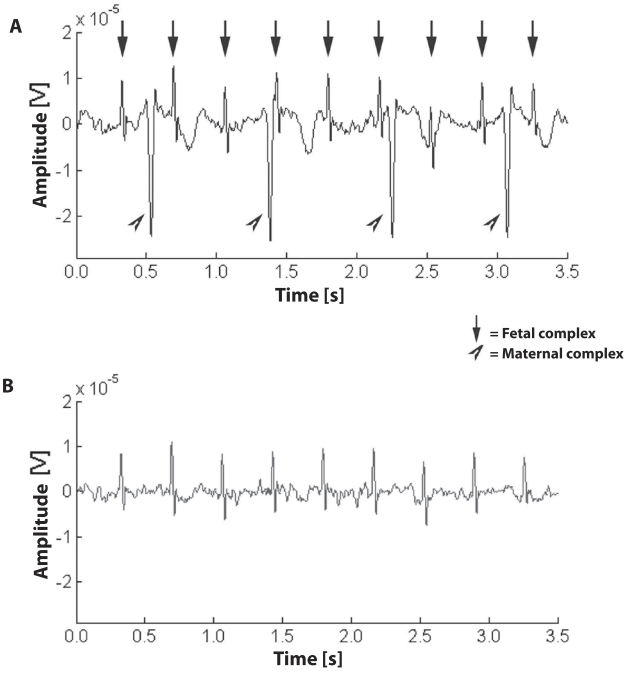
The aim of fetal heart rate analysis is to describe changes in heart rate objectively. Heart rate variability is depicted as a function of the fluctuation of the R-R interval (length between two successive R waves)[11]. By means of analysis of fetal heart rate variability, the functional state of the autonomic nervous system can be assessed. It is important that the fetal heart rate is acquired on a beat-to-beat basis. In addition, most heart rate analysis methods require equidistant data. Therefore, R-R intervals are resampled at 4 Hz (at least twice the frequency of the highest frequency of interest; 1.5 Hz). There are two distinct approaches in heart rate analysis; analysis in the time-domain or the frequency-domain.

Examples of time-domain indices are short-term variability (STV) and long-term variability (LTV). STV is sensitive to changes in successive heartbeats, and LTV gives a measure for the overall variability in the heart rate. Over the years, multiple definitions have been proposed[12]. In general, STV is calculated based on the difference between successive inter-beat intervals[12,13]. If no beat-to-beat information is available (e.g. in CTG monitoring),

STV can be estimated as the epoch-to-epoch variation in 3.75 second epochs[14]. LTV is generally defined based on the overall variation within one minute and can be calculated as the difference between the maximum and minimum inter-beat interval.

With spectral analysis in the frequency-domain, the energy in specific frequency components of heart rate variability is determined. This reveals the underlying system that controls the heart rate; the autonomic nervous system. Fluctuations in fetal heart rate, and therefore spectral estimates, reflect the influences of the autonomic nervous system. The autonomic nervous system and its influence on fetal heart rate and variability are explained in more detail in chapter 2 – physiological background. With spectral analysis, the signal is decomposed into sinusoids of different frequencies and amplitudes. The magnitude of heart rate variability (power) present at different frequency ranges, is reflected in the power spectrum[13]. The power spectrum can be calculated with one of the following algorithms.

Figure 3. The obtained electrocardiography signal.



A: Filtered abdominal electrocardiogram recording, containing both fetal and maternal electrocardiogram complexes. B: Fetal electrocardiogram, after subtraction of the maternal electrocardiogram.

The Fourier transform describes the relationship between a signal in the time-domain and its representation in the frequency-domain[15], and decomposes the R-R interval signal into its various frequency components as a function of their relative power[11].

A second algorithm that can be used, is the continuous wavelet transformation. Wavelets are used as analytical functions and allow multi-resolution analysis in the time-frequency domain[16]. In this thesis, we used the symlet 5 wavelet.

Impulses from the parasympathetic part of the autonomic nervous system are conducted much faster than impulses from the sympathetic part. Hence, sympathetic modulation causes slow fetal heart rate oscillations, while parasympathetic modulation also causes fast oscillations[19,20]. Therefore, the sympathetic system is solely present in the low-frequency (LF) band[20,21]. The LF peak is attributed to the baroreceptor reflex, and is the result of changes in blood pressure[11,13]. Parasympathetic modulation is present in both the LF and high-frequency (HF) band[20,21]. Following neonatal and adult studies, a HF spectral peak appears at the respiratory frequency, and is the result of respiratory sinus arrhythmia[11,13]. The very low-frequency (VLF) band is described to be related to peripheral vascular resistance fluctuations caused by thermoregulation and humoral systems[11], but seems to have less clinical significance than LF and HF since changes in the VLF band only appear after a delay of almost 6 minutes[23].

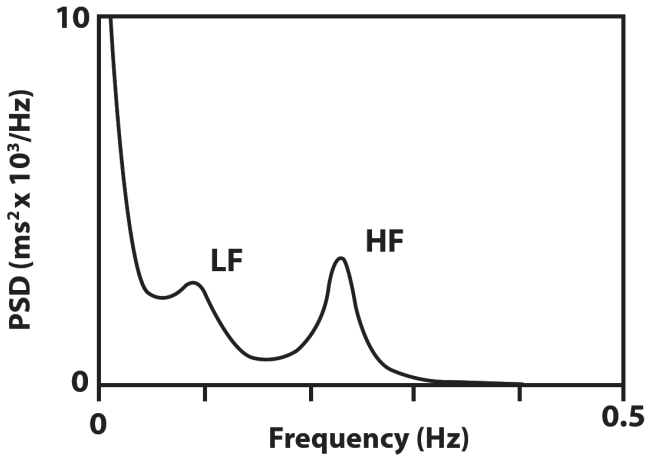
In adult cardiology, the LF band is defined to range from 0.04 – 0.15 Hz and the HF band from 0.15 – 0.4 Hz[22]. In newborns, the parasympathetic nervous system is shown to act in a higher frequency range. Therefore, the HF band is defined to range from 0.4 – 1.5 Hz in both newborns and fetuses. The VLF band is defined to range below 0.4 Hz[22]. Accordingly, these definitions have been used in previous studies[24-27]. HF and LF spectral power are suggested to be clinically similar to STV and LTV in the time-domain, respectively[13].

When absolute units are used, changes in total power influence both LF- and HF-power in the same direction. Normalised LF- and HF-power can be calculated by dividing LF- or HF-power by total power, respectively. By this normalisation, relative changes in LF- and HF-power are not masked by changes in total power and one can distinguish between both branches of the autonomic nervous system[22]. In addition, the LF/HF ratio is a reflection of the sympathicovagal balance[22].

Results are depicted as power spectral density (PSD), which is the squared amplitude calculated for each frequency. Analysis of the power spectrum can be performed by quantifying the area under the spectrum in various bands of frequency[11]. A characteristic

spectrum with a high- and low-frequency band can be distinguished following spectral analysis of heart rate variability, as depicted in Figure 4.

Figure 4. Example of a power spectrum of heart rate variability for human adults.



Adapted from: J.O.E.H. van Laar, Thesis: Fetal autonomic cardiac response during pregnancy and labour[15].
Abbreviations: HF = high-frequency, LF = low-frequency, PSD = power spectral density.

ST analysis

ST analysis is performed using a STAN® monitor (several types available, Neoventa Medical, Mölndal, Sweden). In clinical practice, interpretation of the CTG is combined with automatic analysis of the ST segment of the fetal ECG. The ST waveform is a representation of the repolarisation phase of the myocardium, which is an energy demanding process[28]. The energy metabolism in the myocardium (aerobic or anaerobic) will influence this repolarisation process, and will therefore change the ST waveform. The fetal ECG is recorded with a scalp electrode, which provides a unipolar ECG lead configuration. The monitor detects the R peak of each heartbeat, measures and processes the beat-to-beat R-R intervals.

Before introduction of ST analysis in the labour wards, extensive (animal) studies have been performed. During hypoxia, the heart is one of the organs that is favoured to receive oxygen by autoregulation (as well as the brain and adrenal glands). It is suggested that cardiac signs precede other central organ failure in case of asphyxia, and thus the heart can be used as an indirect indicator of the condition of the fetal brain during labour[28]. The fetal heart compensates by an increase in myocardial blood flow during the initial phase of hypoxia. Eventually,

sustained deprivation of oxygen is followed by enhanced β-adrenoreceptor activity and an adrenalin surge, to switch from an aerobic to an anaerobic cardiac metabolism with glycogenolysis[29,30]. This is accompanied by an increase of potassium ions in the myocard[31], which mainly affects the relaxation phase of the cardiac cycle and leads to an increase in T wave amplitude of the fetal ECG[32]. The oxygen content can fall more than 50% before the anaerobic metabolism is activated, and ST waveform changes occur[30]. A direct correlation between the increase in ST waveform and the rate of myocardial glycogenolysis (lactate production) is seen in fetal lambs[29], as well as a direct correlation between the T/QRS ratio and adrenalin levels[30]. In acidotic fetuses, the increase in T/QRS ratio coincides with the increase in LF-power[33].

In ST analysis, the hypoxia-related rise in T wave amplitude is analysed via a three-step protocol;

1. Of 30 heart cycles, an average ECG signal is rendered. The amplitude of the T wave is normalised against the amplitude of the QRS complex, yielding a T/QRS value.

2. A baseline T/QRS value is determined; this is the median value of at least 20 T/QRS values within a time frame of 20 minutes at the start of the recording. This baseline needs to be determined when there is a normal CTG (normal variability, accelerations) or the fetal status should be verified by fetal blood sampling. The baseline resets if it becomes lower or after three hours of recording.

3. New T/QRS values are compared to this baseline value.

An increase in T/QRS ratio is known to correlate with a surge in catecholamines, activation of β-adrenoreceptors, myocardial glycogenolysis and metabolic acidosis[34]. The STAN® monitor gives an alarm ("event") in case any of the three following changes occur; a rise in baseline T/QRS (during >10 minutes), an episodic rise in T/QRS (during <10 minutes) or a biphasic ST segment. However, there is limited evidence regarding the cut-offs, specificity and sensitivity of these individual items[35]. In addition, dynamic changes in the ST waveform have been reported during repeated brief hypoxic insults[34].

Biphasic ST segments can occur when there is acute hypoxic stress in the fetal heart with no time to respond to the hypoxia, or in case of chronic stress with a reduced capacity to respond in case of lack of resources or already used resources[34,36]. A biphasic ST segment is also associated with disturbances in the function of the heart muscle, infection or congenital malformations[36]. A recent study suggested that biphasic ST events have no additional value in detecting hypoxia[35]. ST depression can occur in case of myocardial ischemia, accompanied by severe fetal acidosis and hypotension[34]. It is possible that the

ischemic-type ST waveforms develop earlier in growth-restricted fetuses due to their limited glycogen reserves and possibly blunted sympathetic responses[34]. In this thesis, we will not discuss biphasic ST evens or ST depression; we will only focus on the T/QRS ratio.

When ST changes occur, the STAN® monitor provides an automatic warning called "ST event". The relevance of such an event is depending on the visual assessment of the CTG. The CTG is classified as normal, suspicious or pathological. Although the FIGO (International Federation of Gynecology and Obstetrics) published an updated CTG classification system[1], the STAN® clinical guidelines are based on a former version of this classification system. Therefore, this former version is included in Table 1. The T/QRS changes that can occur are displayed in Table 2 (biphasic events are not shown). If the T/QRS change is smaller than the alarm threshold, this can be due to normal beat-to-beat fluctuation in the behaviour of the fetal heart, which is unrelated to the fetal condition, and is hence ignored. In case the CTG is classified as normal, any ST event given by the STAN® monitor can be ignored[36,37]. In case of a (pre)terminal CTG, immediate intervention is advised irrespective of ST events[36,37]. When the CTG is suspicious or pathological, the STAN® clinical guidelines indicate if an intervention is advised in relation to the ST event. These guidelines indicate ST changes that prompt a clinical intervention, such as expedite delivery, fetal blood sampling and alleviate possible causes of fetal distress (such as uterine hypertonus and maternal hypotension).

Table 1. Cardiotocography classification[38].

CTG classification	Baseline heart rate	Variability/reactivity	Decelerations
Normal	110-150 bpm	5-25 bpm Accelerations	Early uniform decelerations Uncomplicated variable decelerations (<60 sec, loss <60 beats)
Intermediary	100-110 bpm 150-170 bpm Short bradycardia (<100 bpm for ≤ 3 min)	>25 bpm (saltatory pattern) <5 bpm for >40 min with absence of accelerations	Uncomplicated variable decelerations (<60 sec, loss >60 beats)
	A combination of several intermediary observations will result in an abnormal CTG		
Abnormal	150-170 bpm & ↓ variability >170 bpm Persistent bradycardia (<100 bpm for >3 min)	<5 bpm for >60 min Sinusoidal pattern	Complicated variable decelerations (>60 sec) Repeated late uniform decelerations
Preterminal	Total lack of variability (<2 bpm) and reactivity with or without decelerations or bradycardia		

Abbreviations: bpm = beats per minute, CTG= cardiotocography, min = minutes, sec =seconds.

Table 2. STAN® clinical guidelines[38].

	Intermediary CTG	Abnormal CTG
Episodic T/QRS rise (<10 min)	Increase >0.15 from baseline	Increase >0.10 from baseline
Baseline T/QRS rise (≥10 min)	Increase >0.10 from baseline	Increase >0.05 from baseline

Abbreviations: CTG = cardiotocography, min = minutes.

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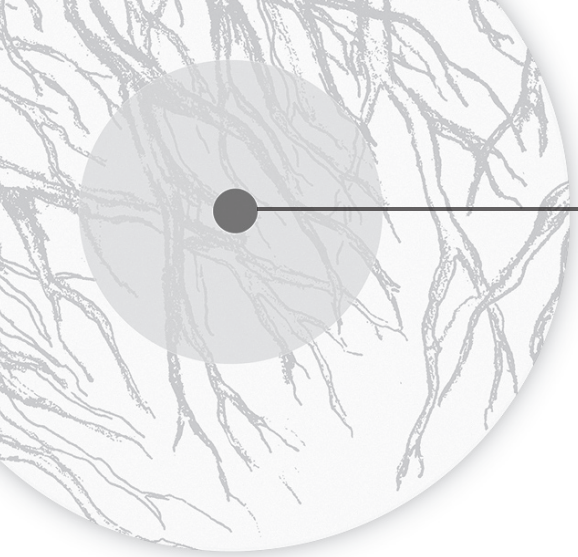
Part I

Fetal ECG and congenital heart disease



Chapter 4

A systematic review of prenatal screening for congenital heart disease by fetal electrocardiography

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Abstract

Background

Congenital heart disease is the most common severe congenital anomaly worldwide. Diagnosing early in pregnancy is important, but the detection rate by two-dimensional ultrasonography is only 65%-81%.

Objectives

To evaluate existing data on congenital heart disease and non-invasive abdominal fetal electrocardiography.

Search strategy

A systematic review was performed through a search of the Cochrane Library, PubMed and Embase for studies published up to April 2016 using the terms "congenital heart disease", "fetal electrocardiogram", and other similar keywords.

Selection criteria

Primary articles that described changes in fetal electrocardiography among fetuses with congenital heart disease published in English were included.

Data collection and analysis

Outcomes of interest were changes in fetal electrocardiography parameters observed for fetuses with congenital heart disease. Findings were reported descriptively.

Main results

Only five studies described changes observed in the fetal electrocardiogram for fetuses with congenital heart disease, including heart rate, heart rate variability, and PR, QRS and QT intervals. Fetal electrocardiography reflects the intimate relation between the cardiac nerve conduction system and the structural morphology of the heart. It seems particularly helpful in detecting the electrophysiological effects of cardiac anatomical defects (e.g. hypotrophy, hypertrophy, and conduction interruption).

Conclusions

Fetal electrocardiography might be a promising clinical tool to complement ultrasonography in the screening programme for congenital heart disease.

Introduction

Congenital heart disease (CHD) is the most common severe congenital anomaly worldwide[1]. CHD is defined as "a gross structural abnormality of the heart or intra-thoracic large vessels, that is actually or potentially of functional significance"[2]. Major CHD is usually defined as a form of CHD that is lethal or requires intervention in the first year of life. The incidence of CHD is estimated at 6-12 per 1000 live births (4 cases of major CHD per 1000 live births), which makes this disorder six times more common than chromosomal anomalies and four times more common than neural tube defects[3-5]. In Europe, the overall rate of mortality due to CHD (both perinatal deaths and termination of pregnancy) was 0.7 per 1000 births in 2000-2005[6]. Of the fetuses affected by CHD, 4.5% die in utero and 21.1% die after birth[7].

Diagnosing CHD early in pregnancy enables the identification of associated extracardiac anomalies (present in 29% of cases) and chromosomal anomalies (26% of cases) that have an effect on fetal and postnatal prognosis[8]. Prenatal and genetic counselling by experts can be offered to parents. Thereafter, parents can decide to terminate or continue with the pregnancy. Studies have shown that the frequency of pregnancy termination is higher if prenatal diagnosis is made at an earlier gestational age (61% and 44% at 19 and 24 weeks of pregnancy, respectively)[8,9]. If pregnancy is continued, an adequate plan of management can be developed, including intra-uterine therapy, timing, mode and location of delivery, and immediate treatment after birth. It has been demonstrated that prenatal diagnosis of CHD increases survival rates and decreases long-term morbidity in both ductus-dependent and foramen ovale-dependent CHD[9-12]. As Yates et al.[13] has pointed out, however, prenatally diagnosed CHD often has a worse prognosis because it is more likely to be severe (i.e. easier to detect by ultrasonography) or associated with extracardiac or chromosomal anomalies.

Fetal cardiac screening during the second trimester was standardised in 2006[14]. The detection rate of CHD varies widely, from 65% to 81%[15-18]. The challenges encountered include the complex anatomy of the fetal heart, its motion, and small size. Specific echocardiography is performed for fetuses with risk factors for CHD, and this technique has a higher detection rate (sensitivity 90%, specificity 98%)[19]. However, up to 90% of all cases of CHD occur in the low-risk population, indicating the necessity of an effective screening procedure that is available to all pregnant women[3,4,20-22].

Therefore, there is need for a reliable non-invasive diagnostic method with improved predictive value for the diagnosis of CHD. Non-invasive transabdominal fetal electrocardiography (ECG) is a new field that is being investigated. This technique can be used early in pregnancy (from 18 gestational weeks), is safe to use, and easy to apply[23]. A big advantage

is that fetal ECG is a potentially non-expensive long-term diagnostic tool, and raw data can be forwarded for evaluation elsewhere.

Extraction of fetal ECG data was first described in 1906 by Cremer et al.[24], and the approach was first reviewed in 1986 by Pardi et al.[25]. Despite this early documentation, the development of fetal ECG has lagged behind other techniques for fetal monitoring, partly because of technical challenges. The fetal signal has low amplitude (2-50 microvolts, 1/50th of the maternal ECG), and is masked by both the maternal ECG and background noises (maternal electromyogram), resulting in a low signal-to-noise ratio[25,26]. The fetus is surrounded by amniotic fluid and maternal tissues, which enlarge the distance to the electrodes and cause a non-homogenous tissue conduction that interferes with signal quality. Additionally, the vernix caseosa is electrically isolating and a main cause of the poor signal-to-noise ratio from 30 to 34 gestational weeks[23,27]. Other challenging factors are the complex three dimensional form of the fetal ECG and the movements of the fetus, which makes it difficult to evaluate the heart from one direction. Furthermore, at 20 gestational weeks, the fetal heart is approximately one-tenth of the size of an adult heart and the fetal heart rate is two to three times faster than the adult heart rate[28]. With improvements in technology and knowledge of information theory, however, fetal ECG is becoming more and more attractive.

In addition to the challenges in the conduction of fetal ECG, it is also difficult to interpret the data. By contrast with postnatal life, the systemic circulation in the fetus is fed from the left and right ventricle in parallel with equal intraventricular pressure[29]. The right ventricular outflow is slightly larger than the left ventricular outflow. The ductus arteriosus propels 40% of the combined cardiac output during the second trimester. Right-sided obstructive lesions (e.g. tetralogy of Fallot or pulmonary stenosis) with a dominance of the right ventricle are difficult to diagnose in utero; however, they are often accompanied by septal defects or by left-side obstructive lesions (e.g. aortic stenosis or coarctation of the aorta), which can be detected more easily. Owing to the fetal circulation in utero, fetuses affected by CHD do not always show overt signs of cardiac failure, because one side of the heart can compensate for an abnormality on the other side. At present, the changes in the fetal ECG amplitudes, segment intervals, and heart axis that are characteristic of CHD are not known. Although the changes due to CHD seen on neonatal ECG are documented, these data are not likely to correspond with those of fetal ECG because the circulation changes markedly directly after birth. The aim of the present review was to evaluate the existing data on CHD and non-invasive abdominal fetal ECG.

Materials and Methods

As part of a systematic review, the Cochrane Library (2016, Issue 4), PubMed and Embase electronic databases were searched to identify all studies published on fetal ECG and CHD up to April 30, 2016. The following keywords were used: "congenital heart disease", "congenital heart defects", "fetal electrocardiogram", "fetal electrocardiography", and "fetal ECG". The outcomes of interest were changes seen in fetal ECG parameters, such as ECG intervals, ECG segments, and the electrical heart axis among fetuses with CHD.

Primary articles that described the changes in fetal ECG among fetuses with CHD were selected. The reference lists of the selected articles were also searched. The study language was restricted to English. Review articles and studies describing diagnostic tools other than non-invasive abdominal fetal ECG were excluded. Articles that solely described fetal arrhythmia were excluded because only few arrhythmias are associated with CHD.

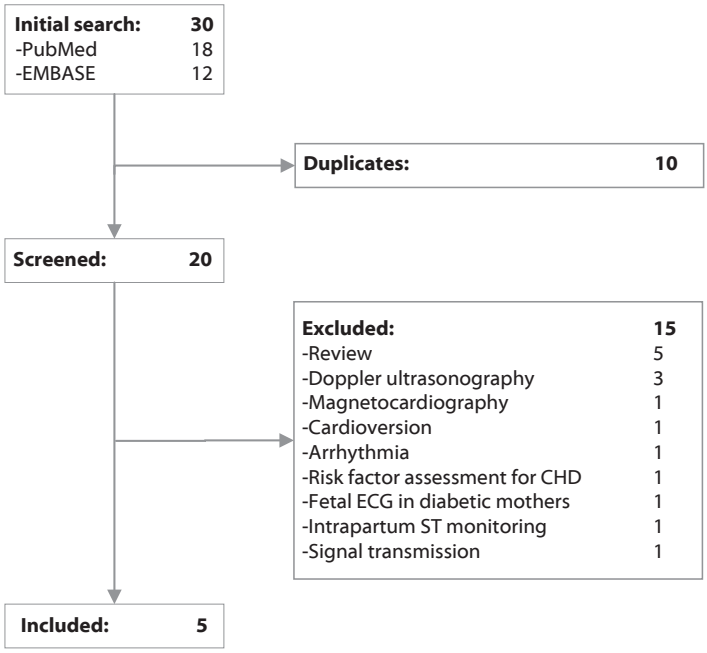
The search and selection of articles were performed independently by two authors (K.M.J.V. and N.B.E.). The guidelines and quality assessment forms of the Dutch Cochrane Centre were used to evaluate the quality of the studies. The findings were reported descriptively and no statistical analysis was performed.

Results

The search and selection of articles is summarised in Figure 1. In total, five articles met the inclusion criteria and were reviewed, including case reports by Hamilton et al.[30] and Brambati and Bonsignore[31]. Three articles by Siddiqui et al.[32], Velayo et al.[33], and Yilmaz et al.[34] were prospective cohort studies, including normal fetuses and cases of CHD. The five studies were published between 1977 and 2016.

Owing to the low number of fetuses, the variation in outcome measures described, and the differences in signal processing techniques used in the five studies, it was not possible to directly compare or pool the results. The basic characteristics and a quality assessment of the two case reports are given in Table 1, whereas the basic characteristics and a quality assessment of the prospective studies are given in Tables 2 and 3. Table 4 presents an overview of the fetal ECG parameters of the fetuses with CHD included in this review.

Figure 1. Flowchart depicting the search and selection of articles.



Abbreviations: CHD = congenital heart disease, ECG = electrocardiography.

Table 1. Characteristics and quality assessment of the two case reports on fetal ECG.

Characteristic	Hamilton et al.[30]	Brambati et al.[31]
Year of publication	1977	1983
Study design	Case report	Case report
Number of patients	1	1
Case	Complete fetal heart block	Fetal cardiac arrhythmia
Gestational age (weeks)	32	34
Prenatal ultrasonography screening	Not described	Not described
Fetal ECG signal processing technique	Unclear; 2 leads	Unclear
Postnatal diagnostics	Auscultation, ECG, radiography, cardiac catheterisation/angiocardiography, autopsy	Auscultation, ECG, radiography
Diagnosis	Multiple cardiac anomalies	Atrial septal defect, mitral insufficiency

Abbreviation: ECG = electrocardiography.

Table 2. Characteristics and quality assessment of the study by Velayo et al.[33]

Characteristics	Overall	Case 1	Case 2	Case 3	Case 4
Year of publication	2011	-	-	-	-
Study design	Prospective cohort study	-	-	-	-
In/exclusion criteria	Clear	-	-	-	-
Risk of selection bias	High	-	-	-	-
Number of patients	179	1	1	1	1
Gestational age (weeks)	18-41	23	32	33	28
Prenatal ultrasonography screening	Normal	Multiple cardiac anomalies	Multiple cardiac anomalies	Multiple cardiac anomalies	Multiple cardiac anomalies
Fetal ECG signal processing technique	Clear; 14 leads				
Other diagnostics prenatally	None	Chromosomal analysis, MRI	None	None	None
Postnatal diagnosis and/or therapy	Unclear	Surgery	Unclear	Unclear	Unclear
Follow-up	Unclear	-	-	-	-
Confounders	Unclear	-	-	-	-
Available as in clinical practice	Yes	-	-	-	-

Abbreviations: ECG = electrocardiography, MRI = magnetic resonance imaging.

Table 3. Characteristics and quality assessment of the studies by Yilmaz et al.[34] and Siddiqui et al.[32]

Characteristics	Yilmaz et al.[34]				Siddiqui et al.[32]			
	Overall	HLHS	TGA	TOF	Overall	HLHS	TGA	TOF
Year of publication	2016	-	-	-	2015	-	-	-
Study design	Prospective cohort study	-	-	-	Prospective cohort study	-	-	-
In/exclusion criteria	Clear	-	-	-	Clear	-	-	-
Risk of selection bias	High	-	-	-	High	-	-	-
Number of patients	92	15	12	14	92	19	12	20
Gestational age (weeks)	20-38	20-38	20-38	20-38	19-38	19-38	19-38	19-38
Prenatal ultrasonography screening	Yes	-	-	-	Yes	-	-	-
Fetal ECG signal processing technique	Clear; 5 leads	-	-	-	Unclear	-	-	-
Other diagnostics prenatally	None	-	-	-	None	-	-	-
Postnatal diagnosis and/or therapy	Unclear	-	-	-	Unclear	-	-	-
Follow-up	Unclear	-	-	-	Unclear	-	-	-
Confounders	Unclear	-	-	-	Unclear	-	-	-
Available as in clinical practice	Yes	-	-	-	Yes	-	-	-

Abbreviations: ECG = electrocardiography, HLHS = hypoplastic left heart syndrome, TGA = transposition of the great arteries, TOF = tetralogy of Fallot.

Hamilton et al.[30] described a case of complex CHD, in which a complete heart block was seen in 1977. They used a cardiotocograph with the capacity to process fetal phonocardiographic and abdominal fetal ECG signals. The bizarre QRS complexes found on fetal ECG (not otherwise specified) suggest that the pacemaker was distal to the bundle of His, with a fetal heart rate of 50 beats per minute. After delivery, cardiac catheterisation and angiocardiography were performed to confirm the existence of complex CHD (Table 4).

Seven years later, Brambati et al.[31] described a case of an atrioventricular septal defect in which cardiac arrhythmia was seen. The signal processing method is not extensively described, but data extraction was mainly performed manually and a median fetal ECG constituting 50 heartbeats was generated. Extrasystoles without a preceding P wave were found, suggestive of ventricular origin. Additionally, a prolonged QRS time was found, which was stated to be suspicious of cardiac enlargement and/or cardiac anomaly. After delivery, ventricular extrasystoles, left axis deviation and right ventricular hypertrophy were found on ECG. The neonate was diagnosed with an atrioventricular septal defect.

Velayo et al.[33] performed a prospective cohort study using simultaneous fetal ECG and cardiotocography (Doppler ultrasonography) recordings. The fetal heart rate information derived from Doppler ultrasonography was used to filter the fetal ECG[35]. Overall, 179 women were prospectively screened from a low-risk population. Twelve (7%) showed an abnormal fetal ECG; of these, 8 (4%) were excluded from further analysis because the fetus had no underlying structural heart defects, whereas 4 (2%) were confirmed to have CHD by an ultrasonography examination performed after inclusion in the study. The remaining 167 women (93%) with normal fetal ECG and no CHD or other anomalies on ultrasonography evaluation were used for standardisation of normal parameters. The fetal ECG was found to have a sensitivity of 100%, specificity of 95%, positive predictive value of 33%, and negative predictive value of 100% for the detection of CHD in a low-risk population.

Velayo et al.[33] described the four cases of CHD that they found in their study population in detail (Table 4). They stated that premature ventricular contractions, as seen in cases one and three, might be caused by a primary developmental anomaly of the conduction system in the presence of endocardial cushion defects or an underlying genetic defect affecting intrinsic myocardial cell physiology. Prolongation of the QT interval, as seen in cases two and four, might be explained by repolarisation dysfunction (alterations in action potential duration), caused by ventricular aberrations[33]. This is also seen in cases of cardiac remodelling due to disease progression. In case four, the various prolonged intervals might have been late signs of the critical condition of the fetus, supported by the cardiomegaly with signs of heart failure.

Yilmaz et al.[34] and Siddiqui et al.[32] both performed a prospective cohort study of the same set of 92 participants: 41 healthy controls and 51 fetuses with CHD, confirmed by fetal echocardiography. The Monica AN24 fetal electrocardiographic monitor was used to perform measurements at three gestational ages (19-27, 28-33 and 34-38 gestational weeks). Tracing quality was analysed in both studies.

Yilmaz et al.[34] calculated the PR, QRS, and QT intervals during gestation. They showed that the PR and QRS intervals both lengthen as gestational age increases among normal fetuses. Among fetuses with CHD, this lengthening during gestation was not seen, but longer PR and QRS intervals were seen at all gestational ages as compared with normal values (Table 4). T waves seemed to be difficult to detect, and were therefore not included in the analysis.

Siddiqui et al.[32] calculated fetal heart rate and fetal heart rate variability during gestation. Among the control fetuses, heart rate decreased during gestation, whereas heart rate variability increased. Fetuses with CHD generally had a lower fetal heart rate than healthy fetuses, but no differences in heart rate variability at 34-38 weeks were observed between the controls and cases, except for fetuses with hypoplastic left heart syndrome (which showed significantly lower heart rate variability during the active fetal state).

Discussion

Overall, the present systematic review revealed that little research has been published regarding the changes seen in fetal ECG parameters observed for fetuses with CHD. The methods of conducting the fetal ECG measurements were different in most studies and evolved with time. Additionally, the fetal ECG parameters described in the studies varied. All the studies included show that fetal ECG can be a valuable tool to diagnose CHD early in utero. However, data on the fetal ECG changes observed among fetuses with CHD remain limited.

Both the case reports by Brambati et al.[31] and Hamilton et al.[30] are from another era, and are therefore not comparable with the signal processing techniques in current use. It is not likely that the two pregnancies described received prenatal ultrasonography screening to detect CHD. Nevertheless, both studies do indicate the potential of fetal ECG in diagnosing CHD and fetal arrhythmias.

Velayo et al.[33] reported a promising sensitivity and specificity of 100% and 95%, respectively; however, the positive predictive value of fetal ECG was only 33%. The low positive predictive value can be explained by the low probability that fetuses in the general population will have CHD. The eight cases with an abnormal ECG that were excluded had other abnormalities,

Table 4. Overview of the fetal ECG parameters of the included fetuses with congenital heart disease.

Study	No.[a]	Type of CHD	Findings fetal ECG (GA, weeks)	PR interval, ms (GA, weeks)	QRS interval, ms (GA, weeks)	QT interval, ms (GA, weeks)
Hamilton et al.[30]	1	Complex[b]	Bizarre QRS complexes; Complete atrioventricular block; Atrial rate: 100 bpm Ventricular rate: 48 bpm			
Brambati et al.[31]	1	Atrial septal defect, mitral insufficiency	Premature ventricular contractions		Extrasystole: 112 ± 22 (34) Normal complex: 72 ± 9 (34)	
Velayo et al.[33]	1	Case 1: Atrioventricular septal defect	Premature ventricular contractions Right axis deviation			
Velayo et al.[33]	1	Case 2: Complex[c]				QTc: 518 (32)
Velayo et al.[33]	1	Case 3: Complex[d]	Polymorphic premature ventricular contractions Prolonged pre-ejection period			
Velayo et al.[33]	1	Case 4: Complex[e]	Prolonged pre-ejection period	115 (33)		QTc:445 (33)
Yilmaz et al.[34]	13-23	Controls	HR, 148 ± 4 bpm (19-27)	93 ± 12 (20-24)	52 ± 5 (20-24)	240 ± 15 (20-24)
Siddiqui et al.[32]			HR, 141 ± 3 bpm (28-33)	102 ± 15 (28-32)	56 ± 7 (28-32)	231 ± 41 (28-32)
			SD, 0.020 ± 0.002 (34-38)	109 ± 18 (34-38)	56 ± 9 (34-38)	233 ± 43 (34-38)
Siddiqui et al.[32]	22	All CHD	HR, 143 ± 5 bpm (19-27)			
Yilmaz et al.[34]	5-9	Hypoplastic left heart syndrome	HR, 143 ± 3 bpm (19-27)	97 ± 16 (20-24)	66 ± 6 (20-24)	
Siddiqui et al.[32]			HR, 136 ± 5 bpm (28-33)	113 ± 12 (28-32)	62 ± 7 (28-32)	
			SD, 0.013 ± 0.003 (34-38)	120 ± 21 (34-38)	61 ± 16 (34-38)	
Yilmaz et al.[34]	2-10	Tetralogy of Fallot	HR, 140 ± 7 bpm (19-27)	119 ± 29 (20-24)	61 ± 3 (20-24)	
Siddiqui et al.[32]				105 ± 14 (28-32)	59 ± 9 (28-32)	
				113 ± 21 (34-38)	67 ± 5 (34-38)	
Yilmaz et al.[34]	4-9	Transposition of the great arteries		92 ± 21 (20-24)	60 ± 2 (20-24)	
Siddiqui et al.[32]				101 ± 10 (28-32)	64 ± 9 (28-32)	
				101 ± 20 (34-38)	64 ± 8 (34-38)	

[a] In the studies of Yilmaz et al.[34] and Siddiqui et al.[32], the number of fetuses included varied by gestational age; therefore, the minimum and maximum number of fetuses per group is indicated.
[b] Common atrium, complete atrioventricular canal, double outlet right ventricle, pulmonic stenosis, aneurysmal right aortic arch with mirror-image branching, interrupted left-sided vena cava with azygous continuation.
[c] Total anomalous pulmonary venous connection, pulmonic stenosis, systemic right ventricular dysfunction, common atrioventricular valve, bilateral superior vena cava, pulmonary venous return anomaly.
[d] Tetralogy of Fallot, ventricular septal defect, pulmonic stenosis, double outlet right ventricle, transposition of the great arteries, multi-aortopulmonary collateral arteries.
[e] Dilated cardiomyopathy, ventricular septal defect, congestive heart failure.

Abbreviations: bpm = beats per minute, CHD = congenital heart disease, ECG = electrocardiography, GA = gestational age, HR = heart rate, ms = millisecond, No. = number of included patients, SD = standard deviation of heart rate during active fetal state (i.e. heart rate variability), QTc = fetal QT interval corrected for heart rate (QT divided by the square root of RR).

including non-immune hydrops fetalis, hypoxemia, or arrhythmia (not otherwise specified). Although CHD was not detected in this group, it is nonetheless important to identify this subset of fetuses that are possibly at risk of fetal distress[36].

Yilmaz et al.[34] and Siddiqui et al.[32] describe the largest case series of fetal ECG measurements among fetuses with CHD published so far. However, only three types of CHD – which were commonly diagnosed and with "distinct anatomical and physiological features that could potentially impact ECG intervals"[34] – were included in those studies. As a result, there is a high risk of selection bias in both studies. Additionally, identification of the P, QRS and T waves is not extensively described by Yilmaz et al.[34]. Siddiqui et al.[32] calculated heart rate variability in three different ways: interquartile range of the fetal heart rate, standard deviation of the fetal heart rate, and root mean square of the standard deviation of the heart rate. Unfortunately, exact values are not given for each type of CHD separately for either fetal heart rate or variability. A new trial with a greater sample population and the inclusion of more types of CHD is needed.

The fetal ECG reflects the intimate relationship between the cardiac nerve conduction system and the structural morphology of the heart[33]. In accordance with Yilmaz et al.[34], other studies also found that the duration of the P wave, QRS complex, and PR interval increases progressively from 18 gestational weeks until term for fetuses with normal cardiac structures[34,37]. This reflects the anatomical development of the atria and ventricles during pregnancy, with gain in the weight and mass of the fetal heart. The increase in PR interval indicates the development of the atrioventricular conducting tissue[38].

Yilmaz et al.[34] showed that, among fetuses with CHD, the normal lengthening in PR and QRS intervals during pregnancy is absent. Additionally, most CHDs are associated with an increased or decreased ventricular mass or cardiac arrhythmias[25,30,31,33]. In case of a severe endocardial cushion defect (atrioventricular septum defect), the abnormal atrioventricular connection affects the conduction system, and this is reflected in a longer PR interval and left axis deviation[25,31,33,39].

The aim of Siddiqui et al.[32] was to characterise autonomic regulation in fetuses with CHD, and to study whether autonomic development is altered in comparison with healthy controls. Although it was not the aim, the study seems to indicate that heart rate variability might not be a good screening tool to detect CHD because heart rate variability was lower only among fetuses with hypoplastic left heart syndrome and only in the measurement at 34-38 gestational weeks. Moreover, there were only minor differences in fetal heart rate between controls and fetuses with CHD.

The rate of prenatal detection by two-dimensional ultrasonography is mainly influenced by the experience of the sonographer. It is relatively difficult to interpret the anatomy of the fetal heart correctly because it is a dynamic, constantly moving structure that rhythmically beats approximately more than twice per second. In addition, some diagnoses (e.g. coarctation of the aorta and CHDs that develop/progress during pregnancy such as pulmonary stenosis, aortic stenosis, ventricular hypoplasia, and cardiomyopathy) remain challenging to diagnose even in experienced centres. Given the fetal circulation, it is difficult to define lesion severity in the presence of the unique fetal shunts that permit redistribution of ventricular preload and output to the contralateral ventricle or great artery[3].

Computerised evaluation of the fetal ECG might eliminate some of the abovementioned problems. First, performer variability – as occurs in the case of ultrasonography – would be absent because the data are analysed by computerised algorithms. Second, the equipment is cheaper and smaller by comparison with ultrasonography equipment. Third, application of the fetal ECG system involves minimum training. Last, at the time of the fetal anomaly scan, CHDs that evolve during gestation might present no anomalies by ultrasonography, but might show fetal ECG characteristics.

The present review has some limitations. Because little research has been published, the amount of ECG recordings that was available per type of CHD was limited. Only two case reports and three prospective trials were found. The methods of conduction the fetal ECG measurements were different in the five studies and evolved during time. Additionally, the fetal ECG parameters that were described varied in every study. Nevertheless, all the studies included show that fetal ECG can be a valuable tool for diagnosing CHD early in utero.

In conclusion, fetal ECG is a promising clinical tool that complements ultrasonography in the screening programme for CHD. It is particularly suitable for the detection of secondary effects due to CHD (i.e. hypotrophy, hypertrophy, and conduction interruption). However, more research establishing normal fetal ECG values and studies concerning the true incidence of fetal ECG anomalies in CHD are needed.

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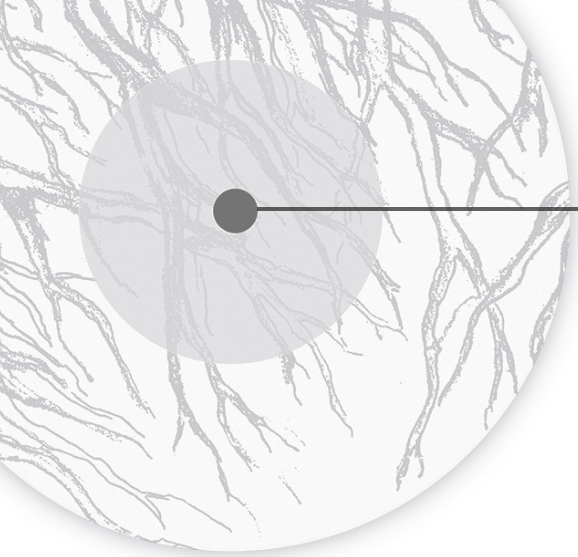

Chapter 5

Normal ranges for fetal electrocardiogram values for the healthy fetus of 18-24 weeks of gestation: a prospective cohort study

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Abstract

Background

The fetal anomaly ultrasound only detects 65-81% of the patients with congenital heart disease, making it the most common structural fetal anomaly of which a significant part is missed during prenatal life. Therefore, we need a reliable non-invasive diagnostic method which improves the predictive value for congenital heart diseases early in pregnancy. Fetal electrocardiography could be this desired diagnostic method. There are multiple technical challenges to overcome in the conduction of the fetal electrocardiogram. In addition, interpretation is difficult due to the organisation of the fetal circulation in utero. We want to establish the normal ranges and values of the fetal electrocardiogram parameters in healthy fetuses of 18 to 24 weeks of gestation.

Methods/Design

Women with an uneventful singleton pregnancy between 18 and 24 weeks of gestation are asked to participate in this prospective cohort study. A certified and experienced sonographist performs the fetal anomaly scan. Subsequently, a fetal electrocardiogram recording is performed using dedicated signal processing methods. Measurements are performed at two institutes. We will include 300 participants to determine the normal values and 95% confidence intervals of the fetal electrocardiogram parameters in a healthy fetus. We will evaluate the fetal heart rate, segment intervals, normalised amplitude and the fetal heart axis. Three months postpartum, we will evaluate if a newborn is healthy through a questionnaire.

Discussion

Fetal electrocardiography could be a promising tool in the screening programme for congenital heart diseases. The electrocardiogram is a depiction of the intimate relationship between the cardiac nerve conduction pathways and the structural morphology of the fetal heart, and therefore particularly suitable for the detection of secondary effects due to a congenital heart disease (hypotrophy, hypertrophy and conduction interruption).

Background

During pregnancy, the condition of the fetus is assessed with different techniques. One of these techniques is ultrasound examination. Between week 18 and 22 of gestation the fetal anomaly ultrasound is performed. During this examination, the fetus is screened for all kind of possible congenital anomalies, including congenital heart disease (CHD). CHD is defined as a "gross structural abnormality of the heart or intra-thoracic large vessels, (possibly) with functional significance"[1]. CHD is the most common severe congenital anomaly worldwide[2]; the incidence is estimated at 6-12 per 1000 live births[3-5]. CHD is six times more common than chromosomal anomalies and four times more common than neural tube defects[4,6].

The fetal anomaly ultrasound, including planes of the ventricular outflow tracts and the three-vessel view, only detects 65-81% of the patients with CHD[6-9]. That makes CHD the most common structural fetal abnormality of which a significant part is missed during prenatal life. Therefore, we need a reliable non-invasive diagnostic method which improves the predictive value for the diagnosis CHD. This diagnostic technique should be able to diagnose CHD early in pregnancy for multiple reasons. First, we get the opportunity to identify associated extracardiac and chromosomal anomalies that affect fetal and postnatal prognosis. Second, parents get the chance to opt for termination of pregnancy in case of a severe CHD. Third, one can develop an adequate treatment plan including intra-uterine therapy, timing, mode and location of delivery and planning of immediate treatment after birth. In ductus- and foramen ovale dependent CHDs, it is demonstrated that prenatal diagnosis increases the survival rates and decreases long term morbidity[10-13].

The currently used two-dimensional ultrasonography provides multiple anatomic planes, relying on the sonographists mental reconstruction of these planes to define the fetal cardiac anatomy. The antenatal diagnostic value is therefore to a great extent depending on the experience of the performer. As stated by Gardiner[5]; "you only see what you look for and identify what you already know". Three- and four-dimensional ultrasonography gives a more fluid and representative image of the fetal cardiac structures, and therefore aids in this mental reconstruction[14]. Spatio-temporal image correlation (STIC) is a new modality using automated volume acquisition of the fetal heart with one sweep of the probe, further facilitating the examination of the fetal heart. Disadvantages of these ultrasound modalities are that they are extremely expensive and only applicable in centres with experienced personnel.

The non-invasive fetal electrocardiogram (ECG) could be a valuable tool for the detection of CHD early in pregnancy. In 1906, Cremer and colleagues[15] were the first to describe fetal ECG extraction through the maternal abdomen and 80 years later, Pardi and colleagues[16]

were the first to write a review considering fetal ECG and, amongst others, CHD. Compared to other techniques for fetal monitoring, the development of the fetal ECG lagged behind. This is mainly because there are multiple technical challenges to overcome. First, at a gestational age of 20 weeks, the fetal heart is about 1/10th of the size of an adult heart. Due to the low voltage of the fetal ECG (1/50th of the maternal ECG), there is a low signal-to-noise ratio. In addition, identifying the fetal signals is challenging due to masking by the maternal ECG and high background noises caused by the maternal electromyogram. The amniotic fluid and maternal tissues that surround the fetus enlarge the distance to the electrodes, and cause a non-homogenous tissue conduction that interferes with signal quality. In addition, the vernix caseosa causes electrical isolation and further diminishes the signal amplitude[17]. This is the main cause of the poor signal-to-noise ratio from 30 to 34 weeks of gestation[18,19]. Second, the fetal ECG has a complex three-dimensional shape, alternating with changes in fetal presentation. Following fetal movements, the electrical signal from each electrode changes frequently. Another challenging factor is the speed of the fetal heart rate, which is two to three times faster compared to the adult heart rate[20].

Besides the technical difficulties encountered when conducting a fetal ECG, it is also challenging to interpret the fetal ECG. In contrast with postnatal life, the systemic circulation in the fetus is fed from both the left and right ventricle in parallel, with equal intraventricular pressures[21]. The outflow in the right ventricle is slightly larger compared to the outflow in the left ventricle, and increases during gestation; 53% vs 47% at 20 weeks of gestation, 57% vs 43% at 30 weeks of gestation and 60% vs 40% at 38 weeks of gestation[21]. In utero, the O_2-rich blood flows from the umbilical vein to the right atrium. There, the formen ovale propels a major part of the O_2-rich blood to the left side of the heart and into the systemic circulation, bypassing the fetal lungs. In addition, in the second trimester the ductus arteriosus propels 40% of the combined cardiac output. Because of these major differences between the systemic circulation in utero and postpartum, it is difficult to predict what a normal fetal ECG looks like. Furthermore, due to this organisation of the fetal circulation in utero, in case of a CHD one side of the heart can compensate for an abnormality on the other site, and fetuses affected by a CHD do not always show signs of cardiac failure.

However, before we are able to detect CHD with the fetal ECG, we need to establish the normal range and values of amplitudes and segment intervals of the fetal ECG in a healthy fetus.

Methods/Design

Aim

The aim of this study is to establish the normal ranges and values (mean with 95% confidence intervals) of fetal ECG parameters in a healthy fetus of 18 to 24 weeks of gestation.

Study design

We will perform a prospective cohort study. The study protocol is approved by the medical ethical committee of the Máxima Medical Centre, Veldhoven, the Netherlands (NL48535.015.14).

Setting

Measurements are performed at the Máxima Medical Centre, Veldhoven, the Netherlands and "Diagnostiek voor U" (DvU), Eindhoven, the Netherlands. The Máxima Medical Centre is a tertiary care teaching hospital for obstetrics. DvU is a diagnostic centre which, amongst others, performs blood tests and ultrasounds. Measurements are performed directly before or after the sonographist performed the fetal anomaly scan. The fetal anomaly ultrasound is performed by a certified and experienced sonographist.

Participants

Patients with an uneventful pregnancy, carrying a singleton fetus with a gestational age between 18 and 24 weeks, are included in the study after written informed consent. At the Máxima Medical Centre, this will be patients who visit the outpatient clinic for an appointment. At DvU, this will be patients who visit the centre for their fetal anomaly ultrasound. These patients are generally seen by a midwife or by a doctor at the Máxima Medical Centre for their obstetrical care. Pregnant women must be aged older than 18 years. If any of the fetuses turn out to have a form of CHD, they are excluded from the cohort. Other exclusion criteria are multiple pregnancies, insufficient understanding of the Dutch language, and any known fetal congenital anomalies.

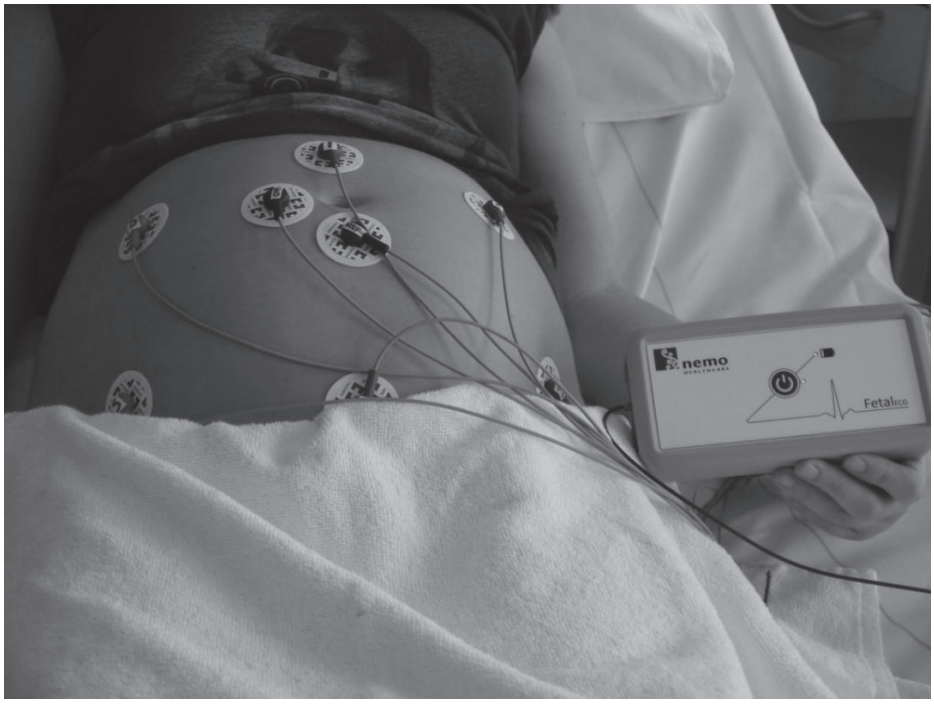
Three months postpartum we will evaluate if the newborn is healthy, which is defined as absence of CHD, through a questionnaire. If the neonate turns out to have a CHD, which was missed at the time of the structural anomaly ultrasound, we will exclude the patient from the cohort.

Procedures

The fetal ECG is a non-invasive, transabdominal research method. The pregnant women is lying down in a semi-recumbent position to prevent aortocaval compression. The fetal ECG

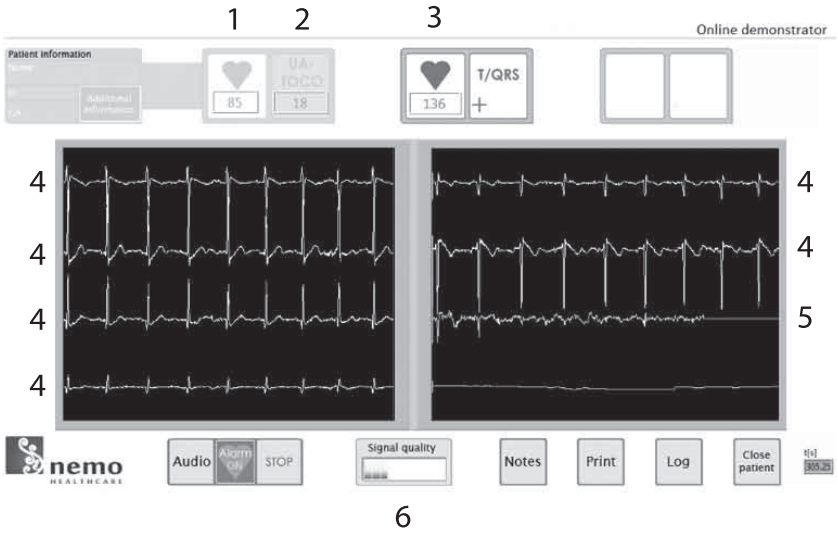
is conducted with eight electrodes on the maternal abdomen, placed in a fixed configuration (Figure 1). Before applying the electrodes on the abdomen, the skin is cleaned and prepared by scrubbing the skin areas with abrasive paper to optimise the skin-electrode impedance. The impedance is measured after the skin is prepared and before the fetal ECG recording is started. A ground and reference electrode are placed near the belly button. The six recording electrodes give bipolar signals that, among others signals, contain the fetal ECG. The placement of the electrodes is chosen in order to assess the fetal heart with as much accuracy as possible. With the fetus able to move freely in the uterus, at least some of the six electrodes will be close to the fetal heart and thus will give a usable bipolar signal. We will record the fetal ECG for 30 minutes. During this recording, the fetal position is determined four times by ultrasound assessment. Good signal quality is verified via the real-time bedside monitoring system (Figure 2).

Figure 1. Configuration of the electrodes on the maternal abdomen.



The fetal electrocardiogram is recorded with eight electrodes on the maternal abdomen, placed in a fixed configuration. A ground and reference electrode are placed near the belly button. The electrodes are connected to our fetal ECG system, which is connected to a computer. This system records 6 channels of fetal ECG data.

Figure 2. Real-time bedside monitoring system.



Good signal quality can be verified via the real-time bedside monitoring system. Depicted in the screen are; 1. maternal heart rate, 2. uterine activity, 3. fetal heart rate, 4. output from the six abdominal electrodes, 5. computation of the fetal signal, after subtraction of the maternal signal, 6. estimate of the signal quality. The user interface can be switched to a different screen in which the cardiotocogram is depicted.

The fetal ECG signals are digitised and stored by a prototype fetal ECG system (Nemo Healthcare BV, the Netherlands). This prototype system comprises of a six-channel amplifier that is dedicated for electrophysiological recordings during pregnancy. After digitisation, the acquired signals are processed by PC-based dedicated signal processing techniques as previously described by Vullings et al.[22,23] to suppress interferences such as maternal ECG, powerline, and electromyographic signals from within the maternal body, and retrieve the fetal ECG. Following, we can calculate the fetal ECG for each of the six electrodes. However, before we can compare ECG values between patients we need to normalise the ECG for different orientations of the fetus within the uterus. A specific electrode would record a different ECG waveform for a fetus in cephalic position versus for a fetus in breech position, also yielding differences in some of the ECG parameters mentioned below.

To normalise for fetal orientation, we calculate the vectorcardiogram (VCG) of the fetus[24]. This VCG entails a three-dimensional representation of the fetal electrical cardiac activity. As described by Frank et al.[25], in adult electrocardiography the VCG can be used to calculate standardised ECG leads such as Einthoven 1-3, aVF, aVL, and aVR. By mathematically rotating

the fetal VCG prior to calculating the ECG, we can create standardised fetal ECG leads. The amount of rotation required is determined based on a simultaneously performed ultrasound assessment of the fetal presentation. Via these mathematical rotations, we are also capable of detecting and correcting for fetal movements in between the ultrasound assessments, as described previously by Vullings et al.[26]. The four ultrasound assessments during the measurements are used to correct for cumulative errors in this correction method and to determine the initial orientation of the fetus. To enhance the signal quality of the measurements, the fetal ECG is filtered further (amongst others by averaging of the ECG waveforms). The detection of segments and intervals is performed semi-automatically. The detection of fetal ECG complexes is computerised, while marking of the fetal ECG intervals (P top, QRS complex, T top) is performed manually by two independent researchers following a protocol that is verified by an experienced paediatric cardiologist. We will calculate the inter-observer variability between the two researchers.

Normal heart rhythm is assumed to show variations in heartbeat intervals smaller than 20% between consecutive beats. In case these variations are larger, this is assumed to be the result of either fetal arrhythmia or erroneous detection of the heartbeat interval, e.g. because of poor signal quality. Assessment of erroneous detection is based on energy of the ECG signal and correlations between consecutive ECG waveforms. The ECG is a quasi-periodic signal, meaning that consecutive ECG waveforms have a similar appearance and similar amplitude/energy. In case of poor ECG signal quality, the energy of the ECG signals is expected to differ from the energy during good quality recordings. Present artefacts or noise cause the energy of the ECG to increase beyond physiologically plausible ranges. Likewise, correlations between consecutive ECG waveforms are reduced in the presence of poor signal quality.

It has to be noted here, that fetal arrhythmia can also cause poor correlation between ECG waveforms. Some arrhythmias are hence expected to be incorrectly classified as poor signal quality. This misclassification affects the detection of fetal arrhythmia, but will not have any impact on other study parameters as these are determined only during normal rhythm and good signal quality. The recording must contain a minimum of 200 ECG complexes that were assessed to have good signal quality and that were corrected for fetal movement[26].

Study parameters

Multiple outcome values are evaluated:

- Fetal heart rate; mean, standard deviation, 95% confidence intervals and heart rate arrhythmia
- Segment intervals (PQ, QRS, ST etc.); mean, standard deviation and 95% confidence intervals
- Normalised amplitudes (P, QRS, T); mean, standard deviation and 95% confidence intervals
- Fetal electrical heart axis
- % of total patients in which the recording contains the required amount of data to perform the analysis

Heart rate arrhythmia is defined based on heuristic rules that dictate that during normal rhythm subsequent heartbeat intervals cannot differ more than 20%. Any rhythm not complying with this rule, and assessed to not be caused by erroneous detection of heartbeats, e.g. as a result of poor signal quality, is labelled as a fetal arrhythmia.

Sample size

There are previously published studies (see Discussion for more details) that describe fetal ECG parameters. However, these studies use different methods for obtaining the fetal signal and do not correct for the fetal position in the uterus. Therefore they are not able to calculate the fetal electrical heart axis. Moreover, all studies describe another parameter of the fetal ECG. Statistical experts calculated that we need a study population of 200 pregnant patients in order to determine normal values and 95% confidence intervals of a healthy fetus[27]. Anticipating on loss to follow-up and insufficient data quality, we will include 300 patients in the initial cohort.

Statistical analysis

The collected data is analysed through SPSS. With the collected data, we perform several analyses. We calculate the normal values and ranges of the fetal heart rate, segment intervals (PQ, QRS, ST etc.), normalised amplitudes (P, QRS and T) and the fetal heart axis. Initially, we will calculate the values and ranges for all included patients as one group (18 to 24 weeks of gestational age). Thereafter, we will perform a subanalysis for every group per week of gestational age.

Discussion

Previous studies have been published regarding the normal values and ranges of the fetal ECG. In their review, Pardi et al.[16] summarised the normal evolution of the cardiac cycle during gestation. From the 17th week of gestation up to term, the duration of the P wave increases progressively. This reflects the anatomical development of the atria during pregnancy. Similar, the duration of the QRS complex increases progressively, parallel with the weight gain of the fetal heart and in particular with the gain in ventricular mass. In fetal life, the intraventricular conduction is delayed compared to adult values, most likely due to anatomical differences of the ventricular conduction tissue. There is a slight increase in PR interval during pregnancy, indicating development of the atrioventricular conduction tissue.

Recently, longitudinal studies followed pregnancies from 14 to 41 weeks of pregnancy and performed fetal ECG measurements during different stages of gestation[18,28,29]. In the 1960s, Larks and colleagues[30-33] described the orientation of the electrical fetal heart axis. All mentioned studies performed fetal ECG recordings with different conduction and analysis techniques. The amount of electrodes on the maternal abdomen varied from three to sixteen. Average fetal ECG complexes were generated from segments of 60 seconds up to 2.5 minutes. Analyses were performed manually or by computerised signal processing programs. These studies did not take the fetal position in the uterus into account.

In a group around 20 weeks of gestation, the following mean values were found by Chia and Taylor[28,29], respectively: P wave length 43.9 ms, PR interval 102.1/91.7 ms, QRS duration 47.2/40.7 ms, QT interval 224.0/242.3 ms and T wave duration 123.8 ms. Larks[33] found a normal range of the fetal heart axis between +100 and +160 degrees, with a mean value of +134 degrees in term fetuses during labour. Due to the lack of correcting for the fetal position in utero, fetuses in breech position showed a negative electrical heart axis (-180 to 0 degrees)[32]. In fact, due to the lack of correcting for fetal position, also findings for fetuses in vertex position were unreliable. In their analysis, Larks implicitly assumed that every fetus was facing the frontal plane. In cases where this assumption was incorrect, the measured heart axis must have been incorrect as a consequence. For example, a fetus with an electrical heart axis at +135 degrees will indeed be measured as +135 degrees when facing the frontal plane. When this same fetus, still in vertex position, rotates to face the sagittal plane, the measured heart axis will be +90 degrees. When opposing the frontal plane, the measured heart axis will be +45 degrees.

Up to our knowledge our study is the first to calculate the fetal electrical heart axis, taken the fetal position into account. A reliable calculation of the electrical heart axis is important in interpreting the fetal ECG. In addition, changes in the orientation of the fetal electrical heart axis might be able to aid in the diagnosis of CHD in the future.

The fetal ECG can be used from early gestation, it is non-invasive, easy to apply and safe to use[18]. One of the big advantages of the fetal ECG is that it potentially is a non-expensive diagnostic test in the long term. In addition, it creates the opportunity to perform measurements anywhere in the world and transmit the raw ECG data to be evaluated elsewhere. The equipment is smaller in comparison to ultrasound machines. Moreover, the fetal ECG is evaluated by semi-computerised algorithms, taking away some of the performer-dependent variability in diagnostic value. The fetal ECG system takes minimum training to be applied.

The fetal ECG could be a promising clinical tool in the screening programme for CHD. It is a depiction of the intimate relationship between the cardiac nerve conduction pathways and the structural morphology of the fetal heart[8,34]. The fetal ECG is likely to be particularly suitable for the detection of secondary effects due to a CHD; hypotrophy, hypertrophy and conduction interruption.

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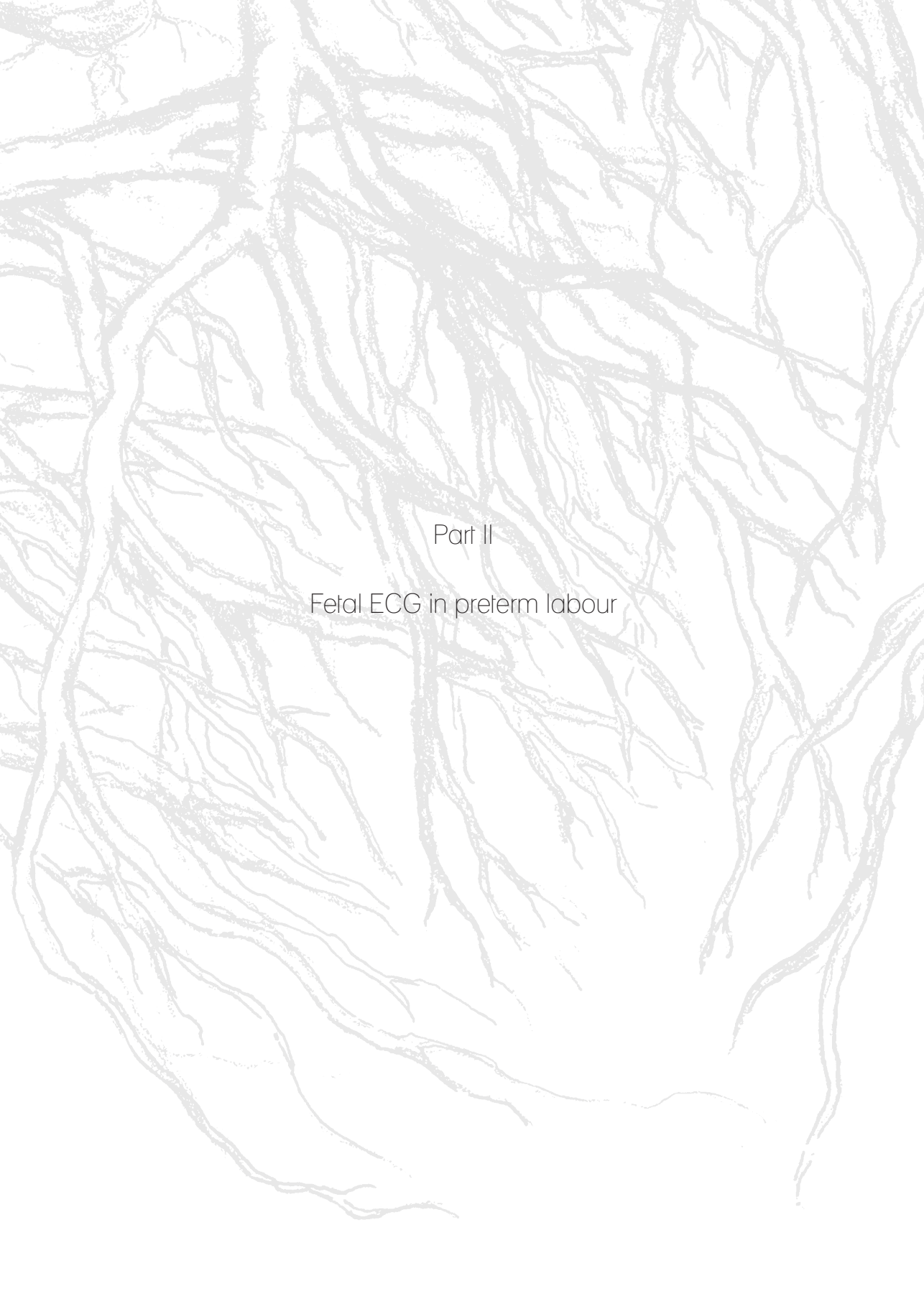
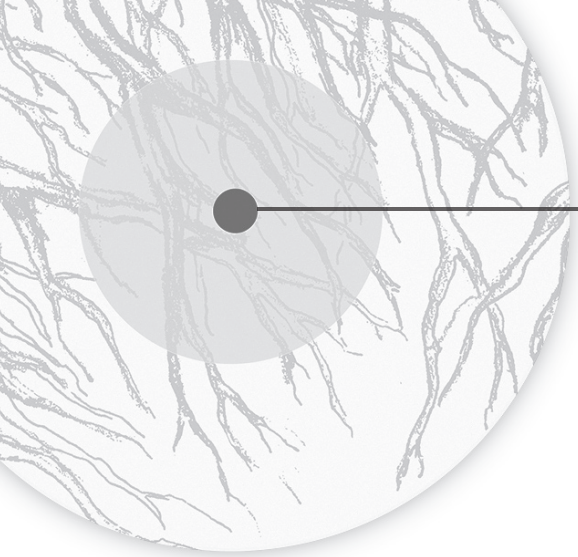


Part II

Fetal ECG in preterm labour



Chapter 6

The influence of corticosteroids on fetal heart rate variability: a systematic review of the literature

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Abstract

Corticosteroids play an important role in the clinical management of threatened preterm delivery between 24 and 34 weeks of gestational age. It is known that corticosteroids have a direct, transient effect on fetal heart rate parameters. Fetal heart rate variability is a reflection of autonomic nervous system activity and a useful marker for fetal wellbeing. Therefore, it is important to interpret the changes that occur in fetal heart rate parameters during corticosteroid treatment correctly, to avoid unnecessary iatrogenic preterm delivery. We performed a systematic review of the literature in CENTRAL, PubMed, and EMBASE, including 15 articles. In this review, we discuss the influence of corticosteroids on fetal heart rate parameters, in particular fetal heart rate variability, and fetal behaviour. Furthermore, we explain possible mechanisms of action and confounding factors.

Background

Antenatal corticosteroids are administered to enhance fetal lung maturation in cases of threatened preterm delivery between 24 and 34 weeks' gestational age (GA)[1-3]. In 1972, Liggins and Howie[4] first described this breakthrough in obstetric care. A significant reduction in neonatal mortality and morbidity, due to a reduction in respiratory distress syndrome, respiratory support/intensive care admissions, cerebroventricular hemorrhage and necrotising enterocolitis, has been demonstrated in the 2006 Cochrane review by Roberts and Dalziel[5].

As elucidated by van Runnard Heimel et al.[6], endogenous corticosteroids are converted into their inactive metabolites by the $^{11}\beta$-hydroxysteroid dehydrogenase (HSD) enzyme. This enzyme limits the fetal exposure to prednisone and methylprednisolone, making them ideal for maternal treatment (e.g. treatment of preterm HELLP [hemolysis, elevated liver enzymes, and low platelet count] syndrome). In contrast, betamethasone and dexamethasone are not converted into inactive metabolites by the $^{11}\beta$-HSD enzyme and can therefore easily cross the placenta in active form[6-8]. This makes them specifically useful for fetal treatment in case of threatened preterm delivery. Confirming this, Blanford and Murphy[9] demonstrated that cortisol and prednisolone were significantly converted into their inactive metabolites in an in vitro study, whereas the conversion of betamethasone and dexamethasone into inactive metabolites was low or negligible.

After administration of a single course of antenatal corticosteroids, no associated long-term negative effects have been reported[10-12]. However, it is known that corticosteroids have a direct, transient, effect on fetal heart rate (HR) and fetal heart rate variability (HRV)[13].

In cases of threatened preterm delivery, objective information concerning the fetal condition is important for clinical decision making. During hypoxia, the autonomic nervous system (ANS) is activated and modulates the beat-to-beat fetal HR[14]. A fetus is not able to adapt its single stroke volume because of the small size of the fetal heart. Therefore, fetal HR is the primary variable for controlling cardiac stability and is primarily regulated by the ANS[15]. It is known that fetal HRV is a reliable marker of fetal wellbeing[16,17]. In 1963, Hon and Lee[18] observed that, in cases of fetal distress, changes in beat-to-beat heart rate interval occur before changes in heart rate itself. Assessing the variability of the fetal HR is therefore useful in fetal monitoring and determining fetal wellbeing.

Autonomic modulation and therefore fetal HRV are influenced by several medications commonly used in obstetric care[19]. With regard to corticosteroids, it is known that a transient

but significant decrease in fetal HRV occurs[20]. It is important to understand and appreciate the exact effects of corticosteroids on fetal HR parameters so that these changes are not misinterpreted as non-reassuring fetal status, with iatrogenic preterm delivery as a consequence.

In this review, we will focus on literature describing the effect on fetal HRV of corticosteroids administered in the setting of potential preterm delivery. We will describe the changes in fetal HR parameters and discuss the proposed mechanisms of action.

Material and Methods

Inclusion and exclusion criteria

Published studies that describe the influence of corticosteroids (betamethasone and dexamethasone) on fetal HRV, assessed by computerised analysis, were included in this review. Review articles were excluded. Participants of interest were human fetuses at risk for preterm delivery, receiving corticosteroids.

Search

We performed a systematic search in the electronic databases CENTRAL (the Cochrane Library; 2013, Issue 3), PubMed, and EMBASE through June 2013. The study language was restricted to English. The following keywords were used: fetal HRV, fetal HR variation, betamethasone, dexamethasone and corticosteroid. In addition, references of selected and related articles were searched.

Two authors (K.M.J.V. and J.R.) independently abstracted the data. There were no discrepancies regarding inclusion or data extraction of the reviewed articles. Included studies were critically assessed using the review guidelines for cohort studies and randomised trials from the Dutch Cochrane Centre.

A quality assessment of the included cohort studies was performed. The risk of selection bias was determined taking into account the study type, description of inclusion and exclusion criteria, and the methods for recruitment of the study population and is described as “high” or “low”. The duration of follow-up was scored as “adequate” when follow-up lasted at least 4 days after the first dose of the corticosteroid, to assess for both short- and longer-term direct effects on fetal HR parameters. Important confounders included administration of other drugs, intra-uterine growth restriction (IUGR), GA, and the influence of diurnal rhythm. In the column “confounding variables described”, the number of confounding factors addressed in the study is given.

A quality assessment of the included randomised trials was also performed. We described blinding of randomisation and compared the description of baseline characteristics of the different treatment groups. Baseline characteristics included demographic characteristics, reason for hospitalisation and fetal HR parameters at baseline. Comparability was described as the combination of co-interventions, contamination, and compliance. This was scored as "yes", "partially" or "no", with the number of factors described in parentheses. The final conclusion concerning the overall quality of the included studies was based on internal validity and clinical applicability of the study. The internal validity was a summary of the previously assessed factors.

The outcome measures of interest were fetal HR and variability of the fetal HR, assessed by computerised analysis. Mean fetal HR (mfHR) is expressed in beats per minute. Long-term variation (LTV) is calculated as the average of 1-minute pulse-interval differences, while short-term variation (STV) is calculated as the average of sequential 1/16th minute (3.75 seconds) pulse-interval differences in all studies.

Results

Our search in the Cochrane Database revealed no reports applicable for this review. In PubMed, we found 35 reports. Of these, 20 articles were excluded because they did not meet our inclusion criteria. Among the remainder, seven articles described other effects rather than fetal HRV, three articles described effects of other drugs rather than corticosteroids, two articles assessed only fetal HRV in fetuses at term or in newborns who were previously treated with corticosteroids, and two articles described visual analysis of fetal HRV. In EMBASE, two additional articles were found that were not present in PubMed. Both of these articles did not meet our inclusion criteria; one article was a conference abstract, and one article described the effect of a congenital heart block on fetal HR patterns. Eventually, 15 articles were included in this review. A quality assessment of the included studies is shown in Tables 1 and 2. Characteristics and basic fetal HR parameters of the included studies are shown in Table 3.

In all studies, day 0 is defined as the "control day", before administration of the first dose of corticosteroids. Subsequently, day 1 is defined as the next day after the first dose of corticosteroids (approximately 24 hours later), day 2 is the second day (approximately 48 hours later), and so on. All values are compared with the baseline value, measured on day 0.

Table 1. Quality assessment of the included cohort studies.

	……..……..Selection bias……..……			Intervention	……...Outcome…..……		……..……..Follow-up…….…..….....			Confounding		Conclusion
Reference	**Study design**	**Description in/exclusion criteria**	**Risk of selection bias**	**Description of administered medication**	**Data analysis description**	**Beat-to-beat fetal heart rate**	**Duration of follow-up**	**Missing results reported**	**Withdrawals explained**	**Confounding variables described**	**Data available as in clinical practice**	**Low/ medium/ high quality**
Dawes et al.[28] 1994	Retrospective longitudinal	No	High	Yes	Yes	No	Adequate	No	No	1	Yes	Low
Derks et al.[13] 1995	Prospective longitudinal	No	High	Yes	Yes	No	Adequate	No	No	3	Yes	Medium
Frusca et al.[30] 2001	Prospective longitudinal	No	High	Yes	Yes	No	Adequate	No	No	1	Yes	Low
Lunshof et al.[21] 2005	Prospective longitudinal	Yes	Low	Yes	Yes	No	Inadequate	Yes	Yes	3	Yes	Medium
Mulder et al.[20] 1994	Prospective longitudinal	No	High	Yes	Yes	No	Adequate	Yes	No	3	Yes	Low
Mulder et al.[25] 2004	Retrospective longitudinal	Yes	High	Yes	Yes	No	Adequate	No	No	4	Yes	Medium
Mulder et al.[23] 2004	Prospective longitudinal	Yes	Low	Yes	Yes	No	Adequate	No	No	4	Yes	Medium
Multon et al.[26] 1997	Retrospective longitudinal	No	High	Yes	Yes	No	Adequate	No	No	1	Yes	Low
Schneider et al.[15] 2010	Prospective longitudinal	Yes	High	Yes	Yes	Yes	Inadequate	Yes	No	1	No	Medium
Ville et al.[31] 1995	Prospective longitudinal	Yes	High	Yes	Yes	No	Adequate	Yes	No	3	Yes	Medium

Table 2. Quality assessment of the included randomised trials.

		……Randomisation……				Baseline	Outcome	……Follow-up……		Analysis	Comparability	Conclusion
Reference	**Study design**	**Randomisation blinding**	**Patient blinding**	**Treatment staff blinding**	**Observer blinding**	**Comparison of groups**	**Beat-to-beat fetal heart rate**	**Missing results reported**	**Withdrawals explained**	**Intention-to-treat analysis**	**Co-interventions, contamination and compliance described**	**Low/medium/high quality**
Magee et al.[22] 1997	Randomised trial	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes (3)	High
Mulder et al.[27] 1997	Randomised trial	Yes	No	No	No	Yes	No	Yes	No	No	Partially (1)	Low
Rotmensch et al.[29] 1999	Randomised trial	Yes	No	No	Yes	No	No	No	No	No	No (0)	Low
Senat et al.[1] 1998	Randomised trial	Yes	No	No	No	Yes	No	No	No	No	No (0)	Low
Subtil et al.[24] 2003	Randomised trial	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Partially (1)	Medium

Table 3. Characteristics and basic fetal heart rate parameters of the included studies.

Reference	No. patients	Patient characteristics (No. patients)	wGA	fHR analysis	Corticosteroid (interval)	Time of measurements	fHR parameters: mfHR	fHR parameters: LTV	fHR parameters: STV
Dawes et al.[28] 1994	28	PE (21), IUGR (5), HT (2)	27-32	CTG	Dexamethasone 2x12mg (12h)	- Daily 2 days before 1st dose - Daily for 4 successive days	=	No information	↑* (day 1)
Derks et al.[13] 1995	31 (5x repeat; 38)	PE (5), IUGR (7), TPL (9), PROM (5), VBL (5)	26-32	CTG	Betamethasone 2x12mg (24h)	- Before 1st dose - Daily for 4 successive days	=	↓* (day 2+3)	↓* (day 2+3)
Frusca et al.[30] 2001	50	IUGR (50)	26-33	CTG	Betamethasone 2x12mg (24h)	- Before 1st dose - Daily for 4 successive days	=	↓* (day 3)	↓* (day 3)
Lunshof et al.[21] 2005	36 (6x repeat; 43)	PE and/or IUGR (11), TPL (11), PROM (5), other (9)	25-33	CTG	Betamethasone 2x12mg (24h)	- Before 1st dose - 6h-interval during first 48h	↓* (6-12h) = (>15h)	↑* (6-12h) ↓* (day 2)	↑* (6-12h) ↓ (day 2)
Magee et al.[22] 1997	59	PE or HT (24), TPL and/or PROM (25), VBL (10)	26-34	CTG	Betamethasone 2x12mg (12h) Dexamethasone 2x12mg (12h)	- Before 1st dose - Daily for 2 successive days	↓* (day 1) = (day 2)	↑* (day 1) ↓ (day 2)	↑* (day 1) ↓ (day 2)
Mulder et al.[20] 1994	13 (3x repeat; 16)	PE (1), IUGR (5), TPL (4), PROM (1), placenta praevia (2)	26-32	CTG	Betamethasone 2x12mg (24h)	- Before 1st dose - Daily for 4 successive days	= (day 2) ↑ (day 3)	fHRV: ↓* (day 2+3)	
Mulder et al.[27] 1997	60	PE (4), IUGR (10), TPL (11), PROM (4), VBL (10), other (11)	26-33	CTG	Betamethasone 2x12mg (24h) Dexamethasone 2x12mg (12h)	- Before 1st dose - Daily for 4 successive days	↓ (day 1) ↑ (day 2-4) ↓ (day 1) ↑ (day 2)	↑ (day 1) ↓* (day 2+3) ↑ (day 1) ↓ (day 2+3)	↑ (day 1) ↓* (day 2+3) ↑* (day 1) ↓ (day 2+3)
Mulder et al.[25] 2004	63 (7x repeat; 70)	PE (8), IUGR (14), TPL (15), PROM (7), VBL (13), other (6)	26-34	CTG	Betamethasone 2x12mg (24h)	- Before 1st dose - Daily for 4 successive days	↓* (day 1,>30.5 wGA) ↑* (day 3,<27.5 wGA)	↓* (day 2+3)	No information
Mulder et al.[23] 2004	18 (2x repeat; 20)	Twin pregnancies; PE and/or IUGR (13), TPL (3), PROM (1), VBL (1)	26-32	CTG	Betamethasone 2x12mg (24h)	- Before 1st dose - Daily for 4 successive days	↓* (day 1)	↓* (day2+3)	↓* (day2)
Multon et al.[26] 1997	41 (mean 2.2 gifts)	IUGR (41); singleton pregnancies (27), twin pregnancies (14)	26-38	CTG	Betamethasone 4x6mg (12h)	- Before 1st dose - Daily during days 1+2	↑* (day 1) = (day 2 + 4-7)	=	=
					Dexamethasone 4x4mg (12h)	- Daily during days 4-7	=	=	=

Rotmensch et al.[29] 1999	46	HT and/or IUGR (14), TPL (26), PROM (3), VBL (3)	27-34	CTG	Betamethasone 2x12mg (24h)	- Before 1st dose - 48h after 1st dose	=	↓* (day 2)	↓* (day 2)
					Dexamethasone 2x12mg (24h)	- 92h after 1st dose	=	↓(day 2)	↓* (day 2)
Schneider et al.[15] 2010	12	TPL, "low risk" population, not specified	29-34	fMCG	Betamethasone 2x12mg (24h)	- Before 1st dose - Within 6h after 2nd dose	↓*	↓*	=
Senat et al.[1] 1998	82	TPL, not specified (no PROM, no VBL, no other medication)	25-33	CTG	Betamethasone 4x6mg (12h)	- Before 1st dose - 24-48h after 1st dose	↑ (day 1-2 + 4-7)	↑ (day 1-2) ↓ (4-7 days)	↑* (day 1-2) = (4-7 days)
					Dexamethasone 4x4mg (12h)	- Once 4-7 days after 1st dose	↓ (day 1-2 + 4-7)	=	=
Subtil et al.[24] 2003	105	PE and/or IUGR (13), TPL (69), PROM (14), other (9; VBL, DM, etc)	27-35	CTG	Betamethasone 2x12mg / 4x6mg Dexamethasone 4x6mg	- Before 1st dose - once daily for 4 successive days	↓* (day 1) ↑ (day 3)	↑ (day 0+1) ↓* (day 2+3)	↑* (day 0+1) ↓* (day 2+3)
Ville et al.[31] 1995	33 (4x repeat, 2-4 courses)	Dichorionic twin pregnancies, cervical changes (no active preterm labour), "low risk" population	36-33	CTG	Betamethasone 4x6mg (12h)	- Before 1st dose - 24-36h after 1st dose - 4-7 days after 1st dose	= (day 2 + 4-7)	↓* (day 2)	↓* (day 2)

In several studies, patients were allowed to participate multiple times in the study protocol. This is indicated in the column "No. patients" as "repeat"; in case of Derks et al.[13], 31 patients were included, of whom 5 participated multiple times in the study protocol, resulting in a total of 38 sets of observations.

* Significant

Abbreviations: CTG = cardiotocogram, DM= diabetes mellitus, fHR = fetal heart rate, fHRV = fetal heart rate variability, fMCG = fetal magnetocardiography, h = hour, HT = hypertension, IUGR = intra-uterine growth restriction, LTV = long-term variation, mfHR= mean fetal heart rate, No. = number of, PE= pre-eclampsia, PROM = preterm rupture of membranes, STV = short-term variation, TPL = threatened preterm labour, VBL = vaginal blood loss, wGA= weeks of gestational age.

In several studies, patients were allowed to participate multiple times in the study protocol if corticosteroids were administered again after a 10- to 14-day interval. This is indicated in the column "number of patients" in Table 3 as "repeat". In the study by Derks et al.[13], 31 patients were included, of whom 5 participated multiple times in the study protocol, resulting in a total of 38 sets of observations. All included studies were published between 1994 and 2010. A total of 538 fetuses (range; 8-105) were described.

Betamethasone

As shown in Table 3, a decrease in mfHR was found after betamethasone administration on day 1 in eight of the included studies[15,21-27], of which seven showed a significant result. However, this effect was relatively small, with a 3-5% decrease in mfHR[21,27]. On days 2 and 3, a trend was seen towards an increase in mfHR in multiple studies[20,24,27]. This trend was significant only in fetuses younger than 27.5 weeks' GA[25]. Other studies showed no effect on mfHR after corticosteroid administration during the study period[13,28-31].

All studies observing the effects of corticosteroids on fetal HRV during day 1 showed an increase in both LTV and STV (Table 3)[1,21,22,24,27,28]. In addition, nearly all studies showed a decrease in both LTV and STV during days 2 to 3[1,13,15,20-25,27,29-31]. Both Mulder et al.[23] and Ville et al.[31] demonstrated a similar overall response in twin pregnancies compared with singleton pregnancies. There were no significant intertwin differences reported. In IUGR fetuses with redistribution of blood flow (cerebral vasodilation), these modifications were even more profound[30]. In the study reported by Lunshof et al.[21] fetal HRV was decreased by 10% during day 2. The decrease in fetal HRV was also present in more than 80% of the fetuses studied by Mulder et al.[27]. Likewise, Senat et al.[1] demonstrated a significant decrease in both LTV and STV when comparing measurements during days 1 to 2 with measurements during days 4 to 7. Fetal HRV fell below the normal range (30 milliseconds at 30 weeks' GA) in 46% of the cases; however, no fetal HR decelerations occurred[20].

Mulder et al.[20,27] also studied movement patterns of the included fetuses with ultrasound, with activity expressed as a percentage of total observation time. All medians were compared with the fetal HR recording during day 0. Body movements were significantly reduced during days 1 and 2 ($p < 0.01$). After both doses of betamethasone, the incidence of body movements was about 50% of the incidence during day 0 ($p < 0.01$). Breathing movements were decreased by 90% during days 2 and 3 ($p < 0.01$); the incidence of hiccups did not change. The total fetal activity (the sum of body- and breathing movements and hiccups) showed a trend with a minimum during day 2 (median incidence falls from 47.7% during day 0 to 8.3% during day 2). A decrease in body- and breathing movements was demonstrated in 88.5% of all fetuses.

For all parameters measured, there were no significant differences between the subgroups (fetuses with IUGR, preterm onset of labour, pre-eclampsia, placenta praevia, and a miscellaneous group) in all of the included studies. All values returned to baseline during day 4[20,24].

Dexamethasone

Dexamethasone is less well-studied in comparison with betamethasone. Most studies found the same effect of dexamethasone on fetal HR parameters as with betamethasone[22,24,27,29]. Both Senat et al.[1] and Multon et al.[26] concluded no significant changes were present after administration of dexamethasone. Concerning mfHR, Dawes et al.[28] described no significant changes, whereas Mulder et al.[27] found a trend towards decreasing mfHR on day 1 in more than 50% of fetuses following two doses of dexamethasone. STV was increased significantly during day 1 in the reports of both Dawes et al.[28] and Mulder et al.[27], and this increase was present in more than 80% of the fetuses. In addition, Rotmensch et al.[29] found a reduction in fetal HRV during day 2. However, the magnitude of this reduction was less after exposure to dexamethasone as compared with betamethasone. In addition, fetuses exposed to betamethasone had a significantly slower return to baseline LTV as compared with the dexamethasone group ($p < 0.001$). In contrast to reports of betamethasone, no significant differences in fetal movement patterns were observed after the administration of dexamethasone[27].

Discussion

Quality assessment of the included studies

A summary of the quality of the included studies can be found in Tables 1 and 2. In the included cohort studies, a high risk for selection bias was found. This can be attributed to an unclear definition of inclusion and exclusion criteria, the retrospective nature of some studies, and the selection procedure of participants. In the three retrospective studies, only complete data sets were selected for analysis, resulting in a risk for selection bias[23,26,28]. This risk for selection bias is not clearly reported by most authors. However, the consequences of this possible bias are limited, because every fetus is regarded as its own control in these studies.

Most included patients were at high risk for preterm delivery, and in most studies, it takes up to five days to complete the study protocol. Therefore, a considerable loss of participants can be expected, mainly caused by preterm delivery or discharge before completing the final measurements. Unfortunately, this is not described properly in some of the included studies. It is not clear how, or if, this might impact the results of these studies.

Multon et al.[27] used both betamethasone and dexamethasone for fetal lung maturation in fetuses with IUGR; however, this was not in a randomised fashion. Fetuses received 1-7 (mean; 2.2) successive weekly courses of corticosteroids, and six fetuses received both drugs alternatively at weekly intervals. Therefore, this study is different in study design from other included studies.

Randomisation was blinded in all randomised trials, whereas observer blinding was performed in three of five studies. In this type of research, observer blinding is less important because of computerised analysis of the data. In general, the description of baseline characteristics of the study population and fetal HR parameters was sufficient. None of the studies conducted an intention-to-treat analysis, because there was no contamination between betamethasone and dexamethasone in clinical practice. Co-interventions were not clearly described in all studies, except for the study by Magee et al.[22]. The most important co-intervention is the administration of other drugs in addition to corticosteroids.

A point of concern is the small population size in all included studies. Magee et al.[22] performed a power analysis but failed to include enough patients in their final analysis. Subtil et al.[24] used the same values to calculate power and included just enough patients to fulfill their power criteria. A likely challenge to recruitment is that these studies were conducted in tertiary care hospitals, where a substantial number of the preterm patients are transferred from other care settings. In most cases, tocolysis and corticosteroid administration are started before transport, which makes it impossible to conduct a baseline measurement prior to the first dose of corticosteroids.

Another point to consider is the difference in nature and duration of corticosteroid administration in the various studies. Because of the heterogeneous dosing regimens, a direct comparison by pooling the study results is impossible.

A major drawback of all but one of the included studies is that the recordings used for analysis of fetal HRV were all derived from a Doppler ultrasound-based computerised cardiotocogram (CTG), making it impossible to achieve true beat-to-beat interval registration. With a known beat-to-beat interval, fetal HRV can be calculated more accurately. In addition, spectral energy in the high- and low-frequency bands can be calculated, reflecting both branches of the ANS. Schneider et al.[15] used fetal magnetocardiography to obtain beat-to-beat fetal HR parameters non-invasively. Unfortunately, this reliable method is not applicable in daily clinical practice. Direct fetal electrocardiogram (ECG) measurements could be a valuable tool to overcome this problem. Therefore, we suggest further studies on the influence of commonly used medicines in obstetric care on fetal HRV, to focus on electrophysiology of the fetal HR tracings. The

fetal ECG can be recorded non-invasively from the maternal abdomen, using self-adhesive electrodes[32]. Accordingly, the effects of medicines on fetal HRV can be quantified by means of spectral analysis (frequency analysis) objectively[33-35].

In conclusion, most of the included studies are of low to medium quality. This is partly due to high loss to follow-up, which is inherent to the study population. However, a proper description of the inclusion and exclusion criteria, risk of selection bias, and loss to follow-up should ideally be provided by the authors.

Effects of betamethasone versus dexamethasone

As summarised in Table 3, nearly all studies showed a biphasic change in fetal HR parameters after maternal administration of corticosteroids. Mean fetal HR decreases during the first day of corticosteroid administration, whereas there was an increase during days 2 to 3. Fetal HRV, both STV and LTV, showed an increase during the first day of corticosteroid administration, and a decrease during days 2 to 3.

Betamethasone and dexamethasone are stereoisomers, with the C-16 methyl group in the β- or α-position, respectively. Compared to the maternal plasma concentration, the fetal plasma concentration after administration of either betamethasone or dexamethasone is approximately 33%[7,36]. Betamethasone is the corticosteroid best studied in relation to fetal HR parameters and has a more pronounced suppressive effect on most variables concerning fetal HRV in comparison to dexamethasone[29]. Maximal effects were seen during day 2, which coincides with the highest biological activity of corticosteroids[37]. In general, all synthetic corticosteroids have a greater affinity for the glucocorticoid receptor than endogenous cortisol: dexamethasone 7.1- and betamethasone 5.4-fold higher[38]. Betamethasone has a longer plasma half-life compared with dexamethasone, whereas dexamethasone seems to have a higher add-back effect; the subsequent decrease in variability might therefore be attenuated. Subtil et al.[24] did not find any differences in fetal HR parameters between different corticosteroid formulations. Whereas betamethasone causes fetal breathing movements to disappear almost completely, this was not seen following dexamethasone administration[27].

In twin pregnancies, a similar fetal response to betamethasone administration to that described in singleton pregnancies is seen[23,31]. This response appears to be irrespective of modifying effects such as poor fetal growth, chorionicity, Doppler abnormalities, or placental vascular anastomoses. Although placental insufficiency was suspected in some of the twin pairs, this did not seem to affect the transplacental passage of betamethasone.

Proposed mechanisms of action

The exact mechanism of alteration of fetal HRV and fetal behaviour by corticosteroids is unknown. One hypothesis involves the high affinity of corticosteroids for the gonadotropin receptor. Gonadotropin receptors are widely expressed in the central nervous system, including in the brain stem nuclei. They show high affinity to synthetic corticosteroids and suppress neuronal activity when occupied, thus reducing physical activity[39]. Corticosteroids enter the brain slowly and involve cytosolic gonadotropin receptors, accounting for the prolonged range of action from hours to days[40].

The decrease in fetal HR is most likely associated with an increase in fetal systemic blood pressure. Corticosteroids can cause hypertension via augmentation of vascular tone by potentiating the actions of vasoconstrictor hormones and by direct actions on vascular smooth muscle cells[40]. This yields a vagally-mediated baroreceptor response, which triggers a reflex inhibition of the sympathetic branch and activation of the parasympathetic branch and results in a decreased fetal HR.

The increase in fetal HRV can be explained in part by the known inverse relationship between basal fetal HR and its variation. According to Nijhuis et al.[41], about 50% of the differences in fetal HRV can be explained by differences in fetal HR. Furthermore, Bennet et al.[42] found a positive correlation between sympathetic tone and short-term heart rate variation, which is attributed to transiently increased local levels of catecholamines (cardiac or neural), and/or to an increased sensitivity to normal circulating levels of catecholamines. ANS regulation of fetal HRV proves to be complex, because both vagal and sympathetic activation seems to cause an increase in fetal HRV. Accordingly, Frasch et al.[43] described that sympathetic and vagal influences might be superimposed nonlinearly on fetal HRV and can act synergistically.

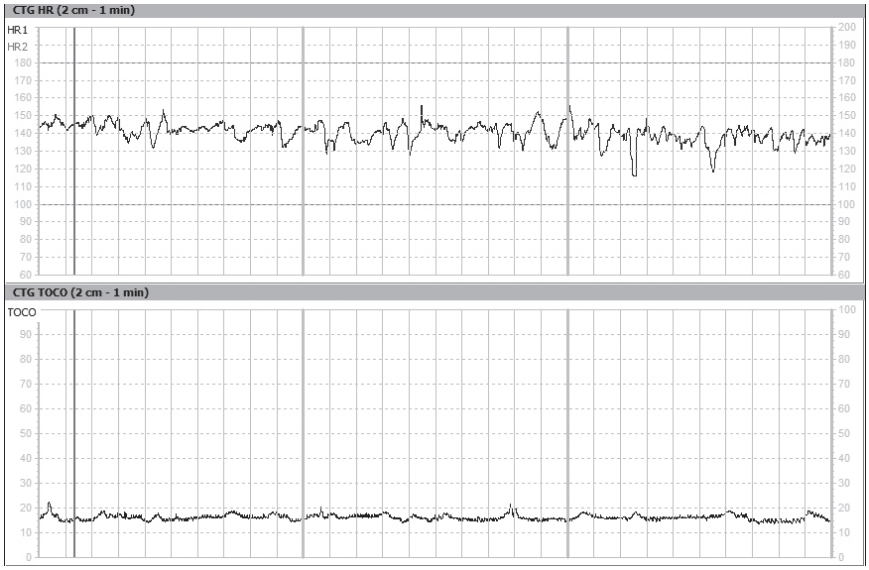
The transient decrease in fetal HRV during days 2 to 4 cannot solely be explained by an increase in fetal HR, and is likely to be related to the reduction in fetal body- and breathing movements[20,27]. This may be caused by occupation of the gonadotropin receptors of the responsible fetal brain areas. The raphe nuclei and locus coeruleus are, among others, thought to control motor activity in the third trimester. Neurons of the nucleus of the solitary tract in the medulla are known to direct respiratory activity. Thus, one can hypothesise that complete gonadotropin receptor occupancy of these fetal brain areas after corticosteroid administration reduces both body- and breathing movements.

The reduction in fetal movements and fetal HRV, both of which are associated with fetal wellbeing, can be misinterpreted as deterioration of fetal status and can therefore potentially lead to unnecessary iatrogenic preterm delivery[13,24]. The suppression in fetal HR parameters

is not only visible with computerised analysis, but also detected by visual analysis of CTG tracings by clinicians[44]. In Figures 1 and 2, the decrease in fetal HRV after corticosteroid administration is illustrated in the case of a 29-week fetus before and 2 days after betamethasone administration.

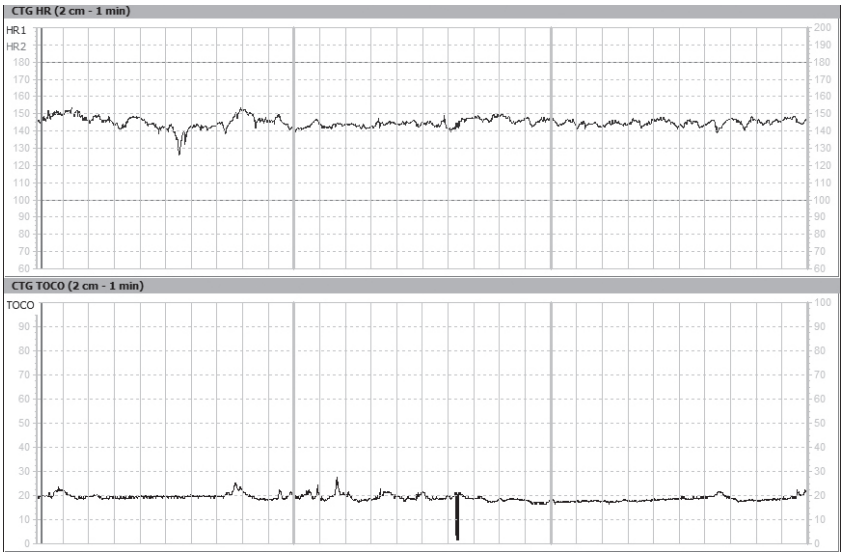
Shenhav et al.[45] demonstrated that if women delivered within 48 hours after betamethasone administration, the reduced fetal HRV was not related to the fetal acid-base balance at birth. Moreover, no changes have been observed in Doppler flow velocity waveforms of uterine and umbilical arteries - brain-sparing was absent, and no decelerations or reduction in fetal eye movements have occurred after corticosteroid administration[13,46]. Furthermore, there are no signs of any association of steroids with uterine contractions[1,24,27]. In animal studies, no signs of fetal asphyxia were observed following maternal corticosteroid administration[42]. In addition, all parameters returned to normal during day 4. These findings all indicate no fetal deterioration during the course of the study period.

Figure 1. Cardiotocogram, one day before betamethasone administration.



Fetal age: 29 weeks + 2 days of gestation. Paper speed: 2cm/minute.

Figure 2. Cardiotocogram during day 2 after betamethasone administration.



Fetal age: 29 weeks + 5 days of gestation. Paper speed: 2cm/minute.

It seems that the effect of re-administration of corticosteroids is comparable to the primary effect on fetal HR parameters. In several studies, fetuses were exposed to multiple courses of corticosteroids, with a similar response after re-administration[20,31].

In Figure 3, an overview of the effects of synthetic corticosteroids on fetal HR and fetal HRV and the proposed mechanisms of action is illustrated.

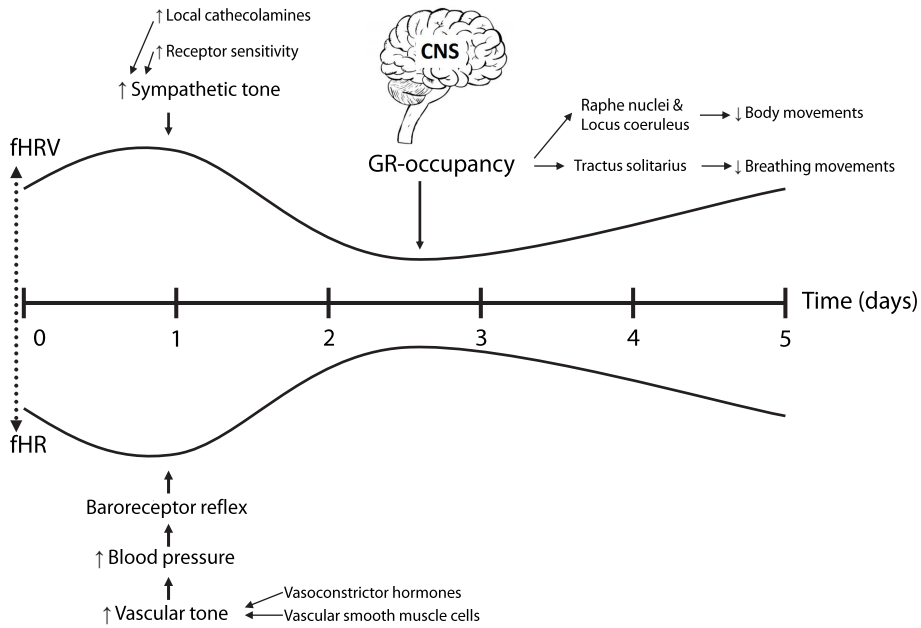
Confounding factors

In assessing the impact of corticosteroids on fetal HR, it is important to account for possible confounding factors that might also affect fetal HR and fetal HRV. We assessed other drugs administered, GA, diurnal rhythm and IUGR as major potential confounders. In Figure 4, an overview of the hypothesised effects of the different confounders is presented. One can correct for these variables by measuring at fixed times during the day and by performing subgroup analyses. Below, we will shortly discuss each of these potential confounders.

To understand some of the underlying confounding mechanisms, it is important to review the ^{11}β-HSD enzyme. This enzyme is an important regulator of fetal glucocorticoid exposure and consists of two distinct iso-enzymes, namely ^{11}β-HSD type 1 and 2[6]. ^{11}β-HSD type 1 acts as a reductase, converting cortisone (inactive metabolite) into cortisol (active metabolite).

This enzyme is located mainly in the liver, but is also present in the decidua, chorion and the endothelium of placental villous tissue, where it modulates the effect of cortisol on other placental pathways (including prostaglandin biosynthesis and metabolism, resulting in an increase in prostaglandin synthesis, which is involved in parturition)[47]. In contrast, ^{11}β-HSD type 2 acts as an oxidising enzyme, converting cortisol to cortisone. ^{11}β-HSD type 2 activity is located mainly in the kidney, but is also found in the placental syncytiotrophoblast during pregnancy, where it functions to limit fetal exposure to maternal corticosteroids.

Figure 3. Overview of the effects of corticosteroids on fetal heart rate and fetal heart rate variability and the proposed mechanisms of action.

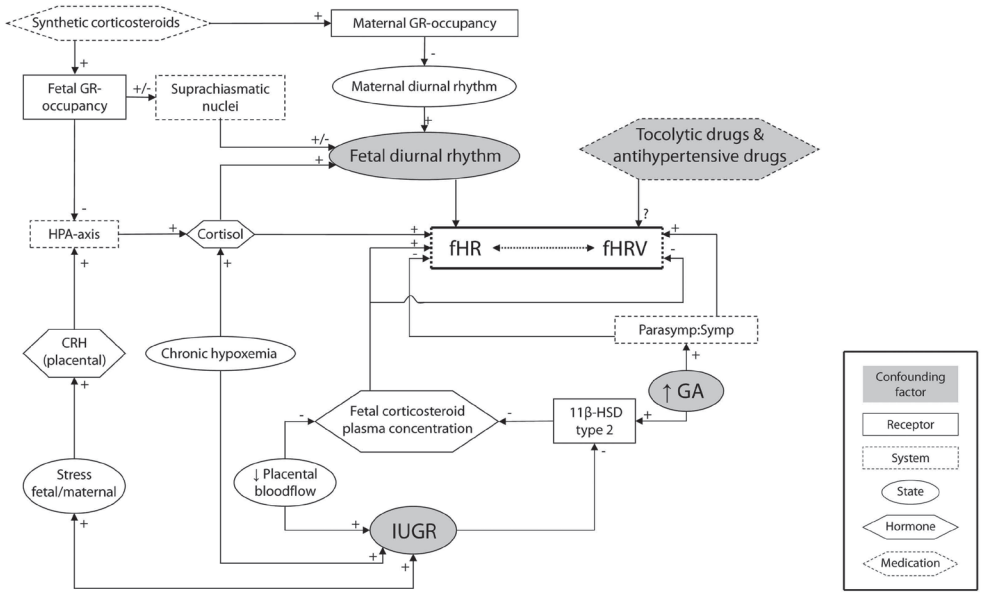


The changes in fetal heart rate and fetal heart rate variability are relative changes, compared with the baseline values on day 0. Therefore, no y-axis is shown. As illustrated, fetal heart rate decreases during day 1 and increases during days 2 to 3, whereas fetal heart rate variability increases during day 1 and decreases during days 2 to 3. All values returned to baseline during day 4.

·····► Indicates the inverse relation between fetal heart rate and fetal heart rate variability.

Abbreviations: CNS = central nervous system, fHR = fetal heart rate, fHRV = fetal heart rate variability, GR = glucocorticoid receptor.

Figure 4. The complex interactions between confounding factors and fetal heart rate and/or fetal heart rate variability.



If arrows attach to the horizontal line above "fHR" and "fHRV", this indicates that the confounding factor has an effect on both fetal HR and fetal HRV. The dashed vertical lines next to "fHR" and "fHRV" indicate an effect solely on fetal HR (left dashed line) or fetal HRV (right dashed line).

·····► Indicates the inverse relation between fetal heart rate and fetal heart rate variability.
+ Indicates a positive correlation, - indicates a negative correlation.

Tocolytic and antihypertensive drugs: the effect of other administered drugs remains unclear, since these are mainly co-administered with corticosteroids. Therefore, we illustrated this as a question mark in the figure. Gestational age: during gestation, fetal HRV increases and fetal HR decreases. This might be caused by a gradual increase in the parasympathetic-to-sympathetic ratio. Besides, there is an increase in ^{11}β-HSD type 2 activity during gestation, yielding to a lower fetal corticosteroid plasma concentration. Intra-uterine growth restriction: in IUGR fetuses, fetal HR was generally higher and fetal HRV was lower compared to a control group. This might be due to a decrease in placental transfer of corticosteroids, premature reduction in ^{11}β-HSD type 2 activity, and maternal/fetal stress. Alternatively, chronic hypoxemia can cause an increased cortisol concentration. Fetal diurnal rhythm: following corticosteroid administration, fetal diurnal rhythm abolishes. However, the exact effects on fetal HR and fetal HRV depend on the time of day. Therefore, it is not possible to indicate this effect as "positive" or "negative". The abolishment of fetal diurnal rhythm might be caused by a direct effect on the suprachiasmatic nuclei (indicated as +/-, since it is not described whether this is an activation or suppression), a temporary suppression of the fetal HPA-axis and/or by simultaneous abolishment of the maternal diurnal rhythm.

Abbreviations: $^{11}\beta$-HSD = $^{11}\beta$-hydroxysteroid dehydrogenase, CNS = central nervous system, CRH = corticotrophin-releasing hormone, fHR = fetal heart rate, fHRV = fetal heart rate variability, GA = gestational age, GR = glucocorticoid receptor, HPA-axis = hypothalamic-pituitary-adrenal axis, IUGR = intra-uterine growth restriction, parasymp:symp = parasympathetic:sympathetic ratio.

Influence of other drugs

A significant potential confounder is the use of other medications that might influence fetal HRV. When administering corticosteroids in threatened preterm labour, tocolytic drugs are commonly co-administered in order to suppress uterine activity. These tocolytic drugs may have an effect on fetal HRV, although de Heus et al.[48] did not report additional changes in fetal HR parameters after administration of atosiban or nifedipine, on top of the changes caused by corticosteroids. However, there are indications that nifedipine might cause fetal tachycardia[49]. Because the combined administration of corticosteroids and tocolytic drugs is common clinical practice and because of the small sample sizes encountered in the described studies, it is not feasible to design a study in which only effects of one of these drugs on fetal HRV could be studied. Consequently, the isolated effect of tocolytic drugs on fetal HRV remains unclear.

Antihypertensive agents are also commonly co-administered with corticosteroids in cases of pre-eclampsia or pregnancy induced hypertension. In a review performed by Waterman et al.[50], it is stated that the available data is inadequate to draw any conclusions concerning the effect on fetal HRV parameters.

In multiple studies, it is stated that the fetal response to maternal corticosteroid administration was not significantly related to the type of pregnancy complication[20,21,23,27]. Therefore, it is unlikely that the observed changes were only due to concomitant factors such as tocolytic or antihypertensive drugs. Nevertheless, a comprehensive analysis of the effects on fetal HR parameters of commonly used medicines in obstetric care, other than corticosteroids, goes beyond the scope of this review.

Influence of gestational age

In healthy fetuses, both LTV and STV increase during gestation, whereas fetal HR decreases[41]. Both Mulder et al.[25] and Lunshof et al.[21] found that older fetuses (29-34 weeks' gestation) show a significant decrease in fetal HR and body- and breathing activity during day 1. These changes were not statistically significant in younger fetuses (26-28 weeks' gestation). However, the relative reduction in fetal HRV during days 2 and 3 was similar in younger and older fetuses, and not related to changes in basal fetal HR[23]. This is suggestive of an immature cardiovascular control mechanism and/or non-functional gonadotropin receptors in the fetal

brain, heart, or vessels at younger ages. In sheep studies, it is demonstrated that the sympathetic branch of the ANS develops and becomes functional earlier in fetal life than the parasympathetic branch[51,52]. However, the parasympathetic system is capable of exerting a strong action on the fetal cardiovascular system when stimulated; this capability increases with GA[52].

The activity of the placental $^{11}\beta$-HSD type 2 enzyme increases during pregnancy, with a decrease in activity from 38-40 weeks' gestation[47]. In addition, there is an increase in $^{11}\beta$-HSD type 1 expression at term. These changes result in a rise of cortisol concentrations at term, regulating the reduction in fetal growth rate and the promotion of fetal organ maturation towards term and activating pathways associated with labour.

Diurnal rhythm

From the second half of pregnancy onwards, there is a fetal diurnal rhythm present with a rise in STV and fetal movements and a decrease in fetal HR in the afternoon and evening compared with the morning[53]. A part of the increase in fetal HRV during the day can be explained by a decrease in fetal HR, because correction for fetal HR resulted in absence of any effect of time of the day on LTV and STV[41]. However, the effect of corticosteroid administration is considerably larger than the observed diurnal variations[20].

De Heus et al.[53] performed daily CTG recordings in both the morning and afternoon, before and 4 days after betamethasone administration. They found a reduction in fetal HRV and fetal movements during day 2 in the afternoon and evening, but not in the early morning. This suggests a transient suppression of the normal fetal diurnal rhythm, induced by corticosteroids. The diurnal rhythm returned to normal during days 3 and 4[54].

The mechanisms by which corticosteroids temporarily influence the fetal diurnal rhythm are still uncertain. They may exert a direct effect on the suprachiasmatic nuclei in the hypothalamus; the same nuclei that regulate the adult biological clock[55]. Or, corticosteroids may temporarily suppress the fetal hypothalamic-pituitary-adrenal (HPA) axis with cortisol functioning as a major "Zeitgeber"[56]. Another hypothesis is the simultaneous abolishment of the maternal diurnal cortisol rhythm[57]. Most likely, there is a combination of direct, reversible effects on the fetal cardiovascular system and diurnal rhythms.

Intra-uterine growth restriction (IUGR)

Nijhuis et al.[41] stated that in IUGR fetuses, fetal HR was generally higher and fetal HRV was lower compared with a control group. In addition, Frusca et al.[30] found an even more pronounced decrease in STV on day 3 after betamethasone administration in fetuses with cerebral vasodilation. This may be explained as a sign of a compromised fetal condition or by

a higher concentration of steroids in the fetal brain due to an increased cerebral blood flow. In IUGR fetuses, it is possible that the placental transfer of corticosteroids is decreased because of a diminution in uteroplacental blood flow. ^{11}β-HSD type 2 is a key factor in determining fetal growth, with a positive correlation between ^{11}β-HSD type 2 activity and birth weight. In addition, IUGR is probably associated with a premature reduction in ^{11}β-HSD type 2 activity, thus increasing the glucocorticoid transfer from mother to fetus[6,58]. In addition, maternal and/or fetal stress stimulates the placental secretion of corticotrophin-releasing hormone, stimulating the HPA axis to secrete glucocorticoids. Alternatively, an increased plasma concentration of cortisol has been found in human fetuses with chronic hypoxemia, possibly protecting some IUGR fetuses from the suppressive effects of synthetic steroids[59]. However, IUGR fetuses show a similar trend in response to corticosteroids as do appropriately grown fetuses[30].

Conclusions

This review indicates that following maternal corticosteroid administration for threatened preterm delivery, fetal HR and fetal HRV show a biphasic course. During day 1, fetal HR decreases and fetal HRV increases, followed by increasing fetal HR and decreasing fetal HRV during days 2 to 3. All parameters typically return to baseline by day 4. This decrease in fetal HRV, combined with a decrease in fetal body- and breathing movements, can be misinterpreted as non-reassuring fetal status. Therefore, the physician should be aware of unnecessary iatrogenic delivery of premature infants because of these pharmacological changes in fetal HR parameters following corticosteroid administration. In future studies, beat-to-beat fetal HR should be obtained, to calculate fetal HRV more accurately and to interpret these findings in conjunction with the ANS. Direct fetal ECG measurements could be a valuable tool to overcome this problem.

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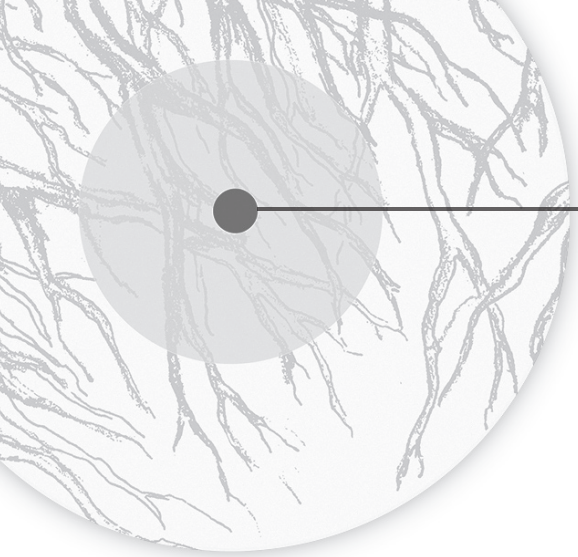

Chapter 7

Effect of tocolytic drugs on fetal heart rate variability: a systematic review

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Abstract

Introduction

Tocolytics may cause changes in fetal heart rate pattern, while fetal heart rate variability is an important marker of fetal wellbeing. We aim to systematically review the literature on how tocolytic drugs affect fetal heart rate variability.

Material and Methods

We searched CENTRAL, PubMed, and EMBASE up to June 2016. Studies published in English, using computerised or visual analysis to describe the effect of tocolytics on heart rate variability in human fetuses were included. Studies describing tocolytics during labour, external cephalic version, pre-eclampsia and infection were excluded. Eventually, we included six studies, describing 169 pregnant women.

Results

Nifedipine, atosiban and indomethacin administration show no clinically important effect on fetal heart rate variability. Following administration of magnesium sulphate, decreased variability and cases of bradycardia are described. Fenoterol administration results in a slight increase in fetal heart rate with no changes in variability. After ritodrine administration increased fetal heart rate and decreased variability is seen. The effect of co-administration of corticosteroids should be taken into account.

Conclusion

In order to prevent iatrogenic preterm labour, the effects of tocolytic drugs on fetal heart rate variability should be taken into account when monitoring these fetuses.

Introduction

In case of threatened preterm delivery between 24 and 34 weeks of gestation, short-term tocolytic therapy is commonly used in combination with corticosteroids. The aim is to postpone delivery for at least 48 hours, in order to gain time for transferring women to a centre with neonatal intensive care facilities and administering and awaiting maximal beneficial effect of corticosteroids. The tocolytic agent of first choice is still a topic of debate and varies considerably in different parts of the world. The most commonly used tocolytic drugs in clinical practice nowadays are nifedipine, magnesium sulphate ($MgSO_4$), atosiban, indomethacin, fenoterol and ritodrine. Table 1 summarises the most important properties of these tocolytics.

Table 1. Overview of the most important tocolytic drugs and their properties.

Working mechanism	Tocolytic agent	F/M ratio	Maternal side effects	Fetal side effects	Half life
Calcium channel blocker	Nifedipine[1]	0.93	a.o. hypotension, tachycardia, headache	No fetal side effects reported	81 min
	Magnesium sulphate[2-4]	1.00	a.o. flushing, nausea, headache, palpitations	Hypermagnesemia: a.o. respiratory depression	5 h
Oxytocin receptor antagonist	Atosiban[5,6]	0.124 ± 0.025	No systemic effects reported	No fetal side effects reported	17 min
Prostaglandin antagonist	Indomethacin[3]	1.00	a.o. headache	a.o. oligohydramnios, premature closure of the ductus arteriosus	2 h
Selective β_2-adrenergic agent	Fenoterol[7,8]	0.40	a.o. palpitations, tachycardia, hypotension	Tachycardia	Two-phased: 11 min and 5 h
	Ritodrine[3,9]	1.17 ± 0.48	a.o. tachycardia, hypotension, cardiac dysrhythmia	Tachycardia	Two-phased: 6 and 156 min

Abbreviations: a.o. = amongst others, F/M ratio = fetal/maternal ratio, h = hours, min = minutes.

In 1989, the American College of Obstetricians and Gynecologists acknowledged that fetal heart rate variability (HRV) is a reliable marker for fetal wellbeing[10]. In accordance with other studies, Williams and Galerneau[11] concluded that minimal or absent variability is the most significant intrapartum fetal heart rate (HR) parameter to predict acidemia. Since the fetus is unable to adapt its single stroke volume due to the small size of the heart, the fetal HR is the primary variable to control the cardiac stability and is the major regulative of the autonomic nervous system[12]. Therefore, we should be aware of the influence of commonly used medicines in obstetric care on fetal HRV. For example, corticosteroids are known to cause a decrease in fetal HRV that can be interpreted as deterioration of the fetal condition[13]. As with corticosteroids, tocolytics may also cause changes in fetal HR pattern, which can be

erroneously interpreted as a sign of fetal distress. This could lead to iatrogenic preterm delivery. In this review, we will focus on the influence of tocolytic drugs on fetal HRV in human fetuses.

Material and Methods

We performed a systematic search in the electronic databases CENTRAL (the Cochrane Library, 2016, Issue 6), PubMed, and EMBASE up to June 2016. The search strategy is attached in the Appendix.

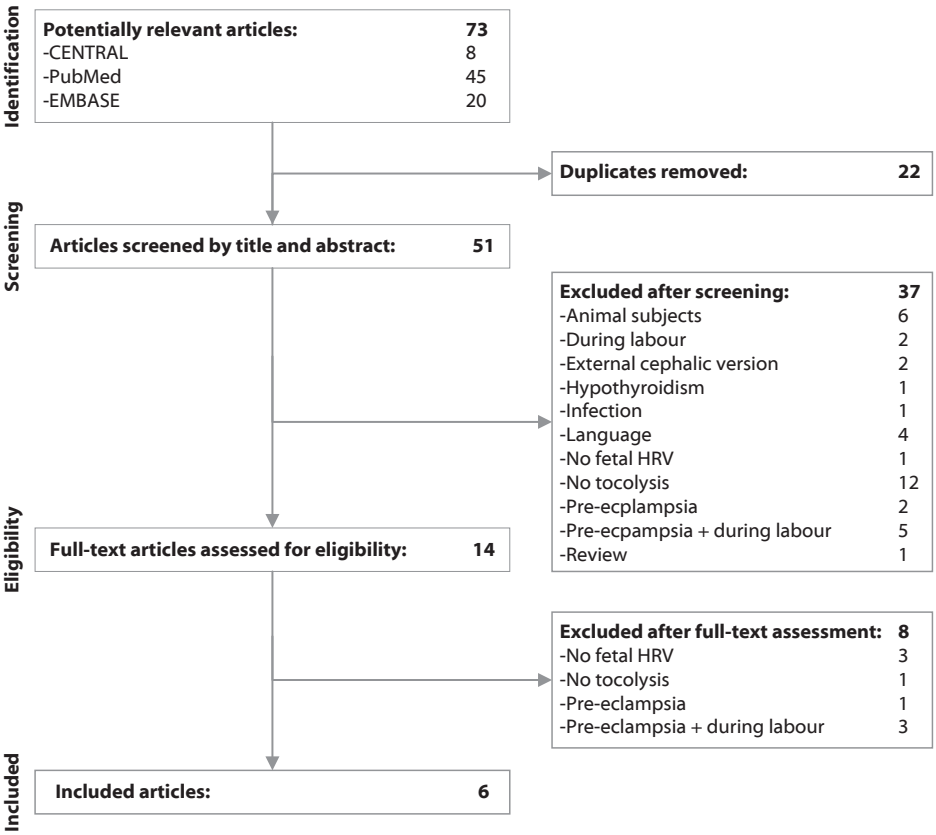
All published studies that describe the influence of tocolytic drugs on HRV of the human fetus, assessed by computerised or visual analysis, were included in this review. The outcome measure of interest was variability of the fetal HR. There were no restrictions on publication dates. We excluded review studies, studies that described pre-eclamptic women or women with an intra-uterine infection and studies that performed measurements during labour or during external cephalic version. The study language was restricted to English.

Two reviewers (KV and AH) independently performed the search and abstracted the data. Any discrepancies were resolved by discussion. Articles were initially screened by title and abstract, when appropriate a full-text evaluation was performed. Qualitative analysis, including description of the women enrolled, description of the intervention and outcomes, and possible risks of bias, were based on the review guidelines of the Dutch Cochrane Centre.

Results

The screening and inclusion process is depicted in Figure 1. Eventually, six out of 72 articles were included in this review (169 women). Study characteristics and basic fetal HR parameters are shown in Table 2.1 (computerised analysis of fetal HR parameters) and Table 2.2 (visual analysis of fetal HR parameters). Three of the included studies are randomised controlled trials, two are case reports and one is a prospective cohort study. Table 3 includes the quality assessment of the included randomised trials. We considered the trials by de Heus et al.[14] and Neri et al.[15] as medium quality evidence, as blinding was not appropriate or not described. The trial by Hallak et al.[16] was considered high-quality evidence. Table 4 includes the quality assessment of the included prospective cohort study by Wright et al.[17]. This study was considered low-quality evidence since there was no description of exclusion criteria and there was a high risk of selection bias: the tocolytic agent used was the choice of the individual physician and co-administration of corticosteroids was not described.

Figure 1. Flowchart of the included and excluded articles.



Abbreviation: HRV = heart rate variability.

Calcium channel blocker: nifedipine and magnesium sulphate

Fourteen women were randomised to receive nifedipine in the study by de Heus et al.[14]. On days 1 and 2, a significant decrease in fetal HR (-7 bpm) and a significant increase in both short- and long-term fetal HRV on days 1 and 2 (+2 ms and +12 ms, respectively) were seen. This effect was observed in both the atosiban and nifedipine groups, there was no difference between these tocolytic agents. During days 3 and 4, all values (basal fetal HR, short- and long-term variability) returned to normal (pre-medication values). The authors found no significant changes in fetal body- and breathing movements or uteroplacental blood flow during the 5-days study period. Fetuses below 29 weeks of gestation showed higher basal fetal HR and lower fetal HRV in comparison to older fetuses. However, the initial increase of fetal HRV and return to baseline were independent of gestational age.

Table 2.1 Characteristics and basic fetal heart rate parameters of included studies concerning administration of tocolytic drugs, assessed by computerised analysis.

Study characteristics	De Heus et al.[14] 2009	Neri et al.[15] 2009
Study type	Randomised trial	Randomised trial
Research question	Effect atosiban and nifedipine on fetus in time	Effect ritodrine versus atosiban on fetus at one moment
No. participants	31	54
Characteristics	Threatened preterm labour	Threatened preterm labour
Gestational age	25-33 weeks	26-33 weeks
Medication		
Tocolytic agents	Atosiban (n = 17) 6.75mg i.v. bolus + 54mg in 3h + 288mg in 48h Nifedipine (n = 14) 4x10mg orally (15min interval) + 30mg slow-release orally each 8h	Atosiban (n = 29) 6.75mg i.v. bolus + 10.8mg in 3h + 57.6mg in 48h Ritodrine (n = 25) i.v. 100 – 350 µg/min until disappearance of uterine contractions or maternal HR ≥ 140 bpm
Other	Betamethasone 2x12mg (24h interval)	Betamethasone 2x12mg (24h interval)
Timing of measurements	1. Prior to 1st dose 2-5. 1h daily for 4 successive days	1. ≥ 12h after last corticosteroid administration
Fetal HR analysis	Doppler, computerised analysis	Doppler, computerised analysis
Fetal HR parameters		
Mean fetal HR	↓* (day 1+2) (atosiban & nifedipine) = (day 3+4) (atosiban & nifedipine)	↑*(<30 weeks of gestation) (ritodrine)
Long-term variation	↑* (day1+2) (atosiban & nifedipine) = (day3+4) (atosiban & nifedipine)	↓*(<30 weeks of gestation) (ritodrine)
Short-term variation	↑* (day1+2) (atosiban & nifedipine) = (day3+4) (atosiban & nifedipine)	=

Long-term variation (0.08-0.2 Hz), short-term variation (0.4-1.7 Hz).
Symbol: *, significant; =, no significant difference.
Abbreviations: HR = heart rate, i.v. = intravenous, No. = number of.

Hallak et al.[16] included 34 women with an uneventful pregnancy in their randomised trial; 16 in the control group (receiving NaCl-infusion) and 18 in the $MgSO_4$-group. Following three hours of $MgSO_4$-infusion, they observed a significant decrease in both baseline fetal HR (136 vs 132 bpm) and fetal HRV (2.82 vs 2.67 bpm). They also observed a trend towards less accelerations after three hours (11 vs 7.4 per hour). Wright et al.[17] found a significant decrease in both fetal HR (140.8 vs 137.3 bpm) and fetal HRV ("decreased" in 2/48 vs 12/48) after the $MgSO_4$ loading dose in their prospective cohort group. "Decreased" variability was defined as a band width ≤5 bpm. They found a trend towards less accelerations after $MgSO_4$ was initiated. Cardosi et al.[18] described a case in which fetal bradycardia (100-110 bpm, initial baseline 140-150 bpm), decreased maternal temperature (-3.1°C) and decreased fetal HRV followed when serum $MgSO_4$ levels increased. After discontinuing $MgSO_4$, all values returned

Table 2.2 Characteristics and basic fetal heart rate parameters of included studies concerning administration of tocolytic drugs, assessed by visual analysis.

Study characteristics		Wright et al.[17] 1996	Cardosi et al.[18] 1998	Hamersley et al.[19] 1998	Hallak et al.[16] 1999
Study type		Prospective cohort	Case report	Case report	Randomised trial
Research question		Effect $MgSO_4$ on fetus	Effect $MgSO_4$ on fetus	Effect $MgSO_4$ on fetus	Effect $MgSO_4$ on fetus
No. participants		48	1	1	34
Characteristics		Threatened preterm labour	Threatened preterm labour	Threatened preterm labour	Uncomplicated pregnancy
Gestational age		24-35 weeks	29 weeks	32 weeks	>30 (mean 34.4) weeks
Medication	Tocolytic agents	$MgSO_4$ 4-8g i.v. bolus	$MgSO_4$ 6g i.v. bolus + 2g/h first 4h + 3g/h maintenance	$MgSO_4$ 4g i.v. bolus + 2g/h maintenance	$MgSO_4$ (n=18) 6g i.v. bolus + 2g/h maintenance Placebo (NaCl) (n=16)
	Other	Not described	"Parenteral steroids"	Betamethasone 2x12mg (24h interval) Ampicillin	Not described
Timing of measurements		1. Prior to 1st dose 2. 30min after loading dose	Intermittently first 22h	1. Prior to 1st dose 2. Intermittently 3 days	1. Prior to 1st dose 2. 1h after start infusion 3. 3h after start infusion
Fetal HR analysis		Doppler, visual analysis	Doppler, visual analysis	Doppler, visual analysis	Doppler, visual analysis
Fetal HR parameters	Mean fetal HR	↓*	Fetal bradycardia	Fetal bradycardia	↓* ($MgSO_4$, after 3h)
	Variability	↓*	↓	=	↓* ($MgSO_4$, after 3h)
	Accelerations	↓	Not described	Not described	↓ ($MgSO_4$, after 3h)

Symbol: *, significant; =, no significant difference.
Abbreviations: HR = heart rate, i.v. = intravenously, $MgSO_4$ = magnesium sulphate, n = number, No. = number of.

Table 3. Quality assessment of the included randomised trials.

Quality assessment item	Hallak et al.[16] 1999	De Heus et al.[14] 2009	Neri et al.[15] 2009
Randomisation;			
Study design	Randomised trial	Randomised trial	Randomised trial
Randomisation blinding	Yes	Not described	Yes
Patient blinding	Yes	Not described	No
Treatment staff blinding	Yes	Not described	No
Observer blinding	Yes	Not described	No
Baseline; comparison of groups	Yes	Yes	Yes
Outcome; beat-to-beat fetal HR	No	No	No
Follow-up;			
Missing results reported	Not applicable	Yes	Yes
Withdrawals explained	Not applicable	Yes	Yes
Analysis; intention-to-treat analysis	Unclear	No	No
Comparability; co-interventions, contamination and compliance described	Yes (3)	Yes (3)	Yes (3)
Conclusion; low/medium/high quality	High	Medium	Medium

Abbreviation: HR = heart rate.

Table 4. Quality assessment of the included cohort study.

Quality assessment item	Wright et al.[17] 1996
Selection bias;	
Study design	Prospective cohort study
Description inclusion criteria	Yes
Description exclusion criteria	No
Risk of selection bias	High
Intervention; description of administered medication	Yes
Outcome;	
Data analysis description	Yes
Beat-to-beat fetal HR	No
Follow-up;	
Duration of follow-up	30 minutes
Missing results reported	Yes
Withdrawals explained	Not applicable
Confounding;	
Confounding variables described	No
Data available as in clinical practice	Yes
Conclusion;	Low quality

Abbreviation: HR = heart rate.

to pre-$MgSO_4$ levels within 24 hours. Hamersley et al.[19] also described a case of fetal bradycardia where baseline dropped from 140 bpm to 110 bpm following 30 minutes of $MgSO_4$ infusion and to 100-105 bpm following 90 minutes. The fetal HRV remained good in this case. After discontinuing $MgSO_4$-infusion on the third day, fetal HR baseline returned to 140 bpm.

Oxytocin receptor antagonist: atosiban

A total of 46 included women with threatened preterm delivery received atosiban in combination with betamethasone. De Heus et al.[14] randomised 17 women to the atosiban group and found no difference in changes between the atosiban and the nifedipine group: on days 1 and 2, both short- and long-term fetal HRV increased significantly, and returned to premedication values on days 3 and 4. Fetal HR showed a transient significant decrease during days 1 and 2, that returned to premedication values on days 3 and 4.

Neri et al.[15] performed their measurements at least twelve hours after the last corticosteroid administration. They found no significant differences between the atosiban group (n=29) and the ritodrine group considering fetal HR (148.5 vs 152.5 bpm), long-term variability (18.3 vs 18.9), and short-term variability (5 vs 5.1).

Prostaglandin synthesis inhibitor: indomethacin

We did not find any studies describing the effect of indomethacin on fetal HRV that matched our inclusion criteria.

Selective β2-adrengergic agent: fenoterol and ritodrine

We did not find any studies describing the effect of fenoterol on fetal HRV that matched our inclusion criteria.

Neri et al.[15] observed no differences between 25 women who received ritodrine and those who received atosiban. Subgroup analysis showed that fetuses before 30 weeks of gestation treated with ritodrine had a significant higher fetal HR (154 vs 148 bpm), lower long-term fetal HRV (15.7 vs 21.6 ms) and lower low-frequency/high-frequency ratio (18.5 vs 29.9) than those treated with atosiban.

Discussion

General Comments

First of all, our search revealed that little research has been published regarding the influence of tocolytic drugs on fetal HRV. Tocolysis is nearly always combined with corticosteroids that are known to have transient but considerable effects on fetal HRV[13]. This makes the interpretation of the sole effect of tocolytics difficult. However, the combination of these medicines

is daily clinical practice and therefore we chose to include studies that describe the effect of tocolytics, regardless of the co-administration of corticosteroids. We chose to include studies that used visual interpretation of fetal HR tracings, despite the well-known inter- and intra-observer variations in visual fetal HR tracing interpretation. Those study results are valuable, since visual analysis is common clinical practice and computerised analysis is only used for research so far.

All included studies used Doppler ultrasound-based cardiotocogram recordings for fetal HRV analysis (visual or computerised). To perform spectral analysis and obtain more complete and reliable information on fetal HRV, the fetal HR must be acquired on a beat-to-beat basis. Standard Doppler recordings cannot derive the fetal HR on a beat-to-beat basis, but produce an average fetal HR. It is feasible to use Doppler ultrasound for beat-to-beat fetal HR measurements, although this is technically challenging and requires special algorithms[20]. These are not described in the included studies. We recommend future studies to focus on beat-to-beat analysis, to calculate fetal HRV more accurately and to interpret the findings in conjunction with the autonomic nervous system.

We excluded women during labour, since the stress of labour is known to influence fetal HRV (the sympathicovagal balance)[21] and a woman is likely to receive other pharmacologic agents in addition to tocolytics which can interfere with the fetal HR. In addition, we did not include women with pre-eclampsia. This pathological state with abnormal placental-fetal circulation and hemodynamical fetal stress is known to influence fetal HR tracings due to changes in cardiovascular regulation[22]. Women with (suspicion of) intra-uterine infection were excluded as well, since it is demonstrated in fetuses that reduced HRV and transient decelerations are an important physiomarker and can precede clinical signs of sepsis[23,24]. We also chose to exclude studies that performed measurements during or after external cephalic version, since the effect of the version may interfere with the observed fetal HR parameters[25-27].

Calcium channel blocker: nifedipine and magnesium sulphate

Nifedipine crosses the placenta easily and contradictory results have been reported regarding changes in uteroplacental blood flow. In the study by de Heus et al.[14], the number of participants steadily decreased during the study period due to preterm delivery. On day 4, 77% (24/31 women) remained available for analysis. Due to this small amount of women, study results were depicted as the influence of both atosiban and nifedipine together. A subanalysis showed no differences in fetal parameters between the two tocolytics, but details are not shown. The decrease in fetal HR and increase in short- and long-term fetal HRV on days 1 and 2 were attributed to the known effect of corticosteroids by the authors. However, our review considering the effects of corticosteroids on fetal HRV showed a decrease in fetal

HR and increase in fetal HRV during day 1, and an increase in fetal HR and decrease in fetal HRV during days 2 and 3[13]. This difference might be attributable to the low number of women included in the study by de Heus et al.[14]. The nifedipine administration was "progressively decreased" after 48 hours. However, the authors did not exactly describe in what time course or dosages this was performed.

In summary, it seems that nifedipine has no clinically important effect on fetal HRV.

$MgSO_4$ crosses the placenta rapidly, and reaches an equilibrium after two hours of administration between maternal and fetal plasma levels[4]. Moreover, fetal levels seem to increase proportionally with maternal levels[16,28]. It is assumed that $MgSO_4$ crosses the fetal blood-brain barrier, as it does in the mother. It suppresses the central nervous system and inhibits cardio-accelerating pathways via the cerebral cortex, hypothalamus and the cardioaccelerator center in the medulla oblongata[29].

Hallak et al.[16] studied healthy pregnant women, without any indication for treatment with $MgSO_4$ in their randomised trial. Therefore, their measurements were not influenced by conditions like pre-eclampsia, premature contractions or co-administration of corticosteroids. Besides decreased fetal HR and fetal HRV, they found that the positive correlation between gestational age and the number of accelerations observed in the control group (treated with NaCl) was missing in women treated with $MgSO_4$. An animal study confirmed a significant decrease in both baseline fetal HR as well as long- and short-term variability four hours after $MgSO_4$ administration, compared to the control group (5% glucose infusion)[29]. The included prospective study by Wright et al.[17] found similar results regarding fetal HR and fetal HRV. They also state that a lower gestational age increases the likelihood of decreased variability (odds ratio 0.75, $p = 0.03$). Cardosi and Hamersley both described a case report with fetal bradycardia following $MgSO_4$-infusion in a preterm fetus. Cardosi et al.[18] state that the effect on fetal HR might indirectly be related to the hypothermic effect of $MgSO_4$. Hamersley et al.[19] suggested a pharmacological depression of the central nervous system. The decrease in fetal HRV can be interpreted as a sign of compromised fetal condition and expedite iatrogenic preterm delivery, while Duffy et al.[30] showed that the decreased variability is associated with exposure to $MgSO_4$, since they excluded adverse fetal outcomes. This indicates a transient medication effect (central nervous system depression) rather than a marker of deteriorating fetal condition, as confirmed by other studies[31,32].

In summary, decreased fetal HRV and cases of fetal bradycardia are described after $MgSO_4$ administration.

Oxytocin receptor antagonist: atosiban

Atosiban is known to be highly specific for the oxytocin receptors in the uterus, with low placental passage and few maternal and fetal side effects. Both de Heus et al.[14] and Neri et al.[15] found no other changes than the changes known to be caused by corticosteroids.

Neri et al.[15] performed one measurement, at least 12 hours after the last corticosteroid administration. They state this would avoid the adverse effects on fetal behaviour following corticosteroid administration. However, it can take up to 96 hours for fetal HR parameters to return to baseline values following corticosteroid administration[13]. Therefore, the effect of corticosteroids is still likely to overwhelm the effect of atosiban and ritodrine. No baseline (premedication) measurements were performed, but two medication groups were compared at one moment. A direct comparison between two drugs was performed, instead of comparison with a placebo or pre-medication group. Thus, potential changes in fetal HR parameters could be overlooked and it is difficult to conclude if atosiban or ritodrine have any effect on fetal HRV, based on this study.

A sheep study demonstrated that atosiban does not influence fetal or maternal cardiovascular parameters[33]. These findings also agree with the study by Valenzuela et al.[5], who found no differences in arterial umbilical cord blood gases in women who did or did not receive atosiban intravenously before elective caesarean section.

In summary, it seems that atosiban has no clinically important effect on fetal HRV.

Prostaglandin antagonist: indomethacin

We did not find any studies describing the effect of indomethacin on fetal HRV that matched our inclusion criteria. In a sheep study, there were no significant changes in maternal and fetal HR or blood pressure following administration of indomethacin[34]. In summary, animal studies show no effect on fetal HRV.

Selective β2-adrenergic agent: fenoterol and ritodrine

β-adrenergic receptors are divided in three subtypes; β1-receptors cause positive chronotropic, dromotropic and inotropic effects. β2-receptors cause smooth muscle relaxation and β3-receptors cause relaxation of the detrusor muscle in the bladder. In fetuses, the density of β-adrenoreceptors is low compared to adult values, resulting in a less powerful response. The higher the affinity for the β2-adrenergic receptor, the less cardiac effects are seen.

Fenoterol is a selective β2-adrenergic receptor agonist, which causes receptor desensitisation in the myometrium resulting in relaxation[35]. It has negligible α-adrenergic activity and minimal β1-adrenergic activity[36]. We did not find any studies that describe the effect of fenoterol on fetal HRV that matched our inclusion criteria. Based on visual cardiotocography, a slight increase in fetal HR (up to 10 bpm) with no changes in fetal HRV was found[37]. In accordance, Kast and Hermer[38] found an increase in fetal HR of approximately 10% (maximum 20%) following fenoterol administration in their review. This can be explained by the low affinity for the β1-adrenergic receptor, as well as by the low placental transfer of fenoterol (fetal-maternal ratio 0.40). Overall, little research is published so far concerning the effect of fenoterol on fetal HRV.

In summary, the abovementioned studies show a slight increase in fetal HR, with no changes in fetal HRV.

Ritodrine is a potent β2-adrenergic receptor agonist which causes direct relaxation of the myometrium. The β2-specificity of ritodrine is dose-related[39]. At higher dosages, other β-sympathicomimetic effects occur including cardiac stimulation and vasodilation. Fetal tachycardia, in combination with reduced fetal HRV, was observed by Neri et al.[15] in fetuses below 30 weeks of gestational age. These fetuses were considered in a subgroup analysis, as baseline fetal HR decreases and parasympathetic activity increases in the second and third trimester. In other studies ritodrine was associated with persistent fetal tachycardia[40], which tended to persist in the newborn for several days after delivery[10]. Moreover, a concentration-dependent relation between ritodrine and the fetal HR rise was found, although there was a clear inter-patient variation[41]. It is hypothesised that the immaturity of the nervous system induces an exaggerated response through heart receptor stimulation[15]. Another explanation could be that the sympathetic branch of the autonomic nervous system matures earlier than the parasympathetic branch, resulting in an exaggerated sympathetic reflex with little parasympathetic suppression[42]. In addition, ritodrine can freely pass the placenta and there is even accumulation of ritodrine in the fetal blood (fetal-maternal ratio 1.17). This can explain the more pronounced fetal tachycardia following ritodrine administration compared to fenoterol.

In summary, ritodrine seems to cause an increase in fetal HR and a decrease in fetal HRV.

Conclusions

Our search revealed that little research has been published regarding the influence of tocolytic drugs on fetal HRV. The limited available evidence indicates that both nifedipine and atosiban have no clinically important effect on fetal HRV. A decrease in fetal HRV and cases of fetal bradycardia are described following $MgSO_4$ administration. Animal studies show no effect on fetal HR parameters after indomethacin administration. Studies considering fenoterol show a slight increase in fetal HR, with no changes in fetal HRV. Ritodrine seems to cause an increase in fetal HR and a decrease in fetal HRV. Since most women treated with tocolytics also receive corticosteroids, the known profound effects of corticosteroids on fetal HR parameters should be taken into account and could overwhelm the effect of tocolytics in clinical practice. As with corticosteroids, the changes caused by several tocolytics can be erroneously interpreted as a sign of fetal distress. Therefore, physicians should be aware of these effects.

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Chapter 8

The influence of betamethasone on fetal heart rate variability, obtained by non-invasive fetal electrocardiogram recordings

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Revision pending

Abstract

Introduction

Betamethasone is widely used to enhance fetal lung maturation in case of threatened preterm labour. Fetal heart rate variability is one of the most important parameters to assess in fetal monitoring, since it is a reliable indicator for fetal distress. Spectral analysis of fetal heart rate variability can quantify the modulation of the autonomic nervous system. High-frequency power is parasympathetically mediated, while low-frequency power is both sympathetically and parasympathetically mediated. In this study, we examined the influence of betamethasone on spectral values.

Materials & Methods

We performed a prospective cohort study in a tertiary care teaching hospital. Inclusion: patients with a gestational age from 24 weeks onwards who required betamethasone. Exclusion: maternal age <18 years, fetal congenital malformation and fetal growth restriction. We performed daily non-invasive fetal electrocardiogram measurements, from hospitalisation until delivery, discharge or day 5. Recordings were analysed offline and spectral analysis was performed on extracted fetal heart rates using a continuous wavelet transform. Measurements during days 1, 2 and 3 were compared to a reference measurement (the median of day 0, and/or day 4, and/or day 5).

Results

Following 68 inclusions, 12 patients remained with complete series of measurements and sufficient data quality. Due to the low number of patients remaining, we mainly used descriptive statistics. During day 1, an increase in absolute fetal heart rate variability values (low- and high-frequency power, short- and long-term variability) was seen. During day 2, a non-significant decrease in these values was seen. All trends indicate to return to pre-medication values on day 3. Normalised high- and low-frequency power show little changes during the study period. During days 1 and 2 the number of segments in quiet state increased.

Conclusions

The changes in fetal heart rate variability following betamethasone administration show the same pattern when calculated by spectral analysis of the fetal electrocardiogram, as when calculated by cardiotocography. The change in absolute spectral values is likely to correspond to the change in quiet and active state of the fetus. Since normalised spectral values show little changes, the influence of autonomic modulation is minor.

Introduction

Cardiotocography (CTG) is used for fetal monitoring worldwide. One of the most important parameters to assess in CTG monitoring is fetal heart rate variability (HRV). Normal fetal HRV is a reliable indicator of fetal wellbeing, while decreased fetal HRV is associated with poor neonatal outcome (acidosis, low Apgar score and death)[1]. The fetal heart rate (HR), and thus HRV, is regulated by a complex interplay of the sympathetic and parasympathetic branches of the autonomic nervous system[2]. Spectral analysis (frequency analysis) of fetal HRV can be used to quantify these changes in autonomic regulation[3-8]. The low-frequency (LF)-component reflects baroreceptor reflex activity, and is both sympathetically and parasympathetically mediated[9]. The high-frequency (HF)-component is associated with fetal respiration, and is solely parasympathetically mediated[9].

Antenatal betamethasone administration plays an important role in the clinical management of threatened preterm delivery between 24 and 34 weeks of gestation (wG). It enhances fetal lung maturation and results in a significant reduction in, amongst others, neonatal mortality and respiratory distress syndrome[10]. However, betamethasone can easily cross the placenta and influence fetal autonomic modulation and thus fetal HRV[11]. Since fetal HRV is an important marker for fetal distress, knowledge on the influence of betamethasone on autonomic regulation is needed to avoid misinterpretation of changes in fetal HRV following betamethasone administration, and therefore prevent unnecessary iatrogenic preterm delivery.

Results of previous studies describing the effect of betamethasone on fetal HRV indicate that fetal HRV increases during the first day, followed by a decrease during days 2-3[12]. Values returned to baseline during day 4. However, these studies were performed using CTG and measured the fetal HR by Doppler-ultrasound. With CTG, the fetal HR is averaged over several heartbeats and therefore beat-to-beat information is lacking. As a consequence, it is not possible to perform reliable spectral analysis.

The aim of this study is to quantify the effects of maternally administered betamethasone on spectral values of fetal HRV. To perform a reliable calculation of LF- and HF-power, we extracted beat-to-beat fetal HR information from non-invasive abdominal fetal ECG recordings.

Materials and Methods

We performed a prospective, longitudinal cohort study at the Máxima Medical Centre, Veldhoven, the Netherlands. This is a tertiary care teaching hospital for obstetrics. The study protocol was approved by the Medical Ethical Committee of the Máxima Medical Centre. Participants were included after written informed consent.

Study population

As described in our study protocol, we aimed for at least 50 inclusions and expected to end with 10-20 complete sets of measurements due to the anticipated loss to follow-up in this study group. From March 2013 until July 2016, women with a singleton pregnancy, at risk for preterm delivery and admitted to the Obstetric High Care unit were asked to participate in this study. All women requiring 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. In case of threatened preterm labour, co-administration of tocolytic drugs was allowed. Nifedipine was used to attenuate uterine contractions, occasionally complemented by indomethacin in case of continuous uterine contractions when betamethasone administration was not yet completed. In case of preterm prelabour rupture of membranes, patients also received antibiotics (erythromycin 250mg 4 times daily during 10 days) as part of the standard treatment protocol. Women were excluded in case of maternal age <18 years, multiple pregnancy, fetuses with a known congenital malformation or fetal growth restriction (defined as the estimated weight of the fetus below the 5th percentile for gestational age).

The following data was gathered prospectively: maternal gravidity and parity, indication for betamethasone administration, obstetrical and general medical history, gestational age at inclusion and administered medication during the study period. Follow-up measurements of study participants lasted from the date of informed consent until five days after the first measurement, discharge or delivery, whichever occurred first. Postpartum, neonatal charts were checked for any indications of congenital anomalies that might have influenced the measurements and for missed cases of growth restriction defined as birth weight below the 5th percentile (corrected for gestational age, parity and sex of the neonate).

Outcome measures

The primary outcome was fetal HRV, which was quantified using both time-domain features (short-term variability [STV] and long-term variability [LTV]) and frequency-domain features (LF- and HF-power). As secondary outcomes, we calculated the fetal HR (in beats per minute, bpm). In addition, based on the HR variance, segments were classified into periods of

quiet state (fetal HR variance <15 bpm^2) and periods of active state (fetal HR variance >30 bpm^2)[4,13,14].

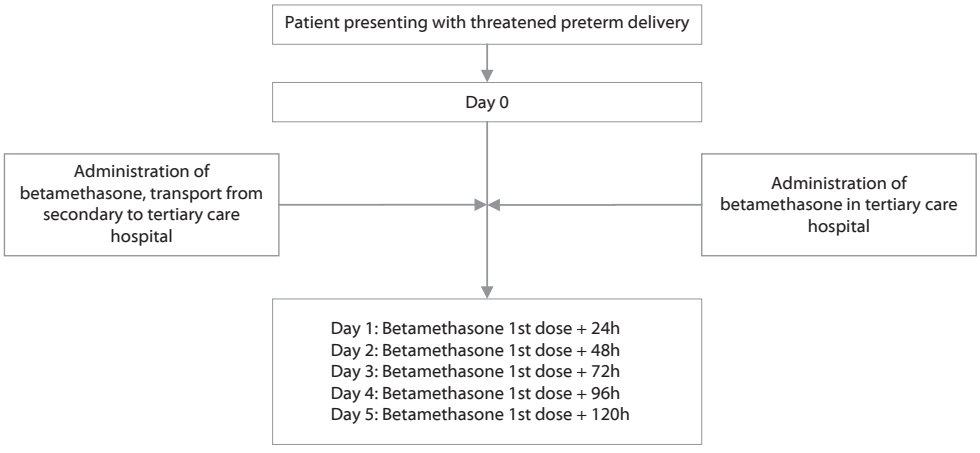
Measurements

We performed series of measurements as visualised in Figure 1. Recordings were obtained while the patient was lying in a semi-recumbent position, to prevent supine hypotension syndrome. The duration of a measurement was approximately 30 minutes in pregnancies <34 wG and 45 minutes in pregnancies ≥34 wG, to account for the influence of fetal behavioural states[4]. The total measurement was divided in segments of 60 seconds, and per segment HRV parameters were calculated. The median value of all available segments was used for statistical analysis.

To reduce the influence of diurnal variations, the timing of measurements within a series was fixed for each patient (between 20 and 28 hours after the previous measurement). In order to respect the patient's night rest, no measurements were performed between 24.00h and 7.00h.

Complete series were defined as series including a reference measurement, and measurements during at least days 1, 2, and 3. In case one or more of these measurements was missing, the patient was excluded.

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



Reference measurement

Most patients were transferred from secondary care hospitals in the region. Since for these patients betamethasone treatment was initiated prior to transport, they had no baseline measurement (0-measurement, on day 0). Former research showed that all changes in fetal HR and HRV returned to baseline values from day 4 onwards (96 hours after the first dose of betamethasone)[12]. Therefore, we included transferred patients if we were able to conduct a measurement during day 4 or 5 following the first dose of betamethasone. We used the median value of the measurements during day 0, and/or day 4, and/or day 5 as the "reference measurement". By means of a full range plot, we verified whether our reference measurement was comparable with the real 0-measurement in a separate subset of patients. Included cases with good quality measurements on day 0, and day 4, and/or day 5 were selected.

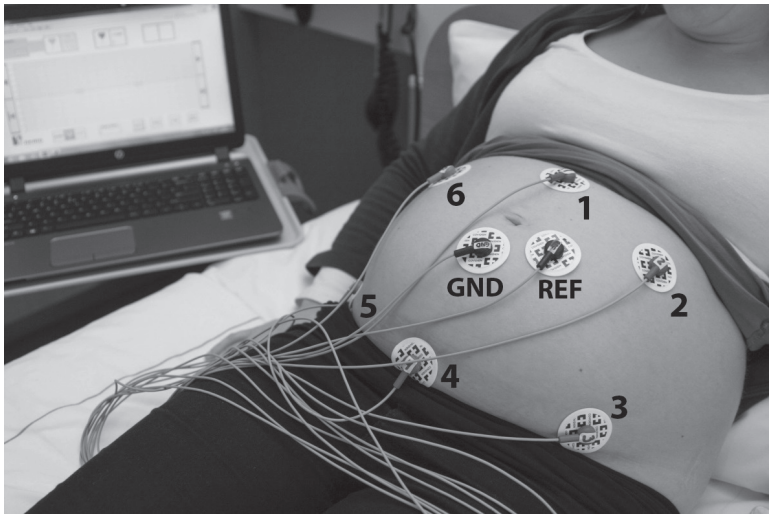
Data acquisition and signal processing

The fetal ECG was recorded on six channels, using a fixed configuration on the maternal abdomen as illustrated in Figure 2. The abdominal signals were recorded by two non-invasive electrophysiological monitoring devices; the Nemo fetal monitor (Nemo Healthcare BV, Eindhoven, the Netherlands) and the Porti system (TMSi, Enschede, the Netherlands), operating at sampling rates of 500 Hz and 512 Hz, respectively. Both devices were approved by the Medical Technical Service Department of the Máxima Medical Centre.

The recordings were analysed offline. Recordings were first pre-processed to suppress the maternal ECG using a dynamic template subtraction technique[15]. 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)[16,17]. Finally, a wavelet-based R peak detection was performed to obtain a beat-to-beat fetal HR[18]. In case no R peaks were detected using all six channels, channels with good quality fetal ECG were selected manually to avoid negative effects on the spatial combination of those channels that were dominated by interferences.

Prior to HRV analysis, the obtained heart rates were automatically analysed 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[18]. Furthermore, if an R-R interval deviated more than 12% from a running average R-R interval, it was also assumed to be incorrect[19]. 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[19]. We only included measurements with at least three segments that met the quality criteria.

Figure 2. The fetal electrocardiogram.



The six channel fetal electrocardiogram is recorded with electrodes on the maternal abdomen, placed in a fixed configuration. The ground (GND) and reference (REF) electrode are placed near the belly button. The electrodes are connected to a battery operated data acquisition system (Nemo Healthcare BV), which filters, amplifies, and digitises the data for further processing. This system is connected to a computer.

Heart rate variability analysis

Since spectral analysis requires signals that are equidistantly distributed in time, the obtained heart rates are resampled at 4 Hz by linear interpolation. Spectral analysis is performed using a continuous wavelet transform[20]. Based on previous studies, the following frequency bands were selected: total frequency 0.04 - 1.5 Hz, LF 0.04 - 0.15 Hz and HF 0.4 - 1.5 Hz[4,6,9,21,22]. LF- and HF-power was expressed in absolute units (ms^2) and normalised units (LFn = LF-power/total power, HFn = HF-power/total power).

In addition to spectral powers, STV and LTV were calculated to compare our results to prior research performed with CTG measurements. LTV was calculated as the difference between the maximum and minimum R-R interval in every 60 seconds segment[23,24]. STV was calculated as the mean of absolute differences between consecutive R-R intervals in every 60 seconds segment[24]. Note that in CTG (ultrasound) monitoring, STV is defined based on epochs (e.g. 1/16th of a minute) because fetal HR is not acquired beat-to-beat. However, since the gold standard for STV is beat-to-beat variation[23], we used the aforementioned ECG-based STV calculation.

Statistical analysis

Descriptive statistics were used to describe the study population. Statistical analysis was performed using SPSS software version 23 (IBM Corp., Armonk, NY, USA). For each fetus a different number of segments were available during the study period, mainly due to variations in ECG signal quality. Median values and interquartile ranges were calculated for HR, LTV, STV and the different spectral values (LF, HF, LFn, HFn). The results were plotted over the four day measurement period. The result on each day was compared to the reference measurement. Statistical analysis was performed using the Wilcoxon signed-rank test. Statistical significance was assumed at the two-sided p-value of <0.05.

Results

Initially, 68 women were included in this study. The inclusion process is depicted in Figure 3. Three patients requested withdrawal from the study because of poor prognosis for an extreme premature child (1), technical issues (1) and inconvenient timing of measurements for the patient (1). In one patient unexpected intra-uterine fetal death occurred during the study period. Extensive evaluation revealed no evident cause. In 28 patients we were able to obtain a complete set of measurements, of which 16 were excluded due to insufficient data quality (fewer than three good quality segments per measurement) in one or more of the measurements. Eventually, 12 patients with a complete set of sufficient data quality were included for analysis. Table 1 shows the patient characteristics of the 12 included cases.

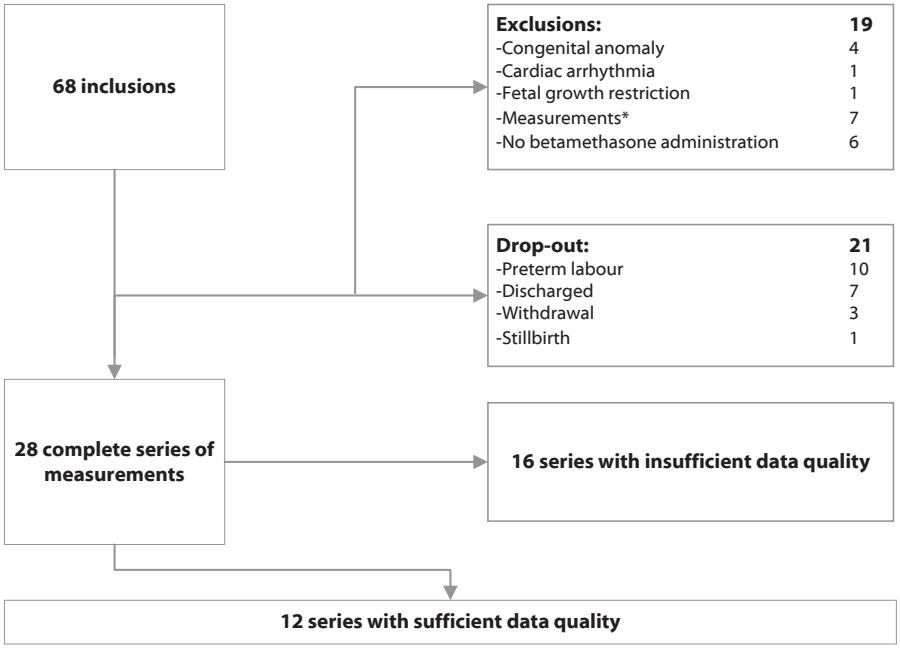
Reference measurement

Measurements during day 0, and/or day 4, and/or day 5 were compared in five patients. In Figure 4, absolute LF, HF, LFn and HFn are displayed. As expected, the absolute fetal HRV values showed some inter- and intra-patient variation, which can mainly be explained by variation in the segments that were recorded during active and quiet states and by variation in gestational age of the fetuses. LFn and HFn showed rather good comparability during day 0, 4, and 5.

Primary outcome

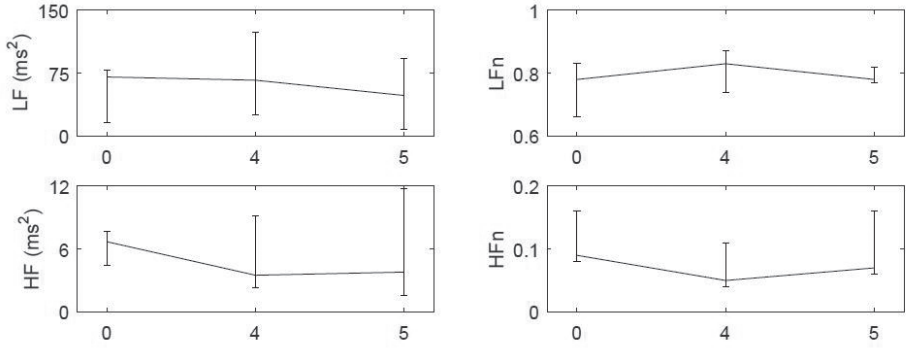
Our primary outcome was fetal HRV. Figure 5 shows the changes in LTV, STV, absolute LF and HF and normalised LFn and HFn. Only the increase in HF-power during day 1, compared to the reference measurement (day 0) was statistically significant ($p = 0.025$). All other trends were not statistically significant.

Figure 3. Overview of the inclusion process.



* Patients were excluded if the measurements were not performed within the time window (between 20 and 28 hours after the previous measurement), had one or more missing measurement in the series, or were insufficient in data quality.

Figure 4. Verification of the reference measurement.



Median value and full range plot of low-frequency (LF)-power, high-frequency (HF)-power, normalised LF-power (LFn) and normalised HF-power (HFn) on days 0, and/or day 4, and/or day 5 for five patients.

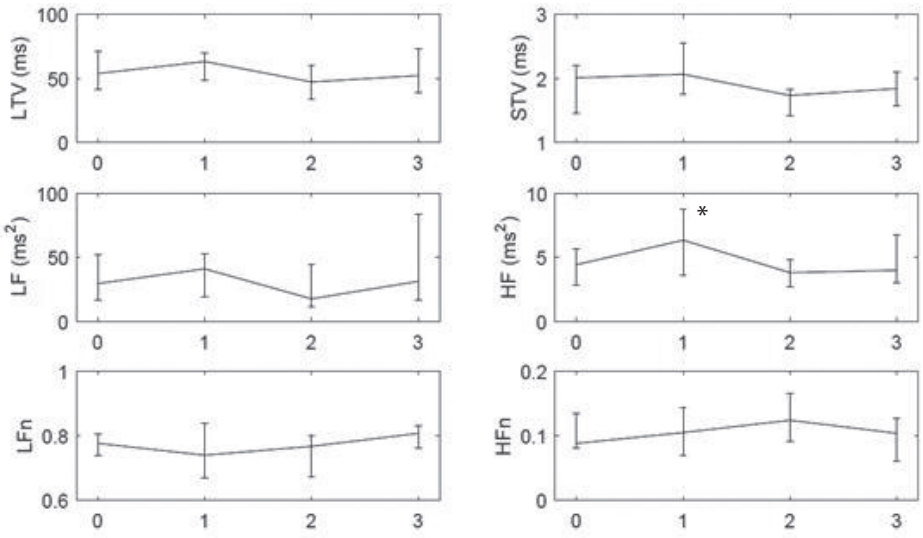
Table 1. Patient characteristics and pregnancy outcome.

Case	Maternal gravidity, parity	Indication	Relevant history	wG at inclusion	Medication during study period (other than betamethasone)	wG at delivery	Birth weight percentile	Apgar Score 1'/5'	NICU admission
1	G1P0	TPL	-	24+4	Nifedipine, indomethacin, LMWH	25+4	50	7/8	Yes
2	G1P0	PE	May-Turner, thrombosis	33+4	LMWH, methyldopa	34+3	5-10	9/10	No
3	G2P1	VBL	Gestational diabetes	31+1	Progesterone (vaginal), nifedipine, augmentin	33+5	50-80	9/10	No
4	G2P1	PPROM	-	33+0	Nifedipine, erythromycin	34+1	50-80	8/9	No
5	G2P1	TPL	-	26+2	Nifedipine	39+5	50-80	5/9	No
6	G1P0	TPL	LEEP	29+2	Nifedipine	40+1	80	9/10	No
7	G1P0	VBL	-	25+2	-	38+1	20-50	9/10	No
8	G2P1	TPL	Pre-existent hypertension	26+1	Nifedipine, labetalol, magnesium sulphate, indomethacin	36+6	50-80	8/10	No
9	G2P1	TPL	-	25+6	Nifedipine, progesterone (vaginal)	40+4	50	9/10	No
10	G2P1	VBL	-	33+0	Iron tablets	37+5	90-95	9/10	No
11	G1P0	TPL	-	30+6	Nifedipine	32+6	>97	9/10	No
12	G1P0	VBL	LEEP	26+6	-	33+5	50-80	?/10	No

Birth weight percentile: percentiles are corrected for parity, gestational age at delivery and sex, and apply to the Dutch population. Source: Perined.

Abbreviations: LEEP = loop electrosurgical excision procedure of the cervix, LMWH = low molecular weight heparin, NICU = neonatal intensive care unit, PE = pre-eclampsia, PPROM = premature prelabour rupture of membranes, TPL = threatened preterm labour, VBL = vaginal blood loss, wG = weeks of gestation.

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



The x-axis shows the number of days after the first administration of betamethasone. Day 0 is the median value of the measurements during day 0, and/or day 4, and/or day 5. The outcomes are depicted as median values with interquartile ranges.
* ; statistically significant result.

Abbreviations: LF = low-frequency power, LFn = normalised low-frequency power, LTV = long-term variability, HF = high-frequency power, HFn = normalised high-frequency power, STV = short-term variability.

Secondary outcomes

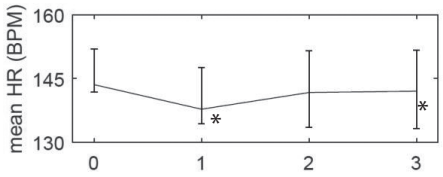
Figure 6 shows the changes in mean fetal HR during the study period. There was a statistical significant decrease in fetal HR during both day 1 ($p = 0.007$) and day 3 ($p = 0.040$), compared to the reference measurement.

The changes in the number of segments measured during quiet state (fetal HR variance <15 bpm^2) and active state (fetal HR variance >30 bpm^2) during the study period are displayed in Figure 7. During days 1 and 2, the number of segments in quiet state increased, while the number of segments in active state decreased. The number of segments in quiet and active state seemed to return to pre-medication values again from day 4.

Segments available for analysis

The amount of segments that was available for analysis is displayed in Table 2.

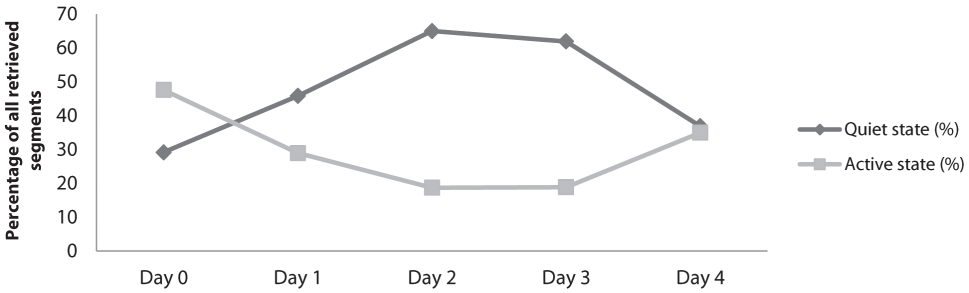
Figure 6. Changes in fetal heart rate during the study period.



The x-axis shows the number of days after the first administration of betamethasone. Day 0 is the median value of the measurements during day 0, and/or day 4, and/or day 5. Data are shown as median values with interquartile ranges.
* ; statistically significant result.

Abbreviations: HR = heart rate, BPM = beats per minute.

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



Overview of the changes in periods of quiet state (fetal heart rate variance <15 bpm^2) and active state (fetal heart rate variance >30 bpm^2). Results are displayed as a percentage of the total number of analysed good-quality segments.

Discussion

General discussion

Up to our knowledge, this is the first study to report on the influence of betamethasone on spectral estimates of fetal HRV measured by non-invasive fetal ECG recordings. As we anticipated, over 80% of our inclusions could not be used in the final analysis. This was mainly due to loss to follow-up and insufficient data quality. Therefore, our study results should be interpreted with appropriate caution, since only a limited number of series (12) could be used for data analysis.

Table 2. Amount of segments available for analysis.

	Segments available for analysis/ total recorded segments	Percentage of segments available for analysis
Reference measurement		
Day 0[a]	103/110	94%
Day 4	201/305	66%
Day 5[b]	162/278	58%
Day 1	332/580	57%
Day 2	214/403	53%
Day 3	223/407	55%

[a] Day 0: measurements performed in 3 out of 12 patients.

[b] Day 5: measurements performed in 9 out of 12 patients.

On the other study days, measurements were performed in all 12 patients.

Primary outcome measures

We found a similar trend in LTV and STV with fetal ECG analysis as compared to previous studies that used CTG analysis[12]. No significant differences were found between the successive study days. This might be due to the small number of analysed series. A more accurate way to evaluate autonomic modulation is spectral analysis of the beat-to-beat fetal HR. LF- and HF-power are absolute spectral estimates, that relate to LTV and STV. As expected, the same trends are seen during the study period for these parameters. Only the increase in HF-power on day 1 was statistically significant. No significant changes were seen in LFn and HFn. Due to normalisation, relative changes in LF- and HF-power are not masked by changes in total power. Both LFn and HFn show little changes during the study period. This indicates that the influence of autonomic modulation is minor.

Secondary outcome measures

The significant changes seen in fetal HR are unlikely to resemble a clinically important effect, since the median HR was 144 bpm on the reference day, 138 bpm on day 1, and 142 bpm on day 3. In prior studies with CTG monitoring, the significant decrease on day 1 was also observed[12].

Figure 7 shows an increase in the number of segments in quiet state, while the number of segments in active state decreases. As described in a previous study, LF- and HF-power are significantly lower in the quiet state, compared to the active state[25]. This can explain the changes seen in absolute spectral values in our study. In addition, it corresponds with the reduced fetal motility that patients report during betamethasone treatment[26-29]. However, one should take into account that in Figure 7, the amount of available segments is limited and varies between the study days.

Segments available for analysis

As shown in Table 2, the mean available amount of segments per day was always more than 50%. One has to bear in mind that this is in selected series with sufficient quality of the performed measurements. There are no obvious differences between the measurement days; the amount of available segments is steady between 52% and 57%. Only the measurements performed on day 0 show a higher percentage of available segments. However, only 3 out of 12 patients were eligible for a measurement during day 0.

Considerations

We defined the reference measurement as the median value of the measurements during day 0, and/or day 4, and/or day 5. Although good comparability was seen for fetal HRV values, this remains second best with regard to a true baseline measurement. The high number of measurements that had to be excluded due to poor signal quality, can mainly be explained by presence of vernix caseosa. This fatty layer surrounds the fetus and results in an electrical isolation, which diminishes the signal amplitude of the fetal ECG. Especially between 30 and 34 wG, this layer causes a poor signal-to-noise ratio[25,30].

By including patients receiving other pregnancy-related drugs rather than betamethasone, we aimed to obtain information that is applicable in daily clinical practice. Nifedipine and indomethacin seem to have no clinically important effect on fetal HRV, while magnesium sulphate can cause decreased fetal HRV and cases of bradycardia have been described[31]. In one case, magnesium sulphate was administered during days 1, 2 and 3 of the study period. Since magnesium sulphate was not administered during the reference measurement, this might have had some influence on the study results. In one case labetalol was administered to the patient; this was already started prior to the measurements and no changes in dosage occurred during the study period. Therefore, it is not likely that this had major influence on the study results. It is unlikely for augmentin, low-molecular weight heparin, methyldopa and progesterone to have any influence on fetal HRV parameters due to their mechanism of action.

Apart from pathological conditions, two major factors that one should consider when assessing fetal HR patterns are gestational age and fetal behavioural states[32]. Previous studies show that gestational age significantly affects the fetal HRV power spectrum, with a gradual increase in LF- and HF-power during gestation[13,25,33]. In this study, the included fetuses had a gestational age varying from 24 to 33 wG. Since we studied fetuses on successive days and were interested in relative changes in fetal HRV parameters, the influence of the increase in LF- and HF-power during gestation is likely to be minor. This study demonstrated an increase

in time spent in the quiet state following betamethasone administration. This might be caused by disturbance of the maternal glucose metabolism[34], which is a known side effect of corticosteroids.

Fetal HRV and fetal movements are two parameters associated with fetal wellbeing. The reduction in both, due to betamethasone administration, can be misinterpreted as fetal deterioration and can therefore possibly lead to unnecessary iatrogenic preterm delivery[35,36]. No other signs of fetal hypoxia, like decelerations or abnormalities in Doppler flow velocity waveforms, have occurred after corticosteroid administration[29,35-38]. In addition, Shenhav et al.[39] demonstrated that reduced fetal HRV was not related to the fetal acid-base balance at birth when delivery occurred <48 hours following betamethasone administration. This study confirms these results, since the influence of autonomic modulation was found to be minor (reflected as no evident changes in normalised spectral powers during the study period). Therefore, administration of betamethasone is not related to fetal distress. However, in fetal monitoring it is important to be aware of the side-effects, such as reduced fetal HRV and fetal movements.

Conclusion

The changes in fetal HRV following betamethasone administration show the same pattern when calculated by spectral analysis of the fetal ECG, as when calculated by Doppler-ultrasound CTG. The change in absolute spectral values is likely to correspond to the change in quiet and active state of the fetus. Since normalised spectral values show little changes, the influence of autonomic modulation is minor.

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Part III

Fetal ECG to prevent asphyxia

Chapter 9

Orientation of the electrical heart axis in mid-term pregnancy

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Letter to the Editor – Brief communication

Introduction

The unique fetal shunting system causes an increased cardiac muscle mass in the right ventricle[1]. Cardiac currents initiating each contraction are measured from the outside as the electrocardiogram (ECG), the main direction of propagation is referred to as the electrical heart axis. Ventricular depolarisation involves the largest cell mass, yielding the largest ECG signal. Therefore, the QRS segment amplitude mainly defines the electrical heart axis. Due to the increased right ventricular mass in fetuses, the electrical heart axis is expected to point towards the right. This has been confirmed in term fetuses during labour and in neonates directly postpartum[2,3]. In contrast, the electrical heart axis of adults points towards the left[4]. However, it is well-known that in both adults and newborns the orientation of the electrical heart axis can vary widely from person to person[2].

For term fetuses during labour, the orientation of the electrical heart axis has been described by Larks et al.[3] in the 1960s. Their recording techniques are outdated, and they did not take the fetal orientation into account. Despite these shortcomings, they already acknowledged the possibilities of the electrical heart axis to contribute in distinguishing between normal intra-uterine development, congenital heart disease and fetal distress.

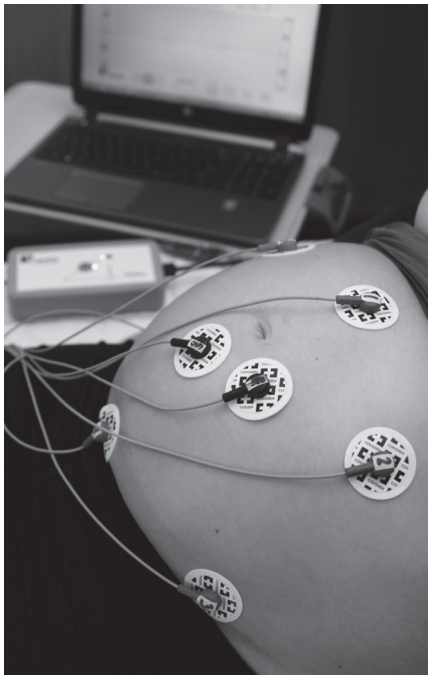
The orientation of the fetal electrical heart axis during gestation has never been described. The relevance of the electrical heart axis increased, since fetal ECG is used to study fetal wellbeing more often. The aim of this study is to determine the direction of the fetal electrical heart axis in mid-term pregnancy.

Materials and Methods

We performed a post-hoc analysis on data of two (prospective) studies, both approved by the ethical committee of the Máxima Medical Centre[5]. Informed consent was obtained in both studies. Women between 18 and 29 weeks of pregnancy, carrying a singleton fetus were included. Exclusion criteria were maternal age <18 years, multiple pregnancy, any known fetal congenital anomaly, fetal growth restriction (birth weight <p10 for gestational age) and women receiving medication known to have any cardiac side effects. The absence of severe cardiac malformations was confirmed after birth by review of medical charts.

We conducted a single fetal ECG recording of approximately 30 minutes with eight adhesive electrodes on the maternal abdomen, placed in a fixed configuration (Figure 1). Recordings were performed using a fetal ECG data acquisition system (Nemo Healthcare BV, the Netherlands), operating at a sampling frequency of 1 kHz. The fetal ECG was obtained and analysed from the abdominal recordings to yield a vectorcardiogram that is normalised for the fetal

Figure 1. Configuration of the electrodes on the maternal abdomen.



orientation via a series of signal processing methods, as depicted in Figure 2 and previously described in other studies[6-10].

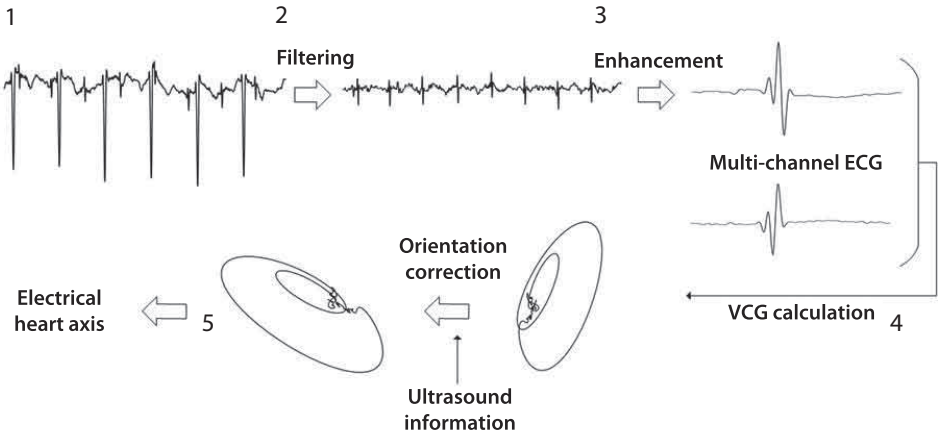
From this normalised fetal vectorcardiogram we obtained the orientation of the electrical heart axis expressed as degrees ranging from -180 to +180, as the direction in which the vectorcardiogram has its maximum amplitude. This direction was defined as the average direction of dominant vectors in the QRS complex. These dominant vectors were selected from the point where the R wave exceeded 70% of its maximum value for the first time until the point where the R wave fell below the 70% again[11]. Per fetus, a mean value of the orientation of the electrical heart axis was calculated from the time period of 50 seconds prior to and 50 seconds following the ultrasound localisation of the fetus in case of good signal quality (at least 80 fetal ECG complexes).

To enable statistical analysis of our results, we categorised the orientations of the electrical heart axis. Both in the frontal and left-sagittal plane we defined 12 categories of possible orientations, the first ranging from 0-30°, the second from 30-60°, and so on. The mean orientation of the electrical heart axis per fetus is displayed in a histogram. Matlab (The Mathworks, Natick, MA) was used to perform the statistical analysis. Kolmogorov-Smirnov test was used to test whether the distribution of scores was significantly different from a normal distribution. A p-value ≤0.05 was considered to be statistically significant.

Results

We included a total of 25 pregnant women between 18+1 and 28+1 weeks of gestation. Patient characteristics and neonatal outcome are summarised in Table 1. There were no cases of asphyxia or perinatal death. Three pregnancies ended in very preterm labour. Two, at 27+2 and 28+6 weeks respectively, because of vaginal blood loss due to placenta praevia, and one at 31+3 weeks due to spontaneous preterm labour. The interval between the fetal ECG recording and the preterm birth was more than three weeks in all cases.

Figure 2. Signal processing steps.



From top left, via a clockwise rotation to bottom left;

1. The signal is recorded by the electrodes on the maternal abdomen. Note that the large peaks are maternal QRS complexes, the small peaks that occur approximately twice as frequent as the maternal QRS are the fetal QRS complexes.

2. The signal obtained after filtering the maternal ECG and other interferences. First, interferences such as powerline and (uterine) muscle activity were suppressed by bandpass filtering the recorded signals between 1 and 70 Hz and applying a notch filter that was centered around the powerline frequency. Second, the maternal ECG was suppressed using a technique that dynamically generates a template of the maternal ECG[8] and subsequently subtracts this template from the recorded data. Third, we detected the individual fetal ECG complexes by firstly spatially combining the various recorded channels[9] and subsequently detecting the fetal QRS complexes using a low-complexity R peak detection method[7].

3. The fetal ECG is enhanced by averaging the ECG across multiple heartbeats, where the number of heartbeats is dynamically varied by an adaptive Kalman filter and depends on the quality and stationarity of the ECG signal[6]. For every electrode an average ECG signal is determined.

4. Using knowledge on the placement of the electrodes, we calculated the fetal vectorcardiogram by spatial combination of multi-channel fetal ECGs[10]. In case the fetus would change its orientation in the uterus, the vectorcardiogram would rotate with the fetus.

5. Rotated version of the fetal vectorcardiogram. To determine the vectorcardiogram in the fetal frame of reference, similarly as an adult vectorcardiogram would be determined, we performed an ultrasound examination to determine the fetal orientation simultaneously with the ECG measurements. The rotated fetal vectorcardiogram represents a standardised view of the fetal vectorcardiogram (i.e. as if it were recorded with electrodes placed directly on the fetal body). From the standardised view, the fetal electrical heart axis is calculated.

Abbreviations: ECG = electrocardiogram, VCG = vectorcardiogram.

Table 1. Characteristics of the study population.

Variable		n
Maternal age (years)	30 ± 4.5	25
BMI (kg/m^2)	24.7 ± 4.7	25
Nulliparous	18 (72%)	25
GA at measurement (weeks)	24.1 (22.3-24.5)	25
GA at delivery (weeks)	39.3 (37.6-40.9)	25
Birthweight (g)	3285 (2950-3730)	25
Sex (n male)	16 (64%)	25
Apgar score at 1 minute	9 (9-9)	25
Apgar score at 5 minutes	10 (10-10)	25
Cord artery pH	7.27 (7.21-7.29)	23
Cord vene pH	7.33 ± 0.07	17
Metabolic acidosis (n)	0 (0%)	25

Data is presented as mean with standard deviation (±), median with interquartile range (Q1-Q3), or number with percentage (%).

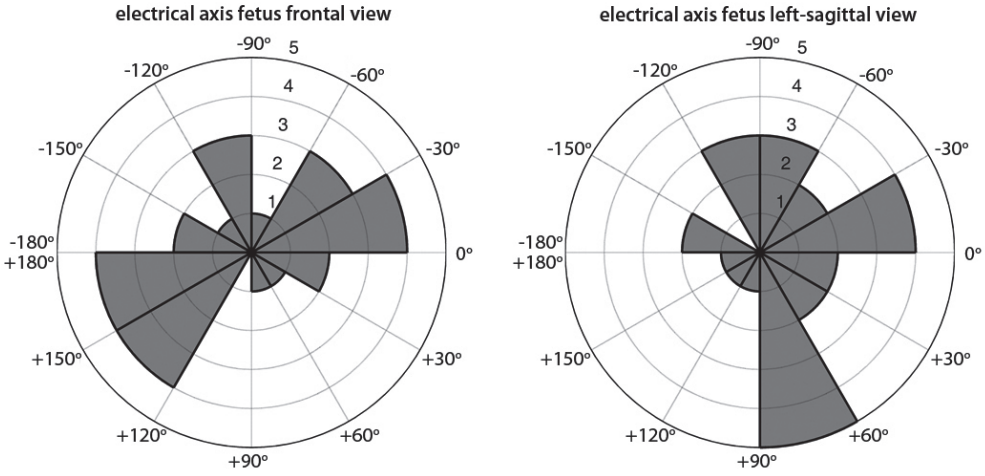
Abbreviations: BMI = Body Mass Index, GA = Gestational Age, n = number.

Figure 3 presents the observed orientation of the fetal electrical heart axis, which shows a considerable amount of variation. In the frontal view, the heart axis points towards the right in most cases. In the left-sagittal view, the heart axis points towards the back in most cases. The orientation of the electrical heart axis in the frontal view varied significantly from a normal distribution; p = 0.016, Kolmogorov-Smirnov test. In the sagittal view, the orientation of the electrical heart axis did not differ significantly from a normal distribution (p = 0.22, Kolmogorov-Smirnov test).

Comment

Although our study population is relatively small, the results are in line with our hypothesis that the fetal heart axis points towards the right due to the increased mass of the right ventricle. In term fetuses during labour, the main direction of the fetal heart axis is to the right (between +100° and +160°)[12]. In neonates directly postpartum, the QRS axis in the frontal view varies between +60° and +160° and the vectorcardiogram points mainly to the right-inferior-anterior direction[2,13,14]. As the mass of the left ventricle increases with age, the orientation of the electrical heart axis gradually deviates toward the left. At the age of one year, the electrical heart axis points to the left (between +10° and +100°)[13]. Normal values in adults vary between -30° and +90°[4]. This all indicates that there is a shifting continuum between the orientation of the electrical heart axis in fetal, neonatal and adult life.

Figure 3. Histograms of the orientation of the electrical heart axis in 25 healthy fetuses.



For every fetus, the orientation of the electrical heart axis was determined in both the frontal plane (left histogram) and left-sagittal plane (right histogram). This orientation was subsequently scored in the corresponding histogram, which were defined by dividing all possible orientations, which range between -180° and +180°, in 12 bins of each 30° width. The number of counts per bin are displayed by means of the grey areas in the histogram plots.

In addition, the distribution of orientations of the electrical heart axis in Figure 3 shows that during mid-term pregnancy, this orientation varies as much as it does in newborns and in adults. Because the electrical heart axis determines the fetal ECG waveform, it is extremely important for fetal ECG interpretation that the electrical heart axis is taken into account. Alternative direction of the main fetal electrical heart axis has direct consequences for the fetal ECG.

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Chapter 10

The electrical heart axis and ST events in fetal monitoring: a post-hoc analysis following a multicentre randomised controlled trial

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Abstract

Objective

Reducing perinatal morbidity and mortality is one of the major challenges in modern health care. Analysing the ST segment of the fetal electrocardiogram was thought to be the breakthrough in fetal monitoring during labour. However, its implementation in clinical practice yields many false alarms and ST monitoring is highly dependent on cardiotocogram assessment, limiting its value for the prediction of fetal distress during labour. This study aims to evaluate the relation between physiological variations in the orientation of the fetal electrical heart axis and the occurrence of ST events.

Methods

A post-hoc analysis was performed following a multicentre randomised controlled trial, including 1097 patients from two participating centres. All women were monitored with ST analysis during labour. Cases of fetal metabolic acidosis, poor signal quality, missing blood gas analysis, and congenital heart disease were excluded. The orientation of the fetal electrical heart axis affects the height of the initial T/QRS baseline, and therefore the incidence of ST events. We grouped tracings with the same initial baseline T/QRS value. We depicted the number of ST events as a function of the initial baseline T/QRS value with a linear regression model.

Results

A significant increment of ST events was observed with increasing height of the initial T/QRS baseline, irrespective of the fetal condition; correlation coefficient 0.63, $p < 0.001$. The most frequent T/QRS baseline is 0.12.

Conclusion

The orientation of the fetal electrical heart axis and accordingly the height of the initial T/QRS baseline should be taken into account in fetal monitoring with ST analysis.

Introduction

Fetal asphyxia is associated with severe perinatal morbidity and mortality. The cardiotocogram, a simultaneous recording of the fetal heart rate and uterine contractions, is used worldwide for fetal surveillance. However, the poor specificity of this method has resulted in increased rates of operative deliveries without a decrease in perinatal mortality or cerebral palsy[1]. ST analysis (STAN®, Neoventa Medical AB, Mölndal, Sweden) was introduced in 1992 as a promising technique that analyses the ST segment of the fetal electrocardiogram (ECG), acquired using an invasive scalp electrode[2]. ST analysis combined with cardiotocography was reported to significantly lower the rates of metabolic acidosis[3] and operative delivery in two randomised controlled trials[3,4]. However, subsequent multicentre trials, including the recently published large American ST analysis trial, could not reproduce these initial findings[5-9]. Recent meta-analyses show conflicting results regarding the decrease in metabolic acidosis, which indicates the need for more research[8,10-13]. Meanwhile, Kwee et al.[14] reported that the STAN® monitor gives as many ST events in cases of proven uncompromised fetal condition as in situations with deteriorating fetal condition. This is countered by the STAN® guidelines that state that ST events must be ignored when cardiotocography shows a reassuring pattern. However, the high inter-observer variability in cardiotocogram interpretation makes this a highly unsatisfying strategy[15]. The correct interpretation of a method as subjective as the cardiotocogram determines whether or not to ignore the ST event or to act upon the alarm, making the success of ST monitoring dependent on cardiotocogram assessment.

Background information and hypothesis

Prior to the introduction of ST analysis, the diagnostic value of the fetal ST segment was clearly demonstrated in animal studies[16-18]. Sustained deprivation of oxygen is followed by a surge of adrenalin to induce glycogenolysis, which is accompanied by an increase of potassium ions in the myocardial cells[19]. These potassium ions mainly affect the relaxation phase of the cardiac cycle and lead to an increase in the T wave amplitude of the fetal ECG[20].

STAN® uses this hypoxia-related rise in T wave amplitude in a three-step protocol;

1. The T wave amplitude is normalised against the amplitude of the QRS complex (mean of 30 ECG complexes), yielding a T/QRS value.

2. A baseline T/QRS value is determined (median of at least 20 T/QRS values within 20 minutes) to gauge future T/QRS values.

3. New T/QRS values are compared to the baseline.

In case a T/QRS value exceeds the baseline by 0.05, a baseline ST event is reported. Smaller exceedings of the baseline can be due to normal beat-to-beat fluctuation in the behaviour of the heart, which is unrelated to the fetal condition. With regard to the detection of rises in T wave amplitude due to oxygen deprivation, this alarm protocol seems plausible.

The ECG recorded from the fetal scalp electrode is a one-dimensional presentation of the electrical activity of the heart. However, the propagation of electrical currents over the cardiac muscle occurs in all three spatial dimensions. The main direction of this propagation is referred to as the electrical axis of the heart. The orientation of the electrical heart axis with respect to the fetal scalp electrode hence affects the shape and amplitude of the recorded ECG. Similarly, (adult) ECG signals recorded at different locations yield different shapes and amplitudes, as already demonstrated many years ago[21].

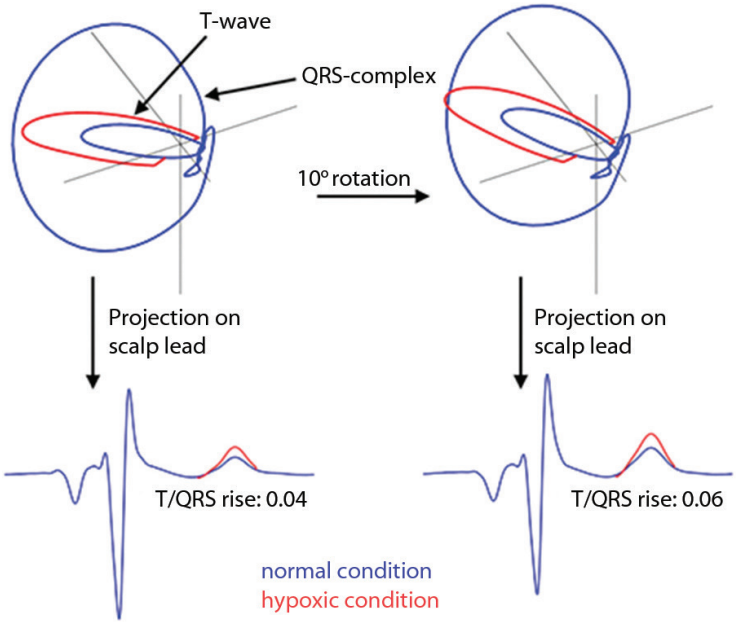
It is known that the orientation of the fetal electrical heart axis can vary between +100° and +160° in mid-term fetuses[22] and between +90° and +180° in term fetuses during labour[23]. Similar inter-person variation in the orientation of the electrical heart axis is present in neonates and adults[24-27]. The STAN® monitor attempts to correct for the orientation of the electrical heart axis with the first step in its protocol (normalisation). However, the propagation of the electrical currents during the contraction (QRS) phase of the cardiac cycle has a different orientation than during the relaxation (T) phase. Consequently, normalisation cannot fully compensate for inter-patient differences in the orientation of the electrical heart axis. As a result, fetuses for whom the scalp lead is almost perpendicular to the direction of propagation in the relaxation phase have a very small T wave amplitude, and typically also low T/QRS values and T/QRS baseline. Similarly, fetuses for whom the electrical heart axis is oriented in a manner creating a propagation during relaxation almost aligned with the scalp lead, typically have a high T/QRS value and T/QRS baseline.

When the hypoxia-induced release of potassium ions affects the electrical current in the relaxation phase in the fetuses with a low T/QRS baseline value, the absolute effect in T wave amplitude will only be marginal as we look at it from an almost perpendicular direction. In fetuses with high T/QRS values, the rise in T wave amplitude will be relatively large. Based on this, we hypothesise that normal fluctuations in the electrophysiological behaviour of the heart can stay below the 0.05 threshold, in case the scalp lead is oriented more perpendicular to the relaxation currents. Similarly, the hypoxia-related fluctuations in the electrical behaviour can more easily exceed the 0.05 threshold, when the alignment between the electrical heart axis and scalp lead is axial. We explain this phenomenon in Figure 1. Previously, Becker et al.[28] described that the initial T/QRS baseline is not related to the fetal condition. The incidence of ST events was stated to be related to the fetal condition[3], and therefore not

related to the baseline. This is in contrast with our hypothesis that the STAN® monitor will raise fewer ST events for fetuses with a low baseline, and more ST events for fetuses with a high T/QRS baseline.

This paper aims to explain how false ST events can occur, based on normal variations in human physiology. Based on this explanation, clinicians might be able to make a better informed decision whether or not to act upon a ST event in case of inconclusive cardiotocogram assessment.

Figure 1. The fetal vectorcardiogram for different orientations of the electrical heart axis.



In the top panels, the electrical currents within the heart during a cardiac cycle are depicted in terms of their vectorcardiogram; ventricular contraction (QRS complex = large loop), relaxation phase (T waves = small loop). From left to right, the entire vectorcardiogram has been rotated over 10° to simulate a different orientation of the electrical heart axis. Note that these vectorcardiograms are 3-dimensional images and the 10° rotation was performed in 3-dimensional space. In the bottom panels, the fetal scalp electrocardiogram has been calculated by projecting the vectorcardiograms onto the scalp lead. Before rotation, the baseline T/QRS is 0.05 and the T/QRS rise resulting from hypoxia is 0.04, yielding no ST event. After rotation, the baseline T/QRS is 0.09 and the T/QRS rise resulting from the same level of hypoxia is 0.06, yielding a ST event.

Materials and Methods

We performed a post-hoc analysis with data derived from a large multicentre randomised controlled trial, the Dutch ST analysis trial[7]. The initial study was approved by the Institutional Review Board of the University Medical Centre Utrecht and was performed between January 2006 and July 2008. After written informed consent, women were randomised to the index group with ST monitoring (STAN® S21 or S31 monitor) or to the control group, using a conventional fetal heart rate monitor (cardiotocography). The randomisation was performed on a 1:1 basis, web-based with stratification for centre and parity. Since the trial was pragmatic in nature, there was no blinding of patients or caregivers. All gynaecologists, residents and midwives in the participating centres were trained and certified as STAN®-users, and decisions were made following the STAN® clinical guidelines. Fetal blood sampling was allowed, yet restricted to specific scenarios in the index group. Inclusion criteria were maternal age over 18 years, singleton pregnancy, cephalic presentation, gestational age beyond 36 weeks and an indication for internal electronic fetal monitoring. The included women were assigned to a "high-risk pregnancy" group, since they all received secondary care. In the Netherlands, "low-risk pregnancies" are monitored by midwives or general practitioners (primary care). In both groups, the umbilical cord was double clamped immediately after birth, in order to sample both arterial and venous cord blood.

For this post-hoc analysis, we included data from two tertiary hospitals: the University Medical Centre Utrecht and the Máxima Medical Centre Veldhoven, both participating in the multicentre randomised controlled trial. Anonymised information from the initial database was used for this analysis. Following consultation of the Medical Ethical Department in the Máxima Medical Centre, no separate ethical approval was warranted for this study. We only included patients from the index group (with ST monitoring). We excluded patients in whom no STAN® registration was performed or no T/QRS baseline value could be determined, cases of metabolic acidosis, cases in which no blood gas analysis was performed postpartum and registrations performed in fetuses with congenital heart disease. Metabolic acidosis was defined as umbilical cord artery blood pH <7.05 and base deficit of the extracellular fluid compartment >12 mmol/l in two blood samples with a minimal pH difference of 0.03. In cases of only one blood sample or smaller differences between samples, metabolic acidosis was set as cord blood pH <7.10 and base deficit of extracellular fluid >12 mmol/l.

The initial baseline T/QRS value was determined the same way as done in the STAN® monitor; as the median of all T/QRS values recorded within the first 20-minute window of the recording, that contained a minimum of 20 T/QRS values. We counted the incidence of ST events throughout the entire registration. Patients were excluded in case a STAN® registration

was temporarily stopped and more than one STAN® file was stored for the patient. For each initial baseline T/QRS value encountered in our data set, we counted the number of patients with that particular baseline. We grouped women with the same initial baseline T/QRS value. Hereafter, we calculated the relative incidence of ST events (defined as the number of ST events per 1000 T/QRS values) as a function of the initial baseline value.

Additionally, we calculated the mean pH and mean base deficit of the extracellular fluid for all women with the same initial baseline T/QRS value. Even though our dataset entails a subset of the data used by Becker et al.[28], it needs to be confirmed that the conclusions from this study, that the height of the initial baseline is not related to fetal outcome, apply to our dataset as well.

Matlab (The Mathworks, Natick, MA) was used to perform the statistical analysis. For analysis of the baseline characteristics, mean, median, standard deviation and interquartile ranges were calculated using IBM SPSS statistics 22.0 for Mac (IBM corp. Armonk, NY, USA). A linear regression model was used to calculate the correlation coefficient for the relation between the number of ST events and the baseline T/QRS value.

Results and Discussion

Initially, 1401 patients were screened; in 273 cases ST information was missing, more than one STAN® file was available for the same patient, or no T/QRS baseline value had been determined due to short duration of the measurement or poor quality of the data. These cases were therefore excluded. In addition, we excluded 11 cases of fetal metabolic acidosis. Further, no blood sample was available in 12 patients, whom were therefore excluded. In addition, six women gave birth to neonates with congenital heart disease, one labouring woman younger than 18 years and one prior to 36 weeks of gestation during labour were excluded. Eventually, we analysed the number of ST events in 1097 women. In this group, a total of 1.027.054 T/QRS ratios and 2066 ST events were reported.

The baseline characteristics of the included women are summarised in Table 1.

Figure 2 shows the distribution of patients across the various initial baseline T/QRS ratios. In Figure 3, we present the number of ST events as a function of the initial baseline T/QRS value. The results show an average increment of 1.42 ST events per 1000 T/QRS values for a rise of 0.1 of the initial baseline T/QRS. The correlation coefficient between data points and fit was 0.63 ($p < 0.001$), as calculated with the linear regression model.

Table 1. Baseline characteristics of the included patients.

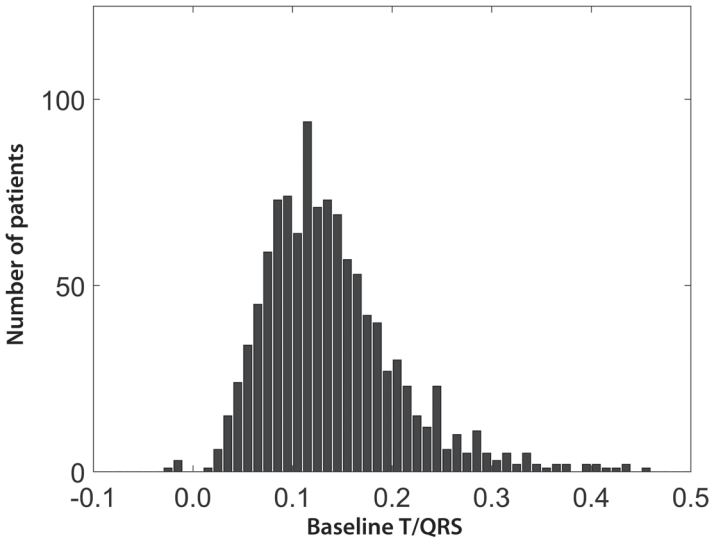
Variable		
Centre UMCU (%)	47.4	
MMC (%)	52.6	
Maternal age (years; mean, [SD])	31.9	[4.6]
Nulliparous (%)	53.4	
Gestational age at delivery (weeks; mean, [SD])	40+0	[1+3]
Spontaneous onset of labour (%)	65.4	
Induction (%)	34.6	
Fetal blood sampling (%)	10.4	
Spontaneous delivery (%)	77.6	
Operative vaginal delivery (%)	10.1	
Caesarean section (%)	12.3	
Apgar score 1' (median, [IQR])	9	[1]
Apgar score 5' (median, [IQR])	10	[0]
pH arterial (mean, [SD])	7.22	[0.07]
Base deficit arterial (median, [IQR])	6	[4]
Birth weight (gram; mean, [SD])	3562	[509]
NICU admission (%)	1.7	
Medium care admission (%)	13.8	
Perinatal mortality (%)	0	

Abbreviations: IQR = interquartile range, MMC = Máxima Medical Centre, SD = standard deviation, UMCU = University Medical Centre Utrecht.

In Figure 4, we present the pH of the arterial cord blood and base deficit of the extracellular fluid as a function of the initial baseline T/QRS value. The results show no dependency between pH and base deficit on the one hand, and height of the initial baseline on the other hand. The non-significant correlation coefficient between pH and initial baseline height and between base deficit and baseline height was -0.04 ($p = 0.14$) and 0.03 ($p = 0.34$), respectively. These results are in line with the results of Becker et al.[28].

This study suggests that variations in the orientation of the fetal electrical heart axis affect the height of the initial T/QRS baseline and that the height of this baseline determines the occurrence of ST events. This finding could explain for the false ST events that are experienced in everyday clinical practice.

Figure 2. Distribution of patients across the baseline T/QRS values.

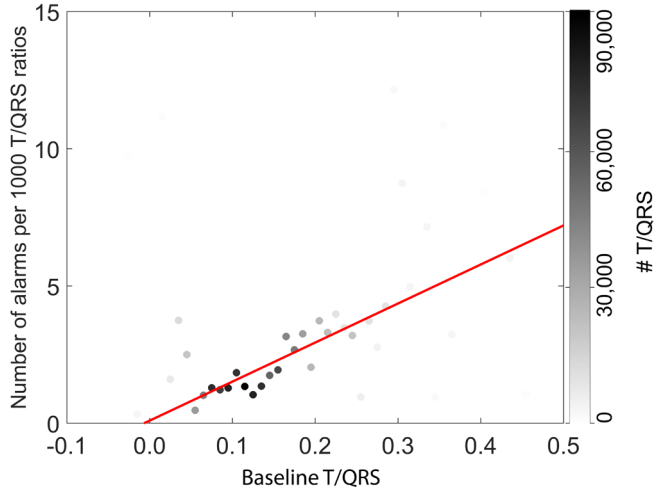


For each initial baseline T/QRS value encountered in our data set, we counted the number of patients with that particular baseline, showing a non-symmetric distribution with the most frequent encountered baseline T/QRS ratio at 0.12.

Our aim was to demonstrate that ST events can occur due to normal variations in human physiology; due to variation in electrical fetal heart axis. Therefore, we chose to exclude all cases of metabolic acidosis in this post-hoc analysis. The ST events included in our study were therefore not related to fetal distress.

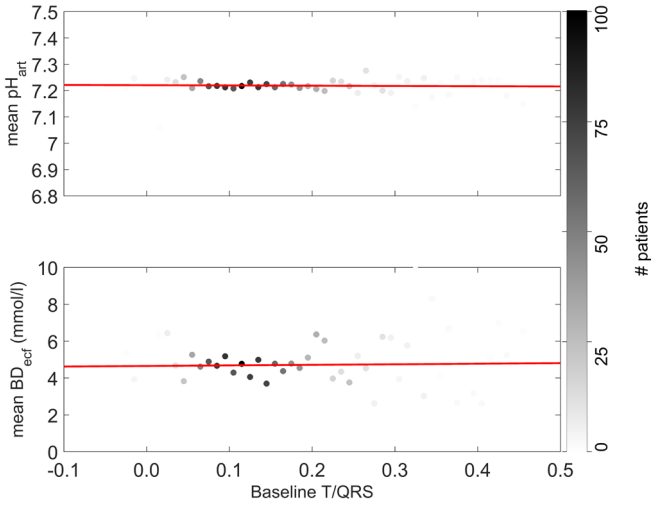
The distribution of initial T/QRS baseline values in Figure 2 shows that relatively high baselines are encountered more often than low baselines. Since high baselines are hypothesised to lead to false positive ST events (i.e. alarms while good fetal condition) and low baselines are hypothesised to lead to false negative ST events (i.e. no alarms while compromised fetal condition), this distribution of baseline values can explain why more false positive than false negative ST events are encountered in clinical practice. Since higher baselines do not relate to higher incidences of fetal distress (see Figure 4 and Becker et al.[28]) and considering the large patient population we analysed, we conclude that the presented results support our hypothesis. In other words, some fetuses have a relatively high probability of getting ST events and some fetuses have a relatively low probability, irrespective of their condition. Whether the relatively low probability of getting ST events in case of low initial T/QRS baseline indeed leads to more false negative ST events needs to be confirmed on a dataset including more cases of metabolic acidosis.

Figure 3. The number of ST events per 1000 T/QRS values as a function of the initial baseline T/QRS value.



Cases with the same initial baseline T/QRS were grouped. The intensity of the black colour of the data points relates to the total number of T/QRS ratios that occurred in the group (right column in the graph). The red line represents a linear fit through the data points. There is an average increment of 1.42 ST events per 1000 T/QRS values for a rise of 0.1 of the initial baseline T/QRS. The correlation coefficient between data points and fit was 0.63 ($p < 0.001$), as calculated with the linear regression model.

Figure 4. The pH of arterial cord blood and base deficit of the extracellular fluid as a function of the initial baseline T/QRS value.



Cases with the same initial baseline T/QRS value were grouped. The intensity of the black colour of the data points relates to the total number of patients that were represented in the group (right column in the graph). The red line represents a linear fit through the data points. The fit suggests a reduction in the pH of 0.0009 and an increase in the base deficit of 0.03 for a rise in 0.1 of the initial baseline T/QRS. The respective correlation coefficients between data points and fit are -0.04 (p = 0.14) and 0.03 (p = 0.34), as calculated with the linear regression model.

Abbreviations: BD_{ecf} = base deficit in the extracellular fluid, pH_{art} = pH of the arterial cord blood.

In addition, we propose that ST events are unreliable in case of high or low baseline T/QRS values. In case of an average T/QRS baseline value, the incidence of false ST events will be lower. When using the STAN® monitor in clinical practice, clinicians should be aware of this limitation. In case of inconclusive cardiotocogram assessment in combination with a high or low baseline T/QRS, fetal blood sampling can be used for complementary diagnostic information. However, the additional value of fetal blood sampling is uncertain and repeated fetal blood sampling is an independent risk factor for caesarean delivery[29]. In case of average baseline T/QRS, ST events can be considered more reliable and could be considered as complementary diagnostic information. ST analysis based on relative elevations of the T/QRS ratio with respect to the baseline or standardised non-invasive fetal ECG recordings[30] might be feasible solutions that warrant further research. In addition, the relation between signal quality and T/QRS reliability needs to be explored in future research, including analysis of the effects of signal quality of small variations in the ECG that are caused by e.g. rotation of the fetal head at the end of labour.

Conclusions

This study showed a significant increment of ST events with increasing height of the initial T/QRS baseline; correlation coefficient 0.63, p <0.001. The orientation of the fetal electrical heart axis affects the height of the T/QRS baseline, and therefore the incidence of ST events. This should be taken into account in fetal monitoring with ST analysis.

Acknowledgements

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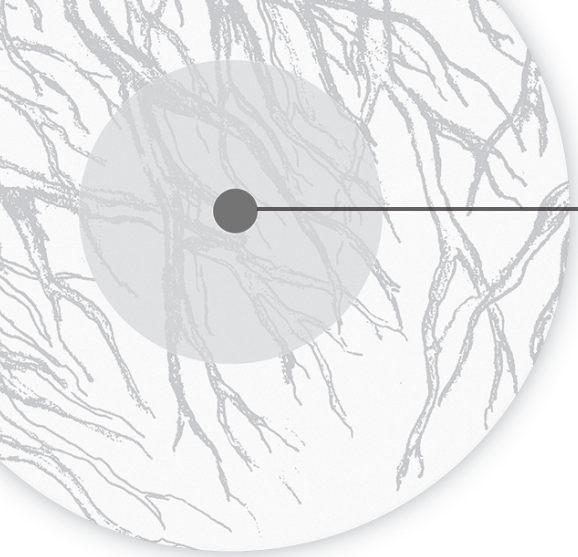

Chapter 11

Relative versus absolute rises in T/QRS ratio: a case-control study

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Submitted for publication

Abstract

Introduction

Conflicting results have been reported regarding the additional value of ST analysis during labour. In ST analysis, a T/QRS baseline value is calculated from the fetal electrocardiogram and successive T/QRS ratios are compared to this baseline. Variation in the orientation of the electrical heart axis between fetuses yields different T/QRS baseline values. In case of a higher T/QRS baseline value more ST events are encountered, irrespective of perinatal outcome. We hypothesised that we can partly correct for this effect by analysing T/QRS rises as a percentage from baseline (relative ST analysis). This study aims to explore whether relative ST analysis improves the diagnostic characteristics of ST analysis to detect metabolic acidosis.

Material and Methods

A case-control study was performed in 20 term human fetuses during labour; 10 cases (cord artery pH <7.05) and 10 controls (cord artery pH >7.20) were included. The fetal electrocardiogram was recorded using a STAN® monitor. We extracted all baseline and episodic ST alarms, T/QRS values, and calculated the relative T/QRS changes. The cut-off for relative ST alarms was determined in a receiver operator characteristic (ROC) curve at optimal specificity. Parameters of interest were area under the curve of the ROC curve for relative ST alarms and test characteristics of both conventional and relative ST analysis.

Results

Relative ST analysis showed an area under the curve of 0.99 (95% confidence interval 0.96-1.00). The optimal cut-off value for relative T/QRS rise was determined at 0.70. Relative vs conventional ST analysis showed a specificity of 100% vs 40% ($p = 0.031$); sensitivity 90% vs 90%; positive likelihood ratio infinity vs 1.5; negative likelihood ratio 0.10 vs 0.25, respectively.

Conclusion

In this study relative ST analysis provides a good distinctive value for metabolic acidosis, with better specificity and comparable sensitivity in comparison to conventional ST analysis. Relative ST analysis seems to be a promising method to detect metabolic acidosis during labour. However, further research and validation are highly recommended.

Introduction

Due to poor specificity of cardiotocography (CTG), which is used for fetal monitoring during labour, unnecessary caesarean deliveries are performed without improvement in long-term neonatal outcome[1]. ST analysis of the fetal electrocardiogram (ECG) was introduced in the 1990s as a promising technique to accurately detect metabolic acidosis and improve perinatal outcome[2]. Two large randomised trials (RCTs), both comparing CTG monitoring to CTG monitoring plus ST analysis, showed promising results with a decrease in metabolic acidosis[3] and operative deliveries[2,3]. Subsequent RCTs did not confirm these results[4-7], and meta-analyses report conflicting results[8-12].

The physiological basis for ST analysis was found in sheep studies. Rosén et al.[13-15] found that hypoxia in fetal lambs leads to an adrenalin surge in the fetal heart, resulting in local glycogenolysis and potassium release. This local increase in potassium ions leads to an increase in T wave amplitude in the fetal ECG[13,15,16]. In ST analysis (STAN®, Neoventa Medical AB, Mölndal, Sweden), the T wave amplitude is normalised against the QRS amplitude, resulting in the T/QRS ratio. In case there is a rise in T/QRS ratio, an alarm is generated. The STAN® method discriminates three types of events (alarms): episodic, baseline, and biphasic events. Biphasic ST events will not be considered in this paper.

The relevance of a ST event depends on the visual assessment of the CTG. In case the CTG is classified as normal, all ST events given by the STAN® monitor can be ignored[17-19]. In this case, the ST event can be classified as a false event. In clinical practice, these false events are encountered frequently[20]. In case the CTG is classified as suboptimal or abnormal, ST events are considered to be significant and a clinical intervention should be prompted[19]. The dependence on subjective CTG interpretation, which is known to have a large inter- and intra-observer variability[1,21], has a negative impact on the practical value of ST analysis.

Previously, we described a physiological explanation for false ST events. We demonstrated that the orientation of the fetal electrical heart axis varies considerably between fetuses[22]. The relation between the orientation of the electrical heart axis and the orientation of the scalp electrode, yields different T/QRS baseline values, due to differences in ECG morphology. We found that fetuses with a higher T/QRS baseline are more prone to ST events, independent of the fetal condition[23]. In contrast, we found that fetuses with a lower T/QRS baseline are less prone to exceed the threshold for a ST event. Becker et al.[24] described that higher T/QRS baseline values are not related to poor neonatal outcome or hypoxia. In other words, it is expected that a high initial T/QRS baseline increases the incidence of false positive ST events and that a low initial T/QRS baseline increases the incidence of false negative ST events.

Both the T/QRS baseline value and the rise in T wave amplitude are affected by the orientation of the electrical heart axis. We hypothesise that analysing relative, rather than the conventional, "absolute" T/QRS rises from baseline, could improve the diagnostic value of ST analysis. In case of relative ST analysis (T/QRS rises as a percentage from baseline), there is a correction for the "ease" of increment of the T wave amplitude. In conventional ST analysis, an absolute rise in T/QRS value will lead to an event; irrespective of the height of the T/QRS baseline. This study aims to explore whether relative ST analysis has a distinctive value in detecting metabolic acidosis. In addition, we aim to compare the test characteristics of both relative and absolute ST analysis. This is the first study that describes relative ST analysis. In order to directly compare both methods, we only focussed on objective information. Therefore, we omitted subjective CTG interpretations.

Material and Methods

Patient inclusion

We performed a case-control study on a dataset collected by van Laar et al.[25]. We included fetuses of at least 36 weeks of gestation with intrapartum fetal ECG recordings, whose arterial and venous umbilical cord blood gasses were determined directly after birth. The included mothers were healthy, had an uncomplicated pregnancy and did not use any medication except oxytocin or epidural analgesia. Only good quality fetal ECG recordings were included, defined as absence of ectopic beats and no missing data in the last 10 minutes before birth. We excluded fetuses with fetal growth restriction (defined as birth weight below the 10th percentile) and congenital heart disease.

Cases had an arterial cord pH <7.05 and controls had an arterial cord pH >7.20. Cases were consecutively selected between January 2006 and December 2007 in the Máxima Medical Centre, Veldhoven, the Netherlands. As a result of the strict inclusion and exclusion criteria, only five fetuses with acidemia could be included. In addition, five fetuses with acidemia from the University Medical Centre Utrecht, the Netherlands were selected between January 2001 and July 2002. Both hospitals are tertiary-care teaching hospitals. The ten controls were consecutively selected between January 2007 and August 2007 in the Máxima Medical Centre, Veldhoven, the Netherlands.

Data acquisition and signal processing

Fetal ECG recordings were obtained during labour with a single helix scalp electrode (Goldtrace™), a maternal skin electrode, and a STAN S31® monitor (Neoventa Medical AB, Mölndal, Sweden). For every heartbeat, the STAN® detects an ECG complex. After 30 good quality ECG complexes, an average ECG complex (aECG) is calculated. This aECG is used to

determine the amplitudes of the T wave and QRS complex which, in turn, are used to calculate the T/QRS ratio. For every registration, we extracted all T/QRS ratios.

In absolute ST analysis, first a T/QRS baseline is determined. Following T/QRS ratios are compared to this baseline and in case they exceed the baseline by 0.05 for at least 10 minutes[16], a baseline ST event is generated. When the T/QRS ratio exceeds the baseline by 0.10 within 10 minutes, an episodic ST event is generated. We used the "event log" window in the STAN® viewer software (Neoventa) to determine whether baseline and episodic ST events occurred. For relative ST analysis, instead of assessing the difference between T/QRS ratios and the baseline, we calculated the quotient. We defined the baseline via a two-step procedure, which is similar to the STAN® method. First, for every T/QRS ratio the median over the last 20 preceding T/QRS ratios was calculated. Second, the T/QRS baseline was defined as the minimum value of this median T/QRS ratio within a three hour window preceding the current T/QRS ratio. In case the 20 preceding T/QRS ratios did not fall within a 20-minute window from the current T/QRS ratio, we classified the signal as low quality and did not update the baseline.

As mentioned previously, we want to assess the test characteristics of absolute and relative ST analysis in a cohort of 10 cases and 10 controls. Ideally, for cases both methods give at least one ST event. For controls, both methods should give no ST events. Hence, in this study we analysed whether the largest rise from baseline exceeds the absolute and/or the relative threshold for generating an event. In case the largest rise does not exceed the threshold, none of the other T/QRS ratios will trigger an event. In case the largest rise exceeds the threshold, at least one event was triggered. Based on whether the patient was a case or a control, we classified the event as true or false.

Outcome measures

The primary outcome was neonatal acidosis, defined as umbilical artery pH <7.05. Secondary outcomes were neonatal intensive care admission and 5 minute Apgar scores. Relative and absolute ST analysis were compared with respect to sensitivity (Sn), specificity (Sp), positive likelihood ratio (LR+) and negative likelihood ratio (LR-).

Statistical analysis

Baseline characteristics were compared with a Mann-Whitney U test for continuous variables and a Fisher exact test for categorical variables. To determine the optimal threshold for relative ST analysis, the largest rise from baseline per patient was plotted in a receiver operating characteristic curve (ROC curve) in SPSS 22 for Mac (IBM corp. Armonk, NY, USA). The threshold to predict neonatal acidosis was determined at the optimal cut-off in the ROC

curve (the point closest to 0.1). This threshold was subsequently used to compute other test characteristics. We used a McNemar test to compare true positives and true negatives. A p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

For all 20 fetuses, good quality ECG data were available until nine minutes before birth. In nine fetuses (four cases, five controls), fetal ECG data could be obtained until the last minute before birth. Table 1 shows the baseline characteristics of the included patients. Significant differences were found between both groups regarding the frequency of fetal blood sampling, Apgar score after 1 minute, Apgar score after 5 minutes, umbilical cord artery and venous pH and umbilical artery base excess.

Relative versus absolute ST analysis

Figure 1 shows the ROC curve for relative ST analysis. The area under the ROC curve for relative T/QRS ratio changes in this population was 0.99 (p <0.001; 95% CI 0.96-1.00), with a standard error of 0.016. The cut-off value was determined at a relative T/QRS rise of 0.70.

We compared the test characteristics of absolute and relative ST analysis in our study population (Table 2). Sensitivity was equal for both methods, while specificity, LR+, and LR- were better for relative ST analysis.

Table 3 shows the number of correctly defined patients. When using a cut-off value of 0.70 as threshold for relative ST analysis, the detection of healthy fetuses is significantly better in comparison to absolute ST analysis (p = 0.031). We did not find significant differences between both methods to discriminate in neonatal hospital admission or Apgar score <7 at 5 minutes.

Table 1. Baseline characteristics and outcome of included patients.

Characteristic n (%) or mean [SD]	Cases (n=10)	Controls (n=10)	p-value
Nulliparous	8 (80%)	4 (40%)	NS[a]
GA – weeks + days	40+3 [1+1]	39+5 [1+4]	NS[b]
Analgesia	5 (50%)	6 (60%)	NS[a]
Oxytocin	7 (70%)	4 (40%)	NS[a]
FBS – frequency	1.4 [1.3]	0	0.023[b]
Birth weight – gram	3414 [432]	3643 [562]	NS[b]
Apgar score, 1′	6 [2.0]	9 [0.7]	<0.001[b]
Apgar score, 5′	8 [1.3]	10 [0.4]	0.001[b]
Arterial pH	6.98 [0.07]	7.26 [0.03]	<0.001[b]
Arterial BE – mmol/l	-17.3 [4.0]	-5.2 [2.0]	<0.001[b]
Venous pH	7.08 [0.10]	7.33 [0.04]	<0.001[b]
Hospital admission	4 (40%)	0 (0%)	NS[a]
Medium care	2 (20%)		
NICU	2 (20%)		
Operative delivery	4 (40%)	0 (0%)	NS[a]
VE	4 (40%)		
CS	0 (0%)		

[a] = Fisher exact test

[b] = Mann-Whitney U test

Abbreviations: BE = base excess, CS = caesarean section, FBS = fetal blood sampling, GA = gestational age, NICU = neonatal intensive care unit, NS = not significant, α = 0.05, SD = standard deviation, VE = vacuum extraction.

Table 2. Test characteristics of absolute and relative ST analysis.

	Sn (95% CI)	**Sp (95% CI)**	**LR+**	**LR-**
Absolute ST analysis	0.9 (0.54 – 0.99)	0.4 (0.14 – 0.73)	1.5	0.25
Relative ST analysis*	0.9 (0.54 – 0.99)	1.0 (0.66 – 1.00)	∞	0.1

*: cut-off value 0.70

Abbreviations: CI = confidence interval, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, Sn = sensitivity, Sp = specificity.

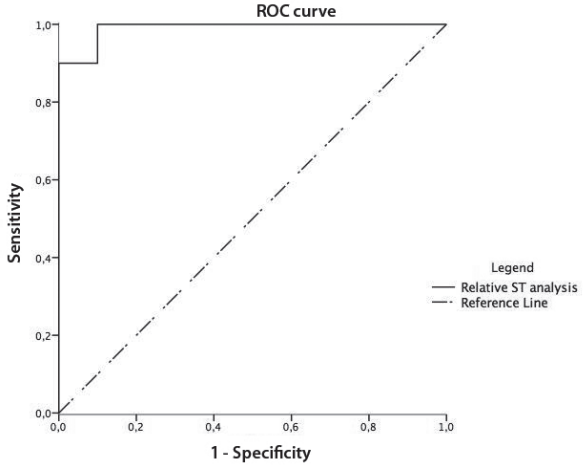
Table 3. Number of correctly defined patients.

	Relative ST analysis	Absolute ST analysis	McNemar p-value
Fetal condition			
Healthy (n=10)	10 (100%)	4 (40%)	0.031*
Acidemia (n=10)	9 (90%)	9 (90%)	1.000
Hospital admission			
None (n=16)	11(69%)	5 (31%)	0.070
MC or NICU (n=4)	4 (100%)	4 (100%)	1.000
Apgar score at 5'			
≥7 (n=18)	11 (61.1%)	5 (27.8%)	0.070
<7 (n=2)	2 (100%)	2 (100%)	1.000

* Significance was set as α = 0.05

Abbreviations: MC = medium care, NICU = neonatal intensive care unit.

Figure 1. ROC curve of relative ST analysis.



Discussion

ST analysis is used to obtain additional information regarding the fetal condition during labour. In current clinical practice, absolute ST analysis has a good sensitivity, but is known to generate false events[20]. The aim of this study was to explore whether relative ST analysis has a distinctive value in detecting metabolic acidosis, while restricting the number of false events. This study demonstrates that relative ST analysis can identify fetuses with metabolic

acidosis at birth, as evidenced by the high AUC in the ROC curve. To explore whether relative ST analysis could be a solution for the false events encountered currently, we compared the test characteristics of both relative and absolute ST analysis. In the studied population, relative ST analysis showed to be superior in specificity, LR+ and LR-. Sensitivity was equal in both methods.

Neonatal hospital admission and low 5 minute Apgar score prevalence were low in our population. Nevertheless, we can observe a non-significant trend that relative ST analysis is more accurate in detecting false events; relative ST analysis is better in correctly defining patients with no hospital admission and a good Apgar score (>7 at 5 minutes). However, hospital admission and low Apgar score can both be caused by numerous other factors that are not necessarily related to acidosis, such as neonatal infection, respiratory insufficiency, meconium aspiration, and so on. Therefore, these factors should be assessed taking the abovementioned in consideration.

In absolute ST analysis, false events are encountered regularly[20]. This could lead to alarm fatigue, which can have life threatening consequences in the labour room. This study shows that ST monitoring is capable of identifying fetuses with acidosis without many false events, once one corrects for the orientation of the electrical heart axis.

In clinical practice, ST analysis is used in addition to CTG and therefore, the effect of false events can be limited by strict CTG interpretation. However, CTG interpretation is known to have a high intra- and inter-observer variability[1,21]. This can lead to different decisions regarding obstetric management following the same objective information.

As previously described, biphasic events were not evaluated in this study. The aim of our study was to compare baseline dependent ST events, since these are known to be related to the orientation of the electrical heart axis[23]. In addition, a recent study showed that biphasic events do not discriminate in the prediction of fetal distress or adverse outcome[26].

The difference between absolute and relative ST analysis is based on different analyses of the same raw data. In both methods the fetal ECG is acquired by a fetal scalp electrode, and thus invasiveness of the technique is equal for patients. In addition, there is no difference in application or work load for the obstetric caregiver.

Although the results from this first study describing relative ST analysis are promising, there are some important limitations. This study was designed as a case-control study, to determine if relative ST analysis could detect metabolic acidosis with a high sensitivity and low number

of false events (high specificity). As a result of this study design, we did not evaluate the full spectrum of patients. Only cases with evident metabolic acidosis and controls with normal blood gas values at birth were included. A middle group with a pH between 7.05 and 7.20 is missing, while this group represents the majority of neonates born in clinical practice. In addition, the studied sample size was small; 10 cases and 10 controls. This can be explained by the low prevalence of metabolic acidosis (0.1-1%)[3-7], combined with our strict inclusion criteria (availability of good quality fetal ECG recordings until at least 10 minutes before birth and availability of umbilical cord blood gasses).

Taken the limitations of our study into account, validity of relative ST analysis should be evaluated in a larger patient group, including the full spectrum of perinatal outcome. This allows to determine a more reliable and representative threshold value for relative ST analysis. Subsequently, this threshold needs to be validated in a different group of patients. We expect that the test characteristics of relative ST analysis determined in the latter group will be slightly less optimistic as those presented in the current work. In addition, only patients with good quality fetal ECG recordings and available umbilical cord blood gasses were included in this study. In following studies these conditions are likely to be less optimal, which might influence the test characteristics. Future studies could also focus on non-invasive abdominal registration of the fetal ECG, since this can also be used for fetal monitoring during pregnancy, before the onset of labour.

Conclusion

This study shows that relative T/QRS analysis provides a good distinctive value to detect metabolic acidosis during labour. In comparison to conventional absolute ST analysis, relative ST analysis shows better specificity with a comparable sensitivity. Therefore, relative ST analysis is a promising method for monitoring of fetal wellbeing during labour and needs to be studied in a larger population.

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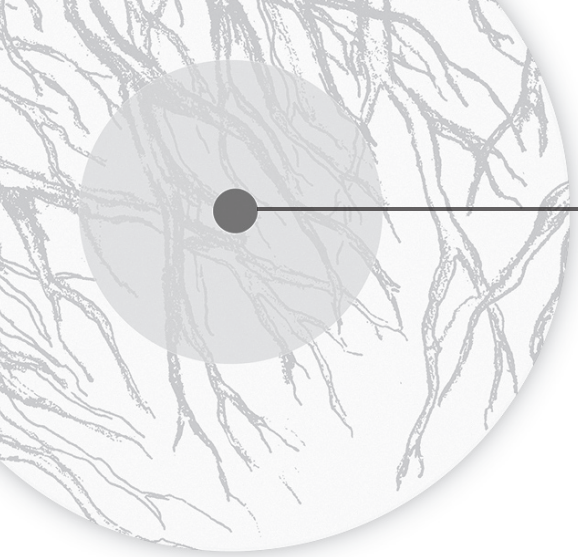

Chapter 12

General discussion

12

In this thesis, the prospects of fetal electrocardiography (ECG) during pregnancy and labour are described. Fetal ECG is a technique that is still evolving. It can be applied non-invasively via electrodes on the maternal abdomen during pregnancy, or invasively with a fetal scalp electrode during labour.

Congenital heart disease (CHD) is the most common severe congenital anomaly worldwide[1]. The detection rate following fetal cardiac screening during the anomaly ultrasound around 20 weeks of gestation, varies between 65% and 81%[2]. Diagnosing CHD early in pregnancy is important, and therefore there is need for a reliable non-invasive diagnostic method that can complement ultrasonography.

Nowadays, we mainly use cardiotocography (CTG) to assess the fetal condition. However, it is known that the specificity and positive predictive value of CTG are rather poor[3] and no improvement in long-term neonatal outcome is seen[4]. During pregnancy, besides a biophysical profile and Doppler ultrasonography there are no complementary diagnostics to give us information concerning the fetal condition. During labour, fetal scalp blood sampling and ST analysis of the fetal ECG can be performed to give additional information. Yet, these methods are both invasive and not applicable in case of prematurity. Therefore, there is need for a non-invasive method that provides more reliable information concerning the fetal condition.

Chapter 1 discusses the abovementioned issues considering fetal monitoring, that are encountered in daily clinical practice. This thesis aims to answer the following questions;

1. Is fetal electrocardiography valuable in diagnosing congenital heart disease in fetuses?

2. What is the influence of corticosteroids and tocolytics on fetal heart rate variability?

3. Are the changes in fetal heart rate variability following corticosteroid administration in the time-domain (obtained by Doppler ultrasound cardiotocography) comparable to the changes in fetal heart rate variability in the frequency-domain (obtained by non-invasive fetal electrocardiogram recordings)?

4. Is the variation in orientation of the fetal electrical heart axis in premature fetuses comparable to the variation seen in term fetuses?

5. Is variation in orientation of the electrical heart axis the cause of false ST events in ST analysis during labour?

6. Can we improve the method of ST analysis for fetal monitoring during labour?

Background information considering the physiology of the fetal heart is provided in **chapter 2**. The embryology, circulation of the fetal heart and the postnatal changes in circulation are described. In response to hypoxia, chemoreceptors and baroreceptors influence the autonomic nervous system. It is known that changes in the ECG that are seen following hypoxia precede cerebral damage, and can therefore be seen as a marker for fetal distress[5]. The counteracting autonomic influences of the sympathetic and parasympathetic nervous system cause the variability in the fetal heart rate[6].

In **chapter 3**, technical background information is provided regarding the CTG, the fetal ECG, spectral analysis of fetal heart rate variability, and ST analysis. The transabdominal CTG derives fetal heart rate information via Doppler ultrasound. The fetal heart rate is averaged over several heartbeats and beat-to-beat information is not available. From fetal ECG recordings, beat-to-beat fetal heart rate information can be extracted and therefore accurate spectral analysis (frequency analysis) can be performed with these recordings. By means of spectral analysis, changes in the autonomic regulation can be quantified[7-12]. The low-frequency (LF)-component reflects baroreceptor reflex activity, and is both sympathetically and parasympathetically mediated[13]. The high-frequency (HF)-component is associated with fetal respiration, and is solely parasympathetically mediated[13].

In case of sustained hypoxia, there is a switch from aerobic to anaerobic metabolism with glycogenolysis. This is accompanied by an increase in potassium ions in the myocard[14], causing an increase in T wave amplitude in the fetal ECG[15]. The consequent rise in T/QRS ratio is the basis of ST analysis.

This thesis is divided in three parts, that all describe one prospect of fetal ECG.

Part I: fetal ECG and congenital heart disease

CHD is six times more common than chromosomal anomalies and four times more common than neural tube defects[16,17]. The detection rate following the congenital anomaly scan that is performed around 20 weeks of gestation varies from 65-81%[16,18-20]. Diagnosing CHD in pregnancy is important, since it enables the identification of associated anomalies, it gives parents the option to decide for a termination of pregnancy, and an adequate treatment plan can be developed, which is known to increase the survival rates and decrease long-term morbidity[21].

In **chapter 4**, the possibilities of fetal ECG as a screening tool for the detection of CHD are reviewed. Not much research has been performed in this field; only five studies could be

included. Fetal ECG is described to reflect the intimate relation between the cardiac nerve conduction system and the structural morphology of the heart[22]. In case of CHD, arrhythmias and changes in PR, QRS and QT interval have been described. Fetal ECG is particularly helpful in detecting the electrophysiological effects of cardiac anatomical defects (e.g. hypotrophy, hypertrophy, and conduction interruption) and it seems to be a promising clinical tool to complement ultrasonography in the screening for CHD. However, before we can detect CHD with fetal ECG we need to establish the normal range and values of amplitudes and segment intervals of the fetal ECG in the healthy fetus. Therefore, we designed a prospective cohort study, including patients with an uneventful pregnancy. Non-invasive fetal ECG measurements were performed between 18 and 24 weeks of gestation. The study protocol is described in **chapter 5** of this thesis.

Part II: fetal ECG in preterm labour

Preterm birth, defined as birth before 37 weeks of gestation, is one of the major causes of perinatal mortality and morbidity worldwide. In Europe, the preterm delivery rate is approximately 5-9%[23]. In case of threatened preterm labour between 24 and 34 weeks of gestation, fetal lung maturation can be enhanced by maternal administration of corticosteroids. This is associated with a reduction in neonatal mortality and morbidity[24]. In case of spontaneous preterm labour, tocolytics can be administered in order to attempt to postpone delivery for at least 48 hours. This will gain time to transfer the patient to a centre with neonatal intensive care facilities and to await maximal beneficial effect of corticosteroids.

Both corticosteroids and most tocolytics are known to have influence on fetal heart rate and fetal heart rate variability. It is known that fetal heart rate variability is one of the most important markers to assess fetal wellbeing[25]. Therefore, it is important to know the exact effects of corticosteroids and tocolytics on fetal heart rate parameters. Only then we can prevent iatrogenic preterm delivery due to misinterpretation of the CTG.

In **chapter 6**, the influence of corticosteroids (betamethasone and dexamethasone) on fetal heart rate parameters is described. We performed a review of the literature, eventually including 15 articles. During the first day after corticosteroid administration, there was a decrease in fetal heart rate, and an increase in fetal heart rate variability. During days 2 and 3, fetal heart rate increased while fetal heart rate variability decreased. All parameters returned to baseline by day 4. We also described confounding factors like the influence of other drugs, gestational age, diurnal rhythm, and fetal growth restriction. Since the administration of corticosteroids is often accompanied by the administration of tocolytics, their influence on fetal heart rate parameters is described in **chapter 7**. In this review, it was found that nifedipine,

atosiban and indomethacin administration show no clinically important effect on fetal heart rate variability. Magnesium sulphate can result in a decrease in fetal heart rate variability and cases of bradycardia were described. Fenoterol causes a slight increase in heart rate, with no changes in fetal heart rate variability. Following ritodrine, an increase in fetal heart rate and a decrease in variability was seen.

The measurements in the studies regarding the influence of corticosteroids on fetal heart rate variability, as described in chapter 6, used CTG (Doppler ultrasound). As a consequence, it is not possible to perform reliable spectral analysis with these measurements. We designed a prospective cohort study, including patients that required betamethasone during pregnancy. During five successive days, non-invasive abdominal fetal ECG recordings were performed. The aim of this study was to quantify the effects of maternally administered betamethasone on spectral analysis of fetal heart rate variability. In **chapter 8**, the results of this study are described. The changes in fetal heart rate variability following betamethasone administration show the same pattern when calculated by spectral analysis of the fetal ECG, as when calculated by CTG. The change in absolute spectral values is likely to correspond to the change in quiet and active state of the fetus. Since normalised spectral values show little changes, the influence of autonomic modulation is minor.

Part III: fetal ECG to prevent asphyxia

Analysis of the ST segment of the fetal ECG complex can give additional information regarding fetal hypoxia during labour. In chapter 3, the technical details considering ST analysis are described. Initially, the combination of CTG and ST analysis was described to significantly lower the rates of metabolic acidosis[5] and operative delivery[5,26]. However, subsequent trials could not reproduce these findings[27-30] and conflicting results have been reported in recent meta-analyses[31-35]. In addition, false positive alarms are often encountered in clinical practice[36].

In this thesis we hypothesise that the abovementioned issues might be related to the orientation of the fetal electrical heart axis, since this orientation alters the shape and amplitude of the ECG. It is known that in term fetuses, neonates, and adults, there can be a significant inter-person variation in the orientation of the electrical heart axis[37-41]. The orientation of the fetal electrical heart axis during mid-pregnancy has never been described before. As elaborated in **chapter 9**, we performed a post-hoc analysis containing inclusions from two prospective cohort studies. This study showed that the main direction of the electrical heart axis is towards the right in mid-pregnancy fetuses, and that the variation in this orientation varies significantly from a normal distribution ($p = 0.016$).

The orientation of the electrical heart axis can cause a relatively high, or a relatively low T/QRS baseline value. In case of fetal hypoxia, the efflux of potassium ions in the myocard causes a rise in amplitude of the T wave. This results in a rise in T/QRS value, which is repetitively compared to the baseline value. In case of an initial high baseline value (due to the orientation of the electrical heart axis), the subsequent rise in T wave amplitude following hypoxia will be higher in comparison to a case where the initial baseline value is low, where the same amount of hypoxia will cause a smaller rise in T wave amplitude. In ST analysis, an alarm is generated following an absolute rise in T/QRS value above the baseline value. Therefore, in case of a high baseline the threshold for an alarm will be exceeded more often compared to a lower baseline where the T/QRS value rise is smaller.

In **chapter 10**, we test our hypothesis that the orientation of the electrical heart axis (and thus the height of the T/QRS baseline) is related to the occurrence of ST events. We performed a post-hoc analysis following a randomised trial. Only healthy fetuses, born in good condition without metabolic acidosis (defined as cord artery pH <7.05 and base deficit >12 mmol/l) were included. We found that there was a significant increment in ST events with increasing height of the T/QRS baseline; p <0.0001, which was irrespective of the fetal condition. Following this finding, we hypothesised that we can correct for the effect of the electrical heart axis by analysing the T/QRS rise following hypoxia as a percentage from baseline (yielding a relative ST event). A retrospective case-control study was performed, including 20 term fetuses during labour. Ten fetuses were cases with a cord artery pH <7.05 and ten were controls with a cord artery pH >7.20. As described in **chapter 11**, in this highly contrasting study population the optimal cut-off value for relative T/QRS ratio rises was determined at 0.70. The specificity of relative and absolute ST analysis was 100% and 40% (p = 0.031) respectively, while the sensitivity was 90% for both methods. Following this first explorative study, relative ST analysis seems to be promising.

Clinical implications and future directions

The results of the fundamental research reported in this thesis show that fetal ECG has multiple promising prospects, both during pregnancy and labour. Although the first studies describing fetal ECG measurements date back to 1906[42], the development of fetal ECG lagged behind in comparison to other techniques for fetal monitoring. Multiple technical challenges had to be overcome, as described in chapter 3. In 1942, it was already suggested that the effect of drugs, hypoxia, and labour could be conveniently studied by fetal ECG[43]. Nowadays, it is feasible to conduct a fetal ECG relatively easy, and it has been demonstrated that the recordings obtained by non-invasive measurements correlate very well with fetal ECG signals obtained directly via a scalp electrode[11]. With the fetal ECG technique being available, more

sophisticated, easy to apply and safe to use, more and more research with this technique has been performed. Not all possible applications of fetal ECG are yet known, and researchers from all over the world are currently performing studies to elaborate these possible applications[44-46].

In our review as described in chapter 4, it was confirmed that fetal ECG can be a promising tool to complement ultrasonography in diagnosing CHD. This is intuitively logical, since it has been long known in children and adults that ECG can aid in the diagnosis of heart diseases. In particular, it seems that secondary effects due to CHD can be detected; hypotrophy, hypertrophy and conduction interruption. However, the fetal circulation is markedly different in comparison to the neonatal and adult circulation, as described in chapter 2. In order to distinguish abnormal fetal ECGs from normal ECGs, it is first required that we know the normal ECG in healthy fetuses. In chapter 5, the study protocol is described that will investigate the normal ranges for fetal ECG values around 20 weeks of gestation.

The collected data regarding the changes observed in fetal ECG in case of CHD is still limited. There is need for future trials that include multiple types of CHDs and have a reasonable sample size per type of CHD. In order to achieve this, these studies will most likely have to be performed as a collaboration between multiple expert centres. The ECG characteristics found in case of CHD should be compared to the characteristics found in healthy fetuses. When conducting these trials, one should take the gestational age of the fetus into account. The duration of the P wave, QRS complex and PR interval increase progressively from 18 weeks of gestation onwards until term[47,48].

If pregnancy is complicated by threatened preterm labour, multiple drugs are administered. This is done in a highly vulnerable population, since preterm fetuses can tolerate contractions and labour less well compared to term fetuses. In addition, only non-invasive fetal monitoring is available which can be complicated due to movements of the fetus in-utero. Further, it is important to be aware of the effects that the administered medication can have on fetal heart rate parameters, to prevent iatrogenic preterm delivery. In this thesis, the effects of corticosteroids and tocolytics were studied. However, in clinical practice some patients receive other drugs like antihypertensive agents or antibiotics. The effects of these drugs on fetal heart rate parameters should be studied as well. In addition, other confounding factors should be taken into account when studying the preterm fetus, such as gestational age, diurnal rhythm and fetal growth restriction. A challenging factor in studies including fetuses at risk for preterm labour is time of inclusion (most patients are transferred from secondary care hospitals, where medication is already started) and loss of study participants, e.g. due to preterm labour or discharge before the end of the study period. Nearly all studies considering this topic

published so far used CTG (Doppler ultrasound) to perform measurements and evaluate fetal heart rate parameters. However, as previously described in this thesis, CTG measurements do not acquire fetal heart rate information on a beat-to-beat basis. Future studies should perform measurements using fetal ECG equipment that can extract the fetal heart rate on a beat-to-beat basis, since only then reliable spectral analysis can be performed and more reliable estimates for fetal heart rate variability can be calculated.

During term labour, ST analysis of the fetal ECG was developed to provide additional information regarding fetal wellbeing. However, in clinical practice it appeared that false positive events were encountered regularly[36]. This made some clinicians and researchers wonder whether the STAN® monitor was indeed a reliable method for fetal monitoring. In this thesis, we described that our hypothesis that false alarms can be caused by the variation in orientation of the electrical heart axis indeed holds true. In addition, we provide a possible solution; relative ST analysis. Our study results should be verified in a study with a larger sample size, including the whole patient spectrum. In this group a reliable cut-off value for relative ST analysis can be defined, which should be validated in a second study. If the results of relative ST analysis are still promising, a prospective or randomised controlled trial can be performed. In addition, the clinical value of relative ST analysis in conjunction with CTG should be evaluated.

What can be learned from the above, is that when a new technique is introduced in clinical practice, we should not take this technology for granted. When unexpected findings arise, one should go back to basic physiology and anatomy and wonder if some influence might have been overlooked.

With multi-lead fetal ECG recordings being available, the applicability of antepartum ST analysis in preterm deliveries should be a field of future studies[49].

Advantages of fetal ECG

A major advantage of fetal ECG measurements is that they can provide additional and objective information; e.g. ECG segment intervals, values for spectral analysis, and ST analysis. This objective information can aid current technologies. Thereby, the influence of, for instance, performer variability (in ultrasonography) and inter- and intra-observer variability (in CTG assessment) might be decreased. Spectral analysis can objectively quantify the changes in fetal heart rate variability that can be obscured in visual interpretation of fetal heart rate tracings. Spectral analysis might also be added to ST analysis; it has been described that a relative change in LF/HF ratio >30%, in combination with a significant ST event is a better predictor for metabolic acidosis in the arterial cord blood than a significant ST event alone[50].

Another advantage is that fetal ECG has the potential to be widely versatile. A fetal ECG is easy to conduct, by placing electrodes on the maternal abdomen. The electrodes are attached to small and mobile equipment, which is likely to be relatively cheap in the future. Application of the fetal ECG system requires minimum training. In addition, the raw information can be analysed by computerised algorithms or can be sent for analysis elsewhere.

Since the fetal ECG can be conducted both invasively (with a fetal scalp electrode) and non-invasively (with electrodes on the maternal abdomen), the fetal ECG is applicable from early pregnancy (from 18 weeks of gestation onwards) until delivery. Since it can be applied non-invasively and can provide additional information such as spectral estimates, it could be used for fetal monitoring in high-risk pregnancies; e.g. in case of extreme prematurity, fetal growth restriction and fetuses from mothers with diabetes. In addition, home monitoring with non-invasive fetal ECG measurements in high-risk pregnancies is an additional field that has been studied recently[51]. When this would be feasible, it would lead to a significant reduction in health care costs due to less hospitalisation.

Disadvantages of fetal ECG

Despite all efforts to enhance the signal quality in fetal ECG measurements, there is still a lot to gain in this area. Therefore, future research should keep focussing on further progress in signal acquisition and processing. The signal quality is reduced due to presence of vernix caseosa on the fetal skin. This fatty layer surrounds the fetus and results in an electrical isolation, which diminishes the signal amplitude of the fetal ECG. Especially between 30 and 34 weeks of gestation, this layer causes a poor signal-to-noise ratio[46,52].

As with all new techniques, differences in acquiring and processing of the data exist. It is highly recommended that all future studies regarding fetal ECG measurements and spectral analysis use a standardised method. This will enable comparability, reproducibility, reliable physiological interpretation and clinical applicability.

In addition, every study regarding fetal ECG should consider the influence of the orientation of the electrical heart axis on their study results. For instance in case of ST monitoring, as described in this thesis, the physiological variation in orientation of the electrical heart axis might be responsible for the encountered false alarms. When calculating the electrical heart axis, it is important to take the fetal position in the uterus into account.

In the studies described in this thesis, data processing and calculation of spectral estimates, the electrical heart axis, etc. was performed off-line. In order to be clinically applicable, real-time monitoring should become available in the future.

In conclusion, this thesis describes the prospects of fetal ECG during pregnancy and labour. Although non-invasive fetal ECG is not yet clinically applied, this thesis shows that fetal ECG is promising in providing complementary diagnostic information. The additional value of fetal ECG in multiple fields has been addressed, and it has been shown that it can be used both during pregnancy and during labour.

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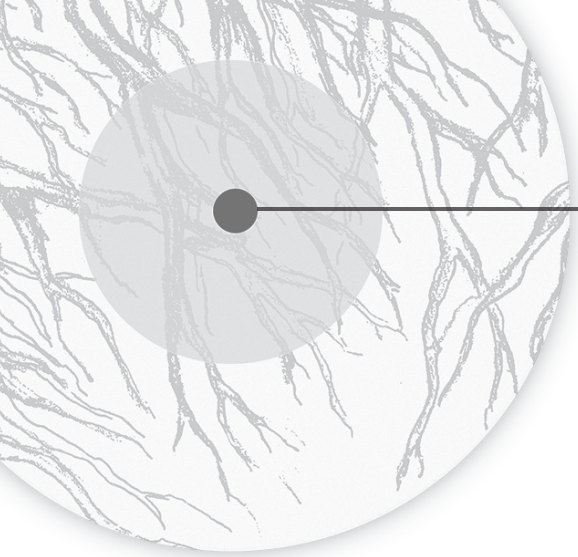

Appendices

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List of abbreviations

aECG	average ECG
ANS	Autonomic nervous system
BDecf	Base deficit in the extracellular fluid
BE	Base excess
BMI	Body Mass Index
BPM	Beats per minute
CHD	Congenital heart disease
CI	Confidence interval
CNS	Central nervous system
CRH	Corticotrophin-releasing hormone
CS	Caesarean section
CTG	Cardiotocography / Cardiotocogram
DM	Diabetes Mellitus
DvU	Diagnostiek voor U
ECG	Electrocardiography / Electrocardiogram
FBS	Fetal blood sampling
fHR	fetal heart rate
fHRV	fetal heart rate variability
fMGC	fetal magnetocardiography
GA	Gestational age
GR	Glucocorticoid receptor
HELLP	Hemolysis, elevated liver enzymes, and low platelet count syndrome
HF	High-frequency (power)
HFn	normalised high-frequency (power)
HPA-axis	Hypothalamic-pituitary-adrenal axis
HR	Heart rate
HRV	Heart rate variability
HSD	Hydroxysteroid dehydrogenase
HT	Hypertension
IQR	Interquartile range
IUGR	Intra-uterine growth restriction
i.v.	intravenous
LEEP	Loop electrosurgical excision procedure of the cervix
LF	Low-frequency (power)
LFn	normalised low-frequency (power)

LMWH	Low molecular weight heparin
LR +	Positive likelihood ratio
LR -	Negative likelihood ratio
LTV	Long-term variability
MC	Medium care
mFHR	mean fetal heart rate
$MgSO_4$	Magnesium sulphate
NICU	Neonatal intensive care unit
NS	Not significant
PE	Pre-eclampsia
pH_{art}	pH of the arterial cord blood
PPROM	Premature prelabour rupture of membranes
PROM	Preterm rupture of membranes
PSD	Power spectral density
QTc	Fetal QT interval corrected for heart rate
RCT	Randomised controlled trial
ROC	Receiver operator characteristic
SD	Standard deviation
Sn	Sensitivity
Sp	Specificity
STAN	ST analysis
STV	Short-term variability
TPL	Threatened preterm labour
VBL	Vaginal blood loss
VCG	Vectorcardiogram
VE	Vacuum extraction
VLF	Very low-frequency (power)
wG	weeks of gestation
wGA	weeks of gestational age

List of publications

Journal papers

K.M.J. Verdurmen, J. Renckens, J.O.E.H. van Laar, S.G. Oei. The influence of corticosteroids on fetal heart rate variability: a systematic review of the literature. Obstet Gynecol Surv. 2013;68(12):811-24. doi: 10.1097/OGX.

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K.M.J. Verdurmen, J.O.E.H. van Laar, S.G. Oei. "Corticosteroids and fetal heart rate variability." European Congress of Perinatal Medicine, Florence, 4-7 June, 2014.

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Nederlandse samenvatting

In dit proefschrift worden drie verschillende toepassingsmogelijkheden van het foetale electrocardiogram (ECG) tijdens de zwangerschap en de bevalling beschreven. Ten eerste wordt het foetale ECG als screeningsmethode bij aangeboren hartafwijkingen bestudeerd. Ten tweede onderzoeken we wat het effect van medicatie bij een dreigende vroeggeboorte is op het foetale hartritme, en ten derde toetsen we onze ideeën over valse alarmen bij het gebruik van foetaal ECG tijdens de bevalling (ST-analyse). Het foetale ECG is een techniek die nog in ontwikkeling is. Het kan niet-invasief verkregen worden met behulp van elektroden op de maternale buikhuid tijdens de zwangerschap, en invasief middels een foetale schedelelektrode tijdens de bevalling. Bij gebruik van foetaal ECG wordt slag-tot-slag informatie verkregen van het foetale hartritme. Hierdoor is het mogelijk om spectraalanalyse (frequentie analyse) te verrichten op het hartritme. Door middel van deze spectraalanalyse kunnen veranderingen in het autonome zenuwstelsel (sympathische en parasympathische activiteit) gekwantificeerd worden.

Aangeboren hartafwijkingen

Wereldwijd zijn aangeboren hartafwijkingen de meest voorkomende ernstige aangeboren afwijkingen. Deze hartafwijkingen komen zes keer vaker voor dan chromosomale afwijkingen (bijvoorbeeld syndroom van Down) en vier keer vaker dan neurale buisdefecten (bijvoorbeeld open rug). Momenteel wordt op aangeboren hartafwijkingen gescreend tijdens de 20-weken echo. Echter, deze echo spoort slechts 65-81% van de aangeboren hartafwijkingen op. Het diagnosticeren van een aangeboren hartafwijking vroeg in de zwangerschap is belangrijk; er kunnen extra onderzoeken plaatsvinden naar bijkomende aandoeningen, ouders hebben de mogelijkheid om te opteren voor een zwangerschapsafbreking en er kan voor gekozen worden de zwangere in een gespecialiseerd ziekenhuis te laten bevallen. Daarom is het van belang dat er onderzoek gedaan wordt naar een aanvullende, betrouwbare, niet-invasieve methode om aangeboren hartafwijkingen op te sporen.

We hebben een literatuurstudie uitgevoerd, waaruit bleek dat er tot nu toe weinig onderzoek verricht is naar het foetale ECG als screeningsmethode voor aangeboren hartafwijkingen. Wel wordt beschreven dat het foetale ECG de nauwe relatie tussen het cardiale geleidingssysteem en de structurele morfologie van het hart weergeeft. In het geval van een aangeboren hartafwijking worden onder andere hartritmestoornissen en veranderingen in PR, QRS en QT interval beschreven. Het foetale ECG is geschikt voor het opsporen van elektrofysiologische effecten van hartafwijkingen; hypotrofie of hypertrofie van de hartspier en onderbreking in het geleidingssysteem. Het lijkt er dus op dat het foetale ECG een veelbelovende aanvullende methode zou kunnen zijn voor het opsporen van aangeboren hartafwijkingen.

Voordat we aangeboren hartafwijkingen met behulp van het foetale ECG kunnen opsporen, is het belangrijk dat we een goed beeld hebben van de normaalwaarden van, onder andere, intervallen en amplitudes van het foetale ECG. In dit proefschrift wordt het studieprotocol beschreven van een prospectieve cohortstudie, waarin zwangeren met een ongecompliceerde zwangerschap geïncludeerd worden. Bij deze zwangeren wordt een niet-invasief foetaal ECG gemaakt tussen de 18 en 24 weken zwangerschap. De resultaten van deze studie zijn nog niet bekend.

Dreigende vroeggeboorte

Op dit moment wordt de conditie van het ongeboren kind tijdens de zwangerschap bewaakt met behulp van het cardiotocogram (CTG). Tijdens de zwangerschap kan dit transabdominaal, via de buik van de moeder, verkregen worden met behulp van een echo-Doppler signaal. De foetale hartslag wordt hierbij gemiddeld over een aantal opeenvolgende hartslagen, waardoor er bij deze registratie geen slag-tot-slag informatie beschikbaar is. Het is bekend dat de specificiteit en positief voorspellende waarde van het CTG beperkt is. Tijdens de zwangerschap zijn er naast echografie geen aanvullende onderzoeken die verricht kunnen worden om ons meer informatie te geven over de foetale conditie.

Een vroeggeboorte, gedefinieerd als een geboorte voor de 37 weken zwangerschap, is één van de belangrijkste oorzaken van perinatale mortaliteit en morbiditeit wereldwijd. In Europa is circa 5-9% van alle bevallingen een vroeggeboorte. Bij een dreigende vroeggeboorte tussen de 24 en 34 weken zwangerschap kan de foetale longrijping bevorderd worden door middel van het toedienen van corticosteroïden aan de moeder. Dit resulteert in een significante afname in neonatale mortaliteit en morbiditeit. Bij een spontane vroeggeboorte wordt dit vaak gecombineerd met het toedienen van weeënremmers; tocolyse. Hiermee wordt geprobeerd de bevalling tenminste 48 uur uit te stellen, zodat een patiënte overgeplaatst kan worden naar een centrum met een neonatale intensive care en om de corticosteroïden te laten inwerken.

Zowel corticosteroïden als weeënremmers hebben invloed op het foetale hartritme en de hartritmevariabiliteit. Uit eerder onderzoek is gebleken dat hartritmevariabiliteit één van de belangrijkste indicatoren is voor een goede foetale conditie. Daarom is het belangrijk om exact te weten wat het effect is van bijvoorbeeld corticosteroïden en weeënremmers op verschillende foetale hartritme parameters. Alleen dan kunnen we een iatrogene vroeggeboorte door misinterpretatie van het CTG voorkomen.

We hebben twee literatuurstudies uitgevoerd waarin zowel het effect van corticosteroïden als dat van weeënremmers op het foetale hartritme wordt beschreven. Na toediening van corticosteroïden is op de eerste dag een afname van het foetale hartritme zichtbaar, terwijl de hartritmevariabiliteit toeneemt. Op dag 2 en 3 zien we een stijging in hartritme en een daling in hartritmevariabiliteit. Op dag 4 zijn alle waarden weer vergelijkbaar met de waarden voor toediening van medicatie. Echter, er zijn ook andere factoren die invloed hebben op deze waarden, zoals het toedienen van andere medicatie, de zwangerschapsduur, het slaap-waak ritme en een eventuele foetale groeivertraging. Als we kijken naar weeënremmers blijkt uit de bestaande literatuur dat nifedipine, atosiban en indometacine geen duidelijk effect hebben op de hartritmevariabiliteit. Magnesiumsulfaat kan een vermindering van hartritmevariabiliteit veroorzaken, en er zijn ook casus met langdurige bradycardie beschreven. Na toediening van fenoterol wordt een geringe toename van het hartritme gezien, zonder veranderingen in variabiliteit. Bij ritodrine wordt een toename in hartritme en een afname in variabiliteit gezien.

Alle studies die tot nu toe zijn verricht, hebben gebruik gemaakt van CTG (echo-Doppler). Daarom is het niet mogelijk om betrouwbaar spectraalanalyse van hartritmevariabiliteit uit te voeren aan de hand van deze metingen. Om het effect van corticosteroïden op het autonome zenuwstelsel meer in detail te kunnen bestuderen, hebben we een prospectieve cohortstudie uitgevoerd waarbij we gedurende vijf dagen een niet-invasief foetaal ECG gemaakt hebben bij zwangeren die corticosteroïden toegediend kregen in verband met een dreigende vroeggeboorte. We zien dat de veranderingen die we meten met behulp van spectraalanalyse overeenkomen met de veranderingen die eerder beschreven zijn bij studies die met CTG verricht zijn. Daarnaast zien we dat genormaliseerde waarden weinig verandering laten zien gedurende de vijfdaagse studieperiode; dit wijst op weinig invloed vanuit het autonome zenuwstelsel. Duidelijk zichtbaar is dat foetussen na toediening van corticosteroïden meer tijd doorbrengen in een rustige gedragstoestand, in vergelijking met de actieve gedragstoestand. Na vier dagen is de verdeling tussen de gedragstoestanden weer zoals voor toediening van de corticosteroïden. We zien dus dat foetussen rustiger zijn en minder hartritmevariabiliteit laten zien, maar dat er geen sprake is van foetale stress (geen veranderingen in autonome modulatie).

Foetale nood tijdens de bevalling

Tijdens de bevalling kan de foetale hartslag bewaakt worden met behulp van een foetale schedelelektrode, waarbij invasief een foetaal ECG verkregen wordt. Deze registratie geeft slag-tot-slag informatie over het foetale hartritme. Tijdens de bevalling kan een micro-bloedonderzoek en/of ST-analyse van het foetale ECG aanvullende informatie geven. Echter, beide methoden zijn invasief en niet toe te passen in het geval van prematuriteit. Daarnaast

is het zo dat ST-analyse in de praktijk veel valse alarmen geeft en uit eerdere studies is niet evident duidelijk geworden dat ST-analyse een positieve invloed heeft op neonatale uitkomsten.

In het geval van (aanhoudend) zuurstoftekort, schakelt de foetus van het aërobe metabolisme over naar het anaërobe metabolisme, waarbij glycogenolyse plaatsvindt. Als gevolg hiervan is er een toename van kalium-ionen in de hartspier. Dit veroorzaakt een stijging in T-top amplitude in het foetale ECG. De stijging in T/QRS-ratio die hierop volgt is de basis van ST-analyse. Er vindt ook activatie van chemo- en baroreceptoren plaats, met als gevolg modulatie van het autonome zenuwstelsel. Deze modulatie, die invloed heeft op het parasympathische en sympathische zenuwstelsel, zorgt voor veranderingen in hartritmevariabiliteit. Het is bekend dat de veranderingen die in het foetale ECG gezien worden in geval van hypoxie vóórlopen op cerebrale schade; daarom kan het foetale ECG gezien worden als een diagnosticum voor foetale stress.

Een deel van de problemen die we ervaren met ST-analyse zou verklaard kunnen worden door de inter-patiënt variatie in oriëntatie, ofwel de richting, van de elektrische hartas. Deze oriëntatie heeft namelijk invloed op de vorm en amplitude van het ECG-complex. Uit eerdere studies is bekend dat de oriëntatie van de elektrische hartas sterk kan variëren tussen personen, zowel bij à terme foetussen, neonaten als volwassenen. We hebben een post-hoc analyse verricht op data van twee prospectieve cohortstudies, om te onderzoeken of deze variatie ook bestaat bij premature foetussen. Hierbij zagen we dat de gemiddelde oriëntatie van de elektrische hartas bij foetussen tussen de 18 en 29 weken zwangerschap richting rechts is, en dat de variatie in deze oriëntatie significant varieert van een normale verdeling ($p = 0.016$).

De oriëntatie van de elektrische hartas kan een relatief hoge of juist relatief lage T/QRS-basiswaarde veroorzaken. Ook de T-top stijging die plaatsvindt in geval van hypoxie kan hoger danwel lager zijn door deze oriëntatie, bij een zelfde mate van zuurstoftekort. Bij een initieel hoge T/QRS-basiswaarde zal de T-top stijging in het geval van hypoxie hoger zijn, in vergelijking met een foetus waarbij de initiële T/QRS-basiswaarde lager is. Op dit moment wordt bij ST-analyse gekeken naar een absolute stijging in T/QRS-waarde ten opzichte van de basiswaarde. Onze hypothese is dat er bij een hogere initiële basiswaarde sneller een alarm gegeven wordt dan bij een lagere initiële basiswaarde, onafhankelijk van de foetale conditie.

Om onze hypothese te onderzoeken hebben we een post-hoc analyse uitgevoerd met data van de gerandomiseerde, Nederlandse ST-analyse studie. Alleen gezonde foetussen die in goede conditie geboren zijn zonder metabole acidose (gedefinieerd als navelstreng pH

arterieel <7.05 en base deficit >12 mmol/l) werden geïncludeerd. We vonden een significante toename in ST-alarmen bij een toename van de hoogte van de initiële T/QRS-basiswaarde (p <0.0001), welke dus onafhankelijk was van de foetale conditie.

Om deze valse alarmen in de toekomst te kunnen voorkomen, was onze volgende hypothese dat we voor de inter-patiënt variatie in oriëntatie van de elektrische hartas kunnen corrigeren tijdens ST-analyse door de T/QRS stijging als gevolg van hypoxie te kwantificeren als een percentuele stijging vanaf de basiswaarde; "relatieve ST-analyse". We hebben een retrospectieve case-controle studie uitgevoerd met 20 à terme foetussen, waarbij invasieve ECG monitoring was tijdens de bevalling. Tien foetussen hadden tekenen van zuurstoftekort bij de bevalling (een arteriële navelstreng pH <7.05) en de tien controles hadden een goede foetale conditie (arteriële navelstreng pH >7.20). In deze specifieke groep bleek de optimale afkapwaarde voor een ST-alarm een relatieve T/QRS stijging van 70% te zijn. De specificiteit van relatieve en absolute ST-analyse in deze groep was 100% en 40% (p = 0.031), respectievelijk. De sensitiviteit van beide methoden was 90%. Aan de hand van deze eerste exploratieve studie kunnen we dus stellen dat relatieve ST-analyse een veelbelovende techniek is om het aantal valse alarmen te reduceren.

Conclusie

Concluderend beschrijft dit proefschrift verschillende toepassingsmogelijkheden van het foetale ECG, zowel tijdens de zwangerschap als tijdens de bevalling. Hoewel het niet-invasieve foetale ECG nog niet klinisch toepasbaar is, laat dit proefschrift duidelijk zien dat het een veelbelovende manier is om aanvullende informatie te verkrijgen over de foetale conditie.

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Curriculum vitae

Kim Verdurmen werd op 17 juli 1989 geboren in Terneuzen. In 2007 haalde zij haar VWO-diploma aan het Reynaertcollege te Hulst. Na aanvankelijk uitgeloot te zijn, kon ze alsnog in hetzelfde jaar starten met de opleiding geneeskunde aan de Universiteit Maastricht. Haar keuzecoschap verloskunde volgde ze in het Mahatma Gandhi Institute of Medical Sciences te Sevagram, India. Hierna volgde haar eerste kennismaking met wetenschappelijk onderzoek tijdens haar wetenschapsstage in het Máxima Medisch Centrum te Veldhoven, onder leiding van prof. dr. Guid Oei. Hierdoor raakte ze betrokken bij de onderzoeksgroep "fundamenteel perinatologisch onderzoek" en werd de basis gelegd voor wat later zou uitmonden in dit proefschrift. In 2013 ging Kim na het behalen van haar diploma als basisarts aan het werk als arts-assistent niet in opleiding bij de afdeling gynaecologie & obstetrie in het Máxima Medisch Centrum. In 2015 startte ze met de opleiding tot gynaecoloog in cluster Maastricht. Haar eerste opleidingsjaar doorliep ze in het Máxima Medisch Centrum. Haar opleiders waren hier prof. dr. M.Y. Bongers en dr. J.W. Maas. Ze is nu aan het eind van haar tweede opleidingsjaar, dat ze doorliep in het MUMC+, met als opleiders prof. dr. R.F.P.M. Kruitwagen en dr. T. van Gorp.

Kim woont in Soerendonk met Stijn Taelman, waar ze samen bouwen aan hun droomhuis.

Promotor:	prof. dr. S.G. Oei
Copromotores:	dr. J.O.E.H. van Laar
	dr. ir. R. Vullings