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Monitoring and management of mother and fetus at risk

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MONITORING AND MANAGEMENT OF MOTHER AND FETUS AT RISK

Suzanne Moors

Monitoring and management of mother and fetus at risk

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 dinsdag 15 december 2020 om 11:00 uur

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Suzanne Moors

geboren te Geldrop

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

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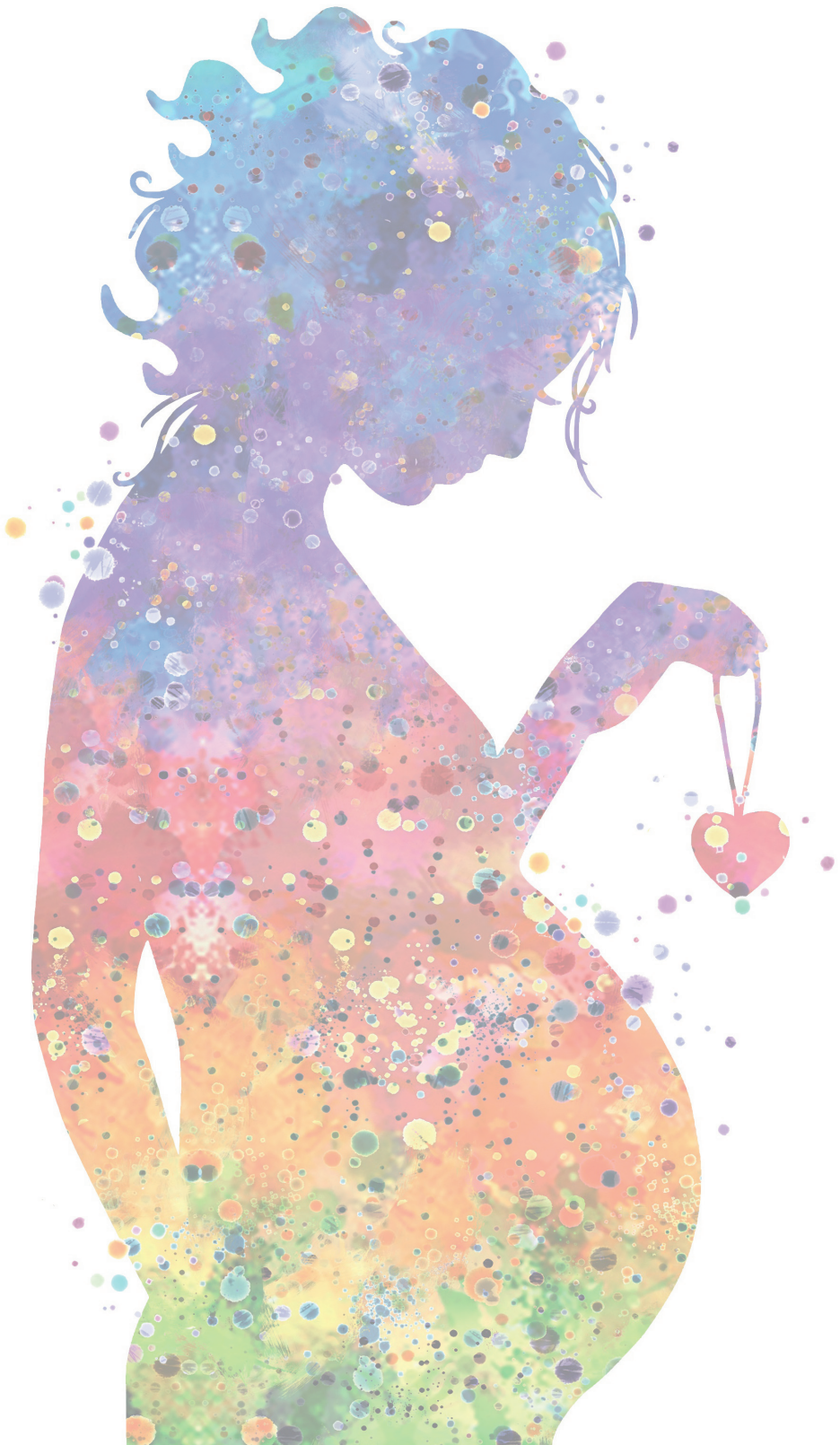

1

General introduction and outline of this thesis

GENERAL INTRODUCTION

There is no moment in the human life cycle when two individuals are more closely physiologically intertwined than during pregnancy. This period thus represents a unique time window where the health of the mother and her baby are very closely related.[1]

Maternal hemodynamics undergo several physiological adaptations during pregnancy to provide for the increased metabolic demands of the mother, as well as to ensure adequate uteroplacental blood supply, nutrient delivery and oxygenation to the fetus for fetal development and growth.[2–4] These maternal hemodynamic changes are mediated through the autonomic nervous system (ANS) and the renin-angiotensin-aldosterone system, and begin as early as four to five weeks of gestation.[4]

Early in pregnancy, the total peripheral vascular resistance reduces.[5] This triggers several compensatory mechanisms.[5] The plasma volume is expended progressively throughout pregnancy by approximately 1100-1500 ml,[6,7] most of this increase has occurred by 34 weeks' gestation.[3,7] Moreover, the maternal cardiac output increases by both an increase in stroke volume and heart rate.[2,3]

These alterations are important to maintain a relatively uniform blood pressure during pregnancy. Besides a mild reduction in blood pressure in the second trimester,[4] the blood pressure can remain stable because the decrease in systemic vascular resistance is matched in magnitude by the increase in cardiac output.[2,8] A stable blood pressure is important for the perfusion of organs.

Along with these hemodynamic changes, the pregnancy also causes anatomical changes through remodeling of the heart and blood vessels.[2,8] Pregnancy-mediated changes in the heart musculature include an increase in left atrial diameter, left ventricular (LV) wall mass, and LV thickness.[8] As early hemodynamic and cardiac changes are very important for a healthy pregnancy, consequently, impairment of these adaptation mechanisms can cause serious fetal and maternal complications.[9]

Hypertensive pregnancy disorders (HPD) are an example of pregnancy complications attributed to inadequate hemodynamic adaptations during pregnancy, probably due to an inability to cope with the vascular load of pregnancy.[6] Moreover, the placenta, which forms the connection between the mother and her baby, also appears to have an important role in the origin of HPD.[10–13] HPD are a major cause of maternal morbidity and mortality and the placenta insufficiency associated with HPD also imposes an important risk for a deprived fetal condition.[13–17]

Hence, although luckily most pregnancies and deliveries are uncomplicated, complications during pregnancy can have extensive consequences for the wellbeing of both the mother

and her baby. Thus it is very important to adequately monitor and manage mothers and their fetuses who are at risk of such complications.

This thesis is subdivided into two parts. In part I, we will discuss the monitoring and management of mothers at risk of pregnancy complications, specifically HPD. Subsequently, in part II we will discuss the monitoring and management of fetal distress during labor.

PART I – MONITORING AND MANAGEMENT OF THE MOTHER AT RISK OF HYPERTENSIVE PREGNANCY DISORDERS

Etiology and consequences of hypertensive pregnancy disorders

HPD are a group of conditions including chronic hypertension during pregnancy, gestational hypertension, preeclampsia (PE), and PE superimposed on chronic hypertension.[17–19] The separate HPD are named based on the moment of onset, either prior to, or developed during pregnancy. Chronic hypertension, also referred to as pre-existing hypertension, consists of hypertension discovered preconception or prior to 20 weeks of gestation.[20] Gestational hypertension is defined as *de novo* hypertension occurring after 20 weeks' gestation with a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg.[17] Gestational hypertension can evolve into PE, when this new-onset hypertension is accompanied by either proteinuria (>300 mg/day), uteroplacental dysfunction, and/or maternal organ dysfunction including renal insufficiency, impaired liver function, thrombocytopenia, and pulmonary edema.[17–19,21] However, PE can also be superimposed on chronic hypertension. Approximately 5-10% of pregnancies are affected by HPD worldwide.[6,10,14,22] The most common HPD is gestational hypertension, followed by PE, chronic hypertension, and PE superimposed on chronic hypertension, respectively.[11]

Although the exact etiology of HPD remains elusive, failure of the maternal cardiovascular system to adapt to pregnancy is hypothesized to be one of the primary mechanisms leading to HPD. Abnormal placentation appears to have an important role in the origin of HPD, as well as increased vascular peripheral resistance.[10–12] It is unknown why these processes occur in women who develop HPD.

HPD are a major cause of maternal and fetal complications during pregnancy, including an increased risk of fetal growth restriction, preterm birth, renal and liver failure, placental abruption, and cardiovascular morbidity including cardiomyopathy.[23–26] Furthermore, HPD are major contributors to maternal death in developing countries.[15]

Moreover, the consequences of HPD are not limited to pregnancy itself. Women who suffered from HPD have a lifelong elevated risk of developing chronic hypertension,

ischemic heart disease, heart failure, stroke, and end-stage renal disease.[27–29] PE has also been identified as an independent risk factor for cardiovascular death, especially early-onset PE.[27,28] Whether HPD unmask an already existing risk of developing cardiovascular disease (CVD) or whether HPD itself is causally related to the maternal risk of CVD, remains uncertain.[30,31] The first hypothesis is supported by shared risk factors between HPD and CVD, such as smoking, obesity, diabetes mellitus, and high cholesterol.[25,31] Furthermore, endothelial dysfunction plays a central role in the development of both disorders.[31] On the other hand, both the pregnancy itself and the stress on the vessels that occurs during pregnancy could contribute to arterial wall inflammation. Furthermore, products of the dysfunctional placenta in HPD could permanently compromise the maternal cardiovascular system, leading to a (further) increased risk of CVD.[25,31] The two hypotheses are not mutually exclusive.

Complications following HPD do not only affect the health of mothers, but also extend to the health of their offspring. Children born after pregnancies complicated by HPD have an increased risk of developing CVD, stroke, elevated blood pressure, higher body mass index, and more subclinical cardiac changes during childhood or adolescence.[32–36]

Early detection of hypertensive pregnancy disorders

Accurate screening for HPD, followed by appropriate treatment, can have major benefits for maternal, fetal, and neonatal health. Identifying women at high risk for HPD provides opportunities to reduce their chance of developing HPD. For example, the daily use of low-dose aspirin and calcium between 12 to 36 weeks' gestation in women at moderate to high risk of HPD can reduce the risk of developing HPD significantly.[37,38]

Currently, risk prediction is mainly based on maternal history, which has limited predictive ability.[39,40] Townsend et al. recently published a review of reviews on the prediction of pre-eclampsia.[41] A total of 126 reviews were included, reporting on over 90 predictors and 52 prediction models. No single marker in this meta-analysis showed a test performance suitable for clinical practice. Prediction models that combined markers are promising to accurately predict HPD. However, none of those models including multiple markers have undergone external validation. Therefore, there is still a need for adequate strategies to identify women at risk of HPD.

One of the methods that has not been included by Townsend et al. is the measurement of changes in cardiac function.[41] Pregnancy is associated with several physiological changes to adapt to the increased plasma volume, increased cardiac output, and decreased peripheral vascular resistance.[2,3,5] In HPD, the maternal cardiovascular system fails to adequately adapt to pregnancy.[6,42] This failure to adapt causes subtle changes of the myocardial tissue shape, size, and function.[6,43–45]

Unfortunately, conventional echocardiography is shown to be unsuitable for the detection of early subclinical myocardial changes because measures such as left ventricular ejection fraction (LVEF) and diastolic function provide only an indirect estimate of myocardial contractile function. Moreover, in case of subclinical myocardial dysfunction, these parameters remain within normal range due to compensatory mechanisms activated in the heart.[9,46]

Speckle tracking echocardiography (STE) might be considered as a diagnostic tool to overcome these conventional echocardiography problems. This relatively new echocardiographic method analyzes the motion of tissues by tracking the position of acoustic reflections called speckles, which appear in the myocardium as a result of scattering of the ultrasound beam by the tissue (see Figure 1).[46,47] By directly quantifying the extent of myocardial contraction function, it appears to be suitable for detecting subclinical cardiac changes.[9,42,48,49] Although the use of STE is not yet widespread during pregnancy, its use for various other clinical settings has increased remarkably over recent years.[47]

One of the advantages STE has over conventionally used technique is its relative independence of loading conditions.[9,46] During pregnancy, there is a continuous variation of loading conditions of the heart, which affects conventional chamber function parameters such as LVEF and stroke volume.[9,46] Thus, STE seems to be a promising method to study changes in myocardial function during pregnancy.

Previously, STE abnormalities were found to have prognostic value in patients with hypertension, heart failure, and hypertensive heart disease.[50–54] Furthermore, Shahul et al. showed that in women with chronic hypertension a decrease in LV global longitudinal strain, has a predictive value for developing superimposed PE.[55] Therefore, differences in STE parameters between HPD and normotensive pregnancies might help in risk stratification of HPD.

Besides evaluation of cardiac function using STE, the search for methods to aid in the early detection and prediction of HPD may also focus on advanced analytics of physiological measurements. The ANS has a prominent role in several of the adaptive changes that occur during pregnancy, especially in the cardiovascular, gastrointestinal, and urinary system control.[29,56] Therefore, the inadequate adaptation of the cardiovascular system to pregnancy, which may ultimately lead to HPD, might be associated with a dysfunction of the ANS.[29,57–59] Measuring this dysfunction of the ANS can possibly be used as a precursor of developing HPD.

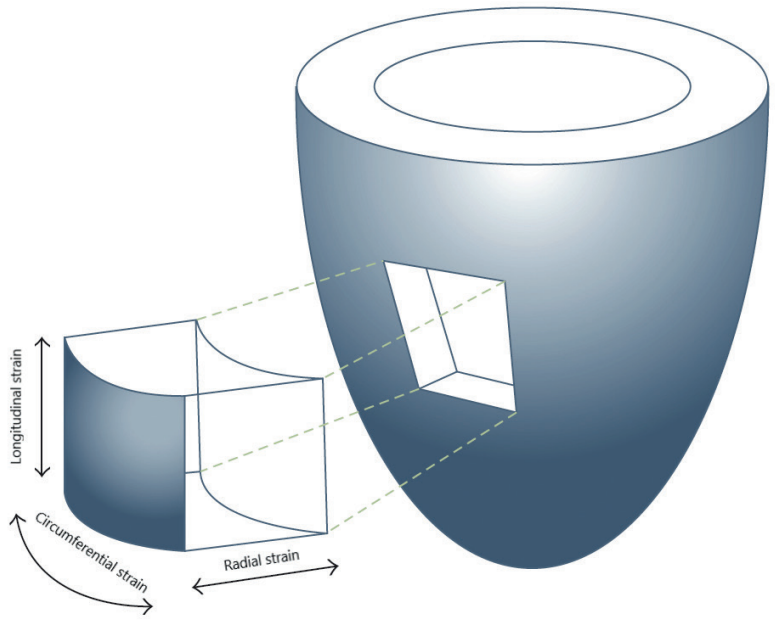

Figure 1. Speckle tracking echocardiography. The cardiac deformation is measured in three directions, namely the longitudinal, radial, and circumferential strain. Adapted from Visentin et al.[9]

Various tests and techniques can be used to assess the function of the ANS. However, not all tests are suitable for routine use due to their invasive character.[60] In contrast, heart rate variability (HRV) is a non-invasive, widely used clinical method to assess cardiac autonomic functions.[61] The assessment of the oscillations in the heart rate signal provides an estimate of the sympathetic and parasympathetic activity, as well as the balance between those two. Several studies state that HPD are associated with a sympathetic overdrive, that might already occur before the onset of clinical symptoms.[62,63] When measuring HRV, it is important to take possible confounders into account, such as the circadian rhythm, physical exercise.[61] The use of long-acting medication, such as antenatally administered corticosteroids, could also have a confounding effect on HRV. However, the effect of such medication on HRV is not fully known.

In addition to (early) detection of HPD, techniques like STE and HRV might also help in better differentiating regarding the risk of CVD in the high-risk group of women with HPD. Indeed, the American Heart Association already recommends that pregnancy history should be part of the evaluation of the risk of CVD in women.[64] However, women with HPD and alterations in HRV or STE might need a more strict follow-up, as this could possibly indicate an even higher chance of developing CVD in later life. Thereby, these techniques might enable better screening and treatment based on each women's personal risk profile.

In conclusion, new methods for prediction and early detection of HPD are needed, as currently used methods are limited in their predictive abilities. As HPD are associated with dysfunction of the ANS and changes in cardiac function, HRV and STE might be able to detect early, subclinical changes. Both of these methods are non-invasive and their use can be easily integrated into the clinical workflow. Furthermore, STE and HRV might also play a role in the risk stratification of developing CVD after a pregnancy complicated by HPD.

PART II – MONITORING AND MANAGEMENT OF THE FETUS AT RISK FOR FETAL DISTRESS

Fetal oxygenation

During pregnancy, the fetus depends on its mother for nutrients and oxygenation. The main source of fetal energy production is cellular aerobic metabolism, for which oxygen and glucose are needed. The oxygen flow towards the fetus is obtained via the maternal respiration and circulation, through placental perfusion, placental gas exchange, and the umbilical cord.[65] The oxygen exchange via the placenta is visualized in Figure 2.

The fetal oxygen tension (or partial pressure of oxygen, pO_2) is lower than the maternal oxygen tension. This difference in pO_2 between the maternal and fetal circulation facilitates the maternal-to-fetal transfer of oxygen via diffusion over the placental membranes.[65,67]

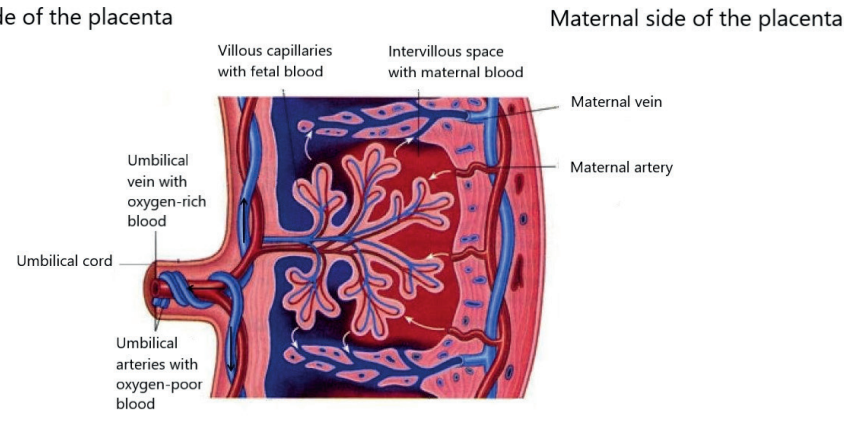

Figure 2 Placental structure and circulation. Maternal blood enters the intervillous space via the spiral arteries. Transport of oxygen and nutrients from the maternal to the fetal blood occurs from the intervillous space towards the villous capillaries, respectively. Oxygenated blood reaches the fetus through the umbilical vein. The deoxygenated blood from the fetus is carried back to the placenta via the umbilical arteries. Adapted from Lofthouse.[66]

Several adaptive mechanisms allow the fetus to function in a low-oxygen environment, like the higher affinity for oxygen in fetal hemoglobin at the same pO_2, a higher cardiac output, and the delivery of blood with the highest oxygenation levels to the most vital organs.[65,67] Despite these adaptive mechanisms, continuous oxygen supply is still very important for the fetus, as oxygen cannot be stored and later mobilized. Hence, even a short interruption of a few minutes can put the fetus at risk of oxygen deficiency.

Birth asphyxia

There are three categories of oxygen deficit, depending on the severity of the oxygen deficiency[65];

1. Hypoxemia, in which the reduced oxygen supply causes a reduction in arterial oxygen concentration without affecting cell and organ function.
2. Hypoxia, in which reduction in oxygen causes anaerobic metabolism and subsequently leading to a decrease in pH, accumulation of lactate, and an increased base excess, mainly in the peripheral tissues.
3. Asphyxia, the last phase of oxygen deprivation in which hypoxia extends to the central organs (i.e. the brain, heart, and adrenal glands). Asphyxia can potentially lead to metabolic acidosis and death.

The risk of compromised fetal oxygenation is increased during labor,[65] which can have lifelong consequences due to neuronal damage. During labor, uterine contractions temporarily decrease the perfusion of the placental bed. Furthermore, these contractions cause compression of the umbilical cord thus reducing umbilical blood flow.[65,68] Both mechanisms may lead to decreased oxygen delivery to the fetus, and when lasting too long may ultimately lead to perinatal hypoxia and eventually to asphyxia.[65,68]

Worldwide, birth asphyxia is one of the main causes of neonatal mortality,[69,70] causing approximately 0.69-0.92 million neonatal deaths each year.[69,71] Asphyxia can cause severe morbidities, such as brain damage, renal and hepatic failure and cardiac dysfunction.[72–78]

Each year, approximately four million babies are born worldwide showing signs of perinatal asphyxia.[78] Annually, in the Netherlands, approximately 400 term babies are born with asphyxia (0.3%).[79] Asphyxia imposes a huge burden on patients, their families, and society, and presents an important challenge to clinical and research professionals to establish effective diagnosis and treatment methods.

Assessment and treatment of deprived fetal oxygenation

To reduce the occurrence of perinatal asphyxia, adequate recognition of fetal distress is needed, allowing timely intervention to manage the effects of hypoxemia and hypoxia before asphyxia occurs. However, it is not yet possible to directly measure fetal oxygenation during labor, and methods for continuous intrapartum monitoring of fetal

oxygen saturation (SpO_2), pO2, partial carbon dioxide pressure (pCO_2), and pH are either not effective or not yet suitable for clinical practice.[80–82] Therefore, evaluation of the fetal heart rate (FHR) pattern, with additional fetal scalp blood sampling on indication, is still one of the most used methods of intrapartum fetal monitoring.[83,84]

FHR is regulated by the ANS. When oxygen delivery towards the fetus is impaired, the fetal ANS is activated as a compensation mechanism.[65,85] This ANS activation results in changes in FHR and blood flow distribution to maintain blood pressure and economize oxygen consumption.[68,83,86] Several studies show that a non-reassuring FHR pattern is considered to be indicative of potential fetal hypoxia.[83,87–90]

Unfortunately, evaluation of FHR has a high false-positive rate in the prediction of fetal hypoxia.[83,91] This implies that a non-reassuring FHR pattern is not always reflecting a compromised fetus. This limitation in the prediction of fetal hypoxia makes it challenging for clinicians to decide when interventions are indicated. Monitoring the fetal condition using continuous FHR could lead to many unnecessary emergency operative deliveries or instrumental vaginal deliveries,[88] which are associated with an increased risk of adverse maternal and neonatal outcome.[92–94] Instead of aiming for immediate delivery in case of suspected fetal distress, interventions can be used to restore fetal oxygenation while keeping the fetus inside the uterus. When successful, these interventions, i.e. intrauterine resuscitation, can avoid unnecessary invasive interventions.

Depending on the presumable cause of fetal distress, the intrauterine resuscitation technique should be focusing on increasing oxygen delivery to the fetus, improvement of uteroplacental blood flow and/or alleviation of umbilical cord compression. For example, adjustment or discontinuation of oxytocin infusion or the use of tocolytic drugs can alleviate umbilical cord compression caused by prolonged or frequent uterine contractions, whereas intermittent pushing and maternal repositioning improve the uteroplacental blood flow, while maternal hyperoxygenation focusses on increasing the oxygen delivery towards the fetus.[95,96]

Even though these interventions are widely used in clinical practice, solid evidence regarding their beneficial effect on neonatal outcome is limited and sometimes contradictory.[95,96] As a result, there is no consensus on the use of these intrauterine resuscitation techniques during labor. Consequently, recommendations on the management of fetal distress may vary in international guidelines. This may lead to variations in clinical practice between hospitals.

Intrauterine resuscitation through maternal hyperoxygenation

One intrauterine resuscitation technique that raises discussion is maternal hyperoxygenation, in which the mother receives additional oxygen to treat fetal distress. The rationale behind this intervention is that, even though the oxygen saturation of

healthy women in labor is nearly 100%, the additional oxygen causes an increase in maternal pO_2, which results in an increase in oxygen transfer towards the fetus.[97,98] Vasicka et al. showed that five minutes of maternal hyperoxygenation with 100% oxygen results in an increase in pO_2 in maternal arterial blood, as well as a 52% increase in pO_2 in the umbilical artery.[97] Maternal hyperoxygenation may thus contribute to improved fetal oxygenation and prevention of fetal hypoxia and acidosis.

Measurements with non-invasive blood oxygen level-dependent magnetic resonance imaging (MRI) demonstrated increased oxygenation in a number of fetal organs during maternal hyperoxygenation, specifically the fetal liver, spleen, and kidneys.[99] In addition, several small, non-randomized studies showed an improvement of FHR pattern and/or fetal scalp pH when additional oxygen was applied in the event of suspected fetal distress.[100–105]

Despite these positive effects of maternal hyperoxygenation, there have been posed counter-arguments, especially concerning the potentially harmful effects of this therapy. One of the arguments to plead against maternal hyperoxygenation is a possible lowering of umbilical cord arterial pH. Thorp et al. performed a randomized controlled trial (RCT) to investigate the effect of prophylactic oxygen administration during the second stage of uncomplicated labor.[106] In this study, women with reassuring fetal heart rate tracings were randomized between breathing room air or maternal hyperoxygenation. The mean umbilical cord arterial pH did not differ between the groups, however, significantly more umbilical cord arterial pH levels below 7.20 were found in the oxygenation group, compared to controls.[106] Two other RCTs on the use of prophylactic oxygen administration during the second stage of uncomplicated labor did not find any significant differences in arterial cord blood pH.[107,108] Furthermore, a recent noninferiority RCT among patients with non-reassuring FHR during the active phase of labor compared maternal hyperoxygenation to breathing room air.[109] This study showed no difference in umbilical artery lactate.

Another possible detrimental effect of maternal oxygen supplementation is the potential increase in free radical activity in both the mother and fetus.[110–112] Free oxygen radicals are reactive atoms with one more unpaired electron in their outer orbit. To a certain degree, free oxygen radicals are formed under physiologic conditions.[113] During labor, uterine contractions might be regarded as a small series of ischemia-reperfusion injuries causing free oxygen radicals, especially in case of non-reassuring FHR.[114]An increase in free radical activity due to oxidative stress may lead to cell damage and altered cellular function.[115] Unfortunately, the brief lifespan of free oxygen radicals makes it extremely difficult to measure them directly. To measure free oxygen radical activity, more stable derivatives can be used as proxy measurements.[116] For instance, malondialdehyde (MDA), a by-product of lipid peroxidation, appears to be an accurate non-invasive biomarker for free radical damage.[114,116]

In an RCT on the prophylactic use of maternal hyperoxygenation during elective cesarean delivery, the levels of MDA in maternal blood and in arterial umbilical cord blood were found to be significantly higher in the oxygen group compared to the group of women breathing room-air.[112] This raises concerns about a possible increase in free oxygen radical activity.

Yet, the effect and clinical implication of maternal hyperoxygenation in case of fetal distress on free radical activity is not known. What we do know is that after birth, neonatal resuscitation using 100% oxygen may lead to higher morbidity and mortality compared with resuscitation with room-air consisting 21% oxygen.[117,118] However, oxygenation of the fetus is facilitated by the large gradient over the placenta between the pO_2 in the maternal blood and the umbilical blood.[119] Therefore, the increase in fetal pO2 due to maternal hyperoxygenation will never reach the levels obtained by the direct application of 100% oxygen directly to either the fetus or neonate.[120]

The conflicting literature has resulted in different recommendations on the use of maternal hyperoxygenation between international guidelines. The American College of Obstetricians and the Gynecologists (ACOG) and the Society of Obstetricians and Gynaecologists of Canada (SOGC) support the use of maternal hyperoxygenation as an intrauterine resuscitation technique during labor.[121,122] In contrast, the British guideline, provided by the Royal College of Obstetricians and Gynaecologists (RCOG) advises against the use of maternal hyperoxygenation in clinical practice.[123] The Dutch Society of Obstetricians and Gynecologists (NVOG) has updated its recommendation in July 2019 and also advises against the routine use of maternal hyperoxygenation to treat suspected fetal distress due to knowledge gap regarding this intervention.[124]

To our knowledge, no RCT has studied the effect of maternal hyperoxygenation in case of fetal distress on FHR pattern or neonatal outcome. The lack of robust evidence regarding the effect of maternal hyperoxygenation is also addressed in a Cochrane review, which concludes there is insufficient evidence to support the use of maternal hyperoxygenation for the treatment of fetal distress and emphasizes the need for a randomized controlled trial to study the effect of maternal hyperoxygenation in the compromised fetus during the second stage of labor.[125]

In conclusion, the fetus depends on oxygen delivery from the placenta. During labor, the risk of compromised fetal oxygenation is increased, and when lasting too long may ultimately lead to perinatal hypoxia and eventually to asphyxia. Therefore, it is important to monitor the fetal condition and, if needed, optimize the fetal condition before hypoxia and asphyxia occur. To do so, several intrauterine resuscitation techniques can be used. However, solid evidence regarding their beneficial effect on neonatal outcome is limited and sometimes contradictory. One intrauterine resuscitation technique that raises discussion is maternal hyperoxygenation, of which the effect during the second stage of labor has only been studied in small, non-randomized studies.

OUTLINE OF THIS THESIS

This thesis aims to answer the following questions:

1. Is STE a suitable method to detect differences in cardiac function in pregnant women with HPD or women with a history of HPD compared to normotensive women?

Chapter 2 aims to answer this research question by systematically reviewing and summarizing the literature on STE in HPD.

2. Does HRV detect differences in the function of the autonomic nervous system in pregnant women with HPD or women with a history of HPD compared to normotensive women?

Chapter 3 gives a systematic overview of currently available literature regarding HRV in HPD in order to answer this research question.

3. What is the effect of routine obstetric medication on maternal HRV?

Chapter 4 presents the study protocol of an observational cohort study to investigate the effect of routine obstetric medication on maternal HRV, to provide an answer to this research question.

4. Which methods are recommended in international guidelines regarding the monitoring and management of fetal distress during labor?
5. Which fetal monitoring methods are used in Dutch clinical practice, and which intrauterine resuscitation techniques are utilized in case of suspected fetal distress?

Chapter 5 reports on the practice variation in fetal monitoring and management of fetal distress during labor in Dutch hospitals. Furthermore, it provides a comparison of recommendations of the national guidelines of various Western countries regarding fetal monitoring and management of fetal distress during labor. This study was set up to answer research questions 4 and 5.

6. What is the effect of intrauterine resuscitation by maternal hyperoxygenation during the second stage of term labor on neonatal and maternal outcome?
7. Does maternal hyperoxygenation, applied in case of suspected fetal distress during the second stage of term labor, affect FHR?

Chapter 6 describes the study protocol of an RCT, the INTEREST O2 study, to investigate the effect of maternal hyperoxygenation as an intrauterine resuscitation technique during the second stage of labor. This RCT is set-up to answer research questions 6 and 7.

Chapter 7 presents the results of the INTEREST O2 study on perinatal and maternal outcome as a result of maternal hyperoxygenation, and this chapter thus contributes to answering research question 6.

Chapter 8 presents the detailed FHR analyses of the INTEREST O2 study, using specific technical FHR features related to poor neonatal outcome. The goal of this study was to contribute to answering research question 7.

Chapters 2 to 8 have been published, or are submitted for publication. These chapters are written to be self-contained which might cause some overlap between these chapters.

Chapter 9 contains a general discussion of the results presented in this thesis and provides suggestions for future research.

Chapters 10 and 11 provide an English and Dutch summary of the data presented in this thesis, respectively.

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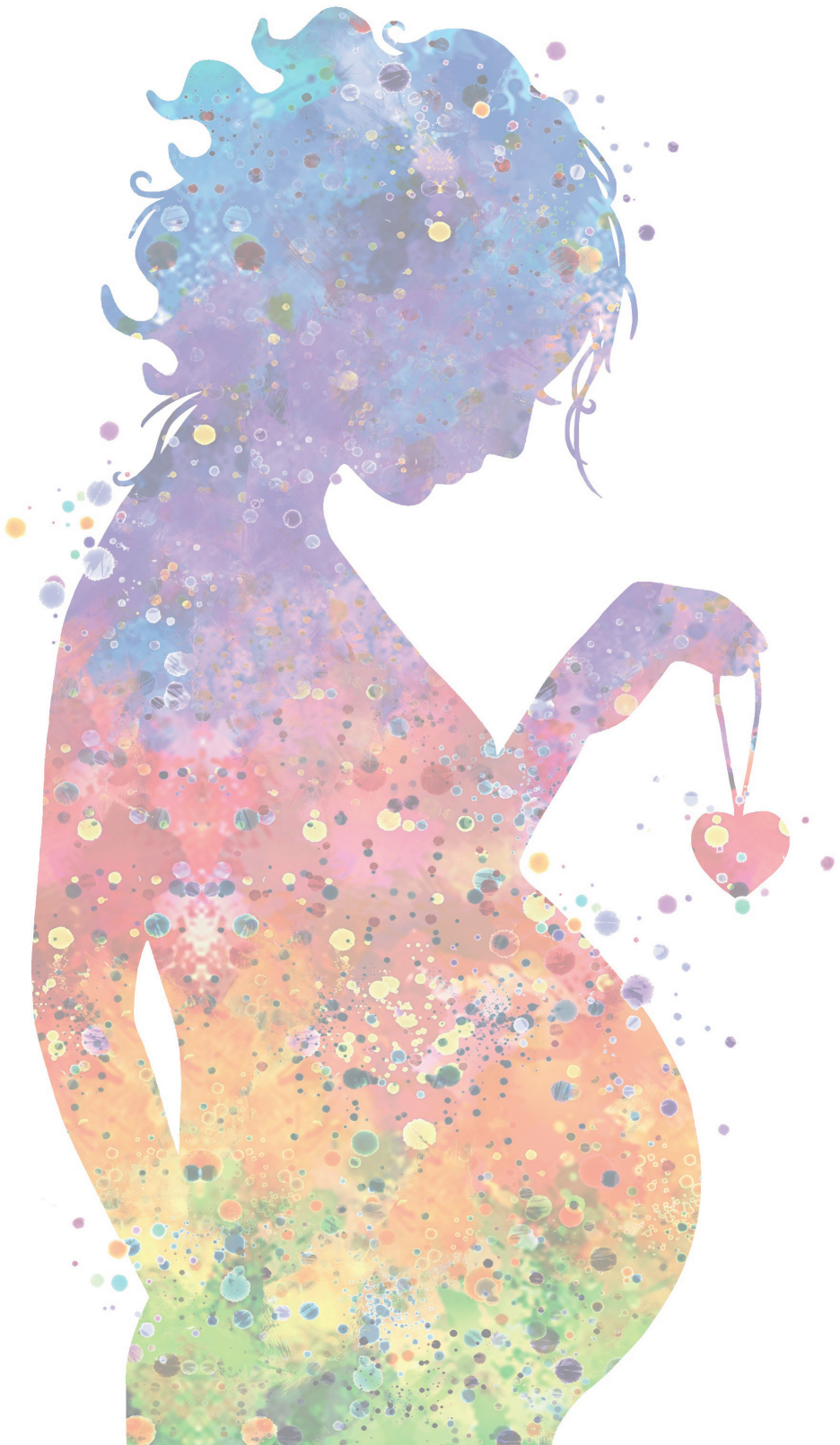

2

Speckle tracking echocardiography in hypertensive pregnancy disorders: a systematic review

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ABSTRACT

Importance

Hypertensive pregnancy disorders (HPD) are associated with an increased risk of long-term cardiovascular disease. Speckle tracking echocardiography (STE) might be useful in the early detection of pre-clinical cardiac changes in women with hypertensive pregnancy disorders.

Objective

To study whether STE is a suitable method to detect differences in cardiac function in pregnant women with HPD compared to normotensive pregnant women or between women with a history of a pregnancy complicated by HPD compared to women with a history of an uncomplicated pregnancy.

Evidence Acquisition

The databases Medline, EMBASE, and Central were systematically searched for studies comparing cardiac function measured with STE in pregnant women with HPD or women with a history of HPD and women with (a history of) normotensive pregnancies.

Results

The search identified 16 studies, including 870 women with (a history of) HPD and 693 normotensive controls. Most studies during pregnancy (n=12/13) found a decreased left ventricle (LV) global longitudinal strain (GLS) in HPD compared to normotensive pregnant controls. LV global radial strain (GRS) and LV global circumferential strain (GCS) are decreased in women with early-onset and severe preeclampsia. Women with a history of early-onset preeclampsia show lasting myocardial changes, with significantly decreased LV-GLS, LV-GCS, and LV-GRS.

Conclusions and relevance

LV-GLS is significantly decreased in pregnant women with HPD compared to normotensive pregnant women. Other deformation values show a significant decrease in women with severe or early-onset preeclampsia, with lasting myocardial changes after early-onset preeclampsia.

INTRODUCTION

Hypertensive pregnancy disorders (HPD) are one of the most common medical problems encountered during pregnancy, affecting 5-10% of pregnancies. [1-4]

HPD, defined as gestational hypertension (GH), chronic hypertension (CH), preeclampsia (PE), or superimposed PE,[5] provoke serious maternal and fetal complications and are the leading cause of maternal death worldwide. [5-7] Besides increased maternal cardiovascular complications in pregnancy, HPD are also associated with an increased risk of long-term cardiovascular disease (CVD). [8-10] Failure of the maternal cardiovascular system to adapt to pregnancy is hypothesized to be the primary mechanism leading to HPD. [11,12] Due to this inability to adapt, the maternal myocardium changes subtly in shape, size, and function.[11,13-15] Early detection of these subtle changes, with the institution of appropriate screening and treatment, may reduce the risk of future CVD.[16,17] Myocardial changes can be identified by ultrasound.[10,12,18] However, conventional echocardiography, measuring left ventricular ejection fraction (LVEF) and diastolic function, was shown to be unsuitable for the detection of early subclinical myocardial changes, as these measures provide an indirect estimate of myocardial contractile function and change late in the cascade of myocardial dysfunction due to compensatory mechanisms.[17,19] Speckle tracking echocardiography (STE), a relatively new echocardiographic method, could overcome this problem.

STE is a grey-scale based ultrasound technique, based on frame-by-frame tracking of acoustic reflections, speckles. STE is increasingly used in the assessment of left ventricular cardiac function,[20,21] as it has advantages over conventionally used techniques.[17,19,22,23] It directly quantifies the extent of myocardial contraction function and STE has equal to superior reproducibility.[24,25] STE is proven to be suitable for the detection of subclinical cardiac changes.[12,17,20,22] STE abnormalities are also shown to have prognostic value in patients with hypertension and hypertensive heart disease.[26,27] Therefore, STE might also be useful in the detection of cardiac changes in HPD affected mothers. The aim of this systematic review is to study whether STE detects differences in cardiac function between pregnant women with HPD compared to normotensive pregnant women and between women with a history of a pregnancy complicated by HPD compared to women with a history of an uncomplicated pregnancy.

MATERIALS AND METHODS

Inclusion and exclusion criteria

All published studies that compared cardiac STE features between human females with (a history of) HPD and a normotensive control group were included in this review. We included studies that compared pregnant women with HPD to normotensive pregnant

women and we included studies that compared women with a history of a pregnancy complicated by HPD to women with a history of an uncomplicated pregnancy.

Studies that compared pregnant women with HPD with normotensive non-pregnant women were excluded. Studies that used other ultrasound techniques than STE to measure maternal heart function were excluded. Furthermore, review studies, guidelines, editorials, comments and conference abstracts were also excluded. No language restrictions or restrictions imposed on year of publication were applied. In the event an article in a language other than English or Dutch was found eligible based on title or abstract, the full text was retrieved and translated by a native speaker.

Search strategy

The databases of Medline (Pubmed), EMBASE, and CENTRAL were systematically searched from inception up to and including September 2019. The search consisted of the following terms and a wide variety of their synonyms: preeclampsia, hypertensive pregnancy disorders, speckle tracking echocardiography, and strain. A professional medical research librarian assisted to set the search strategy. The search strings are shown in Appendix S1. The review process was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (PRISMA),[28] and prospectively registered in the international prospective register of systematic reviews, PROSPERO *(CRD42019124031, Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019124031)*

Study selection and data extraction

Two reviewers, SM and NvO, independently reviewed the titles and abstracts to judge their eligibility for inclusion. The full text of these potentially eligible studies was retrieved and independently assessed for eligibility. Disagreement was solved by consensus; if needed, a third reviewer, MW, was consulted. After, we hand-searched all references and related articles of the selected articles to identify additional relevant publications.

Relevant information was extracted from each paper by two researchers (SM and NvO) independently, using a pre-determined form. The retrieved data comprised study characteristics such as year of publication, number of included women, in- and exclusion criteria and methods including study design, timing of echocardiography, and ultrasound device and STE software used.

Outcome measures

STE is an imaging technique that analyzes the motion of tissues in the heart by using the naturally occurring speckle pattern in the myocardium resulting from scattering of the ultrasound beam by the tissue.[19,29] The STE software measures the change in distance between speckles over time, which is expressed as strain.[19,21] Strain rate (SR) is the rate at which the myocardial deformation occurs in 1/sec. In cardiac STE, strain represents the myocardial shortening and lengthening during a cardiac cycle of contraction and relaxation and can be measured in different directions where it is expressed as a percentage.[19,21,29] The outcome measures of interest were the following parameters measured by STE; left ventricular (LV) global longitudinal strain (GLS), LV global radial strain (GRS), LV global circumferential strain (GCS), and SR. The GLS is measured in the apical long-axis images and the short-axis images are used to measure GRS and GCS.[19,21,29]

Quality assessment and data analysis

The methodological quality of the eligible studies was assessed using the Newcastle-Ottawa Quality Assessment Form for Case-Control Studies (NOS) according to the guidelines of the Dutch Cochrane Center. [30-32] The NOS is a qualitative assessment tool for observational studies. Assessment is done using the following three dimensions; selection, comparability, and exposure. A maximum of nine stars can be awarded to a single study.[30] The studies were classified in categories as suggested by Losilla et al.,[33] by which studies with 0-3, 4-6, or 7-9 stars were classified as low, moderate, and high quality, respectively. Two authors (SM and NvO) completed the quality and risk of bias assessment independently. Disagreement was solved by consensus; if needed, a third reviewer, MW, was consulted. Data from the included studies were aggregated to provide a narrative synthesis of the findings.

RESULTS

Search results

A total of 200 studies were identified through database searching. The process of study inclusion according to the PRISMA statement is shown in figure 1. After removing duplicates, 158 studies remained. From these articles, 63 articles were found eligible for full-text assessment. When multiple articles from the same authors were found eligible, authors were contacted to ensure no duplicate study populations would be included. One study was excluded for this reason.[34] After full-text assessment, 16 articles were included in this review.[12,16,18,35-47] No additional articles were identified by hand searching the references of the included articles. One article was published in Chinese[42] and translated to English by a native Chinese speaker.

The study characteristics of the included studies are summarized in Table 1. All included studies had an observational case-control design, of which three were longitudinal studies. HPD were defined according to the definition by the International Society for the study of Hypertension in Pregnancy, [12,38-40,43,47] American College of Obstetricians and Gynecologists, [16,18,35-37,46] the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy,[41,45] the definition as stated in Obstetrics & Gynecology by Xie and Gou,[42] or by the classification by Davey et al.[44,48]

The 16 selected studies included a total number of 1563 patients. Ten studies evaluated women during their pregnancy, including 601 women with a pregnancy complicated by HPD and 523 controls with a normotensive pregnancy. In three studies cardiac function was measured postpartum only, including 128 women with a history of HPD and 86 controls with a history of normotensive pregnancy. Three studies analyzed women both during their pregnancy and as well as postpartum. Of these, 141 women had HPD and 84 had a normotensive pregnancy. The characteristics and quality of the included studies are presented in Table 1.

The type of ultrasound machine and STE software used to perform STE varied among the studies. The patients in the studies performed during pregnancy varied with regard to the gestational age included (Table 1). The included gestational ages varied from 23 to 42 weeks. Most studies included both preterm and term women,[16,18,35-39,41,42,45-47] whereas one study included term women only.[12] The population in the studies concerning postpartum women showed a wide variation with regard to the period between delivery and the timing of the study measurement, ranging from 6 weeks to 13 years postpartum.[35,40,43-46]

Three studies differentiated between early-onset PE (EO-PE) and late-onset PE (LO-PE), i.e. occurring before or after 34 weeks of gestation, respectively.[39,40,43]

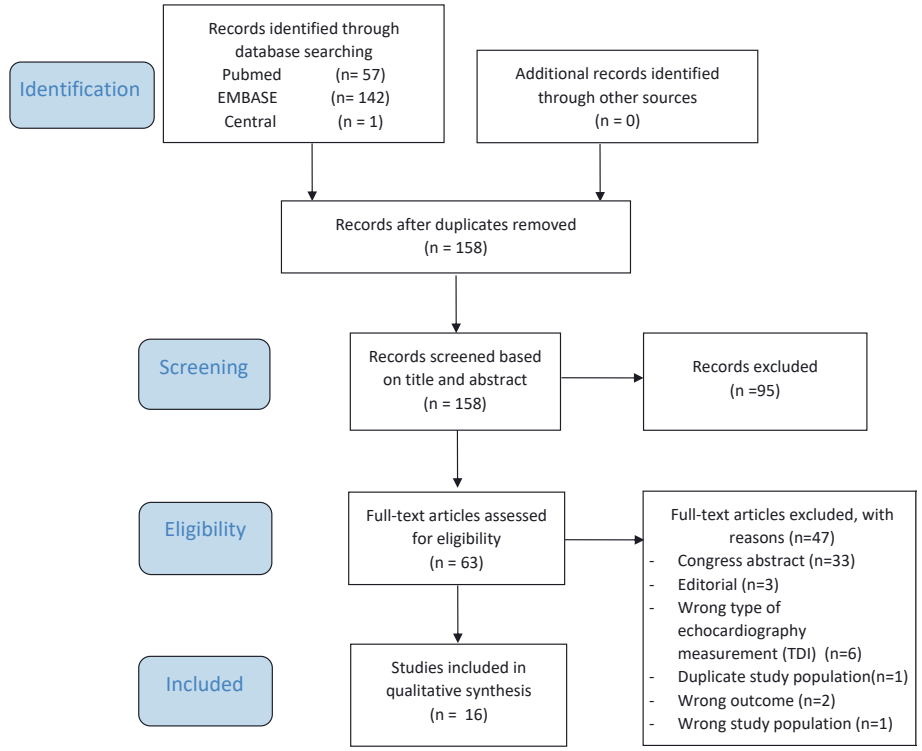

Figure 1. PRISMA Flow diagram demonstrating an overview of the selection process.

Table 1. Characteristics and Quality of Included Studies.

Author Year	Total number of women	Population (n=)	HPD definition Inclusion and exclusion criteria	Methods	Mean GA (weeks) or period postpartum at assessment	Quality assessment and risk of bias (NOS)	Losilla quality categories
Studies examining women during their pregnancy							
Ajmi et al.[18] 2018	60	**Cases:** HPD (30) **Control:** NTP (30)	- **HPD definition**: ACOG - **Inclusion**: Age 18-42, GA 28-38 weeks - **Exclusion:** preexisting hypertension, cardiac, pulmonary, renal disease or other pathology that may influence ultrasound data. EF <55%, difficult interpretation or poor quality of photographs	**Study design:** case control **Machine:** Vivide TM E9, GE **STE software**: not described	**Cases:** 32 **Control:** 33	7 (3/2/2)	High quality
Buddeberg et al.[12] 2018	70	**Cases:** PE (30) **Control:** NTP (40)	- **HPD definition:** ISSHP - **Inclusion:** GA at term, before start of any antihypertensive medication - **Exclusion**: any cardiovascular co-morbidity	**Study design:** case control **Machine:** Vivd Q, GE. **STE software**: EchoPac	**Cases:** 39.3±1.0 **Control:** 38.3±1.5	5 (3/0/2)	Moderate quality
Cho et al.[41] 2011	199	**Cases:** GH (106) **Control:** NTP (93)	- **HPD definition:** NHBPEPWG on HBPP - **Inclusion**: pregnancy - **Exclusion**: DM, essential hypertension, or symptomatic coronary artery disease	**Study design:** case control **Machine:** Vivid 7, GE **STE software:** EchoPac	**Cases:** 33.3±3.6 **Control:** 35.1±3.4	4 (2/0/2)	Moderate quality

Table 1. Continued.

Author Year	Total number of women	Population (n=)	HPD definition Inclusion and exclusion criteria	Methods	Mean GA (weeks) or period postpartum at assessment	Quality assessment and risk of bias (NOS)	Losilla quality categories
Cong et al.[39] 2015	165	**Cases:** - EO-PE (43) - LO-PE (41) **Control:** -NTP <34weeks (41) -NTP >34weeks (40)	- **HPD definition:** ISSHP - **Inclusion**: singleton pregnancy - **Exclusion:** preexisting medical conditions	**Study design:** case control **Machine**: Vivid E9, GE. **STE software**: Echopac.	**Cases:** **EO-PE:** 28.9±2.7 **LO-PE:** 36.4±1.3 **Control <34:** 28.2±2.9 **Control ≥34**: 36.4±1.3	7 (3/2/2)	High quality
Cong et al.[38] 2018	86	**Cases:** PE (45) **Control:** NTP (41)	- **HPD definition:** ISSHP - **Inclusion**: singleton pregnancy - **Exclusion:** poor quality images, smoking history or any previous medical condition	**Study design:** case control **Machine:** Vivid E9, GE. **STE software**: EchoPAC.	**Cases:** 31.8±4.2 **Control:** 32.7±3.7	8 (3/2/3)	High quality
Pan et al.[47] 2019	53	**Cases:** s-PE (33) **Control:** NTP (20)	- **HPD definition:** ISSHP - **Inclusion:** nonsmoking - **Exclusion:** comorbidities	**Study design:** Case control **Machine:** Vivid E9, GE. **STE software:** Not described	**Cases:** 34.7±5.0 **Control:** 34.7±3.4	7 (3/2/2)	High quality

Table 1. Continued.

Author Year	Total number of women	Population (n=)	HPD definition Inclusion and exclusion criteria	Methods	Mean GA (weeks) or period postpartum at assessment	Quality assessment and risk of bias (NOS)	Losilla quality categories
Shahul et al.[37] 2012	28	**Cases:** PE (11) **Control:** NTP (17)	- **HPD definition:** ACOG - **Inclusion**: Age ≥18, singleton pregnancy, GA 24-41weeks - **Exclusion:** pre-existing CVD, pulmonary disease, DM, or poor image quality	**Study design:** case control **Machine:** Siemens X-300. **STE software:** Tomtec.	**Cases:** 36.6 (32.7-37.4) **Control:** 38.0 (35.6-39.6)	5 (3/0/2)	Moderate quality
Shahul et al.[36] 2016	167	**Cases**: PE (62) **Control:** NTP (105)	- **HPD definition:** ACOG - **Inclusion**: Age ≥18, singleton pregnancy, GA <41weeks - **Exclusion:** preexisting cardiomyopathy, ischemic or valvular heart disease, pulmonary disease, DM, or labor.	**Study design:** case control **Machine:** Philips CX-50. **STE software**: Autostrain, Tomtec.	**Cases:** 32.8±3.7 **Control:** 30.7±4.3	5 (3/0/2)	Moderate quality
Vaught et al.[16] 2018	99	**Cases:** s-PE (63) **Control:** NTP (36)	- **HPD definition:** ACOG - **Inclusion**: Singleton pregnancy, GA >23 weeks - **Exclusion:** SLE, congenital or valvular heart disease, APS, cardiomyopathy, pulmonary hypertension or embolism, cardiac surgery, connective tissue or interstitial lung disease, poor image quality	**Study design:** case control **Machine:** GE or Philips ultrasound machine **STE software:** Epsilon software.	**Cases:** 33.1±3.6 **Control:** 31.8±4.9	6 (3/1/2)	Moderate quality

Table 1. Continued.

Author Year	Total number of women	Population (n=)	HPD definition Inclusion and exclusion criteria	Methods	Mean GA (weeks) or period postpartum at assessment	Quality assessment and risk of bias (NOS)	Losilla quality categories
Xia et al.[42] 2017	197	**Cases:** - m-PE (73) - s-PE (64) **Control:** NTP (60)	- **HPD definition:** as in Obstetrics & Gynecology by Xie and Gou. - **Inclusion**: gestational age ≥32 weeks - **Exclusion:** congenital heart disease, other serious comorbidities	**Study design:** case control **Machine:** Vivid E9, GE **Software:** EchoPac	**Mild PE:** 35.9±3.3 **Severe PE:** 35.2±3.1 **Control:** 34.9±2.7	5 (3/0/2)	Moderate quality
Studies examining women postpartum							
Al-Nashi et al.[44] 2016	31	History of: **Cases:** PE (15) **Control:** NTP (16)	- **HPD definition:** ACOG - **Inclusion**: primiparous women during index pregnancy - **Exclusion**: smoking, cardiovascular risk factors	**Study design:** case control **Machine:** Vivid 7, GE. **STE software**: EchoPac.	**Mean period after index pregnancy** 11.2±0.6 year Years after last pregnancy: **Cases:** 7.9±3.3 year **Control:**6.6±2.4 year	8 (3/2/3)	High quality

Table 1. Continued.

Author Year	Total number of women	Population (n=)	HPD definition Inclusion and exclusion criteria	Methods	Mean GA (weeks) or period postpartum at assessment	Quality assessment and risk of bias (NOS)	Losilla quality categories
Clemmensen et al.[40] 2018	93	History of: **Cases:** **-** EO-PE (31) - LO-PE (22) **Control:** **-** NTP (40)	- **HPD definition:** ISSHP - **Inclusion**: women who gave birth between 1998–2008 - **Exclusion**: new pregnancy, breastfeeding, natural menopause, or address >100km away from study site	**Study design:** case control **Machine:** Vivid E9, GE. **STE software:** EchoPac	**Time since index pregnancy in years** **EO-PE cases:** 13±4 **LO-PE cases:** 12±3 **Control:** 12±3	8 (3/2/3)	High quality
Orabona et al.[43] 2017	90	History of: **Cases:** - EO-PE (30) - LO-PE (30) **Control:** NT (30)	- **HPD definition:** ISSHP - **Inclusion**: women who had normal blood pressure and no pathological proteinuria 6 months after delivery - **Exclusion**: smoking, dyslipidemia, obesity, DM, chronic hypertension, cardiopathy, nephropathy, immune disorders, PE superimposed on CH, multiple pregnancy, chromosomopathy, or fetal malformation.	**Study design:** case control **Machine**: Vivid 7, GE . **STE software**: not described	**Time since delivery in years:** 6 months – 4 years **Mean time since delivery:** **EO-PE:** 2.3±0.7 **LO-PE:** 2.5±0.8 **Control:** 2.2±0.6	9 (4/2/3)	High quality

Table 1. Continued.

Author Year	Total number of women	Population (n=)	HPD definition Inclusion and exclusion criteria	Methods	Mean GA (weeks) or period postpartum at assessment	Quality assessment and risk of bias (NOS)	Losilla quality categories
Studies examining women both during their pregnancy and postpartum							
Levine et al.[46] 2019	58	**Cases:** s-PE (29) **Control**: NTP (29)	- **HPD definition:** ACOG - **Inclusion**: Age ≥18 - **Exclusion**: preexisting CVD, chronic hypertension without superimposed PE, or multiple gestations	**Study design:** Longitudinal case control **Machine:** Vivid E9 and E95, GE. **STE software:** Tomtec	**GA at assessment during pregnancy** **Cases:** 31.3±3.9 **Control:** 31.7±3.6 **Time since delivery at assessment postpartum:** 4-12 weeks postpartum **Cases:** 6 (5-6) **Control:** 7 (6-9)	7 (3/2/2)	High quality
Shahul et al.[35] 2018	85	**Cases:** PE (32) **Control:** - GH or CH (28) - NTP (25)	- **HPD definition:** ACOG - **Inclusion**: Age ≥18, singleton pregnancy, GA <41weeks - **Exclusion:** preexisting cardiomyopathy, ischemic or valvular heart disease, pulmonary disease, DM, or women in labor.	**Study design:** Longitudinal case control **Machine:** Philips CX-50. **STE software:** Autostrain, Tomtec.	**GA at assessment during pregnancy** **PE:** 32.2 (29.1-36.1) **GH or CH:** 37.9 (33.3-39.2) **Control:** 30.7 (26.7-32.3) **Time since delivery at assessment postpartum:** 12 months	5 (3/0/2)	Moderate quality

Table 1. Continued.

Author Year	Total number of women	Population (n=)	HPD definition Inclusion and exclusion criteria	Methods	Mean GA (weeks) or period postpartum at assessment	Quality assessment and risk of bias (NOS)	Losilla quality categories
			- **HPD definition:** NHBPEPWG on HBPP - **Inclusion:** women aged ≥18, singleton pregnancy, and nonsmoking - **Exclusion:** gestational diabetes, previous history of hypertension, CVD, poor images quality.	**Study design:** Longitudinal case control **Machine:** Siemens S2000 (axius, Siemens) **STE software:** Axius, Siemens medical	**GA at assessment during pregnancy** **PE:** 32±6 **GH:** 34±3 **Control:** 33±4 **Time since delivery at assessment postpartum:**		
Yu et al.[45] 2018	82	**Cases**: - GH (27) - PE (25) **Control**: NTP (30)			3 months	5 (3/0/2)	Moderate quality

ACOG= American College of Obstetricians and Gynecologists. APS= Antiphospholipid syndrome. BP= Blood pressure. CVD= Cardiovascular disease. DM= Diabetes Mellitus. GA= Gestational age. GH= Gestational hypertension. HPD= Hypertensive pregnancy disorders. ISSHP= International Society for the study of Hypertension in Pregnancy. NHBPEPWG on HBPP= National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. NTP= Normotensive pregnancy. PE= Preeclampsia. EO-PE= Early-onset PE. LO-PE= Late onset- PE. m-PE= Mild PE. s-PE= Severe PE. SLE= Systemic lupus erythematosus. Data are mean±SD or median (interquartile range)

Quality assessment

The risk of bias of the included studies is reported in Table 1. The risk of bias score varied between four and nine stars on the Newcastle-Ottawa Scale, which corresponds with moderate to high quality.

Echocardiographic measurements

An overview of STE results during pregnancy is presented in Table 2. Table 3 presents an overview of STE results postpartum.

Left ventricle global longitudinal strain (LV-GLS)

Results during pregnancy

All included studies reported results on LV-GLS. Twelve studies showed a significant decrease in LV-GLS in pregnant participants with HDP compared to normotensive participants.[12,18,35-39,41,42,45-47] In one study, the same trend of decreased LV-GLS was observed in women with PE compared to normotensive pregnant women, however, this was not significant.[16]

Results postpartum

Six studies measured LV-GLS postpartum.[35,40,43-46] The measurement timing ranged from 6 weeks[46] to 13 years[40] postpartum. Three studies, evaluating women up to one year postpartum, showed a significant decreased LV-GLS after a pregnancy complicated by PE compared to women after a normotensive pregnancy.[35,45,46] One study, comparing women 11 years after a pregnancy complicated by PE with women with a history of a normotensive pregnancy, did not demonstrate a significant difference in LV-GLS.[44] Two studies differentiated between EO-PE and LO-PE. [40,43] Both studies showed a decreased LV-GLS after EO-PE, whereas LO-PE was shown not significantly different from normotensive controls. [40,43]

Comparing women with a history of a pregnancy complicated by GH or CH to women with a history of a normotensive pregnancy, one study found a decreased LV-GLS in women with either GH or CH,[35] whereas another study showed no significant difference between GH and normotensive controls.[45]

Left ventricle global radial strain (LV-GRS)

Results during pregnancy

LV-GRS was measured in five studies.[18,37,39,42,45] LV-GRS was shown significantly lower in women with PE in two studies,[37,45] whereas one study showed no significant difference.[18] One study differentiated between EO-PE and LO-PE.[39] Compared to normotensive pregnant women, LV-GRS was significantly decreased in EO-PE but comparable in LO-PE.[39] In the fifth study, patients suffering from either severe or mild PE were compared with normotensive pregnant women. LV-GRS was only shown significantly lower in patients with severe PE.[42]

Comparable LV-GRS was shown in two studies in patients with GH compared to normotensive pregnant controls. [18,45]

Results postpartum

LV-GRS was measured postpartum in two studies. [43,45] The measurement timing ranged between 3 months[45] to 4 years[43] postpartum. Women suffering from PE or EO-PE showed decreased LV-GRS in two studies.[43,45] After a pregnancy complicated by LO-PE or CH, however, LV-GRS was shown comparable to normotensive women.[43,45]

Left ventricle global circumferential strain (LV-GCS)

Results during pregnancy

Six studies report results concerning LV-GCS during pregnancy.[18,37,39,42,45,46] Comparing women with a pregnancy complicated by PE to normotensive pregnant women, three studies showed a significantly decreased LV-GCS in PE,[37,39,45] whereas two studies showed no significant difference.[18,46] The fifth study compared women with either mild or severe PE to normotensive pregnant controls.[42] LV-GCS was only significantly decreased in severe PE.[42]

In GH, LV-GCS was increased in one study[45] and comparable to normotensive controls in another study.[18]

Results postpartum

LV-GCS was measured in three studies postpartum.[43,45,46] The measurement timing ranged between 6 weeks[46] to 4 years[43] postpartum. Compared to a history of a normotensive pregnancy, LV-GCS was significantly decreased after PE in one study,[45] and comparable to a history of PE in one study.[46] One study differentiated between a history of EO-PE or LO-PE.[43] Compared to a history of a normotensive pregnancy, LV-GCS was significantly decreased after EO-PE but comparable after LO-PE.[43]

LV-GCS was not shown significantly different between women with a history of GH and women with a history of a normotensive pregnancy.[45]

Left ventricle strain rate (LV-SR)

Only one study reported on LV-SR differences between pregnant women with HPD and normotensive pregnant controls.[12] LV-SR was significantly lower in patients with PE compared to normotensive pregnant women. None of the studies including women postpartum reported results of LV-SR measurements.

Table 2. Echocardiography features during pregnancy

Author Year	Ajmi 2018	Buddeberg 2018	Cho 2011	Cong 2015	Cong 2018	Levine 2019	Pan 2019	Shahul 2012	Shahul 2016	Shahul 2018	Vaught 2018	Xia 2017	Yu 2018
Number of participants	60	70	199	165	86	58	53	28	167	85	99	197	82
GA Cases	32	39±1	33±4	29±3 / 36±1	32±4	31±4	35±5	37	33±4	32	33±4	m-PE 36±3 s-PE 35±3	PE 32±6 GH 34±3
GA Control	33	38±2	35±3	28±3 / 36±1	33±4	31±4	35±3	38	31±4	31	32±5	35±3	33±4
LV-GLS	PE ↓ GH ↓	PE ↓	HPD*↓	PE ↓	PE ↓	s-PE↓	s-PE ↓	PE ↓	PE ↓	PE ↓	s-PE =	PE↓	PE↓ GH ↓
LV-GRS	PE = GH =			EO-PE ↓, LO-PE =				PE ↓				s-PE:↓, m-PE: =	PE↓ GH =
LV-GCS	PE = GH =			PE ↓		s-PE=		PE ↓				s-PE:↓, m-PE: =	PE↓ GH ↑
SR		PE ↓											

↑: significant increase, ↓: significant decrease, =: no significant difference compared to the control group of normotensive pregnant women. Empty cell: parameter not analyzed in the study.GA: gestational age in weeks, PE: pre-eclampsia, GH: gestational hypertension, EO: early-onset, LO: late-onset, s-PE: severe PE, m-PE: mild PE, HPD: hypertensive pregnancy disorders. LV-GLS: left ventricular global longitudinal strain, LV-GRS: left ventricular global radial strain, LV-GCS: global circumferential strain, SR: strain rate. *= study by Cho et al. included patients with GH of whom 10 developed PE.

Table 3. Echocardiography features after delivery

Author Year	Al-Nashi 2016	Clemmensen 2018	Levine 2019	Orabona 2017	Shahul 2018	Yu 2018
Number of participants	31	93	58	90	58	82
Mean period postpartum	11.2±0.6	EO-PE 13±4 year LO-PE 12±3	6 weeks	EO-PE 2.3±0.7 year LO-PE 2.5±0.8	1 year	3 months
Cases						
Control	11.2±0.6	Control 12±3	7 weeks	Control 2.2±0.6	1 year	3 months
LV-GLS	PE =	EO-PE ↓, LO-PE =	s-PE ↓	EO-PE ↓, LO-PE =	PE ↓ GH/CH ↓	PE↓ GH =
LV-GRS				EO-PE ↓, LO-PE =		PE↓ GH =
LV-GCS			s-PE =	EO-PE ↓, LO-PE =		PE↓ GH =
SR						

↑ significant increase, ↓ significant decrease, = no significant difference compared to the control group of postpartum women after a normotensive pregnancy. Empty cell: parameter not analyzed in the study. PE: pre-eclampsia. GH; gestational hypertension, EO: early-onset, LO: late-onset. s-PE: severe PE. HPD: hypertensive pregnancy disorders. LV-GLS: left ventricular global longitudinal strain, LV-GRS: left ventricular global radial strain, LV-GCS: global circumferential strain, SR: strain rate.

DISCUSSION

Main findings

A systematic review concerning STE in women with (a history of) HPD compared to normotensive controls was performed. Our major finding was a significantly decreased LV-GLS in HPD during pregnancy in all studies but one. That study showed a trend towards decreased LV-GLS in PE, however, because multiple-testing correction was used in that study, this was not significant.[16] The use of multiple-testing correction could explain why the results of that study were inconsistent with all other studies.

LV-GLS represents LV myocardial shortening in the longitudinal axis and is an important index of global LV function. LV-GLS is capable of early and accurate detection of cardiac alterations that may affect subendocardial longitudinal fibers.[29] These fibers are involved in the first, subclinical stages of several diseases such as ischemic injury and arterial hypertension, showing a reduced LV-GLS.

Furthermore, LV-GLS is associated with major adverse cardiac events in patients with asymptomatic hypertensive heart disease.[26] Therefore, a decreased LV-GLS in women with HPD can also be an indicator of subclinical deterioration of the myocardium and may be a useful tool for early detection of women at risk for cardiac dysfunction later in life.[26,29] As the currently used cardiac function parameter LVEF is typically still normal in the subclinical phase of these diseases, LV-GLS could be a more useful tool in early detection.[29]

This review showed a difference between EO-PE and LO-PE postpartum. LV-GLS, LV-GRS, and LV-GCS were decreased in women with a history of a pregnancy complicated by EO-PE compared to normotensive controls, whereas LV-GLS, LV-GRS, and LV-GCS were shown comparable in women with a history of LO-PE and women with a history of a healthy pregnancy.[40,43] This suggests lasting myocardial changes in women suffering from EO-PE in pregnancy, up to 13 years postpartum.

Growing evidence suggests that EO-PE and LO-PE have different etiologies and should be regarded as two different types of the disease.[10,11,14,49] EO-PE and LO-PE have a different maternal cardiovascular adaptation to pregnancy.[39,50] Also, EO-PE is associated with a higher risk of morbidity and mortality during pregnancy than LO-PE, which is probably due to differences in the severity of the disease. [9,51]

When distinguishing between the three different HPD (i.e. GH, CH, and PE), STE parameters seem to be altered more in PE than in GH or CH, both during pregnancy as postpartum. This is in line with the findings of the review by Castleman et al. about conventional echocardiography in HPD, which showed that if echocardiographic changes are seen in HPD, these changes are more severe in case of PE compared with GH.[52] This

increased impact on the heart in PE is in line with the increased CVD incidence after a pregnancy complicated by PE compared to after GH or CH.[53]

Although it is not well established whether cardiovascular derangement in HPD is a primary etiological factor or a secondary effect, the differences in STE results between the separate HPD attributes to our understanding of the differences between these disorders.

Strengths and limitations

One of the strengths of this systematic review is our rigorous search without restrictions on language or year of publication. It is conceivable that studies are more likely to be published in an international English-language journal if results are significant, whereas non-significant findings are more likely to be published in a local, non-English journal.[32] Another strength of this review is the moderate to high quality of the included studies.[30,33]

A limitation of this review is that the generalizability of the results remains unclear. Due to heterogeneity of the studies, a meta-analysis was not performed as suggested by the Cochrane handbook for systematic reviews of interventions.[32]

Clinical implications and future research

The use of STE for various clinical settings has increased remarkably over recent years.[29] In the acute phase of myocardial infarction, reduced LV-GLS has been proven to be the single most powerful marker of manifest LV hemodynamic deterioration.[54] Moreover, in heart failure, LV-GLS is an independent predictor of mortality and a superior compared to other echocardiographic parameters. [55,56]

However, the use of STE in pregnancy is not very widespread in clinical practice yet. This review shows a decrease in cardiac function, especially in LV-GLS, starting during pregnancy and lasting up to 13 years after pregnancies complicated by HPD compared to normotensive controls. This could indicate that women with echocardiographic abnormalities measured during their pregnancy may benefit from more strict surveillance and treatment to decrease cardiovascular risks during life.

Since STE might be a tool to detect subclinical cardiac changes, more sensitive than conventional echocardiography,[12,17,20,22] STE might be promising for prediction and prevention of CVD after HPD.

A recommendation for future research is to measure STE in mother and fetus simultaneously. Growing evidence shows that, like the mothers, the offspring of pregnancies complicated by HPD also have increased risk of developing CVD later in life compared to offspring of uncomplicated pregnancies.[57-62] A recent study by Yu et al. already showed signs of diastolic dysfunction in fetuses of mothers with PE compared to

fetuses of healthy mothers.[63] This study also shows that STE appears to be more sensitive than conventional echocardiography for the evaluation of fetal cardiac function.[63] Early identification of children with altered strain measurement during and after a pregnancy complicated by HPD might help to provide adequate screening and treatment for children at risk for CVD.

One study by Shahul et al. studied the predictive value of abnormal strain during pregnancy in women with CH. Women with CH who had a decreased LV-GLS mid-gestation, had a significantly higher risk of developing superimposed PE.[64] Future research should continue to focus on the clinical relevance of an abnormal strain during pregnancy, as well as the association between abnormal strain during pregnancy and the development of CVD later in life. Possibly, abnormal strain measurements might help to differentiate within the high-risk group of women with HPD, making appropriate screening and treatment possible based on each women's personal risk profile. Pregnancy may therefore be considered as a window of opportunity for improvement of future health.[65]

CONCLUSION

STE can detect differences between pregnant women with HPD and normotensive pregnant women, mainly in LV-GLS. This parameter is significantly decreased in pregnant women with HPD compared to normotensive pregnant controls. Other deformation values show a significant decrease in women with severe or early-onset PE, with lasting myocardial changes after early-onset PE. Future research should focus on the clinical relevance of an abnormal strain during pregnancy, and its association with the development of CVD later in life.

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APPENDIX 1

((“Pre-Eclampsia”[Mesh]) OR (pre eclampsia[tw] OR preeclampsia[tw] OR gestosis[tw] OR toxemia*[tw] OR toxicosis[tw]) OR ((“Hypertension, Pregnancy-Induced”[Mesh]) OR (“Pregnancy”[Mesh] AND “Hypertension”[Mesh])) OR ((pregnan*[tiab] OR gestation*[tiab] OR maternal[tiab]) AND hypertens*[tiab])) AND ((speckle*[tw] OR strain*[tw]) AND (echocardiograph*[tw] OR imaging[tw]))

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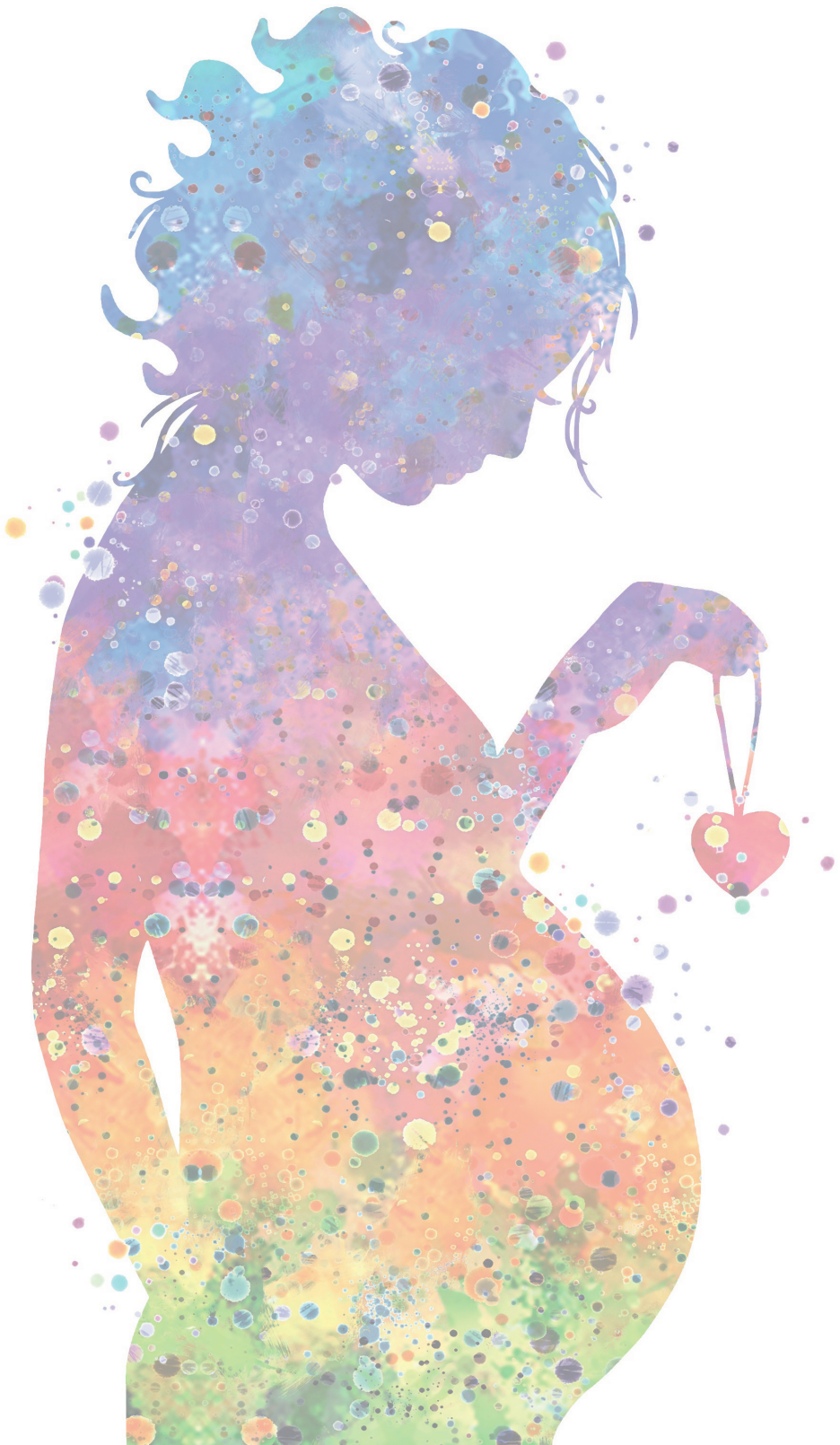

3

Heart rate variability in hypertensive pregnancy disorders: a systematic review

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ABSTRACT

Background

Hypertensive pregnancy disorders (HPD) are associated with dysfunction of the autonomic nervous system. Cardiac autonomic functions can be assessed by heart rate variability (HRV) measurements.

Objective

To study whether HRV detects differences in the function of the autonomic nervous system between pregnant women with HPD compared to normotensive pregnant women and between women with a history of a pregnancy complicated by HPD compared to women with a history of an uncomplicated pregnancy.

Methods

A systematic search was performed in Medline, EMBASE, and CENTRAL to identify studies comparing HRV between pregnant women with HPD or women with a history of HPD to women with (a history of) normotensive pregnancies.

Results

The search identified 523 articles of which 24 were included in this review, including 850 women with (a history of) HPD and 1205 normotensive controls. The included studies showed a large heterogenicity. A decrease in overall HRV was found in preeclampsia (PE), compared to normotensive pregnant controls. A trend is seen towards increased low frequency/high frequency-ratio in women with PE compared to normotensive pregnant controls.

Conclusion

Our systematic review supports the hypothesis a sympathetic overdrive is found in HPD which is associated with a parasympathetic withdrawal. However, the included studies in our review showed a large diversity in the methods applied and their results.

INTRODUCTION

Hypertensive Pregnancy Disorders (HPD), defined as gestational hypertension (GH), chronic hypertension (CH), preeclampsia (PE), and superimposed PE,[1] are pregnancy-specific systematic disorders that globally affect 5-10% of all pregnancies.[2–6]

Hypertension is defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg.[1,7] In GH and PE, hypertension develops after 20 weeks' gestation, with PE also being characterized by proteinuria (>300 mg/day) and/or end organ dysfunction.[1] CH is defined as hypertension discovered preconception or prior to 20 weeks' gestation.[7] Of all HPD, GH and PE occur the most frequent.[8]

HPD are a major cause of maternal and fetal mortality and morbidity worldwide.[1,2,9,10] Furthermore, there is growing evidence that HPD are associated with a higher risk of maternal cardiovascular disease (CVD) later in life.[11–13]

The etiology of HPD is not exactly known, but several studies state that the primary derangement involves the cardiovascular system.[14,15] In normal pregnancy, cardiovascular volume load is increased and cardiovascular pressure load is reduced as an adjustment to the early pregnancy drop in peripheral vascular resistance.[15,16] The autonomic nervous system has a prominent role in these adaptations.[14,16–18]

HPD might originate from abnormal remodeling of maternal spiral arteries and the absence of adequate cardiovascular adaptations to pregnancy,[14,15] resulting in a higher blood pressure and an increase in vascular resistance.[1,19] In addition, women with HPD typically lack the hypervolemia that is associated with normal pregnancy.[1,20,21] Several studies have stated that HPD develop because of dysfunction of the autonomic nervous system.[16,20,22,23]

Cardiac autonomic functions can - amongst others - be assessed by heart rate variability (HRV).[24,25] HRV reflects the impact of central and peripheral circuits of regulation on hemodynamics.[19,26] Therefore, a possible dysfunction of the autonomic nervous system can be shown by measuring HRV.

The objective of this systematic review is to study whether HRV detects differences in the function of the autonomic nervous system between pregnant women with HPD compared to normotensive pregnant women or between women with a history of a pregnancy complicated by HPD compared to women with a history of an uncomplicated pregnancy.

METHODS

HRV definitions

HRV is the oscillation between subsequent heartbeats, which is generated by heart-brain interactions, cardiovascular hormones, and neuronal pathways that exert effects on the heart, blood vessels and kidneys.[25,27,28]

Assessment of HRV is most frequently performed with electrocardiography (ECG). The data acquired from ECG can be evaluated and described by using time-domain and frequency-domain features.[25,29]

Frequency-domain features

Frequency-domain values estimate the distribution of the signal energy within a frequency band. The differences in frequency ranges allows HRV analysis to separate the sympathetic and parasympathetic contributions to the autonomous nervous system.[29] The HRV Task Force defined the frequency-domain bandwidths, shown in Table 1.[25]

The ratio between low frequency (LF) and high frequency (HF) is considered to mirror sympatho/vagal balance or to reflect sympathetic modulations. A low LF/HF-ratio reflects parasympathetic dominance, while a high LF/HF-ratio reflects sympathetic dominance.

The frequency-domain features are usually expressed in absolute values of power (ms^2) or as the natural logarithm (Ln). LF and HF might also be measured in normalized units (n.u.; (LF/(TP-VLF)) and (HF/(TP-VLF))).[23,25,30]

Time-domain features

Time-domain features quantify the amount of variability in the interbeat interval. The normal-to-normal (NN) intervals are determined, i.e. intervals between adjacent QRS complexes.[25]

A wide variety of time-domain features can be calculated.[25,29] Many of these measures correlate closely with each other. Therefore, the HRV Task Force recommended four time-domain features as presented in Table 2.[25]

Table 1. Frequency-domain features according to Heart rate variability Task Force[25]

Band	Frequency	Period recording	Clinical application
ULF	≤0.003 Hz	24 hours	Slow-acting biological processes like the circadian rhythm
VLF	0.003-0.04 Hz	2-5 minutes	The physiological explanation of the VLF component is not defined very strictly and it is questionable whether a specific physiological process attributes to VLF
LF	0.04-0.15 Hz	2-5 minutes	Some studies suggest that LF is a quantitative marker for sympathetic modulations, other studies describe LF as reflecting both sympathetic and vagal activity.
HF	0.15-0.40 Hz	1 minute	Reflects parasympathetic tone
TP	ULF+VLF+LF+HF	24 hours	Sum of all bandwidths

ULF: ultra low frequency, VLF: very low frequency, LF: low frequency, HF: high frequency, TP: total power, Hz: Hertz.

Table 2. Time-domain features according to Heart Rate Variability Task Force.[25]

Time-domain feature	Clinical relevance
SDNN	The estimate of overall HRV.
HRV triangular index	The estimate of overall HRV; permits only casual pre-processing of the ECG-signal.
RMSSD	The estimate of short-term components of HRV.
SDANN	The estimate of long-term components of HRV. Intervals in all 5-minutes segments of the entire recording.

SDNN: Standard Deviation of normal-to-normal (NN)-interval; HRV: Heart Rate Variability; RMSSD: Root Mean Square of Successive Differences; SDANN: Standard Deviation of the Averages of the NN-interval. ECG: electrocardiography

Study design

Eligibility criteria

Our review included studies that examine HRV in women with HPD compared to healthy normotensive pregnant women or studies that measure HRV in women with a history of HPD compared to normotensive women with a history of a normotensive pregnancy. The analyses in which pregnant women with HPD were compared with normotensive non-pregnant women and the studies in which women with a history of a pregnancy complicated by HPD were compared to women who had never been pregnant were excluded. We included studies that described maternal HRV using linear time- and frequency-domain features. We excluded animal studies, case reports, reviews, meta-analyses, conference abstracts, commentaries, and editorials. Also, studies without a control arm or HPD arm were excluded. No restrictions were applied regarding language or date of publication.

Search strategy

This review is conducted in accordance with the PRISMA guideline for systematic reviews,[31] and prospectively registered in the PROSPERO International prospective register of systematic reviews (CRD42019124052, available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019124052). With help of a professional librarian, we performed our search in the electronic databases EMBASE, MEDLINE (PubMed) and CENTRAL. Our search was conducted from inception of databases up until October first, 2019. Our search consisted of the following terms and its synonyms: 'heart rate variability', 'gestational hypertension', 'preeclampsia' and a wide variety of its synonyms. The search strings can be found in Appendix 1.

Study selection and data extraction

All titles and abstracts obtained from our search were independently screened by two reviewers (SM and KS). Based on our selection criteria, eligible studies were identified, and subsequently full texts were retrieved. When multiple articles were published by the same authors, we contacted the authors to avoid duplication of participants and consequently excluded duplicates. Furthermore, we hand-searched all references of the selected articles and related articles to identify additional relevant publications. Any disagreement was resolved by consensus and if necessary, a third reviewer (MW) was consulted. Two reviewers (SM and KS) extracted relevant data using a preliminary designed data form. The retrieved data comprised year of publication, maternal features of HRV and study characteristics.

Assessment quality and risk of bias

Quality of the included studies was assessed by using the criteria of the Newcastle-Ottawa Scale (NOS), as recommended by the Dutch Cochrane Center.[31–33] Nine criteria were assessed, divided over three dimensions: selection, comparability, and exposure. For each criterium, stars can be awarded. As suggested by Losilla et al.,[34] studies scoring 0-3, 4-6, and 7-9 stars were deemed to be of low, moderate, and high quality, respectively.

Two authors (SM and KS) completed the data quality and risk of bias assessment independently. Disagreements were resolved by consensus and if needed, a third author (MW) was consulted.

Data analysis

Data from the included studies were aggregated to provide a narrative synthesis of the findings.

RESULTS

PRISMA Flow Figure 1 shows the search process in steps. A total of 24 studies met all our inclusion criteria and were included in our systematic review. All included studies were observational studies; 20 case-control and four longitudinal case-control studies. All studies combined included a total of 2055 women. 21 studies measured HRV during pregnancy, including 787 women with a pregnancy complicated by HPD and 1142 controls with a normotensive pregnancy. One study measured HRV postpartum, including 20 women who have had a pregnancy complicated by HPD and 20 women with a history of a normotensive pregnancy. Two studies analyzed women both during their pregnancy as well as postpartum. Of these, 43 women had HPD and 43 had a normotensive pregnancy. Detailed information regarding the study characteristics of the included studies, the quality assessment and risk of bias are presented in Table 3.

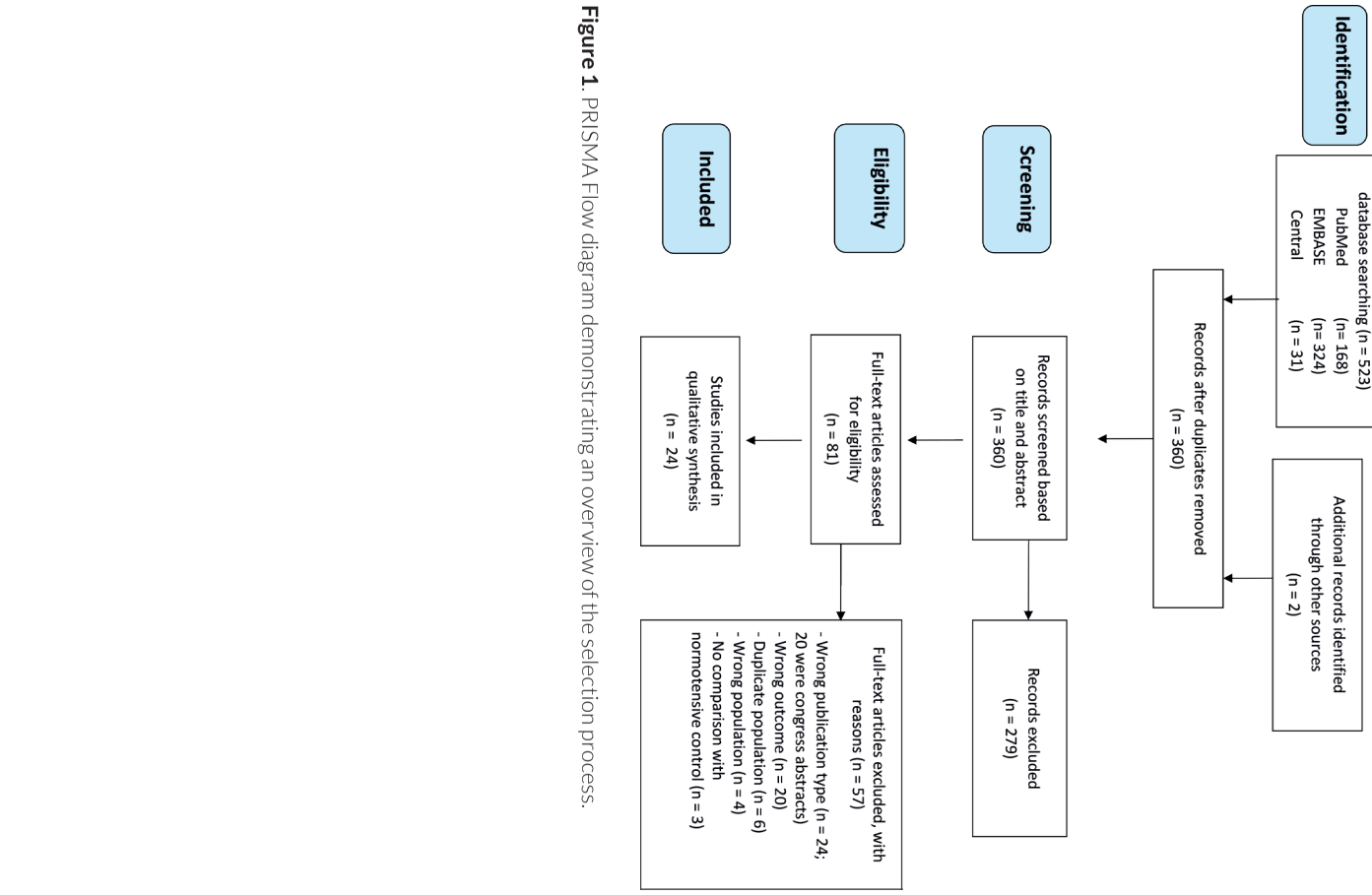

Figure 1. PRISMA Flow diagram demonstrating an overview of the selection process.

Table 3. Characteristics of included studies

Author year	Population§ (n=)	Inclusion criteria (definition)	Exclusion criteria	Mean GA in weeks	Frequency bands in Hz	Medication	Quality NOS + Losilla categories	Study design and measurements
Studies including women during pregnancy								
Brown et al. 2008 [20]	**Cases:** GH (20) **Controls:** NTP (20)	HPD definition: ACOG 2002 Age ≥18 years, GA 33-41 weeks, singleton, maternal weight <114kg, no treated comorbidities (DM,thyroid disease, depression)	Cardiac arrhythmias	GH: 36.5±2.4 NTP: 36± 0.5	LF: 0,04-0,15 MF: 0,12-015 HF: 0,15-0,40	No β-blockers or anti-arrhythmic drugs	5 (3/0/2) Moderate quality	Case-control ECG 10 min CTG 30min
Chaswal et al. 2018 [30]	**Cases:** PE (40) **Controls:** NTP (40)	HPD definition:, ACOG 2013	Multiple pregnancy, DM, CH, liver/ thyroid/auto-immune/ renal/ inflammatory disease	PE: 29±2.4 NTP: 30 ±3.6	VLF: not described LF: 0,04-0,15 HF: 0,15-0,4	Not mentioned	7 (3/2/2) High quality	Case-control ECG 5 min
Ekholm et al. 1997 [38]	**Cases:** GH (14) **Controls:** NTP (16)	HPD definition: BP >140/90 mmHg on two occasions in 3rd trimester, with or without proteinuria ≥0.3 gm/l	Not applicable	GH: 37 (31-40) NTP: 37 (31-40)	LF: 0,00-0,07 MF: 0,07-0,15 HF: 0,15-0,4	No antihypertensive treatment	6 (3/1/2) Moderate quality	Case-control ECG 7 min
Eneroth et al. 1994 [48]	**Cases:** PE (13) **Controls:** NTP (12)	HPD definition: BP ≥140/90 mmHg and proteinuria ≥300mg/24hr or dipstick ≥1+	History of cardiopulmonary disease or DM	PE: 35±3 NTP: 37±4	LF: 0,07-0,15 HF: 0,15-0,4	No medication	5 (3/0/2) Moderate quality	Case-control ECG 5 min

Table 3. Continued.

Author year	Population§ (n=)	Inclusion criteria (definition)	Exclusion criteria	Mean GA in weeks	Frequency bands in Hz	Medication	Quality NOS + Losilla categories	Study design and measurements
Euliano et al. 2018 [50]	**Cases:** PE with severe features (37) **Controls:** NTP (43)	HPD definition: ACOG 2002	Confounding disease state during admission (e.g. vasculitis/renal/ liver disease unrelated to PE), proteinuria before pregnancy, labor beyond 5cm cervical dilation, neuraxial anesthesia	Inclusion:29-41 PE: 32±3.6 NTP: 37±4.3	LF, HF (bandwidth not described)	Antihypertensive drugs and/or MgSO4	4 (2/0/2) Moderate quality	Case-control PPG + ECG 30 min
Faber et al. 2004 [21]	**Cases:** - PE (44) - GH (18) - CH (19) **Controls:** NTP (80)	HPD definition: NHBPEP	Not applicable	PE: 32 (30-36) GH: 36 (31-37) CH: 34 (25-38) NTP: 35 (32-37)	VLF: 0,003-0,04 LF: 0,04-0,15 HF: 0,15-0,4	Not mentioned	5 (3/0/2) Moderate quality	Case-control ECG 30 min
Flood et al. 2015 [52]	**Cases: -** Later developed PE (27) - Later developed GH (26) **Control:** NTP (332)	HPD definition: ACOG	Not applicable	Measurement at 28 week assessment visit	LF: 0,04-0,15 HF: 0,15-0,5	Not mentioned,	5 (2/1/2) Moderate quality	Secondary analysis of prospective cohort ECG 5min
Guo et al. 2018 [40]	**Cases:** - PE (19) - GH (41) **Controls:** NTP (60)	HPD definition: ACOG 2013 Nulliparous, single living fetus after 32 weeks	CH, DM, any endocrinal disorders, cardiac arrhythmias, infectious diseases, cancer, smokers, or drinkers	PE: 35±2.0 GH: 36±3.2 NTP: 35±2.7	LF: 0,04-0,15 HF: 0,15-0,4	Antihypertensive drugs. No other medication	5 (3/0/2) Moderate quality	Case-control Holter 24 hours

Table 3. Continued.

Author year	Population§ (n=)	Inclusion criteria (definition)	Exclusion criteria	Mean GA in weeks	Frequency bands in Hz	Medication	Quality NOS + Losilla categories	Study design and measurements
Khan et al. 2014 [49]	**Cases:** PE (15) **Controls:** NTP (33)	HPD definition: not specified Risk factors for GH	Controls had no risk factors for GH	>20 weeks of gestation, no mean presented	VLF: 0,003-0,04 LF: 0,04-0,15 HF: 0,15-0,4	Not mentioned	5 (3/0/2) Moderate quality	Case-control ECG 10 min
Khlybova et al. 2008 [45]	**Cases:** - Mild PE (12) - Moderate PE (10) - CH: (18) **Controls:** NTP (15)	HPD definition: Not specified	Not applicable	Mild PE: 34±0.5 Moderate PE:33±1.3 CH: 35±0.9 NTP: 34±0.5	LF, HF (bandwidth not described)	Antihypertensive drugs	4 (3/0/1) Moderate quality	Case-control ECG 500 cycles
Lakhno 2017 [26]	**Cases:** - Mild-moderate PE (44) - Severe PE (32) **Controls:** NTP (30)	HPD definition: **Mild-moderate PE:** SBP 140-159 mmHg and DBP 90-109 mmHg **Severe PE:** SBP ≥160mmHg and DBP 110 mmHg, and/ or thrombocytopenia, serum creatinine >1.1 mg/l, liver transaminases >2x↑, pulmonary edema, cerebral or visual disturbances	Multiple pregnancy, eclampsia, pre-existing diseases (e.g. DM, metabolic syndrome, cardiac or renal diseases, thyrotoxycosis and CH)	Inclusion: 34-40 Mild/moderate PE: 37±.3.6 Severe PE: 37 ±2.5 NTP: 37±1.8	VLF, LF, HF (bandwidths not described)	Antihypertensive drugs	6 (4/0/2) Moderate quality	Case-control ECG 10 min Non-invasive fetal ECG
Lewinsky et al. 1998 [53]	**Cases:** PE (15) **Controls:** NTP (25)	HPD definition: BP >140/90 mmHg on two occasions at least 6h apart and proteinuria >300 mg/24hr	History of hypertension, renal disease, DM, medication with exception of iron supplementation	PE: 33±3 NTP: 35±4	VLF: 0-0,05 MF: 0,05-0,15 HF: 0,2-0,5	Measurements before start of MgSO4 or antihypertensive therapy	4 (2/0/2) Moderate quality	Case-control ECG, not mentioned how many min. (short term)

Table 3. Continued.

Author year	Population§ (n=)	Inclusion criteria (definition)	Exclusion criteria	Mean GA in weeks	Frequency bands in Hz	Medication	Quality NOS + Losilla categories	Study design and measurements
Metsaars et al. 2006 [42]	**Cases:** Early-onset HPD (37) Late-onset PE (8) **Controls:** NTP (29)	HPD defined as GH with fetal growth restriction, severe PE, HELLP or eclampsia HPD definition: ACOG 1988 Fetal growth restriction: EFW <p10	Not defined	Inclusion:24-34 EO-HPD: 29 (24-34) LO-PE: 32 (31-33) NTP: 32 (31-33)	LF: 0,04-0,15 HF: 0,15-0,4	MgSO4 and/or antihypertensive drugs	6 (3/1/2) Moderate quality	Case-control Continuous HR non-invasive finger arterial pressure waveform, unknown duration
Musa et al. 2016 [44]	**Cases:** PE (60) **Controls:** NTP (60)	HPD definition: ACOG 2013	Thyroid/renal/liver disease, hypertension, DM, medication for hypertension	PE: 34±4.3 NTP: 33±4.0	LnVLF, LnLF, LnHF (bandwidths not mentioned, ref. Task Force)	All women enrolled before receiving any medication	5 (3/0/2) Moderate quality	Case-control ECG 5 min
Pal et al. 2009 [46]	**Cases:** With risk factors, developed GH (27) **Controls:** NTP (38)	HPD definition: Not defined	Oral contraceptives prior to pregnancy	- 12 - 24 - 31	LF, HF (bandwidths not mentioned)	Not mentioned	6 (3/1/2) Moderate quality	Longitudinal ECG 10 min
Pal et al. 2011 [39]	**Cases:** With risk factors GH, developed GH (31) **Controls:** NTP (38)	HPD definition: Joydev et al.	Not defined	- 12 - 24 - 31	LF, HF (bandwidths not mentioned)	Not mentioned	6 (3/1/2) Moderate quality	Longitudinal ECG 10 min

Table 3. Continued.

Author year	Population§ (n=)	Inclusion criteria (definition)	Exclusion criteria	Mean GA in weeks	Frequency bands in Hz	Medication	Quality NOS + Losilla categories	Study design and measurements
Swansburg et al. 2005 [43]	**Cases:** PE (9) **Controls:** NTP (18)	HPD definition: NHBPEP Maternal age >16years, singleton pregnancy Gestational age 32-40 weeks	No exclusion criteria	PE: 37±2.6 NTP: 36±2.0	LF: 0,04-0,15 HF: 0,15-0,4	Three women used medication (gluticasone, terbutaline sulfate, labetalol, methyldopa, ranitidine)	5 (3/0/2) Moderate quality	Case-control ECG 20 min
Tejera et al. 2012 [47]	**Cases:** - PE (27) - GH (55) **Controls:** NTP (135)	HPD definition: NHBPEP Maternal age >16years, singleton	Not defined	PE: 27 (range 7-40) GH: 25 (range 7-40) NTP: 24 (range 6-40)	VLF: ≤0,04 LF: 0,04-0,15 HF: 0,15-0,4	Antihypertensive drugs	4 (2/0/2) Moderate quality	Case-control ECG 10 min
Weber et al. 2017 [37]	**Cases:** - PE <AD34 (10) - PE >AD34 (14) **Controls:** - NTP <GA34 (30) - NTP >GA34 (42)	HPD definition: ACOG 2013	PE and pre-existing diseases (e.g. insulin-dependent DM, cardiovascular or renal diseases, etc.)	Inclusion: 28-38 EO-PE:31±2 LO-PE: 36±3 NTP: 31±2 and 36±3	LnLF: 0,04-0,15 LnHF: 0,15-0,4	Not mentioned	7 (3/2/2) High quality	Case-control ECG 10 min
Yang et al. 2000 [35]	**Cases:** PE (11) **Controls:** NTP (17)	HPD definition: ISSHP 2000	Diabetic neuropathy, cardiac arrhythmia or other cardiovascular diseases that affect HRV	PE: 35±1 NTP: 34±1	LF: 0,04-0,15 HF: 0,15-0,4	No hypnotics or autonomic blockers	7 (3/2/2) High quality	Case-control ECG 5 min

Table 3. Continued.

Author year	Population§ (n=)	Inclusion criteria (definition)	Exclusion criteria	Mean GA in weeks	Frequency bands in Hz	Medication	Quality NOS + Losilla categories	Study design and measurements
Yokusoglu et al. 2009 [36]	**Cases:** PE (34) **Controls:** NTP (29)	HPD definition: ISSHP 2000	Not described	Inclusion: 27-34 PE: 29±3.8 NTP: 30±3.6	Only time domain	No medication	8 (4/2/2) High quality	Case-control Holter 24 hours
Studies including women postpartum								
Murphy et al. 2015 [51]	**Cases:** PE (20) **Controls:** NTP (20)	HPD definition: Canadian Hypertensive Disorders of Pregnancy Working Group, Magee et al.	HELLP, pre-pregnancy history of hypertension, DM, renal or cardiovascular disease or smoking	6-8 months postpartum	LF: 0,04-0,15 HF: 0,15-0,4	No clear mentioning of medication postpartum	4 (3/0/1) Moderate quality	Case-control ECG 10 min
Studies including women both during pregnancy and postpartum								
Eneroth et al. 1999 [41]	**Cases:** PE (15) **Controls:** NTP (15)	HPD definition: BP ≥140/90 mmHg in at least two readings more than 6h apart and proteinuria ≥300mg/24hr or dipstick ≥1+)	History of hypertension, DM or renal disease	PE: 33±1.6 NTP: 33±2.0 and 3-6 months postpartum	VLF:0,0033-0,04 LF: 0,04-0,15 HF: 0,15-0,4	No medication	5 (3/0/2) Moderate quality	Longitudinal Holter 24 hour

Table 3. Continued.

Author year	Population§ (n=)	Inclusion criteria (definition)	Exclusion criteria	Mean GA in weeks	Frequency bands in Hz	Medication	Quality NOS + Losilla categories	Study design and measurements
Heiskanen et al. 2011 [18]	**Cases:** HPD (GH or PE) (28) **Controls:** NTP (28)	HPD definition: BP ≥140/90 mmHg after 20 weeks GA with previously normal BP and with or without proteinuria, measured three times	Pregnant women with superimposed PE	HPD: 35±0.7 NTP: 34±0.6 and 3 months postpartum	VLF: 0-0,04 LF: 0,04-0,15 HF: 0,15-0,4	Not mentioned	5 (3/0/2) Moderate quality	Longitudinal ECG 10 min

§ population of which the analyses are included in the review. ACOG: The American College of Obstetricians and Gynecologists; BP: blood pressure; CH: chronic hypertension; DBP: diastolic blood pressure; DM: Diabetes Mellitus; GA: gestational age; GH: gestational hypertension; HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelets syndrome; Hz: Hertz; NTP: normotensive pregnancy; ISSHP: International Society of Hypertension in Pregnancy; NHBPEP: National High Blood Pressure Education Program; $MgSO_4$: magnesium sulfate NOS: Newcastle-Ottawa Scale; PE: preeclampsia; PPG: Photoplethysmography; PPI: Partus Prematurus Imminens (Threatened preterm labor); SBP: systolic blood pressure.

Quality assessment

The risk of bias, as assessed by the NOS, ranges from 5 to 8 stars. Four studies were classified as high quality.[30,35–37] The remaining 20 articles were of moderate quality. No study was considered to be of low quality (Table 3).

Frequency-domain features

The results of all frequency-domain features during pregnancy are presented in Table 4. The postpartum results of frequency-domain features are shown in Table 5.

Total Power (TP)

During pregnancy

When comparing GH to normotensive pregnant women, TP showed no difference (2 studies).[20,38] A lower TP was found at 12, 24 and 31 weeks of gestation in women who would develop GH later in pregnancy compared to normotensive pregnant controls (1 study).[39] With regard to natural logarithm of TP (LnTP), a decrease was found in GH compared to normotensive pregnant women.[40]

Comparing women with PE to normotensive pregnant women, TP showed no difference (3 studies)[41–43] or a decrease (1 study).[30] LnTP showed no difference (1 study)[44] or a decrease (1 study)[40] in women with PE compared to normotensive pregnant controls.

Studies comparing women with a variety of HPD to normotensive controls found no difference in TP.[18,42]

Postpartum

No differences were found in TP after either GH or PE compared to after a normotensive pregnancy (1 study).[18] After PE, TP was decreased compared to after a normotensive pregnancy (1study).[41]

Low Frequency (LF)

During pregnancy

In CH, LF was increased (1 study)[45] or comparable (1 study)[21] to normotensive controls.

Comparing GH with normotensive controls, no difference in LF was found (4 studies).[18,20,21,38] LF(n.u.) was increased in women who would develop GH at 12, 24 and 31 weeks of gestation compared to normotensive controls.[39,46] Studies comparing LnLF between GH and normotensive controls found an increase in case of GH (1 study)[40] or no significant difference (1 study).[47]

Studies comparing LF between PE and normotensive women found no difference (5 studies),[21,41,43,45,48] an increased LF in PE (2 studies),[42,49] or a decreased LF in PE (3 studies).[26,30,50] With regard to LF(n.u.), an increase in PE (3 studies)[30,44,49] or no significant difference (1 study)[35] was found compared to normotensive controls. Comparing LnLF between PE and normotensive controls, an increase in PE (2 studies)[40,44] or no difference (3 studies)[35,37,47] was found.

Studies comparing women with a variety of HPD to normotensive controls found no difference in LF. [18,42]

Postpartum

No difference was found in LF postpartum after GH or PE (2 studies)[18,41] compared to normotensive controls, also not when calculated as LF(n.u.; 1 study).[51]

High Frequency (HF)

During pregnancy

Comparing CH with normotensive pregnant women, an increased HF (1 study)[45] or no difference (1 study)[21] was found.

In GH, an increased HF (1 study)[38] or no difference (2 studies)[20,21] was found compared to normotensive controls. HF(n.u.) was decreased at 12 weeks of gestation in women who would develop GH compared to normotensive controls. At 24 and 31 weeks of gestation, no difference in HF(n.u.) was found between these groups.[39,46] One study found a decreased HF at 28 weeks of gestation in women who would later develop GH compared to normotensive controls.[52] No difference in LnHF was found between GH and normotensive controls.[40,47]

In PE, an increased HF (1 study)[43], a decreased HF (5 studies)[26,30,45,48,49] or no difference (3 studies)[21,41,53] was found compared to normotensive controls. One study found no difference in HF at 28 weeks of gestation in women who would later develop PE compared to normotensive controls.[52] All three studies comparing HF(n.u.) between PE and normotensive controls found a decreased HF(n.u.) in PE.[30,44,49] LnHF was found to be decreased in PE (1 study)[35] or comparable to normotensive controls (4 studies).[37,40,44,47]

Studies comparing all HPD with normotensive controls showed an increased HF (1 study)[18] or no difference in HF (1 study)[42].

Postpartum

HF was not different after either PE or GH compared to normotensive controls.[18,41]

Low frequency/High frequency-ratio (LF/HF-ratio)

During pregnancy

In CH, an increased LF/HF-ratio (1 study)[45] or no difference in LF/HF-ratio (1 study)[21] was found compared to normotensive controls.

Comparing GH and normotensive controls, no difference in LF/HF-ratio was found (3 studies).[18,21,47] However, an increased LF/HF-ratio was found in all three trimesters in women who would later develop GH compared to normotensive controls.[39,46] The Ln(LF/HF-ratio) was increased in GH compared to normotensive controls (1 study).[40]

In PE, an increased LF/HF-ratio (3 studies)[26,30,49] or no difference in LF/HF-ratio (2 studies)[21,47] was found compared to normotensive controls. LF/HF-ratio was increased in moderate PE compared to normotensive controls, while it was not different between

mild PE and normotensive controls.[45] The Ln(LF/HF-ratio) was found to be increased in PE (3 studies)[35,40,44] or not different from normotensive controls (1 study).[37] Studies comparing all HPD with normotensive controls found no difference in LF/HF-ratio(2 studies).[18,42]

Postpartum

LF/HF-ratio was not different after a pregnancy complicated by either GH or PE compared to normotensive controls.[18,51]

Table 4. Frequency domain features, during pregnancy women

Author ***Year***	**Brown 2008**	**Chaswal 2018**	**Ekholm 1997**	**Eneroth 1994**	**Eneroth 1999**	**Euliano 2018**	**Faber 2004**	**Flood 2015**	**Guo 2018**	**Heiskanen 2011**	**Khan 2014**
Epoch ***No. patients***	**10 min 40**	**5 min 80**	**7 min 30**	**10 min 25**	**24 hours 30**	**30 min 80**	**30 min 161**	**5min 385**	**24 hours 120**	**10 min 120**	**10 min 48**
TP	GH: =	PE: ↓	GH: =		PE: =					HPD: =	
ULF											
VLF					PE: =					HPD: =	PE: ↓
LF	GH: =	PE: ↓	GH: =	PE: =	PE: =	PE: ↓	PE: = GH: = CH: =			HPD: =	PE: ↑
MF			GH: =								
HF	GH: =	PE: ↓	GH: ↑	PE: ↓	PE: =		PE: = GH: = CH: =	Before PE: = Before GH: ↓		HPD: ↑	PE: ↓
LF/HF		PE: ↑					PE: = GH: = CH: =			HPD: =	PE: ↑
LF/(LF+HF)						PE: ↓					
MF/HF			GH: =								
LF(n.u.)		PE: ↑									PE ↑
HF(n.u.)		PE: ↓									PE: ↓
LnTP									PE: ↓ GH: ↓		
LnVLF											
LnLF									PE: ↑ GH: ↑		
LnHF									PE: = GH: =		
LnLF/HF									PE: ↑ GH: ↑		

Table 4. Continued.

Author	Khlybova	Lakhno	Lewinsky	Metsaars	Musa	Pal	Pal	Swansburg	Tejera	Weber	Yang
Year	2008	2017	1998	2006	2016	2009	2011	2005	2012	2017	2000
Epoch	500 cycles	10 min	Unknown	Unknown	5 min	10 min	10 min	20 min	10 min	10 min	5 min
No. women	55	121	40	74	120	65	69	27	217	96	28
TP				LO-PE = EO-HPD =			GH: GA 12 ↓ GA 24: ↓ GA 31: ↓	PE: =			
ULF											
VLF	Mild PE: = Moderate PE: ↓ CH: ↑	PE: ↓	PE: =								
LF	Mild PE: = Moderate PE: = CH: ↑	PE: ↓	X	LO-PE = EO-HPD ↑				PE: =			
MF			PE: =								
HF	Mild PE: ↓ Moderate PE: ↓ CH: ↑	PE: ↓	PE: =	LO-PE = EO-HPD =				PE: ↑			
LF/HF	Mild PE: = Moderate PE: ↑ CH: ↑	PE: ↑		LO-PE = EO-HPD =		GH: GA 12 ↑ GA 24: ↑ GA 31: ↑	GH: GA 12 ↑ GA 24: ↑ GA 31: ↑		GH: = PE: =		
LF/(LF+HF)											
MF/HF											
LF(n.u.)					PE: ↑	GH: GA 12 ↑ GA 24: ↑ GA 31: ↑	GH: GA 12 ↑ GA 24: ↑ GA 31: ↑				PE =
HF(n.u.)					PE: ↓	GH: GA 12: ↓ GA 24: = GA 31: =	GH: GA 12: ↓ GA 24: = GA 31: =				
LnTP					PE: =						
LnVLF					PE: ↑						
LnLF					PE: ↑				PE: = GH: =	PE: = (eo-PE = lo-PE =)	PE =
LnHF					PE: =				PE: = GH: =	PE: = (eo-PE =, lo-PE ↑)	PE ↓
LnLF/HF					PE: ↑					PE: = (eo-PE =, lo-PE =)	PE ↑

↑: significant increase, ↓: significant decrease, =: no significant difference compared to a control group of normotensive pregnant women.
Empty cell: parameter not analyzed in this study; GA: gestational age; PE: preeclampsia; GH: gestational hypertension; CH: chronic hypertension; HPD: hypertensive pregnancy disorder; eo-PE: early-onset PE; lo-PE: late-onset PE. No. patients: number of patients included in the analyses.

Table 5. Frequency domain features postpartum

Author	**Eneroth**	**Heiskanen**	**Murphy**
Year	**1999**	**2011**	**2015**
Epoch	**24 hours**	**10 min**	**10 min**
No. women	**30**	**56**	**40**
TP	PE: ↓	HPD: =	
ULF			
VLF	PE: =	HPD: =	
LF	PE: =	HPD: =	
MF			
HF	PE: ↓	HPD: =	
LF/HF		HPD: =	PE: =
LF/(LF+HF)			
MF/HF			
LF(n.u.)			PE: =
HF(n.u.)			
LnTP			
LnVLF			
LnLF			
LnHF			
LnLF/HF			

↑: significant increase, ↓: significant decrease, =: no significant difference compared to a control group of women with a history of a normotensive pregnancy.
Empty cell: parameter not analyzed in this study; PE: preeclampsia; HPD: hypertensive pregnancy disorders; No. patients: number of patients included in the analyses.

Time-domain features

The results of the time-domain features of HRV are presented in Table 6. Eleven studies reported results during pregnancy,[21,26,50,30,36,37,39,40,44–46] and one study described results postpartum.[51]

Standard deviation of all NN intervals (SDNN)

During pregnancy

In CH, no difference was found in SDNN compared to normotensive controls.[21]
One study found a decrease in SDNN in GH compared to normotensive controls.[21] The Ln(SDNN) was decreased in GH compared to normotensive controls in one study.[40] A decreased SDNN was found at 12 weeks of gestation in women who would later develop GH compared to normotensive controls,[39] whereas another study showed no difference between these groups.[46] No significant differences were found at 24 or 31 weeks of gestation.[39,46]
In PE, SDNN was found to be decreased (3 studies)[26,30,36] or not different (2 studies)[21,37] from normotensive controls. SDNN was found to be increased in early-onset PE and not different in late-onset PE compared to normotensive controls.[37]
Ln(SDNN) was decreased in PE (1 study) or comparable to normotensive controls (1 study).[44]

Postpartum

Postpartum, SDNN was found to be significantly lower after PE compared to normotensive controls.[51]

HRV triangular index

During pregnancy

In CH, HRV triangular index was significantly higher compared to normotensive controls.[45]
One study showed HRV to be significantly lower in PE compared to normotensive controls.[36] HRV triangular index was found to be lower in moderate PE and comparable between mild PE and normotensive controls.[45]

Standard deviation of the averages of NN intervals (SDANN)

During pregnancy

SDANN was shown to be decreased in PE compared to normotensive controls (1 study).[36]
Another study showed Ln(SDANN) in either PE or GH to be equal to normotensive controls.[40]

Root mean square of successive differences (RMSSD)

During pregnancy

RMSSD was not different between CH and normotensive controls (1 study).[21]
In GH, RMSS was not different from normotensive controls (1 study).[21] No difference in RMSSD between women who would develop GH and normotensive controls at 12 or 24 weeks of gestation was found. At 31 weeks, RMSSD was decreased in women who would develop GH compared to normotensive controls.[39,46]
In PE, RMSSD was increased (1 study),[37] decreased (2 studies),[26,30] or comparable to normotensive women (2 studies).[21,36] The Ln(RMSSD) was not different between PE and normotensive controls.[44]

Postpartum

RMSSD was decreased after a pregnancy complicated by PE compared to normotensive controls.[51]

Table 6. Time domain features, during pregnancy

Author / *Year*	Brown 2008	Chaswal 2018	Euliano 2018	Faber 2004	Guo 2018	Khlybova 2008	Lakhno 2017	Musa 2016	Pal 2009	Pal 2011	Weber 2017	Yokusoglu 2009
Epoch / *No. women*	10min 40	5 min 80	30 min 80	30 min 161	24 hours 120	500 cycles 55	10 min 121	5 min 120	10 min 65	10 min 69	10 min 96	24 hours 63
Mean NN	GH =			PE: = GH: ↓ CH: =					GH: GA 12: ↓ GA 24: ↓ GA 31: ↓	GH: GA 12: ↓ GA 24: ↓ GA 31: =		
SDNN		PE: ↓		PE: = GH: ↓ CH: =			PE: ↓		GH: GA 12: = GA 24: = GA 31: =	GH: GA 12: ↓ GA 24: = GA 31: =	PE: = (total =, <34 =, >34 ↑)	PE: ↓
Ln (SDNN)					PE: ↓ GH: ↓			PE: =				
RMSSD		PE: ↓		PE: = GH: = CH: =			PE: ↓		GH: GA 12: = GA 24: = GA 31: ↓	GH: GA 12: = GA 24: = GA 31: ↓	PE: ↑ (total ↑, <34 =, >34 ↑)	PE: =
Ln(RMSSD)								PE: =				
SDANN												PE: ↓
Ln(SDANN5)					PE: = GH: =							
pNN50												PE: ↑

Table 6. Continued.

Author / *Year*	Brown 2008	Chaswal 2018	Euliano 2018	Faber 2004	Guo 2018	Khlybova 2008	Lakhno 2017	Musa 2016	Pal 2009	Pal 2011	Weber 2017	Yokusoglu 2009
Epoch / *No. women*	10min 40	5 min 80	30 min 80	30 min 161	24 hours 120	500 cycles 55	10 min 121	5 min 120	10 min 65	10 min 69	10 min 96	24 hours 63
pRR50%			PE: =			Mild PE: = Moderate PE ↓ CH: ↑	PE: ↓					
HRV triangular index						Mild PE: = Moderate PE ↓ CH: ↑						PE: ↓
WPSUM13				PE: = GH: = CH: =								
PLVAR20				PE: = GH: = CH: =								

↑: significant increase, ↓: significant decrease, =: no significant difference compared to a control group of normotensive pregnant women.
Empty cell: parameter not analyzed in this study; PE: preeclampsia; GH: gestational hypertension; GA: gestational age; No. patients: number of patients included in the analyses.

Table 7. Time domain features, postpartum

Author	**Murphy**
Year	**2015**
Epoch	**10 min**
No. women	**40**
Mean NN	PE: ↓
SDNN	PE: ↓
Ln (SDNN)	
RMSSD	PE: ↓
Ln(RMSSD)	
SDANN	
pNN50	PE: ↓
pRR50%	PE: ↓
HRV triangular index	
WPSUM13	PE: ↓

↑: significant increase, ↓: significant decrease, =: no significant difference compared to a control group of women with a history of a normotensive pregnancy.
X: parameter not analyzed in this study; PE: preeclampsia; No. patients: number of patients included in the analyses.

HRV changes in GH and PE

A decrease in overall HRV was found in GH and PE, compared to normotensive pregnant controls. A trend is seen towards increased LF/HF-ratio in women with (moderate) PE compared to normotensive pregnant controls. An increased LF/HF-ratio was found in two longitudinal studies in women who would later in their pregnancy develop GH. However, this difference in LF/HF-ratio was not found in other studies in women with GH compared to normotensive pregnant controls.

DISCUSSION

This systematic review provides an overview of the available literature on HRV in HPD. The frequency-domain features results show a wide variety, possibly due to the heterogenicity of the data. Normalized units of LF and HF show more consistency between the studies. In pregnant women with PE, three out of four studies showed an increased LF(n.u.),[30,44,49] and both longitudinal studies showed in increased LF(n.u.) in GH.[39,46] HF(n.u.) was decreased in all three studies measuring it during pregnancy with PE.[30,44,49] The LF/HF-ratio is increased in women with (moderate) PE compared to normotensive pregnant controls in four out of the six studies.[26,30,45,49] No study demonstrated a decrease in the LF/HF-ratio. Similar results were found for GH and CH.

In time-domain features, a decrease in overall HRV was shown in PE, with both SDNN and HRV triangular index being significantly lower compared to normotensive pregnant controls. Postpartum, SDNN was measured in one study showing a significant decrease after PE compared to women with a history of a normotensive pregnancy.

These results may suggest a sympathetic overdrive of the autonomous nervous system in HPD, possibly associated with parasympathetic withdrawal. This could explain the differences in adaptations of the cardiovascular system to pregnancy between HPD and normotensive pregnancies.

Sympathetic overactivity is also stated to be a precursor of essential hypertension and CVD, years before the onset of symptoms.[54–56] The sympathetic overdrive seen in HPD could explain the higher risk of developing essential hypertension and CVD in later life.

However, caution should be applied to these conclusions, given the large diversity in the results of the included studies.

Two previous reviews regarding autonomic function of pregnant women with PE showed the same wide variety in results with a trend towards more autonomic dysfunction in women with HPD compared to normotensive pregnant controls.[17,27] Our review is the first to present the results of all HPD both during pregnancy and postpartum after a pregnancy complicated by HPD. Thereby, it provides a complete overview given the shared pathophysiological mechanisms and the long-term persistent effects of these complicated pregnancies.

We were unable to perform a meta-analysis due to heterogenicity of data in the included studies regarding, amongst others, the used definitions of HPD, the mode and duration of recording HRV, and the gestational age or period postpartum.

In the majority of studies, non-invasive ECG recordings were used. Standard ECG recording is a practical way to assess the autonomic nervous system in a clinical setting.[25] However, there is a wide range in duration of ECG recordings. The “gold standard” is a 24h measurement. Subsequently, the recording should be divided into 5-minute segments.[25] The length of the recording affects both the frequency- and time-domain. Longer recordings show an increased overall HRV. Therefore, comparing and pooling HRV features measured in different time periods is inappropriate.[25,57]

Furthermore, there is a large range in gestational age of the included pregnancies. During early pregnancy, an increase in sympathetic nervous system activity is seen.[58] When gestation advances, the LF/HF-ratio increases during normal uncomplicated pregnancy.[59,60] Therefore, the large variety in gestational age of the included women makes pooling of data even more difficult.

Another contributor to the heterogenicity is the variety in bandwidths used for the frequency-domain features. The bandwidths as recommended by the HRV Task Force were used by all but four studies.[38,48,52,53] Three studies reported no information regarding the bandwidths used.[26,44,45]

For this review, we chose to exclude the analyses in which pregnant women with HPD were compared with non-pregnant women, since HRV is altered in normotensive pregnant women compared to normotensive non-pregnant women.[30,53]

Imbalance autonomic nervous system

A major finding in our systematic review is a trend towards an elevated sympathetic tone in HPD and a reduced parasympathetic tone. Although the pathophysiologic mechanisms that cause HPD remain to be elucidated, the imbalance of the autonomic nervous system could contribute to the origin of HPD. Figure 2 illustrates a schematic overview of how the autonomic imbalance is hypothesized to lead to HPD, based on several studies and reviews.[15,16,19,61–63] Increased sympathetic activity can cause an increase in peripheral resistance, which subsequently leads to high blood pressure.[15,16,19,61–63] Furthermore, an increased sympathetic tone may foster placental ischemic/reperfusion events, leading to the release of abnormal soluble placental factors into the maternal circulation.[61] This results in endothelial dysfunction and adrenergic receptor-induced vasoconstriction, which aggravates placental ischemia.[16,61] In the end, these mechanisms could contribute to the development of HPD.

Effect of medication on HRV

According to standard protocol in several international guidelines, women with HPD are likely to receive routine medication such as antihypertensive drug therapy, and in severe cases also corticosteroids and magnesium sulfate ($MgSO_4$).[1,64] This introduces an important confounding factor in many studies. Khlybova et al. state that administrating antihypertensive drugs may increase maternal HRV, due to inhibition of beta-adrenergic receptors and/or a decrease in the amount of myocardial beta-adrenergic receptors.[45] To our knowledge, there are no studies regarding the effect of $MgSO_4$ and corticosteroids on maternal HRV. The effect of both drugs on fetal HRV, however, has been well documented.[65–69] Given the mechanism of action of both drugs, it is likely that maternal HRV is affected by its admission. However, none of the included studies reported on the administration of corticosteroids, little is reported regarding $MgSO_4$ and whether HRV was measured before or after administration. In order to differentiate between the effect of medication on maternal HRV or merely HPD as a condition, further research regarding the effect of medication on maternal HRV in pregnant women is mandatory.

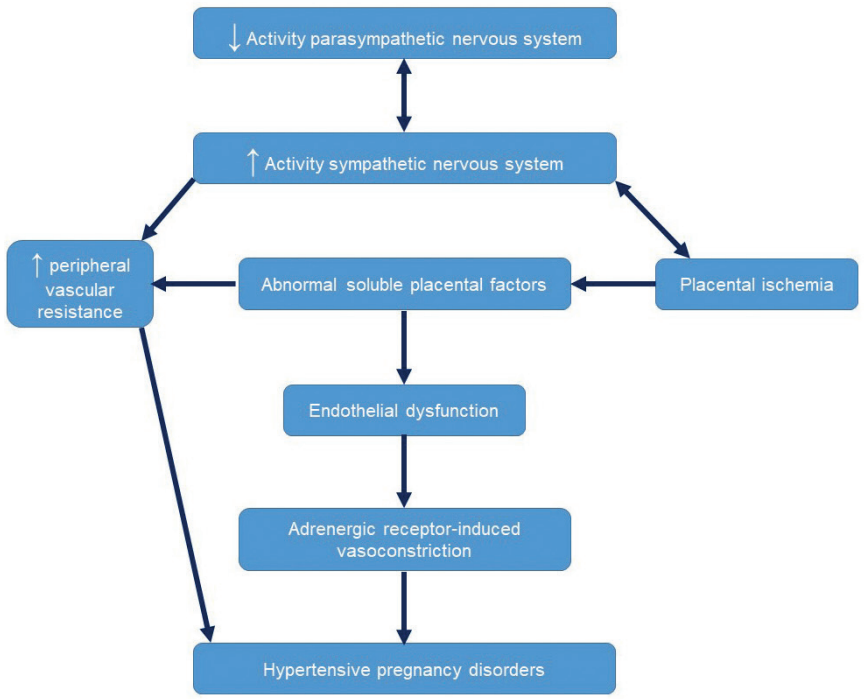

Figure 2. Overview how the autonomic imbalance is hypothesized to lead to HPD.

Strengths and limitations

One of the strengths of this systematic review is our rigorous search with the help of a professional librarian. Furthermore, we applied no restrictions regarding language or year of publication. Another strength of this review is the moderate to high quality of the included studies.

The limitation of this review was the wide variation of the included studies regarding the definitions of HPD, frequency-domain bandwidths, the duration and method of HRV measurement, and gestational age or period postpartum. Due to this heterogenicity, a meta-analysis could not be performed.

HRV is a non-invasive and accurate method to assess autonomic function and is also a good predictor of the risk of CVD.[25,29,70] However, HRV per se has certain limitations. Whereas HF power primarily reflects parasympathetic influence, LF power is not a pure marker of sympathetic drive but reflects both sympathetic and parasympathetic influences.[25,70] Furthermore, HRV is not an ideal index of autonomic activity and reactivity. Therefore, in clinical practice it could be useful to also perform other autonomic function tests, like cardiovascular reflex tests and baroreflex sensitivity, to assess autonomic dysfunctions in HPD.

Recommendations for future research

This review shows a large diversity in used methods to measure HRV. There is urgent need for standardized methods to measure HRV that would preferably use the bandwidths and duration of the measurement as suggested by the HRV Task Force.[25]

Mother and fetus can be measured simultaneously during pregnancy. Lakhno showed that in case of PE, both maternal and fetal HRV were significantly altered compared to normotensive pregnancies, with a decreased SDNN, RMSSD, LF, and HF.[26] Furthermore, less fetal accelerations and more fetal decelerations were demonstrated during complicated pregnancies.[26] There is growing evidence that children born after pregnancies complicated by HPD have a higher risk of developing CVD later in life.[71–74] Compared to the offspring of uncomplicated pregnancies, the offspring of pregnancies complicated by HPD have a higher blood pressure and more subclinical changes in cardiac structure in childhood or young adulthood.[73,75,76] Longitudinal studies with long term neonatal follow-up are needed to investigate the clinical relevance of abnormal fetal HRV measured during pregnancy.

In addition, longitudinal cohort studies can investigate whether HRV is able to predict HPD in a pre-clinical stage. The studies by Pal et al. are the only longitudinal studies included in this review.[39,46] They showed a significantly higher LF/HF-ratio early in pregnancy in women who would later develop GH, compared to normotensive pregnant women of similar gestational age and pregnant women with risk factors for GH who would not develop GH.[39,46] The study by Subha et al. found similar results, with a higher LF/HF-ratio in all three trimesters in high risk women who would develop GH, compared to high risk women who would remain to have a normotensive pregnancy.[60] These results are promising and indicate the need for further research. HRV might be helpful to compose a prediction model to identify women at risk for developing HPD.

CONCLUSION

Our systematic review supports the hypothesis that a sympathetic overdrive is found in HPD which is associated with a parasympathetic withdrawal.

However, the included studies in our review showed large diversity in the methods applied and the results.

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APPENDIX 1

Search string

(((“Heart Rate”[Mesh] OR heart rate*[tiab]) AND variabilit*[tw]) OR HRV[tiab]) AND ((((“Hypertension, Pregnancy-Induced”[Mesh] OR (“Pregnancy”[Mesh] AND “Hypertension”[Mesh])) OR ((pregnan*[tiab] OR gestation*[tiab] OR maternal[tiab]) AND hypertens*[tiab])) OR (“Pre-Eclampsia”[Mesh] OR pre eclampsia[tiab] OR preeclampsia[tiab]))

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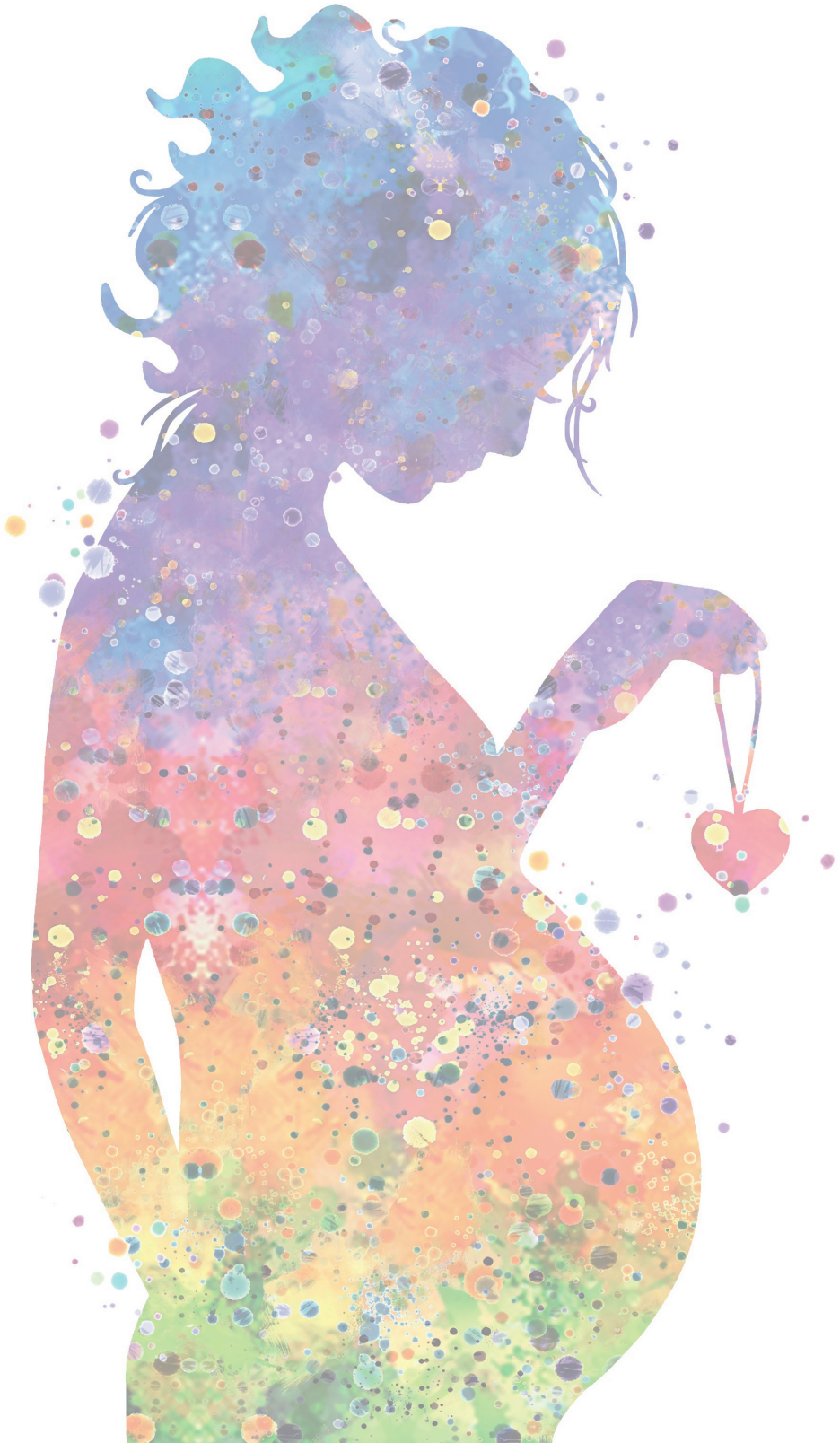

4

Changes in maternal heart rate variability in response to the administration of routine obstetric medications in hospitalized patients; study protocol for a cohort study (MAMA-heart study)

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Submitted

ABSTRACT

Introduction

Pregnancy is a period of continuous change in the maternal cardiovascular system, partly mediated by the autonomic nervous system (ANS). However, the ANS does not always adapt sufficiently to support the increasing demands of pregnancy – a scenario associated with various pregnancy complications, e.g. hypertensive pregnancy disorders (HDP) and preterm birth (PTB). Early detection of these complications (both leading causes of perinatal morbidity and mortality) could enable actionable interventions to mitigate the burden of disease.

Owing to the association of HPD and PTB with autonomic dysfunction, monitoring maternal heart rate variability (mHRV) – a proxy measure for ANS activity – could aid in the early detection of these complications. However, the pathway to mHRV alteration in relation to HPD or PTB remains unclear. Patients diagnosed with these complications are routinely administered obstetric medications, including antenatal corticosteroids, which affect fetal HRV. Little is known on how these medications (particularly corticosteroids) affect mHRV. Subsequently, administering these may confound mHRV measurements in this cohort. Therefore, our study will investigate how these medications affect mHRV.

Methods

A longitudinal, observational cohort study will be conducted in a tertiary obstetric care unit. We will include 61 women admitted between 23 5/7 and 33 6/7 weeks' gestation with an indication to receive corticosteroids antenatally. Continuous photoplethysmography (PPG) measurements will be acquired with a wrist-worn device throughout subjects' hospitalization to determine mHRV, facilitating within-patient comparisons of the effect of corticosteroids and other routinely administered obstetric medications on mHRV. Additionally, 24 hours of PPG measurements will be acquired at home at six weeks postpartum to enable a comparison between antenatal and postpartum mHRV.

Trial registration

Dutch Trial Register, NL8204; registered on December 6, 2019.

INTRODUCTION

Pregnancy is a period of continuous anatomical and physiological changes in both mother and fetus.[1] During this period, most maternal physiological systems undergo considerable adaptation to support the growing fetus. Some of the most prominent changes needed to sustain the increasing metabolic demands of the maternal-fetal dyad occur in the maternal cardiovascular system.[1–3]

These maternal cardiovascular adaptations involve, amongst others, changes in blood pressure and heart rate (HR).[1] The main mechanisms mediating these changes are related to the endocrine and the autonomic nervous systems (ANS).[2,4] However, in some cases, the ANS does not sufficiently adapt to support the increasing demands of pregnancy – a scenario which is associated with various pregnancy complications.[5] Two prominent examples are hypertensive pregnancy disorders (HPD) and preterm birth (PTB), both of which are leading causes of worldwide perinatal and maternal morbidity and mortality.[6–9] Although the exact etiology remains uncertain, both conditions are believed to be associated with dysfunctional autonomic regulation.[5,10–13] Since early detection of HPD and PTB (i.e. birth before 37 weeks of gestation) is challenging, alleviating the burden of these complications remains an important challenge in perinatology.

Early detection of HPD and imminent PTB is important and actionable, since effective risk-mitigating interventions exist. While significant effort has been devoted to developing prognostic models for the early detection of pregnancy complications, clinically implementable progress has been modest.[14] Challenges include, on the one hand, that most of these models have not been clinically validated, while on the other, these models often require clinical markers that are either impractical to acquire or simply unavailable.[14,15]

An alternative practical opportunity for the early detection of deterioration in maternal health is through continuously tracking changes in maternal heart rate variability (mHRV), as a proxy measure for the regulation offered by the ANS.[16–18] mHRV can be readily monitored using unobtrusive wearable technologies at home, e.g. wristwatches employing photoplethysmography (PPG).[19] Hence, it would be worthwhile to investigate whether continuous antenatal monitoring of mHRV may aid in the early detection of pregnancy complications.

Detecting pregnancy complications via mHRV requires a clear understanding of how these complications might affect mHRV. Considering previously published literature on this topic, many studies have explored how mHRV changes in pregnancies complicated by HPD,[16,20–22] though often with conflicting results.[23] Contrarily, only one study describes the relationship between PTB and mHRV.[5] Clearly, this remains an open research area.

An important limitation in studying HRV in this patient cohort is the difficulty in obtaining mHRV measurements that are not confounded by the use of medication. Typically, the onset of HPD and PTB is sudden, resulting in swift hospitalization to obstetric care units (OCUs) where patients frequently receive routine obstetric medications such as tocolytic drugs, magnesium sulfate ($MgSO_4$), corticosteroids, or antihypertensive treatment.[24–26] These medications possibly affect mHRV, thus acting as potential confounders in attempts to assess maternal health from mHRV measurements. However, the changes in mHRV resulting from this confounding effect remains largely unknown.[23]

Several studies have, in fact, urged investigation into the possible confounding effects of these medications on mHRV as this might help in better identifying changes in mHRV related to pregnancy complications.[21,23] Conducting such studies, however, is challenging. One of the primary reasons is because patients admitted to OCUs do not routinely undergo continuous HR monitoring (e.g. via ECG). Other factors include logistical challenges such as the urgent admission of patients to OCU along with, typically, speedy administration of one or more medications. Possibly, because of these reasons, many studies investigating mHRV do not address the use of medication,[20,22] while others only conduct short measurements before the administration of medication.[5,16]

To our knowledge, only two studies – one in hospitalized women, the other in rats – have investigated the changes in mHRV in response to the administration of routinely used obstetric medication. Weissman et al. found that a tocolytic drug (atisoban) – which is used to arrest preterm contractions – had no effect on mHRV.[27] Contrarily, Zhou et al. observed changes in mHRV when administering $MgSO_4$ to rats with medically induced preeclampsia (a type of HPD). While the rats' condition resulted in lowered HRV, this was partly normalized after administering $MgSO_4$.[28]

In addition to tocolytics, another widely used type of medication in obstetrics is corticosteroids. These are antenatally administered to women with threatened PTB between 24 and 34 weeks of gestation to induce fetal lung maturation, thereby reducing the risk of neonatal morbidity and mortality.[29] Fetal HRV (fHRV) is known to be affected by corticosteroids.[30–33] Subsequently, it is likely that these will also affect mHRV. Yet, the effect of corticosteroids on HRV in adults has only been studied in a small group (n = 12) of healthy male subjects.[34] In this study, while the HR of participants increased, HRV remained unchanged. However, we cannot assume a similar response in pregnant women, as HRV not only differs between sexes,[35] but is also impacted by the duration of gestation.[20,36,37]

Consequently, in this paper, we describe a study design to investigate changes in mHRV in response to routinely administered obstetric medications in a cohort of patients with pregnancy complications. Quantifying these changes is important as it not only fills a knowledge gap but could also aid future studies in distinguishing changes in mHRV

owing to pregnancy complications from those resulting from the use of medication. A clearer understanding of how pregnancy complications affect mHRV could in turn enable predictive monitoring of the same, allowing timely implementation of risk-mitigating interventions.

METHODS AND ANALYSIS

Aim of the study

This study aims to investigate the effect of routinely administered obstetric medications on mHRV in patients hospitalized due to pregnancy complications.

Clinical setting

This longitudinal, observational cohort study will be conducted at the OCU of Máxima Medical Center (Máxima MC), Veldhoven, The Netherlands, starting July 2020. The study cohort will comprise patients admitted to the OCU between 23 5/7 and 33 6/7 weeks of gestation with an indication to receive corticosteroids antenatally. Since Máxima MC is a tertiary obstetric referral center, high-risk patients from neighboring secondary care hospitals are often transferred here. Subsequently, the study cohort comprises of patients directly admitted to Máxima MC, as well as those transferred from elsewhere.

Clinical data acquisition

Longitudinal PPG measurements will be continuously acquired with the Philips Data Logger (PDL, Philips Research, Eindhoven, the Netherlands). The PDL – shown in Figure 1 – is a non-invasive wrist-worn device (CE-marked) that acquires PPG data (32 Hz) through optical sensing that measure changes in blood volume. Previous studies have utilized a predecessor of this device to collect PPG measurements in free-living conditions.[38,39]

PPG measurements capture the time intervals between pulses resulting from subsequent heart beats, serving as a measure of HR, from which HRV can be calculated.[40] Furthermore, the PDL also records movement data using a tri-axial accelerometer (range: ± 8 G, sampled at 32 Hz), which can aid in filtering out motion artifacts. The PDL offloads acquired data to a mobile phone via Bluetooth. Data are not displayed on either the PDL or the mobile phone, ensuring that acquired data cannot influence clinical decision making.

In addition to PPG measurements, the study utilizes patient data routinely collected in electronic patient files. These data – detailed in the *Study Parameter* section – include maternal-fetal health parameters and routine measurements, e.g. cardiotocography (CTG).

Figure 1: The Philips Data Logger. This device will be employed in this study to acquire PPG and accelerometer data. The device does not display this PPG and accelerometer data, it only displays the time.

Routinely administered medications in obstetric care settings

Owing to their clinical state, the patient cohort participating in this study will be administered one or more obstetric medications as part of their standard clinical care. All medications administered during this study are part of standard care and not influenced by study participation.

When pregnancy complications are diagnosed before 34 weeks of gestation, patients receive corticosteroids (betamethasone). Owing to its frequent use and effects on fHRV, our study design focuses on this medication. A course of betamethasone (Celestone Chrondose®, Schering AG, Berlin, Germany) consists of two 11.4 mg injections administered intramuscularly, each consisting of 50% betamethasone phosphate for quick uptake (≈ 1 hour) and 50% betamethasone acetate for slow release to facilitate sustained exposure.[41–43] Although the pharmacokinetics of betamethasone in the maternal system are not fully known, its maximum effect and terminal half-life (i.e. time until the drug concentration in plasma reduces by 50%) are believed to lie within 0.5-3 hours and within 6-12 hours after administration, respectively.[43–46] Betamethasone's biological half-life – which relates to its effect on the hypothalamus-pituitary-adrenal axis – is 36-59 hours.[47,48] This medication is cleared from the maternal system within 48 hours.[44]

Patients will typically receive other obstetric medications in addition to corticosteroids. In cases of threatened PTB, patients are likely to receive tocolytic drugs such as nifedipine (taken orally) or atosiban (administered intravenously) to attenuate uterine contractions.[25] Furthermore, patients in the study population can also receive $MgSO_4$, which is given

intravenously and prescribed for either fetal neuroprotection (in case of PTB <30 weeks' gestation) or maternal neuroprotection (in case of severe HPD).[24–26] Patients with HPD might also be administered anti-hypertensive medications such as labetalol, methyldopa, nifedipine, or nicardipine, which are administered either orally or intravenously.

Study design

The study comprises two periods of PPG measurements in the same study population. The *primary phase* will assess the effect of obstetric medications on mHRV, based on PPG data gathered throughout subjects' hospitalization in the OCU. The *secondary phase* – added to compare cardiovascular features between the antenatal and postpartum periods – consists of 24-hour PPG measurements at six weeks postpartum, acquired in free-living conditions at home.

Primary phase: Enrollment in the *primary phase* occurs at patient admission to the OCU at Máxima MC. Due to the typically speedy administration of betamethasone after admission, PPG measurements with the PDL will start as soon as possible. Subjects will in so far as is reasonable wear the PDL throughout their hospitalization. If possible, subjects will wear the PDL on their non-dominant hand to reduce motion artifacts in the PPG measurements.

We define the principal PPG measurement epochs around the administration of the second betamethasone injection (administered 24 hours after the first), as the study population will likely contain patients transferred from other hospitals who have already received their first injection elsewhere. The principal baseline measurement epoch – shown in Figure 2 in light blue – is the two hours leading up to the second injection. Since the terminal half-life of betamethasone is 6–12 hours,[43–46] we plan this baseline measurement 22 hours after the first injection. The principal post-medication measurement epoch is the four hours after the injection (shown as dark red in Figure 2), as betamethasone's maximum effect occurs 30 minutes to 3 hours after administration.[43–46] We will exclude and replace subjects for whom less than 50% of reliable PPG data is available in each of these principal measurements epochs.

Since PPG measurements will be longitudinal, there is a possibility to incorporate multiple measurement epochs to improve the accuracy of the analysis. Subsequently, we define a set of additional baseline and post-medication PPG measurements centered on the first betamethasone injection where possible. A third baseline PPG measurement is defined 48 hours after the second injection, although this might be unavailable if the subject is transferred to another hospital or goes into labor.

Participation in the *primary phase* ends upon discharge from Máxima MC. Where possible, subjects who go into labor during the primary phase will also wear the PDL during delivery.

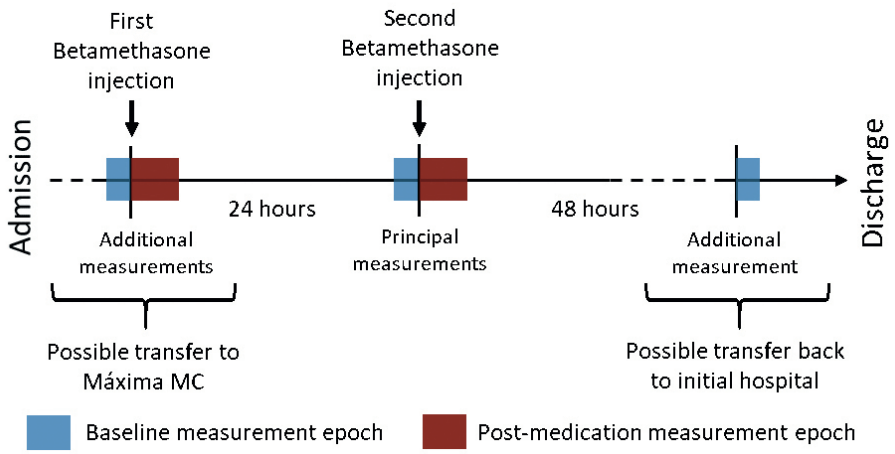

Figure 2: Baseline and post-medication measurements acquired in the primary phase of the study. The principal measurement epochs occur around the second betamethasone injection, while additional measurement epochs are defined around the first betamethasone injection and 48 hours after the second injection.

Secondary phase: Participants from the *primary phase* have the option of participating in the *secondary phase*. This consists of wearing the PDL at six weeks postpartum for a 24-hour monitoring period in free-living conditions at home.

Primary and secondary analyses

Primary phase: The primary analysis will determine the effect of administering betamethasone on mHRV. Secondary analyses will explore the effect of other medications on mHRV, compare cardiovascular parameters between subgroups (e.g. stratified by diagnosis), assess cardiovascular parameters during delivery and evaluate similarities between trends in PPG and CTG measurements.

Secondary phase: PPG measurements acquired in the *secondary phase* will further facilitate secondary analyses, including a within-patient comparison of cardiovascular parameters between the antenatal and postpartum periods. If the sample size allows, we will also compare postpartum parameters between subgroups (stratified by diagnosis).

Study parameters

We will assess cardiovascular parameters derived from the PPG measurements to perform our analyses. These include HR, HRV features (e.g. SDNN, RMSSD, HF, LF and pNN50) and features based on the morphology of the PPG waveform (e.g. pulse area and large artery stiffness index[49]). To describe the study cohort, we will also collect the following data from patient records:

1. Maternal condition:
   - patient characteristics, including age, BMI and ethnicity
   - pregnancy characteristics, including gestational age, results of prenatal screening, and complications in pregnancy
   - obstetric history, including gravidity, parity, and previous pregnancy or labor complications
   - family history, including genetic or congenital diseases or a history of hypertension or preeclampsia
   - medical condition, including preexisting diseases (i.e. cardiovascular disease, pre-existing hypertension, autoimmune disorders, neurologic disorders)
   - routine measurements, including blood pressure, laboratory test results, physical examination results, ultrasound results.
2. Fetal/neonatal condition, including fetal growth, congenital diseases, birth weight, APGAR score, CTG measurements and umbilical cord blood gases.
3. Labor and delivery, including mode of delivery and clinical notes.
4. Administration of medications, including timing, dosage, and reasons for administration.

The electronic medical records only contain information relevant to a patient's hospitalization or appointments at Máxima MC. Subsequently, we will contact subjects who did not deliver at Máxima MC for basic details of their delivery (i.e. birth weight and gestational age).

For subjects who participate in the *secondary phase* and have their postpartum appointments at Máxima MC, information on their postpartum condition (e.g. postpartum complications and standard checkup measurements) will also be collected from their electronic medical records.

Subject inclusion and exclusion criteria

Patients admitted to the OCU at Máxima MC who are going to receive one or both dosages of betamethasone injection(s) are eligible for inclusion. Table 1 outlines the entire inclusion and exclusion criteria.

Table 1: Inclusion and exclusion criteria for MAMA-hart study

Inclusion criteria	Exclusion criteria
- Age 18 years and above - Gestational age 23 5/7 to 33 6/7 weeks - Yet to receive the second betamethasone injection - Proficient in Dutch or English	- History of severe arrhythmia and/or maternal congenital heart disease - Cushing's disease - Known allergies to hard plastic (e.g. used in sport watches) or elastic band material - Wounds, injuries or infectious diseases on wrist where the PDL will be worn - Tattoo location on wrist interfering with the positioning of the PDL - Both wrists unavailable for wearing the PDL (e.g. owing to intravenous lines) - Dexamethasone (another brand of corticosteroid) administered instead of betamethasone

Retrospectively, if subjects are identified to be incorrectly enrolled (i.e. not meeting the full eligibility criteria), they will be excluded from the study analysis and replaced with a new subject.

Sample size

In accordance with the primary analysis (i.e. the effect of administering betamethasone on mHRV during pregnancy), we designed the study to detect the differences in mean maternal HR (mHR) between the baseline and post-medication epochs. Subsequently, we calculated the sample size using a two-sided T-test for a confidence interval of 95% and a power assumption of 80%. The expected variation in HR measurements was estimated from studies assessing HR in pregnant populations.[11,50,51] No prior research was available to guide the decision concerning effect size, but the heterogeneity of the cohort could necessitate being able to detect a small effect. Subsequently, we selected an effect size of 10%.

Based on these parameters, we calculated a sample size of 43 using R (version 3.5.3, RStudio Inc., Boston, MA, USA). Adding in a safety margin of 20% increased the sample size to 61. We will perform an interim analysis after including 43 subjects to assess whether further inclusions are necessary. The study is powered for the primary analysis , and not specifically powered for secondary analyses.

Statistical analysis

A within-subject comparison of cardiovascular features (derived from PPG measurements) in the baseline and post-medication epochs will be carried out for the primary analysis, i.e. determining the changes in mHRV in response to administering betamethasone. For secondary analyses in both *phases*, we will perform within-subject as

well as between-group comparisons. We will test normality assumptions with a Shapiro-Wilk test and subsequently compare continuous variables using a paired T-test or a Wilcoxon matched-pairs test, and categorical variables using a χ^2-test or Fisher's exact test, chosen as appropriate. $P<0.05$ is considered significant for a two-tailed test.

Data handling and storage

We will adhere to the European General Data Protection Regulation (GDPR) and the Dutch Personal Data Protection Act ("Uitvoeringswet AVG") for data processing and analyses. Subsequently, subject data will be de-identified.

We will use Research Manager (version 5.51.0, Research Manager, Deventer, The Netherlands) for the case report form and data handling. Personal data will be stored in accordance with Good Clinical Practice guidelines. Analyses are carried out under the Eindhoven MedTech Innovation Center framework, a collaboration between Máxima MC, Philips Research and the Eindhoven University of Technology.

Ethics and dissemination

The Medical Ethics Committee of Máxima MC, Veldhoven, The Netherlands, confirmed that the study neither imposes any changes in general practice, nor does it burden participants. Therefore, in line with the Declaration of Helsinki, a waiver for ethical approval was granted (N19.112).

All investigators agree to publish the study results in an international peer-reviewed journal, regardless of whether the outcomes align with the stated hypotheses. The full study protocol (version 2.0, dated January 20, 2020) is available upon request.

Patient and public involvement

Patients and the public were not involved in the design or planning of the study.

DISCUSSION

This study is one of only a few to explore the effect of administering routine obstetric medications on mHRV,[27,28] and the first to investigate changes in mHRV resulting from antenatal administration of corticosteroids (betamethasone). Apart from a small number of human and animal studies addressing the effect of this medication on HR and HRV in adult males and in baboons,[34,52,53] research has focused on assessing changes in fHRV – demonstrating that administering betamethasone significantly decreases fHRV parameters.[30,33,54]

A possible reason for this disparity in research interest between maternal and fetal HRV is that fHRV is an established parameter in assessing fetal well-being, while mHRV is not yet

widely used in clinical practice.[55] Even so, fetal HR (fHR) is not continuously monitored in this cohort. Consequently, in a previous study that assessed the effect of betamethasone on fHRV, Verdurmen et al. had to deliberately incorporate fHR measurements into clinical workflow. This, as well as the typical urgency of administrating corticosteroids, imposed logistical challenges on their study.[54] Since our clinical setting is comparable, we will likely encounter similar obstacles. Subsequently, we designed the study to mitigate two main logistical challenges: firstly, acquiring sufficiently long and unconfounded baseline measurements; secondly, ensuring that the study protocol seamlessly fits into standard clinical workflow.

Verdurmen et al.'s baseline fHRV-measurements were planned five days after the second betamethasone injection, since betamethasone affects fHRV for four days.[54] However, many subjects were discharged or gave birth before this time point.[54] It is also impractical to acquire the principal baseline measurement before betamethasone administration since transferred subjects will likely have already received the first injection before inclusion in the study. Even for subjects directly admitted to Máxima MC, the epoch before the first injection could be too short to provide a sufficiently long baseline measurement. Furthermore, since admission is typically urgent and unexpected, patients are likely physiologically stressed during this epoch, which can affect HRV parameter.[56]

Therefore, we define our principal PPG baseline measurement as the epoch preceding the second betamethasone injection. Based on the pharmacokinetics of the drug,[43–46] levels of betamethasone in the maternal system are expected to decrease in the 24 hours between the first and second injection. Consequently, we hypothesize that if betamethasone affects mHRV, comparing epochs before and after the second injection will indicate this.

Still, it is possible that the first betamethasone injection could confound our principal baseline measurement. Even though studies show that the terminal half-life of betamethasone is 6 to 12 hours,[43–46] the medication clears the maternal system only after 48 hours. Considering this, we introduce additional measurements to the analysis where possible to improve accuracy, both before administration of betamethasone as well as 48 hours thereafter.

It is uncertain how long mHRV will remain affected by the medication. It should be noted that the biological half-life of betamethasone is 36 to 59 hours;[47,48] therefore, this could also confound measurements. However, the biological half-life was not determined in a pregnant population, and pregnancy is known to affect the pharmacokinetics of drugs.[57,58] Literature has shown that fHRV remains affected for four days,[54] but Ballard et al. have also demonstrated that betamethasone's terminal half-life in the mother is

half of that in the fetus.[44] Subsequently, it is plausible that there is a less sustained effect on mHRV than on fHRV.

The second logistical challenge concerns ensuring that the study fits seamlessly into standard clinical workflow. Ideally, acquiring measurements should minimally disrupt clinical workflow and not burden patients or clinical staff. To overcome this logistical challenge, a wristwatch-like device (the PDL) is employed for collecting mHR since its ease of use requires minimal clinical intervention.

An ECG Holter monitor is an alternative device that might offer higher accuracy in determining mHRV. However, this approach is, both, more obtrusive and cumbersome for the patient and staff. Furthermore, in addition to high compliance in wrist-worn monitoring in pregnant populations,[19] HRV determined from PPG measurements sampled above 25 Hz (PDL: 32 Hz) can be as reliable as that calculated from ECG.[59]

Our study design not only addresses logistical challenges identified from previous studies, but also offers opportunities for additional exploratory analyses. Since PPG measurements are non-invasive, a dataset representing the periods of hospitalization of participants can be collected. Subsequently, we could analyze trends in mHR in conjunction with trends in routinely collected fHR, potentially offering insights into the utility of mHR monitoring as an indicator for fetal well-being. Ramadam et al. have already demonstrated that mHR mimics fHR characteristics,[60] while Gonçalves et al. have suggested that analyzing both maternal and fetal HR – compared to only fHR – could improve the detection of fetal acidemia.[61]

Furthermore, incorporating measurements from the *secondary phase* (i.e. at six weeks postpartum) allows for analysis of mHRV throughout the perinatal period (i.e. antepartum, intrapartum and postpartum), which – to our knowledge – has not been assessed. Insights into the postpartum period could be particularly useful, since literature on this is limited.[62–64]

For the results of the study to be applicable in clinical practice, participants will represent a cohort of women who typically receive corticosteroids, i.e. patients with varying characteristics and diagnoses (e.g. HDP, threatened PTB), and who subsequently receive multiple medications. The heterogeneity in characteristics and diagnoses could serve as limitations, as they will likely also influence mHRV. We account for this heterogeneity by focusing on within-patient comparisons when assessing the effect of betamethasone on mHRV, emphasizing the relative change between the epoch before and after the administration of medication, and averaging results across subjects. However, the heterogeneity could also be advantageous, as it allows us to explore analyses of subgroups stratified by diagnosis, e.g. differences in cardiovascular parameters of subjects who deliver prematurely and those who deliver at term.

The administration of multiple obstetric medications is an unavoidable limitation in this study design. Although medications administered in conjunction with corticosteroids could confound measurements, there is also the opportunity to explore their effects on mHRV. Limited literature exists in this regard, aside from one study which determined that a tocolytic drug had no significant effect on mHRV.[27]

Still, the most prominent knowledge gap concerns betamethasone. This is the first study to investigate the effect of administering this medication on mHRV. Results from this study could reduce the confounding effect of betamethasone in studies employing mHRV to investigate the autonomic dysregulation associated with pregnancy complications such as HPD or threatened PTB. An improved understanding of how mHRV is altered could facilitate earlier diagnosis through tracking deteriorations in mHRV. In turn, early detection could enable prevention or better management of these complications, alleviating some of the burden they place on women, families and society.

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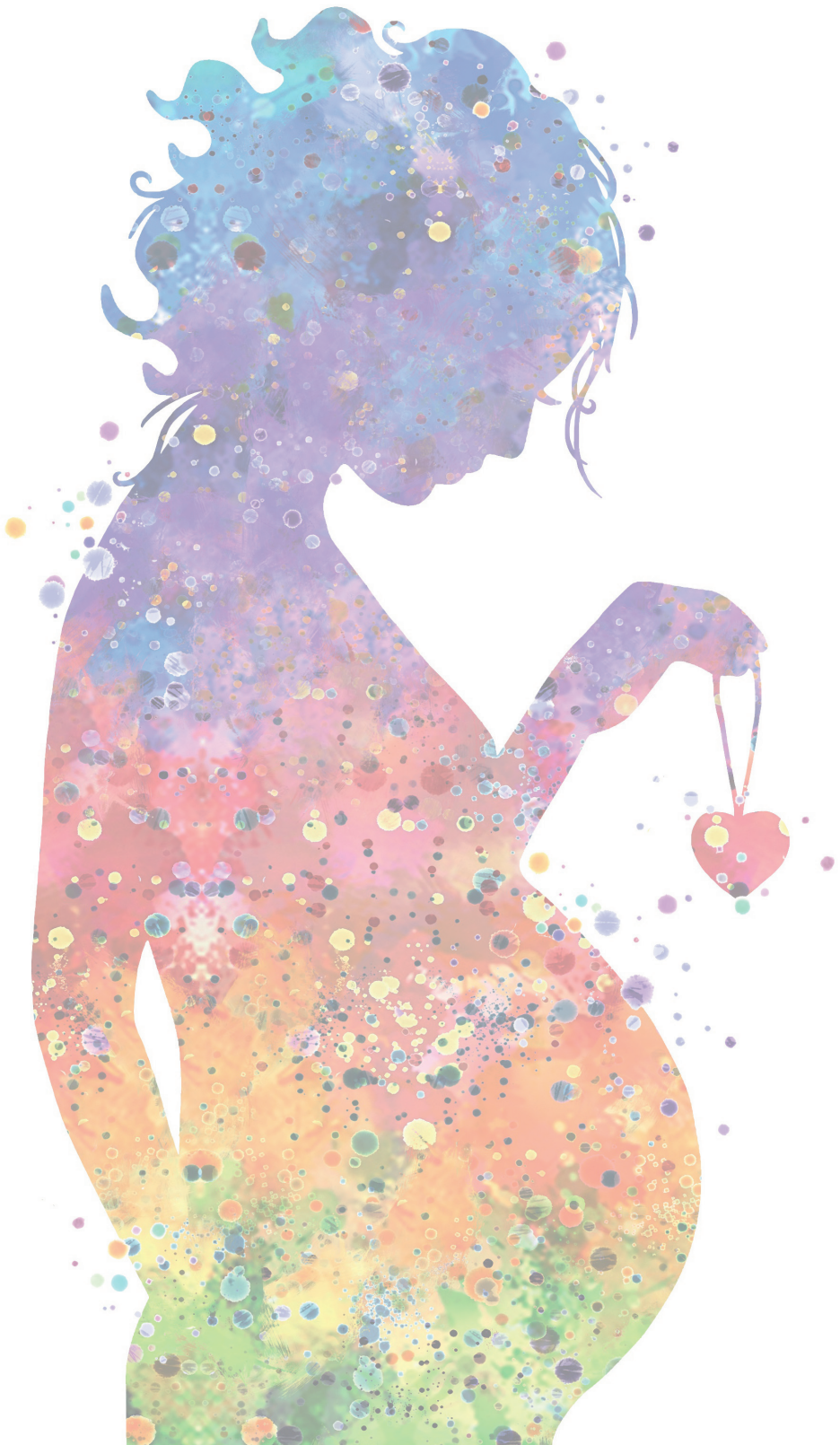

5

Management of intrapartum fetal distress in The Netherlands: a clinical practice survey

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ABSTRACT

Objective

Solid evidence on the effect of intrauterine resuscitation on neonatal outcome is limited, and superiority of one intervention over the others is not clear. We therefore surveyed the clinical practice variation in fetal monitoring and the management of fetal distress during labor, in Dutch labor wards. In addition, we have compared recommendations from international guidelines.

Study design

We conducted a survey among all 86 Dutch hospitals, using a questionnaire on fetal monitoring and management of fetal distress. In addition, we requested international guidelines of 28 western countries to study international recommendations regarding labor management.

Results

The response rate of the national survey was 100%. Labor wards of all hospitals use ctg for fetal monitoring, 98% use additional fetal scalp blood sampling, and 23% use st-analysis. When fetal distress is suspected, oxytocin is discontinued and tocolytic drugs are applied in all hospitals. Nearly all hospitals (98%) use maternal reposition for fetal resuscitation, 33% use amnioinfusion, and 58% provide maternal hyperoxygenation. Management is mainly based on the Dutch national guideline (58%) or on local guidelines (26%). Eight international guidelines on fetal monitoring were obtained for analysis. Fetal scalp blood sampling facilities are recommended in all the obtained guidelines. Use of st-analysis is recommended in three guidelines and advised against in three guidelines. Five guidelines also advised on intrauterine resuscitation: discontinuation of oxytocin and use of tocolytic drugs was advised in all guidelines, amnioinfusion was recommended in two guidelines and advised against in two guidelines, whereas maternal hyperoxygenation was recommended in two guidelines and advised against in one guideline.

Conclusion

Nationwide clinical practice, and recommendations from international guidelines agree on the use of fetal scalp blood sampling in addition to cardiotocography during labor. The opinion on the use of st-analysis differs per clinic and per guideline. Discontinuation of oxytocin, administration of tocolytic drugs and maternal repositioning are rather uniform, on national and international level. However, there is a large variation in the use of amnioinfusion and maternal hyperoxygenation, which may be explained by the contradictory recommendations of the different guidelines.

INTRODUCTION

Non-reassuring fetal heart rate (FHR) patterns frequently occur during labor. They may be indicative for impaired fetal oxygenation, which eventually may lead to fetal asphyxia.[1,2] As fetal asphyxia is associated with hypoxic-ischemic encephalopathy and even fetal death, timely intervention is important to optimize neonatal outcome.

Intrauterine resuscitation is defined as interventions with the intention to improve fetal oxygenation during labor, in the presence of suspected fetal distress. Depending on the presumable cause of the abnormal FHR pattern, these interventions aim to restore oxygenation of the fetus. Possible actions consist of alleviation of cord compression and/or improvement of uteroplacental blood flow.[3,4]

Improvement of the intrauterine condition of the fetus can avoid termination of the delivery, thereby preventing a cesarean section or vaginally assisted delivery. In the case of an emergency cesarean section, intrauterine resuscitation may restore fetal oxygenation during the decision to incision time period.

Several techniques to improve fetal oxygenation are used in clinical practice. The most commonly used interventions are discontinuation of oxytocin infusion, maternal repositioning, amnioinfusion, maternal hyperoxygenation, and the use of tocolytic agents. Unfortunately, solid evidence on the effect of each of these interventions on neonatal outcome is limited, and superiority of one intervention over the others is not clear.[5] This lack of evidence leads to differences in recommendations in two important guidelines on fetal monitoring during labor and intrapartum management.[4,6] For example, the Practice Bulletin of the American Congress of Obstetricians and Gynecologists (ACOG) recommends maternal hyperoxygenation in the presence of fetal distress, whereas the Royal College of Obstetricians and Gynaecologist (RCOG) in the United Kingdom advises against this intervention.[4,6] The Dutch Society of Obstetricians and Gynecologists (NVOG) is currently working on a recommendation regarding the use of maternal hyperoxygenation for fetal distress.[7]

Apparently, different guidelines have different recommendations regarding the management of fetal distress during labor. This may lead to clinical practice variation regarding the management of fetal distress during labor.

We aim to investigate the clinical practice variation in Dutch delivery wards, with specific interest in the local methods used for fetal monitoring, and the actions undertaken in suspected fetal distress. Local guidelines, as well as intervention techniques to improve fetal oxygenation are inventoried. Hence, we conducted a survey among all Dutch hospitals. In addition, we requested the national guidelines from 28 Western countries regarding fetal monitoring and fetal distress.

MATERIALS AND METHODS

A clinical practice survey was conducted from August to October 2015 in all 86 Dutch hospitals. Also, we aimed to obtain international guidelines of 25 European countries, the USA, Canada, and Australia & New Zealand.

Survey among Dutch obstetricians

Per hospital, one obstetrician was asked to complete a survey comprising twelve multiple-choice questions on fetal monitoring and common interventions regarding suspected fetal distress (Appendix A, original version in Dutch).

Topics included: methods used for fetal monitoring; classification method of the cardiotocogram (CTG); how to diagnose fetal distress; the indication and use of intrauterine resuscitation techniques and the use of national and/or international guidelines. Respondents were able to give more than one answer to each question and were free to add more options if their answer was not listed. In case of unclear responses, we contacted the respondent to clarify the answers.

In The Netherlands, low risk deliveries are managed by primary care midwives. These primary midwife practices are excluded from this survey, since most resuscitation techniques are not available during home births. Hence, in the presence of fetal distress, the parturient will be referred to a hospital.

Statistical analysis national survey

After all questionnaires were returned, we analyzed the results using SPSS (IBM SPSS Statistics, version 23). Categorical variables were expressed as frequencies and percentages.

Survey of national guidelines of European countries

We searched the Internet for international guidelines on fetal monitoring and resuscitation of 25 European countries, the USA, Canada, and Australia & New Zealand. If guidelines were not freely available, we approached the corresponding national societies of obstetricians and gynecologists and requested their national guideline on fetal monitoring and/or intrauterine resuscitation during labor.

If a guideline was not available in English, it was translated by a native speaker or by the use of an online translation program. We compared the recommendations as stated in the different guidelines. The following details were abstracted from the guidelines and listed: methods of fetal monitoring systems during labor (intermittent auscultation, fetal heart rate pattern, fetal scalp blood sampling and ST-analysis), the classification system to judge the fetal heart rate pattern, and recommendations on the use of intrauterine resuscitation techniques.

Ethical considerations

As confirmed by the Medical Ethics Committee of Máxima Medical Center, Veldhoven, The Netherlands, our study does not involve any patient data and imposes no changes in general practice. Therefore, according to the Declaration of Helsinki, no ethical approval was required.

RESULTS

Survey among Dutch obstetricians

A total of 86 obstetricians, representing all 86 Dutch hospitals, completed the questionnaire. Hospitals include eight university hospitals, 39 general teaching hospitals, and 39 non-teaching hospitals. The response rate was 100%.

Besides the national guideline on fetal monitoring provided by the NVOG, various local protocols exist on the diagnosis and management of fetal distress during labor. In The Netherlands, the guideline of the NVOG is frequently used (58%), sometimes in combination with a local guideline (26%). In 36% of the hospitals, only local protocols are used. The American guideline, provided by the American College of Obstetricians and Gynecologists (ACOG) is used in one hospital (1%), while the British guideline, provided by the Royal College of Obstetricians and Gynaecologists (RCOG) is used in six hospitals (7%). Results are shown in Fig. 1.

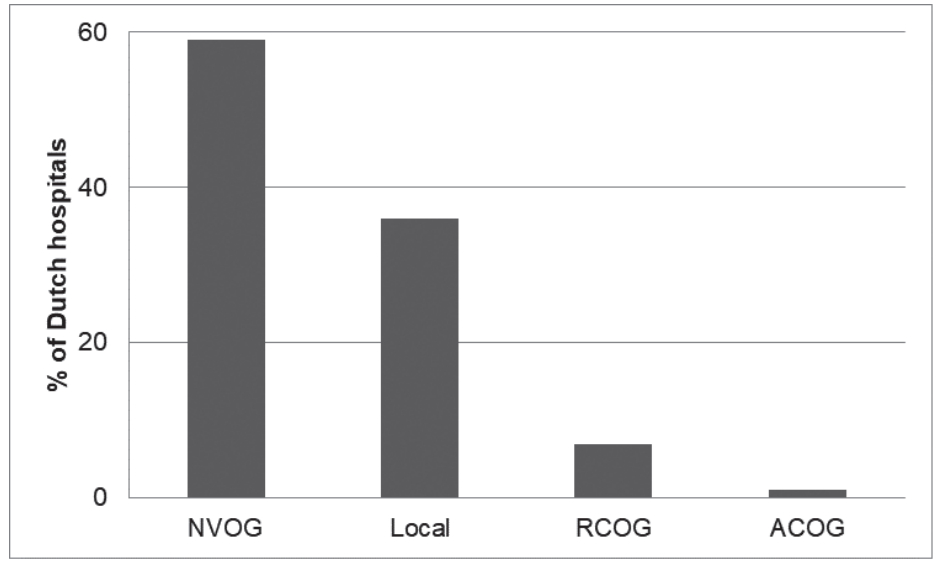

Figure 1. Percentage of Dutch hospitals using the represented guidelines on fetal monitoring and fetal resuscitation.

All hospitals used fetal CTG to estimate fetal well-being during labor. Besides, in 23% (N = 20) of the hospitals ST-analysis is used to monitor fetal condition, while in 98% (N=84) fetal scalp blood sampling is used in addition to CTG.

In most of the hospitals (95%), the (modified) FIGO classification is used to classify the CTG. In two hospitals the Fischer classification is used.[8] In two non-teaching hospitals no structural classification system is implemented.

Preferences regarding the use of resuscitation techniques are different among the hospitals. Fig. 2 shows the percentage of hospitals that use each of the mentioned resuscitation techniques. The most used tocolytic agents are oxytocin antagonists, 6.75 mg atosiban administered intravenously. Furthermore, beta-mimetics, 5-10 mg ritodrine administered intravenously, or nitroglycerin, administered oromucosally with a dose of 0.4 mg are in use.

When fetal distress is suspected, immediate delivery may be expedited, depending on the clinical situation. In almost all hospitals (98%), the attending staff will try to improve fetal oxygenation in expectation of an emergency cesarean section or vaginally assisted birth. Improvement of the intrauterine condition of the fetus may also avoid termination of the delivery, thereby preventing a cesarean section or vaginally assisted delivery. In 86% of the Dutch delivery wards, intrauterine resuscitation techniques are applied as an attempt to prevent immediate delivery.

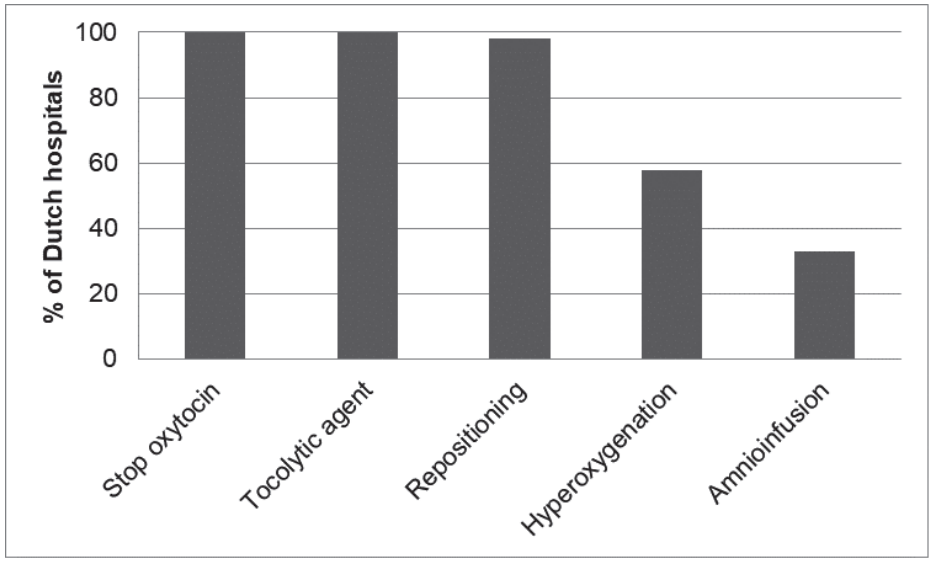

Figure 2. Percentage of Dutch hospitals using the represented intrauterine resuscitation techniques in the presence of suspected intrapartum fetal distress.

Survey of national guidelines of European countries

We were able to obtain national guidelines on fetal monitoring of the following countries: United Kingdom (2015),[6] United States of America (USA, 2009),[4] Canada (2007),[9] Australia & New Zealand (2014),[10] Germany (2013),[11] Ireland (2014),[12] Portugal (2012),[13] and Denmark (2008).[14] The years refer to the date of publication of the most recent version of each guideline. Five of them also contained recommendations on the use of intrauterine resuscitation techniques.[4,6,9,10,12] We were not able to obtain the guidelines of the remaining 20 countries. The national societies of Luxembourg and Finland reported they had no national guideline and used guidelines of surrounding countries.

All the above-mentioned guidelines were freely online available, apart from the Portuguese guideline that was kindly provided by the Portuguese Federation of Obstetrics and Gynecology. Germany and Portugal did have guidelines on fetal monitoring, but not on fetal resuscitations. Denmark did have a guideline on amnioinfusion, but no recommendations regarding the other resuscitation techniques were reported. Recommendations from the obtained guidelines are listed in Tables 1 and 2.

Table 1. Recommendations from national and international guidelines on fetal monitoring during labor.

Country	Intermittent auscultation	CTG	Classification system	FBS	STAN	SpO_2
Netherlands	Low risk	High risk	FIGO	YES	YES	-
USA	-	YES	FIGO	-	-	-
UK	Low risk	High risk	FIGO	YES	-	-
Ireland	Low risk	High risk	FIGO	YES	-	-
Canada	Low risk	High risk	FIGO	YES	NO	NO
Australia & New Zealand	Low risk	High risk	-	YES	NO	NO
Germany	Low risk*	High risk	FIGO	YES	NO	-
Portugal	NO	YES	FIGO	YES	YES	-
Denmark	Low risk*	High risk	FIGO	YES	YES	-

Low risk = recommended in low risk population. High risk = recommended in high risk population.
CTG = cardiotocogram. FIGO = (modified) FIGO classification
FBS = fetal scalp blood sampling. STAN = ST-analysis. SpO_2 = fetal pulse oximetry
- = not mentioned. * = intermittent electronic fetal heart rate monitoring allowed in a low risk population, under certain circumstances.

Table 2. Recommendation from national and international guidelines regarding intrauterine resuscitation during labor.

Country	Maternal repositioning	O_2	Stop oxytocin	Tocolytic agent	Amnioinfusion	IV fluid bolus
Netherlands	YES	-	YES	YES	#	-
USA	YES	YES	YES	YES	YES	YES
UK	YES	NO	YES	YES	NO	YES
Ireland	YES	-	YES	YES	-	NO
Canada	YES	YES	YES	-	YES	YES
Australia & New Zealand	YES	-	YES	YES	NO	YES

O_2 = maternal hyperoxygenation. - = not mentioned. # = not recommended nor discouraged

COMMENT

The Netherlands

The Dutch national guideline on fetal monitoring during labor promotes the use of fetal scalp blood sampling, in combination with CTG.[7] The Dutch national guideline on fetal monitoring provided by the NVOG does not advise on how the individual parameters of the CTG should be measured. Fetal heart rate can be monitored externally, or internally with a fetal scalp electrode. Uterine contractions can be monitored externally with an ultrasound transducer or with an electrode patch.[15] Internal tocodynamometry can be performed using an intrauterine pressure catheter. A Cochrane review by Bakker et al. shows no superiority of internal over external tocodynamometry in induced or augmented labor.[16]

The use of ST-analysis is not promoted, since its use will not decrease the incidence of intrapartum acidosis. However, its use is not discouraged either, since it may be cost-effective in comparison to the use of only CTG and fetal scalp blood sampling.[17-19] As a result, our nationwide survey on the diagnosis and management of intrapartum fetal distress in Dutch labor wards shows a large practice variation on the use of ST-analysis. In contrast, the use of fetal scalp blood sampling is rather uniform. In all but one hospital (98%), fetal scalp blood sampling facilities are available. However, ongoing discussion exists on the use of pH or lactate as a marker for fetal well-being during labor. The Cochrane review by East et al. concludes that fetal scalp blood lactate estimation is more likely to succeed than pH.[20] Nevertheless, due to the lack of long term neonatal follow up, no choice of preference has been made so far. Besides, there is no clear answer yet on the question which level of fetal scalp blood lactate indicates the need for intervention during labor.[21-24] As a consequence, in most Dutch hospitals fetal scalp blood pH is still used as a measure for fetal well-being during labor.

Regarding the use of intrauterine resuscitation techniques, a large practice variation was shown in the use of amnioinfusion and maternal hyperoxygenation. According to the Dutch guideline, the use of amnioinfusion is not helpful to improve neonatal outcome.[7] However, it may decrease the presence of variable decelerations in the fetal heart rate pattern. Therefore the use of this intervention is not promoted, nor discouraged. In 33% of the Dutch hospitals amnioinfusion is used in the presence of fetal distress. So far, no recommendations are made on the use of maternal hyperoxygenation in the Dutch guideline. In 58% of the hospitals, this intervention is commonly used to promote fetal oxygenation.

In almost all hospitals, discontinuation of oxytocin, maternal repositioning and administration of tocolytic drugs is common practice. The administration of tocolytic drugs, preferably atosiban, is actually recommended in the Dutch guideline.[7] Atosiban has a similar effect on uterine pressure as ritodrine, but has significantly less side effects on maternal condition.[25] However, the effect of atosiban on neonatal outcome is not investigated, in contrast to beta-mimetic drugs and ritodrine. A Cochrane review concludes that betamimetic therapy appears to improve abnormal fetal heart rate tracings.[26] They state that there is not enough evidence based on clinically important outcomes to evaluate the use of betamimetics for suspected fetal distress. Another systematic review suggests a positive effect of ritodrine, terbutaline, $MgSO_4$, orciprenaline and nitroglycerine on fetal well-being.[5] Tocolytic drugs may decrease the need for emergency delivery without increasing maternal and fetal adverse side-effects.[27]

The available literature to base practical recommendations on, is scarce. Therefore, local guidelines are typically based on results of small, non-randomized studies and expert opinions. Hence, the difference in delivery ward management regarding intrauterine resuscitation may be caused by the lack of strong evidence to promote or refuse certain techniques. Dutch labor wards use different national and international guidelines for their local protocol.

We believe the results are illustrative for the delivery ward management in our country. The response rate was 100%. Although it is very likely that most respondents are aware of the common delivery ward management in their hospitals, we cannot exclude that other staff members in certain cases practice other policies.

International guidelines

We aimed to compare the recommendations from the Dutch guideline on fetal monitoring and intrauterine resuscitation, with international guidelines. We managed to obtain eight international guidelines on intrapartum monitoring.[4,6,9-14] Five of them also advised on the use of intrauterine resuscitation techniques.[4,6,9,10,12] Canada, the United Kingdom and Australia & New Zealand have elaborate, evidence-based guidelines on antenatal and

intrapartum fetal surveillance.[6,9,10] These guidelines describe various fetal monitoring techniques, extensive CTG interpretation guidelines and management recommendations in case of non-reassuring fetal heart rate patterns. The Irish and American guidelines provide recommendations regarding intrauterine resuscitation, without an overview of the supporting literature.[4,12] Other guidelines we obtained were exclusively on fetal monitoring during labor, or on a specific intrauterine resuscitation technique, e.g. the Danish guideline on amnioinfusion.[28] We assume that more European countries do have national guidelines, but unfortunately we were not able to obtain more than eight guidelines for analysis.

By comparing the eight different guidelines, we identified various contradictory recommendations. For example, the Practice Bulletin of the ACOG recommends maternal hyperoxygenation in the presence of fetal distress, whereas RCOG in the United Kingdom advises against this intervention.[4,6] Also, amnioinfusion is recommended in Denmark, Canada and the United States, but advised against in the United Kingdom, Australia and New Zealand.[4,6,9,10,28] The Netherlands did not state an explicit recommendation on the use of amnioinfusion.[7]

Evidence regarding the effect of the various intrauterine resuscitation techniques is limited, and sometimes contradictory. As a consequence, guidelines are mainly based on low-level evidence and consensus. Also, it is not clear how long the effect of intrauterine resuscitation should be awaited, before an emergency delivery is indicated.

To come to funded recommendations, the effect of the various resuscitation techniques should be investigated in randomized controlled trials. The technique studied could be compared to expectant management, or to another resuscitation technique. Since most of the interventions have become 'common practice', and therefore cannot be withholded, it will be difficult to conduct a randomized controlled trial. In our hospital (Máxima Medical Center), we have started a randomized controlled trial to investigate the effect of maternal hyperoxygenation on fetal distress during labor (EudraCT number 2015-001654-15, Dutch Trial Register number 5461, Central Committee on Research Involving Human Subjects number NL53018.000.15). We hope more studies to investigate the benefit of other resuscitation techniques will follow and lead to clear and uniform recommendations.

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APPENDIX I.

Questionnaire regarding diagnosis and management of fetal distress during labor (original questions in Dutch)

1. Does your hospital have a delivery ward?
   A Yes
   B No (end of the questionnaire)

2. What techniques for fetal monitoring are used?
   A Cardiotocogram
   B Cardiotocogram and/or fetal scalp blood sampling
   C Cardiotocogram and/or fetal scalp blood sampling and/or ST-analysis
   D Other…

3. Is the cardiotocogram classified using a classification system?
   A Yes, the FIGO classification system is used
   B Yes, another classification system is used
   C No, no classification system is used

4. How fetal distress is diagnosed?
   A Suspicion due to an abnormal CTG
   B Confirmed using fetal scalp blood sampling
   C Confirmed using ST-analysis
   D Other…

5. Which action are undertaken in case of suspected fetal distress?
   A Confirmation of impaired fetal condition using fetal scalp blood sampling
   B Immediate delivery (vaginally assisted birth or cesarean section)
   C Application of intra-uterine resuscitation techniques

6. Which intrauterine resuscitation techniques are used in your hospital?
   A Discontinuation of oxytocin infusion
   B Use of tocolytic agents
   C Maternal repositioning
   D Amnioinfusion
   E Maternal hyperoxygenation
   F Other…

7. In case a tocolytic drug is administered, which drug and dose are used?
   A Ritodrine
   B Atosiban
   C Fenoterol
   D Other…
   Dose:

8. Are intra-uterine resuscitation techniques applied while waiting for an emergency cesarean section or vaginally assisted delivery?
   A Yes
   B No

9. If yes, which techniques are applied?
   A Discontinuation of oxytocin infusion
   B Use of tocolytic agents
   C Maternal repositioning
   D Amnioinfusion
   E Maternal hyperoxygenation
   F Other…

10. On what bases one decides which intervention is applied?
    A Based on a guideline
    B Based on my own experience/what I have learnt

11. In case intervention is based on a guideline, which guideline is used?
    A NVOG
    B RCOG
    C ACOG
    D Local guideline
    E Other…

12. Which interventions do *you* think are effective when applied for fetal distress?
    A Discontinuation of oxytocin infusion
    B Use of tocolytic agents
    C Maternal repositioning
    D Amnioinfusion
    E Maternal hyperoxygenation
    F Intravenous fluid administration (not for correction of hypotension)
    G Other…

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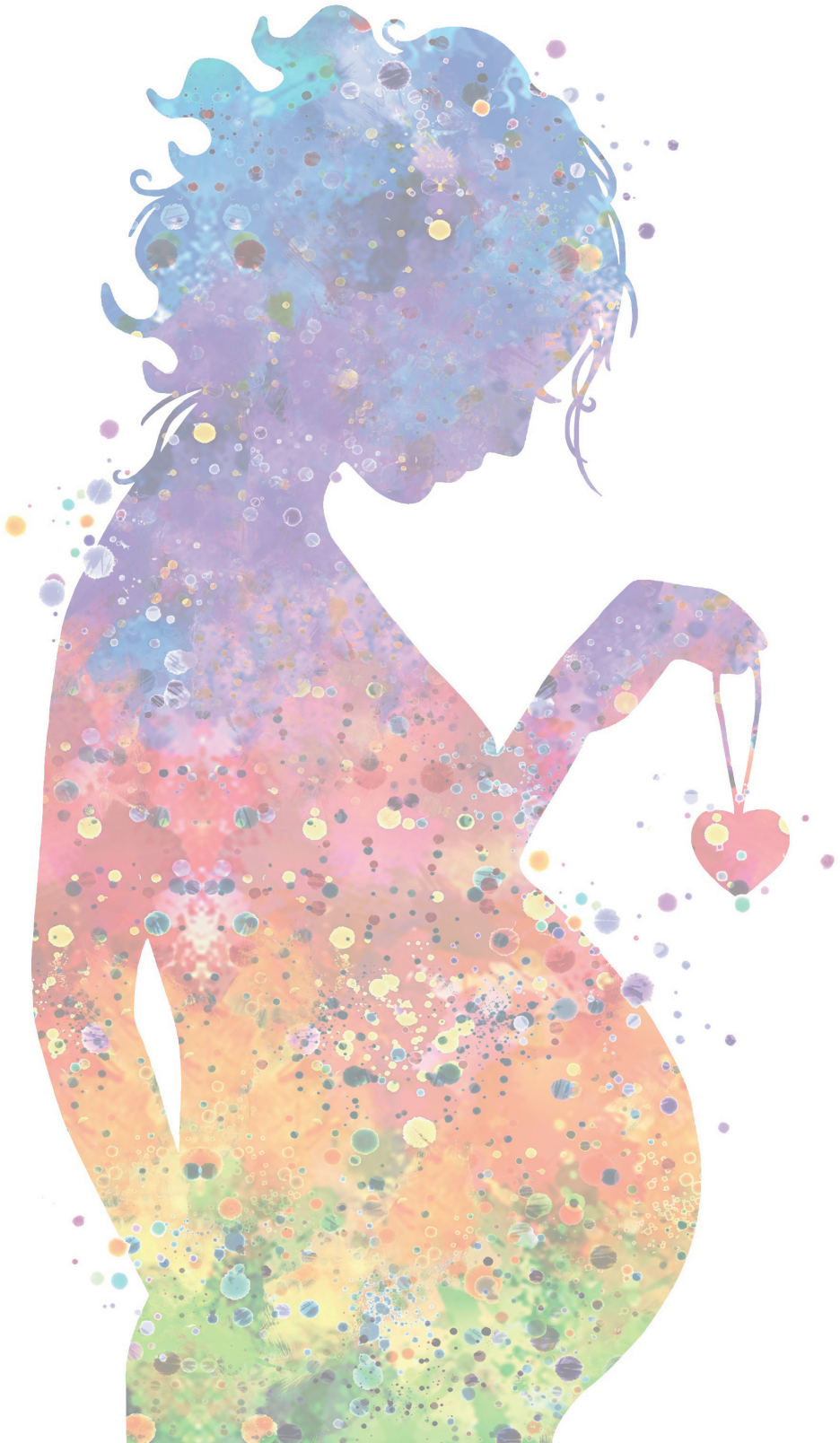

6

Intrauterine resuscitation during term labor by maternal hyperoxygenation: a randomized controlled trial (INTEREST O2)

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ABSTRACT

Background

Perinatal asphyxia is, even in developed countries, one the major causes of neonatal morbidity and mortality. Therefore, if fetal distress during labor is suspected, one should try to restore fetal oxygen levels, or aim for immediate delivery. However, studies on the effect of intrauterine resuscitation during labor are scarce. We designed a randomized controlled trial to investigate the effect of maternal hyperoxygenation on the fetal condition. In this study, maternal hyperoxygenation is induced for the treatment of fetal distress during the second stage of term labor.

Methods

This study is a single-center randomized controlled trial, performed in a tertiary hospital in The Netherlands. In case of a suboptimal or abnormal fetal heart rate pattern during the second stage of term labor, a total of 116 patients will be randomized to the control group, where normal care is provided, or to the intervention group, where before normal care 100% oxygen is supplied to the mother by a non-rebreathing mask until delivery. The primary outcome is change in fetal heart rate pattern. Secondary outcomes are Apgar score, mode of delivery, admission to the neonatal intensive care unit and maternal side effects. In addition, blood gas values and malondialdehyde are determined in umbilical cord blood.

Discussion

This study will be the first randomized controlled trial to investigate the effect of maternal hyperoxygenation for fetal distress during labor. This intervention should only be recommended as a treatment for intrapartum fetal distress, when improvement of the fetal condition is likely and outweighs maternal and neonatal side effects.

BACKGROUND

Labor contractions cause alterations in intrauterine pressure, and can thereby affect uterine and umbilical blood flow.[1-5] These fluctuations in blood flow towards the fetus can negatively influence oxygen flow and blood pressure.[1-5] Through chemo- and baroreceptor responses, these changes in fetal oxygenation and blood pressure affect fetal heart rate (FHR).[1,2,6,7] Hence, non-reassuring FHR patterns, for example, FHR decelerations, may be a sign of fetal hypoxia.[8-10] Prolonged fetal hypoxia may lead to an increased risk of fetal morbidity, including renal insufficiency, pulmonary hypertension, necrotizing enterocolitis and hypoxic–ischemic encephalopathy and fetal death.[11-12] A prospective cohort study of term neonates in 2010 showed that 48% of admissions to Neonatal Intensive Care Units (NICUs) of these neonates were related to perinatal asphyxia (defined by the authors as a 5 minute Apgar score <7). The neonatal mortality rate was 8% in this study, the largest proportion of which (71%, N = 12/17) was related to asphyxia.[13]

Methods to directly measure fetal oxygenation during labor are unavailable, while methods for the continuous intrapartum monitoring of pH, saturation (SpO_2), partial carbon dioxide pressure (pCO_2), and partial oxygen pressure (pO_2) are not yet suitable for clinical practice.[14-16] Therefore, the cardiotocogram (CTG), with occasional fetal scalp blood sampling (FSBS), is still the method of first choice to estimate fetal wellbeing during labor. The CTG has very good specificity but poor sensitivity for fetal wellbeing.[17] In other words, if the FHR pattern is reassuring the fetus is very likely to be well-oxygenated. However, when FHR patterns are non-reassuring, the fetal condition is unclear and fetal distress cannot be ruled out.

Instead of aiming for immediate delivery in the presence of suspected fetal distress, one may try to improve fetal oxygenation to avoid an invasive intervention. Several intrauterine resuscitation techniques are used in clinical practice and described in the literature.[18,19] However, robust evidence regarding their effect on neonatal outcome is limited.[18] One of the interventions that still raises discussion is the administration of additional oxygen to the mother to treat fetal distress during labor.[18,20-23]

Summary of findings from clinical studies

In the past decades, several studies have investigated the effect of maternal hyperoxygenation on maternal and fetal oxygenation. Indeed they found increasing maternal pO_2 and fetal SpO_2 and pO_2 levels,[24] but unfortunately these studies are mainly performed in the non-compromised fetus.[25-27] Furthermore, only a few non-randomized studies of poor quality have been performed in the distressed fetus.[28-32] These studies suggest an improvement in FHR patterns and fetal scalp pH when 100% oxygen is applied to the mother. Based on these publications, a Cochrane review from 2012 concludes that “there is not enough evidence to support the use of prophylactic oxygen therapy

for women in labor, nor to evaluate its effectiveness for fetal distress", due to the lack of randomized controlled trials (RCTs).[33]

An important concern in the use of maternal hyperoxygenation for fetal distress is the potential negative effect on umbilical cord pH. In a study by Thorp et al, 86 term parturients were randomized to receive additional oxygen or normal care, during the second stage of labor.[34] The main outcome measures were cord blood gas and co-oximetry values. The mean cord blood gas values did not significantly differ between the intervention and control group. However, they found significantly more arterial pH values <7.20 in the group receiving extra oxygen. The lowest arterial pH (pHa) value that was found was 7.09. They also found that the duration of oxygen therapy was inversely related to arterial cord pH, while Apgar scores and hospital admission rates did not differ between the groups. The authors concluded that prolonged oxygen treatment during the second stage of labor leads to a deterioration of cord blood gas values at birth. An important remark is the fact that in this study only patients with reassuring FHR patterns were included. Therefore, (ominous) fetal hypoxia at the start of oxygen delivery was very unlikely. Thus, this study did not address the effect of maternal hyperoxygenation in case of suspected fetal distress.

Another frequently stated argument to discourage maternal hyperoxygenation as standard care, is the potential increase in free oxygen radicals in both mother and fetus.[35,36] An increase in the markers for free oxygen radical production has been seen for the use of high fractions of inspired oxygen and in the presence of non-reassuring FHR patterns.[35-38] Also, lipid peroxide concentrations in arterial cord blood are higher after uncomplicated vaginal delivery compared with those after elective cesarean section.[39] To a certain degree, free oxygen radicals are physiological and known to be higher in the presence of several maternal and fetal conditions, such as preeclampsia, diabetes, smoking, intrauterine growth restriction and fetal distress.[37,39-42] The effect of maternal hyperoxygenation on free oxygen radical release, in response to non-reassuring fetal status, has not yet been investigated. What we do know is that neonatal resuscitation with 100% oxygen may lead to an increase in neonatal mortality and morbidity, including bronchopulmonary disease and retinopathy, mainly in premature infants.[43-46] However, the increase in fetal pO_2 due to maternal hyperoxygenation will never reach the levels obtained by the direct application of 100% oxygen directly to the fetus.[23] To our knowledge, the clinical implication of increased free radical production due to maternal hyperoxygenation has not been investigated. Studies that use maternal hyperoxygenation as a treatment for the growth restricted fetus did not report any harmful effects.[47,48]

With regard to the mother, some potential side effects have to be taken into account. The use of high fractions of inspired oxygen in the absence of tissue hypoxia may cause toxic effects as a result of oxidative stress.[49,50] This may for example lead to mucosal inflammation, hypoperfusion and pneumonitis.[51] A reversible vasoconstriction of

approximately 10% in the maternal brain has been described.[52] However, this is not expected to cause any harm.[53,54] Administration of 100% oxygen during labor is not investigated. However, it is well investigated for the treatment of cluster headaches, and no severe side effects (e.g. hypoventilation and fainting) were reported.[54]

Inhaling high fractions of inspired oxygen will increase the concentration of free oxygen radicals in maternal blood.[35] Despite the adverse effects of free oxygen radicals that have been described,[55] it is unlikely these will cause clinically relevant tissue damage due to the mature anti-oxidant system in the adult.[35,36] Also, the Dutch pharmacovigilance center Lareb has not been informed of any side effects due to oxygen therapy.[56]

Current recommendations on the use of maternal hyperoxygenation

Based on current knowledge, it is difficult to determine whether the beneficial effects outweigh the potential side effects. As a consequence, recommendations in international guidelines and use in clinical practice are non-uniform.[20] Maternal hyperoxygenation during labor is often used in the United States of America to increase oxygen transport towards the fetus.[21] The American College of Obstetricians and Gynecologists' (ACOG) guideline on fetal resuscitation recommends the administration of oxygen to the mother in case of fetal distress.[57] In contrast, the Royal College of Obstetricians and Gynaecologists explicitly states in their Green Top Guideline to not apply maternal oxygenation for reasons other than maternal hypoxia, until the beneficial effect is proven.[58] A recent discussion on benefit and harm of maternal hyperoxygenation in the American Journal of Obstetrics and Gynecology (AJOG) emphasises the current lack of evidence.[21,23] In fact, several reviews underline an urgent need for an RCT, investigating the effect of maternal hyperoxygenation on the fetal condition.[21-23,33]

METHODS

Aim

The aim of this study is to investigate the effect of maternal hyperoxygenation with 100% oxygen on the fetal condition during the second stage of labor, in the presence of suspected fetal distress during term labor. Also, we investigate the potential side effects, to formulate recommendations for international clinical practice and future research.

Study design

This study will be a single-center RCT, performed in a tertiary hospital in The Netherlands, comparing maternal hyperoxygenation for the treatment of fetal distress during the second stage of labor with conventional care. All procedures and timeframes are displayed in Figure 1 (according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)).[59] Additional file 2 contains the complete SPIRIT checklist.

Activity/ assessment	CRF[$] (Y/N)	Staff member	Time to complete (minutes)	Pre-study (screening/ consent)	Pre-study (randomization)	Study (during labor)	Study (post partum)	Post-study
Assessment of eligibility	No	Doctor/midwife/ (co)investigator	1	X				
Supply oral and written study information	No	Doctor/midwife/ (co)investigator	5	X				
Obtain and store informed consent	No	Doctor/midwife/ (co)investigator	3	X				
Classification of CTG* and randomization	Yes	Doctor/midwife/ (co)investigator	1		X			
Intervention group: apply O_2 by non-rebreathing mask	Yes	Obstetric nurse	1			X		
Fill in and store CRF[$]	Yes	Doctor/midwife/ (co)investigator	5					X
Draw umbilical cord blood and sent to lab	No	Doctor/midwife	3			X		
Store blood for future examination	No	Laboratory staff	5				X	
Register data on demographics, delivery and neonatal outcome in Research Manager	Yes	(Co)investigator	10					X
Analyse FHR[#] registrations	No	(Co)investigator, experts	15					X
Analyse cord blood for MDA[&]	No	Laboratory staff	?					X
Interim analysis	No	(Co)investigator	60					After including 58 participants
Report SAE/SUSARs	Yes	Principal investigator	?					As needed throughout protocol

Figure 1. The schedule of forms and procedures, according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).
[$]CRF = case report form, [*]CTG = cardiotocogram, [#]FHR = fetal heart rate, [&]MDA = malondialdehyde

Participants

The study population will be drawn from parturients, admitted to the labor ward of a tertiary hospital (Máxima Medical Center, Veldhoven, The Netherlands), where approximately 2200 deliveries occur annually, of which approximately 1900 term births. CTG and, if necessary, FSBS are generally used for fetal monitoring during labor. Maternal repositioning, discontinuation of administration of oxytocin, use of tocolytic drugs and intermittent pushing are common interventions to achieve intrauterine resuscitation, while amnioinfusion and maternal hyperoxygenation are never applied as standard care in our center.

Inclusion criteria

Pregnant women ≥ 18 years, in term labor, and with an intended vaginal delivery of a singleton in cephalic presentation can participate in this study.

Exclusion criteria

Exclusion criteria are determined with focus on the risk of excessive production of free oxygen radicals, and reducing the influence of other factors affecting FHR pattern. These are a recent use of any of the following medication: corticosteroids, antihypertensives, magnesium sulphate, amiodaron, opioids, adriamycin, bleomycin, actinomycin, menadione, promazine, thioridazine or chloroquine, or the use of tobacco, recreational drugs or alcohol during pregnancy. Parturients suffering from pre-existing cardiac disease, pulmonary disease with the use of medication, diabetes, hyperthyroidism or anemia (hemoglobin < 6.5 mmol/l or 10.5 gr/dL) will also be excluded. Fetal factors leading to exclusion are: suspected infection during labor (need for antibiotics), congenital malformations and normal or preterminal FHR pattern, or prolonged bradycardia (according to the modified FIGO classification, Figure 2).[60,61]

	Baseline heart frequency	Variability Reactivity	Decelerations
Normal CTG	• 110–150 bpm	• Accelerations • 5–25 bpm	• Early uniform decelerations • Uncomplicated variable decelerations (loss of <60 beats)
Intermediary CTG	• 100–110 bpm • 150–170 bpm • Short bradycardia episode <100 bpm for > 3 min <80 bpm for > 2 min	• >25 bpm (saltatory pattern) • <5 bpm >40 min	• Uncomplicated variable decelerations (loss of >60 beats)
Abnormal CTG	• A combination of 2 or several intermediary observations will result in an abnormal CTG • >170 bpm • Persistent bradycardia <100 bpm for > 10 min <80 bpm for > 3 min (without an increasing tendency)	• <5 bpm for > 60 min • Sinusoidal pattern	• Complicated variable decelerations with a duration of >60sec • Repeated late uniform decelerations
Preterminal CTG	• Total lack of variability (<2 bpm) and reactivity with or without decelerations or bradycardia		

Figure 2. The modified FIGO classification.

Patient recruitment and randomization

All patients eligible to be included in this study will antepartum be asked to participate when they visit the outpatient's clinic, or when they are admitted to the delivery ward. All patients will receive oral and written information about the study from the attending midwife, doctor or a co-investigator. After informed consent, and only in case of suboptimal or abnormal FHR patterns during the second stage of labor, randomization is performed using sealed, opaque envelops. The allocation sequence is computer-generated using random blocks of four or six patients.

Intervention and control group

Patients will randomly be assigned to one of the two arms of the study:

- Control group: normal care (according to the local standard) is provided, and preferably started at least 10 minutes after the onset a suboptimal or abnormal FHR pattern, according to the modified FIGO criteria (Figure 2).[60,61]
- Intervention group: in case of a suboptimal or abnormal FHR pattern according to the modified FIGO criteria, 100% oxygen is applied to the mother at 10l/min via a non-rebreathing mask, and continued until delivery. Co-interventions (normal care) may be initiated after 10 minutes of oxygen administration without a satisfactory effect on FHR, to investigate the effect of only maternal hyperoxygenation on FHR, without risking prolonged fetal hypoxia. In case a patient needs to undergo a cesarean section, oxygen administration will be continued until the fetus is born.

Obviously, in case the delivery room staff believes additional interventions should be applied for safety reasons, the study protocol can be overruled any time.

Study outcomes and data analysis

The primary outcome is the percentage reduction in the depth and duration of FHR deceleration in the intervention group in comparison with the control group. Secondary outcomes include fetal, neonatal and maternal outcomes.

Fetal outcome

FHR changes

Changes in specific features of the CTG including:

- Decelerations with loss of internal variability (beat to beat variability of <5 beats per minute (BPM))
- Decelerations in combination with tachycardia of bradycardia (> 160 or < 110 BPM)
- Unassignable baseline
- Phase-rectified signal averaging (PRSA); a relatively new technique to determine fetal heart rate variability, by estimating the accelerative (AC_{prsa}) and decelerative capacity (DC_{prsa}) of the fetal heart. This technique is explained in the articles by Bauer and Huhn.[62,63]
- Change in modified FIGO classification (Figure 2).[60,61]

In the next paragraph methodology regarding the comparison of FHR tracings and timeframes are described more detailed.

Neonatal outcome

This includes Apgar score, NICU admission, venous and arterial umbilical cord blood gas analysis (pH, lactate, base excess, pO_2 and pCO_2) and malondialdehyde, (MDA, a marker for free oxygen radical production) in arterial and venous umbilical cord blood. Information on neonatal admission is a standard part of the maternal hospital chart. Determination of 1- and 5-minute Apgar score and venous and arterial umbilical cord blood gas analysis (pH, lactate, base excess, pO_2 and pCO_2) are common practice. A cord blood gas analysis will be performed immediately after birth, by the ABL 90 flex blood gas analyzer (Radiometer Benelux BV, Zoetermeer, The Netherlands), in both venous and arterial cord blood. Two additional blood samples (one venous and one arterial sample) are drawn from the umbilical cord in heparin tubes, and immediately centrifuged and stored at the laboratory of Máxima Medical Center at -20°C. Once all samples are collected, they will be transported to the laboratory of Genetic and Metabolic Diseases of the Academic Medical Center Amsterdam, The Netherlands, where total (free and bound) MDA will be determined as the 2,4-dinitrophenylhydrazine (DNPH) derivative. A stable isotopically labelled analogue ($^2H_2$-MDA) will be added as internal standard, where after alkaline hydrolysation, deproteinisation and derivatisation with DNPH, and MDA-hydrazone will be analyzed by HPLC-MS/MS and positive electrospray. Samples will be injected on an LC-18-DB analytical column (250 × 4.6 mm, 5 µm particles, Supelco) hyphenated to a Quattro Premier XE mass spectrometer (Waters Corporation, Milford, MA), using an Acquity UPLC system (Waters Corporation, Milford, MA). Analytes and internal standard will be eluted with acetonitrile/water/acetic acid (50/50/0.2) and detected in multiple reaction monitoring mode for the transitions m/z 235 → m/z 159; m/z 237 → m/z 161.

Maternal outcome

Maternal outcome measures include the mode of delivery, side effects and reasons for discontinuation of oxygen administration. Side effects include a headache, dizziness, discomfort of the non-rebreathing mask and any other complaint mentioned by the participant. The delivery room staff will register on the case report form (CRF) if the parturient experiences any side effects and/or if there are reasons for eventual discontinuation of oxygen administration. Also, a short questionnaire will be used to investigate experiences of all the participants with this study, to gain insight in how laboring women experience receiving additional oxygen by a non-rebreathing mask, compared to receiving normal care.

Analysis of outcome measures regarding FHR pattern

Changes in FHR pattern

The digital CTG tracings will be extracted from Chipsoft EZIS (Amsterdam, The Netherlands) and analyzed using Matlab 2015a (MathWorks Inc USA). For the computerized CTG analysis we will use a custom-made algorithm, based on the OxSys system,[64] that will first be validated by an expert panel. This expert panel will also manually classify the CTG to one of the FIGO categories.[60,61] Regarding the analysis of specific CTG features, we searched the literature for CTG features that are likely related to neonatal outcome. A large variety of CTG features have been investigated in relation to neonatal outcome, with varying results. However, three features are consistently mentioned as related to neonatal outcome:

- decelerations with loss of internal variability
- decelerations in combination with tachycardia or bradycardia
- periods with unassignable baseline [3,60,64-71]

Besides, AC_{PRSA} and DC_{PRSA} turned out to predict acidemia better than short-term variation.[62,72,73] We therefore include this parameter in as an outcome measure.

What is the timeframe of interest?

All patients serve as their own control with changes in FHR being compared before and after the start of the study protocol, irrespective of whether the patients belonged to the control or the intervention group. Additionally, results of the intervention group and control group will also be compared.

For the analysis where patients serve as their own control, the timeframes of interest for outcomes related to changes in FHR are as follows:

- Control group: 10 minutes before and after the start of the study protocol. In total 20 minutes of data will be analyzed (Figure 3).
- Intervention group: 10 minutes before the start of the study protocol up to 15 minutes after start of the study protocol. The timeframe of interest after the start of the study protocol is determined as the period between 5 and 15 minutes after maternal hyperoxygenation is initiated, motivated by the expectation that it will take 5 minutes for maternal pO_2 to increase to a maximum of approximately 475 mmHg.[24] After that, the effect of the intervention will be observed for 10 minutes. In total 20 minutes of data will be analyzed (Figure 4).

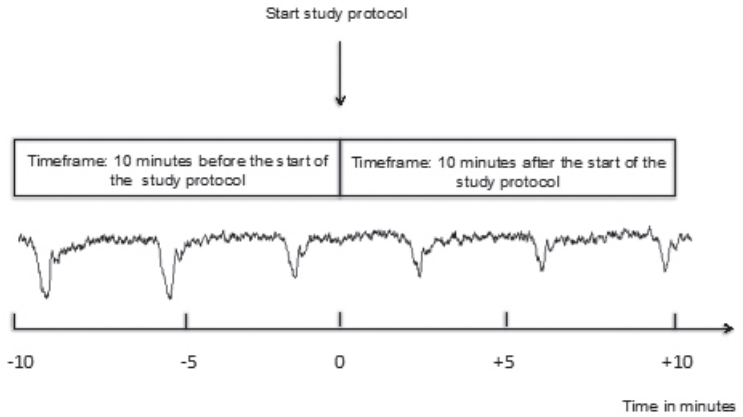

Figure 3. The timeframe of interest for analysis of outcome measures where patients serve as their own control: the control group.

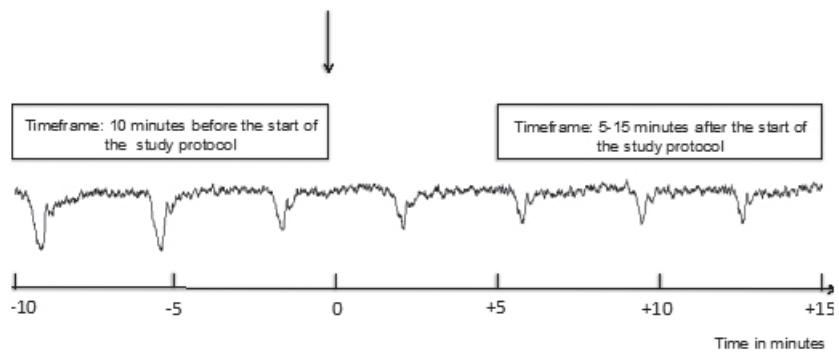

Figure 4. The timeframe of interest for analysis of outcome measures where patients serve as their own control: the intervention group.

These periods are established because during this period, maternal hyperoxygenation can be compared to no treatment. Furthermore, we will also compare the periods from the start of the study until birth, although these results may be influenced by other interventions that may have been applied.

Other study endpoints and parameters

Duration of the second stage of labor, duration of time for which supplemental oxygen was received, baseline characteristics (infant sex, gestational age and birth weight, maternal age and parity) are recorded.

Hypothesis

We hypothesize that maternal hyperoxygenation will improve FHR, without any severe maternal side effects. We do not expect a difference in rates of vacuum-assisted delivery or secondary cesarean sections, nor Apgar scores or umbilical cord pH values, due to the relatively small sample size. Furthermore, we expect larger concentrations of MDA in the intervention group than in the control group.

Handling and storage of data and documents

Data will be handled anonymously and we will adhere to the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, WBP). A secured subject identification code list will be used to link a study number to a patients name and date of birth. This file is password protected available only to the main investigator (LB). All other information will contain only the study number and no data directly referring to the patient. Fetal blood gas values will be stored in the neonates' hospital chart since this is part of conventional care. Laboratory results regarding markers for free oxygen radicals will be coded and will therefore be anonymous. All data will be stored for 15 years, in accordance with the Good Clinical Practice guidelines.

Statistical analysis

Sample size calculation

The study consists of two study groups: one group with suboptimal FHR patterns, and one group with abnormal FHR patterns. We aim for 90% power and a level of significance of 0.05 in both groups. In one small, non-randomized study, a reduction in FHR decelerations (type II dips) of 50 to 100% was noted.[28] This is the only study that reports on FHR changes as a result of maternal hyperoxygenation. Based on the available literature, we expect at least 50% improvement in the oxygen-group and 0% in the control-group in both suboptimal and abnormal FHR patterns.[28] We estimated a mean improvement of 50% with a standard deviation of 50% in each group. A power analysis performed in G*Power 3.0.10 (Kiel University, Germany) for a two-tailed Mann Whitney test (assuming that data will not be equally distributed) resulted in a sample size of 58 patients in each study group, given an anticipated 20% of missing data. Since we have two separate study groups (suboptimal and abnormal FHR group) we need 116 patients to participate.

Data analysis

SPSS (version 24, IBM, Armonk, NY) will be used to perform statistical analysis of the study results. Assuming non-normal distribution, the primary clinical outcome will

be analyzed with a Mann Whitney U test for differences between the intervention and control group, and a Wilcoxon Matched-Pairs test for changes within the same participant. When outcome data is found to be normally distributed, independent samples t-tests (two-tailed) will be used to analyze differences between the intervention and control group, and paired t-tests for changes within the same participant. Outcome measures will be calculated for the combined group and the subgroups of suboptimal and abnormal FHR tracings, and for small for gestational age (SGA, growth percentile <p10) and appropriate for gestational age (AGA) neonates. In the intervention group, oxygen may not be applied due to practical concerns such as very quick progression of labor. Therefore, we will perform both per-protocol and intention-to-treat analysis. In the per-protocol analysis parturients that actually received oxygen will be compared to those who did not receive oxygen. Besides, unjust inclusions will be excluded from this analysis.

Interim analysis

On account of safety concerns, an interim analysis will be performed when 50% of the patients are included in the study. In this analysis, we compare the number of neonates with a 5- minute Apgar score < 7 and/or pHa< 7.05, the number of admission to NICU and perinatal death in both groups (all neonates that received oxygen in both suboptimal and abnormal CTG group versus 'conventional care' group). In case the interim analysis shows a significant difference, we will terminate the study. This interim analysis is performed exclusively for safety reasons: since the primary outcome measure (fetal heart rate) will not be analyzed during the interim analysis, and power analysis is based on the primary outcome, adjustment of the significance level is not required.

Public disclosure and publication policy

All investigators agree to publish the study results in an international peer-reviewed journal, even if the results do not correspond to the hypothesis as stated in the methods section of the protocol. The results will be offered for publication after all the investigators agree on the content of the article. The full protocol (version 8, date 1st March 2017) is available upon request.

DISCUSSION

This study is the first RCT to investigate the effect of maternal hyperoxygenation for fetal distress during labor.[18,33] So far, the effects of supplemental oxygenation in the presence of FHR abnormalities have only been investigated in small, non-randomized studies. Due to the lack of concrete results from clinical trials, it is hard to compare the beneficial effects of maternal hyperoxygenation to the potential side effects. As a result, recommendations on the use this intervention for fetal distress in international guidelines are non-uniform.[20] Thus, the results of this study will help in filling an internationally recognized 'research gap'.

We believe patient safety is carefully addressed in this study, and ethical concerns are limited. One of the major concerns of administering high fractions of oxygen, is the increase in free oxygen radicals. Whether this has a clinical effect remains unclear. We excluded all patients with a higher a priori risk of exposure to increased free oxygen radical levels from this study.

Both practical and safety issues led to limitations of this study. An important limitation is the primary outcome measure. We recognize that changes in FHR as a primary outcome measure is not optimal since FHR does not accurately reflect fetal oxygenation and acid-base balance.[60,75,76] However, we believe this is the 'best available' method to record changes in the fetal condition during labor. Furthermore, we assume that if no beneficial effect on FHR can be shown, an improvement in neonatal outcome is unlikely. Ideally, neonatal outcome measures such as Apgar score and umbilical cord pH are the outcome measures of first choice. However, a study with appropriate power to address these outcome measures would need a very large sample size. Since the potentially harmful effects have not been properly investigated yet, we chose to not expose a large group of women and their fetuses to this intervention. If a positive effect on FHR pattern without severe side effects can be confirmed by this study, we will perform a larger multicenter RCT to investigate the effect on Apgar score and cord blood gas values.

In this study, we focus on the fetal condition during the second stage of labor and short-term neonatal outcome. This implies that abnormalities in FHR patterns during the first stage of labor are not taken into account. We believe that the randomization process will limit its influence. With regard to the neonatal period, we did not arrange long-term follow-up, as we do not expect any clinically relevant side effects that can be attributed to maternal hyperoxygenation. Besides, the sample size is too small to draw firm conclusions on long-term neonatal effects in this study.

Power analysis of the current study is based on the expected effect on the primary outcome measure and is not powered to find any significant differences in Apgar score and umbilical cord blood gas values. In the power analysis, we used an expected improvement in deceleration depth and duration of 50%. This value is based on small, non-randomized studies, and may be overestimated. On the other hand, this is the only available data. Also, we believe it is unlikely that a limited improvement in deceleration depth and duration has clinical relevance. The sample size is calculated for each of subgroups of suboptimal and abnormal FHR tracings. We believe it is important to assess the effect of the intervention in these subgroups as fetuses having lower initial pO_2 levels may profit more from maternal hyperoxygenation.[29]

Regarding the subgroups of AGA and SGA infants, we did not increase our sample size to reach an adequate number of participants in the SGA group. Nevertheless, we find

it interesting to see whether there is a different effect of maternal hyperoxygenation in SGA compared to AGA infants.

Due to organizational challenges, it is not possible to conduct a double-blinded trial. Hence patients and delivery room staff are not blinded to the patients' allocation to a study group and may lead to observer bias. However, analysis of FHR tracings will be done using a computerized algorithm and the investigators judging the CTGs and secondary outcome measures are blinded to the study arm, to minimize bias.

To investigate the effect of maternal hyperoxygenation in the presence of fetal distress on the release of free oxygen radicals, MDA is estimated in umbilical cord blood. MDA is the peroxidation product of membrane polyunsaturated fatty acids. We chose to measure this marker for oxidative stress because it is used in former studies performed during labor and it is related to vaginal birth, non-reassuring FHR tracings, maternal hyperoxygenation and acidemia in arterial cord blood.[36,37,39,41] We realize that differences in values in umbilical cord blood may be confounded by mode and duration of delivery; therefore, we will correct the results for the mode of delivery. A practical ground to choose this marker is that this is the only marker for oxidative stress that can be accurately estimated in Dutch laboratories. In the intervention group, oxygen administration will be continued until delivery to enable analysis of its effect on cord blood gas values and MDA.

Despite some important limitations of this study, we believe this is the best possible way to perform a study while restricting safety issues. If the results do not show any improvement in FHR, we believe maternal hyperoxygenation should not be used as a treatment for fetal distress. However, if a beneficial effect is demonstrated, we will design a multicenter RCT to investigate the effect on neonatal outcome.

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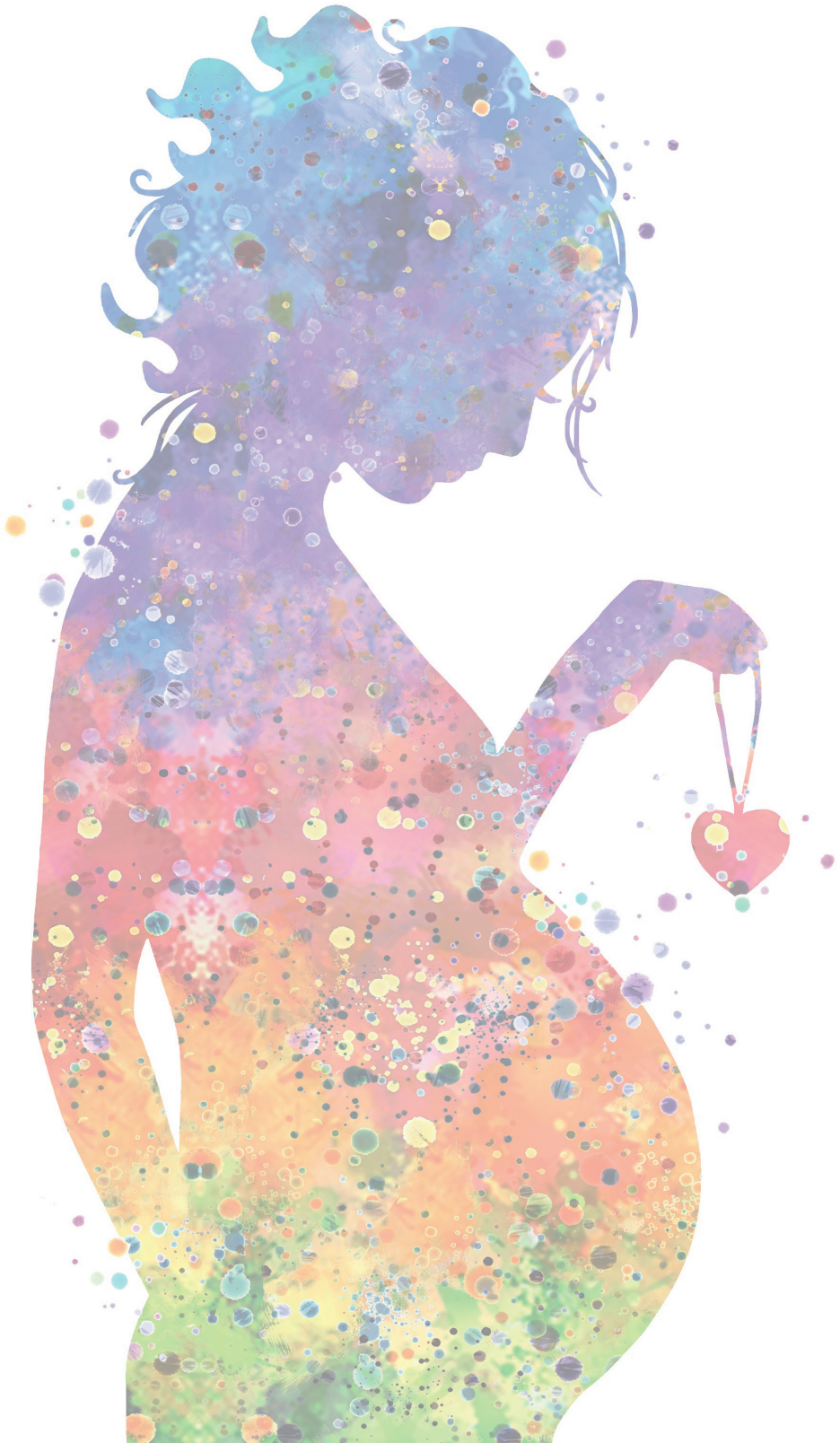

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The effect of intrauterine resuscitation by maternal hyperoxygenation on perinatal and maternal outcome: a randomized controlled trial

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ABSTRACT

Background

Maternal hyperoxygenation is widely used during labor as an intrauterine resuscitation technique. However, robust evidence regarding its beneficial effect and potential side effects is scarce and previous studies show conflicting results.

Objective

To assess the effect of maternal hyperoxygenation upon suspected fetal distress during the second stage of term labor on fetal heart rate (FHR), neonatal outcome, maternal side effects, and mode of delivery.

Study design

In a single-center randomized controlled trial in a tertiary hospital in The Netherlands, participants were randomized in case of an intermediary or abnormal FHR pattern during the second stage of term labor, to receive either conventional care or 100% oxygen at 10 L/min until delivery. The primary outcome was the change in FHR pattern. Prespecified secondary outcomes were Apgar score, umbilical cord blood gas analysis, neonatal intensive care unit admission, perinatal death, free oxygen radical activity, maternal side effects, and mode of delivery. We performed subgroup analyses for intermediary and abnormal FHR, and for small for gestational age fetuses.

Results

From March 2016 through April 2018, 117 women were included. FHR patterns could be analyzed in 71 women. Changes in FHR (defined as improvement, equal, or deterioration) in favor of maternal hyperoxygenation were significant (OR 5.7, 95% CI 1.7-19.1) using ordinal logistic regression. Apgar score, umbilical cord blood gas analysis, free oxygen radicals, and mode of delivery showed no significant differences between the intervention and control group. Among women with an abnormal FHR, there were fewer episiotomies on fetal indication in the intervention group (25%) than in the control group (65%, *P*<0.01).

Conclusion

Maternal hyperoxygenation has a positive effect on the FHR in the presence of suspected fetal distress during the second stage of labor. There was no significant difference in the mode of delivery or neonatal outcome, however, significantly fewer episiotomies on fetal indication were performed following maternal hyperoxygenation in the subgroup with abnormal FHR pattern.

INTRODUCTION

Maternal hyperoxygenation is widely used to improve the fetal condition in case of suspected fetal distress during labor.[1-3] However, robust evidence regarding its effect is scarce and conflicting, and recommendations in international guidelines are inconsistent.[4-6]

Several small, non-randomized studies in distressed fetuses show an improvement in fetal heart rate (FHR) pattern or fetal scalp pH as a result of maternal hyperoxygenation.[7-12] Fetuses with the lowest initial oxygen saturation appear to benefit the most.[9]

In contrast, other studies report potentially harmful effects of prophylactic use of maternal hyperoxygenation,[13-16] such as significantly more arterial cord blood pH levels <7.20 after maternal hyperoxygenation.[15] A recent RCT among distressed fetuses during labor with >6cm cervical dilation (i.e. combined first and second stage of labor) showed no difference in umbilical artery lactate after maternal hyperoxygenation.[17]

Another argument against maternal hyperoxygenation for intrauterine resuscitation is the potential increase in free oxygen radicals, potentially causing cell-damage.[16,18,19] Previous research shows that the production of free oxygen radicals is increased in case of fetal distress, and after inhalation of high fractions of oxygen in the presence of a normal fetal condition.[20] The effect of maternal hyperoxygenation for non-reassuring fetal status on free oxygen radical activity has not been investigated yet.

To our knowledge, there are no RCTs studying the effect of maternal hyperoxygenation in the presence of suspected fetal distress only including women during the second stage of labor. Several reviews underline the need for such a study.[1-3] However, before the safety of maternal hyperoxygenation has been further investigated, it is not desirable to perform an RCT powered for neonatal morbidity, requiring a very large study population.[2] Change in FHR could serve as a surrogate outcome, because a non-reassuring pattern of FHR is considered to be indicative of potential fetal hypoxia.[21-24]

Prior to setting up a clinical trial, we first investigated the effect of maternal hyperoxygenation in the distressed fetus with a mathematical model. Simulations with this model indicate that maternal hyperoxygenation leads to an increase in pO_2 in all placental compartments leading to an increased fetal oxygenation and amelioration of the FHR pattern.[25]

Therefore we performed an RCT in which our objective was to assess the effect of maternal hyperoxygenation in case of suspected fetal distress during the second stage of term labor on FHR, neonatal outcome, maternal side effects, and mode of delivery. We hypothesize that maternal hyperoxygenation will improve FHR, without any severe side effects.

MATERIALS AND METHODS

Study design

This RCT was conducted in a tertiary teaching hospital in The Netherlands. The study protocol has been published previously.[26] We included women aged ≥18 years, in term labor, with an intended vaginal delivery of a singleton fetus in cephalic presentation.

The exclusion criteria were determined with the focus on the risk of excessive free oxygen radical production as well as on reducing the influence of other factors that could affect FHR.

Exclusion criteria were: use of tobacco, recreational drugs, or alcohol during pregnancy, pre-existing cardiac disease, pulmonary disease requiring medication, diabetes, hyperthyroidism, anemia (hemoglobin <10.5 gr/dL) or recent use of corticosteroids, anti-hypertensives, magnesium sulphate, amiodarone, opioids, adriamycin, bleomycin, actinomycin, menadione, promazine, thioridazine, or chloroquine. Fetal factors leading to exclusion were congenital malformations, signs of infection during labor requiring antibiotics, normal or pre-terminal FHR pattern, or prolonged bradycardia according to the modified International Federation of Gynecology and Obstetrics (FIGO) classification (Table 1).[27,28]

Table 1. Fetal heart rate classification according to modified FIGO criteria, adapted from Yli et al.[28]

	Baseline heart frequency	FHR variability and reactivity	FHR decelerations
Normal FHR	• 110–150 bpm	• Accelerations • 5–25 bpm	• Early uniform decelerations • Uncomplicated variable decelerations (loss of < 60 beats)
Intermediary FHR	• 100–110 bpm • 150–170 bpm • Short bradycardia episode < 100 bpm for > 3 minutes < 80 bpm for > 2 minutes	• Saltatory pattern (> 25 bpm) • < 5 bpm for > 40 minutes	• Uncomplicated variable decelerations (loss of > 60 beats)
A combination of two or several intermediary observations will result in an abnormal FHR classification			
Abnormal FHR	• > 170 bpm • Persistent bradycardia < 100 bpm for > 10 minutes < 80 bpm for > 3 minutes (without an increasing tendency)	• < 5 bpm for > 60 minutes • Sinusoidal pattern	• Complicated variable decelerations with a duration of > 60 seconds • Repeated late uniform decelerations
Pre-terminal FHR	• Total lack of variability (< 2 bpm) and reactivity with or without decelerations or bradycardia		

Bpm = beats per minute. FHR = fetal heart rate.

Intervention and randomization

All women eligible were asked antepartum to participate during outpatient visits or when they are admitted to the delivery ward before the delivery started. In the presence of suspected fetal distress during the second stage of labor, as defined by intermediary or abnormal FHR pattern according to the modified FIGO classification,[27] women were randomized to receive either maternal hyperoxygenation with 100% oxygen at 10 L/min delivered by a non-rebreathing mask (fraction of inspired oxygen approximately 0.80)[29] until delivery (intervention group) or conventional care according to local standards without maternal hyperoxygenation (control group). Eligible women were assigned a sealed opaque envelope with treatment allocation, which was opened during the second stage of labor in case of intermediary or abnormal FHR patterns, as classified by the midwife, resident, or obstetrician on duty. Unopened envelopes were reused.

In case co-interventions were required, they were preferably initiated 10 minutes after randomization. A computer-generated allocation sequence is used with random blocks of four or six patients. Stratification was applied for intermediary or abnormal FHR.

Primary outcome

The primary outcome was the change of FHR pattern after randomization into the study. As part of the primary outcome, the depth and duration of decelerations will be analyzed using a computerized algorithm,[26] the results of which will be published separately. For this report, we analyzed the change in FHR as evaluated by clinicians. An expert team of three blinded gynecologists classified the FHR according to the FIGO classification.[27] The time-frame of interest was 10 minutes before and the period 5 to 15 minutes after start of the study protocol (Figure 1). In case of discrepancy, all three reached consensus by discussion. The change in FHR FIGO classification was categorized as deteriorated, equal or improved after the start of the study protocol (for example, when FHR was classified as *abnormal* before start of the study and subsequently classified as *intermediary* or *normal* after start of the study, the change was categorized as improved FIGO classification).

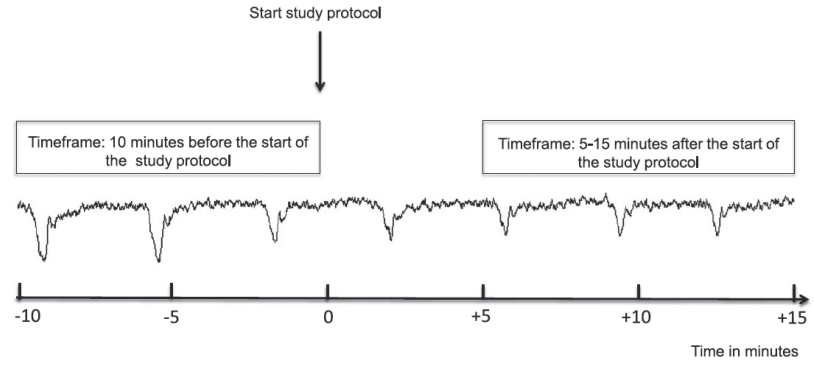

Figure 1. Time-frames of interest. The time-frames of interest for analysis of outcome measures where patients serve as their own controls.

Secondary outcomes

Neonatal outcomes included 1- and 5-minute Apgar score, venous and arterial umbilical cord blood gas (UCBG) values (pH, base excess, pCO_2), neonatal intensive care unit (NICU) admission and perinatal death. Analysis of UCBG was performed using the ABL90FlexPlus blood gas analyzer (Radiometer Benelux BV, Zoetermeer, The Netherlands). To assure validation of accurate paired UCBG samples, the Modified Westgate-Criteria were used.[30,31] In case only one valid sample was available, this was categorized as venous as suggested by White et al..[30]

Due to the brief lifespan of free oxygen radicals, it is extremely difficult to detect these directly.[32] Therefore, we measured Malondialdehyde (MDA) as a surrogate marker of free oxygen radical activity. MDA, a by-product of lipid peroxidation, is considered a non-invasive biomarker for free radical damage.[20] To assess MDA, two additional blood samples (one venous and one arterial) were drawn from the umbilical cord in heparinized tubes and immediately centrifuged and stored at −20°C. Samples were analyzed in duplo by stable isotope dilution with HPLC-tandem mass-spectrometry (Quattro Premier XE (Waters, Milford, MA, USA), and means were determined.

Maternal outcomes included mode of delivery, patient self-reported side effects of oxygen admission, and reasons for discontinuation

Statistical analyses

The sample size calculation was described in detail in the published protocol.[26,33] To detect the expected effect with an α of 0.05 and 90% power, a sample size of 96 was required. To accommodate for 20% missing data, we planned to enroll 116 women. IBM SPSS Statistics software (version 25; IBM, Armonk, NY, USA) was used for the statistical analyses. Change in FHR was analyzed using ordinal logistic regression. A kappa for multiple raters was calculated.[34] For comparison of continuous variables, an independent T-test or Mann-Whitney U test was used as appropriate. For categorical variables, the χ^2-test or Fisher's exact test was used as appropriate. $P<0.05$ for a 2-tailed test was considered significant.

The analyses were performed for the overall study population, as well as for the subgroups of intermediary FHR pattern, abnormal FHR pattern, and small for gestational age (SGA) fetuses (<10th percentile). The primary analyses were intention-to-treat. We anticipated that in some cases it might not be possible to apply oxygen according to the study protocol, due to practical concerns. Therefore, we also performed per-protocol analyses, excluding women receiving oxygen for <5 minutes, since the optimal effect of maternal hyperoxygenation cannot be reached within that period.[35] Furthermore, we also performed a sensitivity analysis to address possible confounding issues due to missingness.

Interim analysis

A pre-planned interim analysis was performed after 50% of the women were included to investigate potential safety issues regarding oxygen administration. There were no significant differences in the number of neonates with 5-minute Apgar score <7, arterial umbilical cord blood pH <7.05, NICU admissions, or perinatal deaths between the intervention and control group.

RESULTS

Between March 2016 and April 2018, a total of 376 women gave informed consent for the study. Of those, 117 women developed abnormal or intermediary FHR during the second stage of labor and were therefore randomized into the study. A total of 57 women were assigned to receive oxygen and 60 women were assigned to receive conventional care (CONSORT flow diagram, Figure 2).
The treatment groups were comparable regarding baseline characteristics (Table 2).

Within the first 10 minutes after randomization, 10 women (8.5%) received additional intrauterine resuscitation techniques: eight (13.3%) in the control group and two (3.5%) in the intervention group (P=0.10). These interventions included maternal repositioning, discontinuation of pushing, and adjustment of oxytocin dosage.

FHR pattern

For all women, FHR was available until birth. Since 46 women (39%) delivered within 15 minutes after enrollment, the FHR data sets were not complete for the post-study time-frame of interest (Figure 1), hence no pre-post analysis could be performed for this group. From 71 of 117 women (61%), the FHR pattern was available for the complete pre and post randomization time-frames of interest and, therefore, change in FHR pattern could be determined. The blinded gynecologists had discrepancy in FHR analyses in 25 cases (35%). The overall kappa was 0.54 [95% CI 0.41-0.68]. To this end, consensus on the final FIGO classification was reached by discussion between all three physicians.

Improvement of FHR was seen over four times more often in the intervention group compared to the control group (2.9 % vs. 13.9%, Table 3). Furthermore, deterioration of FHR was seen four times less often in the intervention group than in the control group (8.3% vs 34.3%). These changes in FHR were significant with an odds ratio (OR) of 5.7 (95% CI 1.7-19.1). None of the subgroup analyses for changes in FHR showed significance.

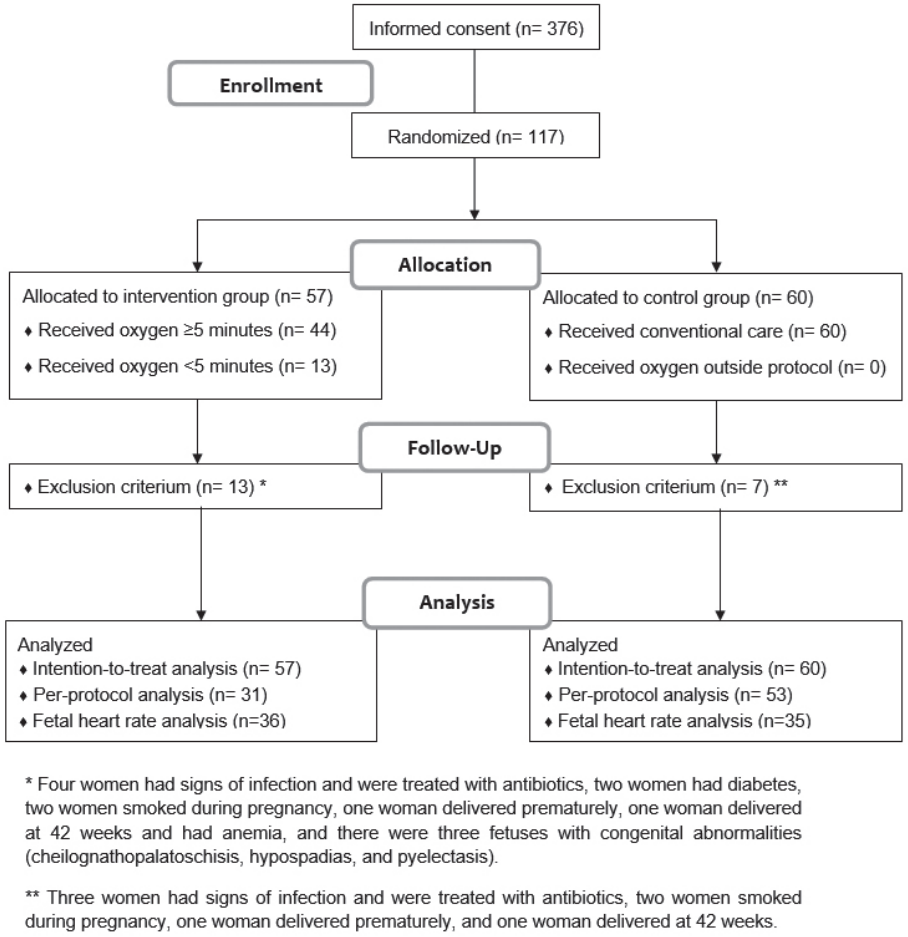

Figure 2. Trial flow diagram. A total of 117 women were allocated to the intervention or control group. Both an intention-to-treat and per-protocol analysis were performed. For the FHR analysis, 71 women were eligible based on availability of complete FHR time-frames.

Table 2. Patient characteristics of women randomized to hyperoxygenation treatment or conventional treatment.

	Maternal hyperoxygenation n=57	Conventional care n=60
Maternal age (years)	31.8 ± 4.2	30.7 ±3.4
Gestational age (days)	279 ±9.0	280 ±8.8
Parity ≥1	22 (38.6%)	27 (45%)
BMI (kg/m2)	25 ± 4.7	24 ± 5.0
Fetal sex male	30 (52.6%)	26 (43.3%)
Birthweight (grams)	3510 ± 471.7	3541.4 ±560.2
SGA	7 (12.3%)	5 (8.3%)
Intermediary FHR pattern	25 (43.9%)	34 (56.7%)
Abnormal FHR pattern	32 (56.1%)	26 (43.3%)

Data are mean±SD or n (%). BMI = body-mass index, SGA = small for gestational age, FHR= fetal heart rate

Table 3. Changes in FHR according to FIGO classification following maternal hyperoxygenation versus conventional care in the total study population.

	Deterioration FHR	Equal FHR	Improvement FHR	*Odds ratio (95% CI)*
Total study population (n=71)				
Maternal hyperoxygenation (n=36)	**3 (8.3%)**	**28 (77.8%)**	**5 (13.9%)**	**5.7 (1.7-19.1)**
Conventional care (n=35)	**12 (34.3%)**	**22 (62.9%)**	**1 (2.9%)**	
Abnormal FHR (n=34)				
Maternal hyperoxygenation (n=20)	1 (5.0%)	15 (75%)	4 (20%)	5.2 (0.9-30.2)
Conventional care (n=14)	4 (28.6%)	9 (64.3%)	1 (7.1%)	
Intermediary FHR (n=37)				
Maternal hyperoxygenation (n=16)	2 (12.5%)	13 (81.3%)	1 (6.3%)	5.0 (0.9-27.3)
Conventional care (n=21)	8 (38.1%)	13 (61.9%)	0	
SGA (n=9)				
Maternal hyperoxygenation (n=6)	1 (16.7%)	3 (50%)	2 (33.3%)	4.5 (0.2-84.6)
Conventional care (n=3)	1 (33.3%)	2 (66.7%)	0	

Data are n (%).CI= confidence interval. FHR= fetal heart rate. SGA = small for gestational age. Odds ratio of ordinal regression analysis

Neonatal outcome and mode of delivery

Four neonates had 5-minute Apgar score <7, three in the control group (5.0%), and one (1.8%) in the intervention group (*P*=0.62, Table 4). In the intervention group 13 neonates (28.9%) had arterial cord blood pH <7.20, compared to 22 (41.5%) in the control group (*P*=0.19). No neonatal deaths occurred in this study.

Table 4. Neonatal outcome and mode of delivery following maternal hyperoxygenation or conventional care in the intention-to-treat analysis.

Outcome parameter	Maternal hyperoxygenation	Conventional care	*P*
Neonatal outcome			
Median 1-minute Apgar score ¥ [n= 57 O2/ 60 control]	9 (8.5-9)	9 (8.25-9)	0.77
Neonates with 1-minute Apgar score <5 ¶ [n= 57 O2/ 60 control]	4 (7%)	4 (6.7%)	1.00
Median 5-minute Apgar Score ¥ [n= 57 O2/ 60 control]	10 (10-10)	10 (10-10)	0.13
Neonates with 5-minute Apgar score<7 ‡ [n= 57 O2/ 60 control]	1 (1.8%)	3 (5.0%)	0.62
Median arterial pH ¥ [n=45 O2/ 53 control]	7.22 (7.19-7.26)	7.20 (7.16-7.27)	0.35
pH arterial <7.05 ‡ [n= 45 O2/ 53 control]	1 (2.2%)	0	0.46
Median venous pH ¥ [n= 57 O2/ 60 control]	7.30 (7.26-7.34)	7.30 (7.26-7.35)	0.94
Arterial base excess ¥ [n=45 O2/ 51 control]	-6 (-8/-3)	-6 (-8/-4)	0.69
Arterial pCO_2 ¥ [n=45 O2/ 52 control]	56 (51.5-59.5)	57 (52-62)	0.54
Arterial Malondialdehyde ¥ [n=41 O2/ 48control]	4.45 (3.68-5.35)	4.15 (3.40-4.75)	0.15
Venous Malondialdehyde § [n=45O2/ 54control]	4.67±1.27	4.38±1.15	0.21
Neonatal Intensive Care Unit admissions ‡ [n= 57 O2/ 60 control]	1 (1.8%)	2 (3.3%)	1.00
Mode of delivery outcome			
Episiotomy all indications ¶ [n=57O2/ 60control]	30 (52.6%)	33 (55%)	0.80
Episiotomy fetal indication ¶ [n=57 O2/ 60control]	17 (29.8%)	27 (45.0%)	0.09
Assisted delivery all indications ¶ [n=57 O2/ 60 control] Of which:	7 (12%)	9 (15%)	0.67
Cesarean section	2 (3.5%)	0	
Vacuum-assisted delivery	5 (8.8%)	7 (12%)	
Cesarean section after failed vacuum-assisted delivery	0	2 (3.4%)	
Assisted delivery fetal indication ‡ [n= 57 O2/ 60 control]	4 (7.0%)	6 (10.0%)	0.74
Active second stage of labor in minutes ¥ [n= 57 O2/ 60 control]	35 (20-64)	25 (14-58)	0.32

Data are mean±SD, median (IQR), or n (%). Data are analyzed by ¥; Mann-Whitney U test, **¶;** χ^2 test, **‡** Fisher's exact test, or §; Independent t-test. pCO_2= Partial carbon dioxide pressure.

In the subgroup analyses, we did not find significant differences between treatment groups in Apgar scores or NICU admissions (Table 5). However, in the subgroup with abnormal FHR patterns, fewer episiotomies for fetal indication were performed in the intervention group than in the control group (n=8, 25% vs n=17, 65%, *P*<0.01).

Table 5. Subgroup analysis of neonatal outcomes and mode of delivery on intention-to-treat basis.

Outcome parameter Subgroup	Maternal hyperoxygenation	Conventional care	*P*
Neonates with 1-minute Apgar score <5 ‡			
Abnormal FHR [n=32 O2/ 26 control]	3 (9%)	3 (12%)	1.00
Intermediary FHR [n=25 O2 /34 control]	1 (4%)	1 (3%)	1.00
SGA [n=7 O2 / 5 control]	1 (14%)	0	1.00
Neonates with 5-minute Apgar score <7 ‡			
Abnormal FHR [n=32 O2/ 26 control]	0	2 (8%)	0.20
Intermediary FHR [n=25 O2 /34 control]	0	1 (3%)	1.00
SGA [n=7 O2 / 5 control]	0	0	-
Arterial pH <7.05 ‡			
Abnormal FHR [n=22 O2/ 24 control]	1 (5%)	0	0.48
Intermediary FHR [n=23 O2 / 29control]	0	0	-
SGA [n=6 O2 / 5 control]	0	0	-
Venous pH <7.10 ‡			
Abnormal FHR [n=32 O2/ 26 control]	1 (3%)	0	1.00
Intermediary FHR [n=25 O2 /34 control]	0	0	-
SGA [n=7 O2 / 5 control]	0	0	-
Arterial pCO_2 ¥			
Abnormal FHR [n=22 O2/ 23 control]	57 (52-61)	54 (49-62)	0.52
Intermediary FHR [n=23 O2 / 29control]	55 (51-59)	57 (53-62)	0.14
SGA [n=6 O2 / 5 control]	55 (49-57)	54 (42-64)	1.00
Venous pCO_2 ¥			
Abnormal FHR [n= 32 O2/ 25 control]	45 (40-49)	44 (41-47)	0.75
Intermediary FHR[n=25 O2/34control]	**38 (36-43)**	**42 (39-45)**	**0.04**
SGA [n=7 O2 / 5 control]	39 (37-45)	41 (36-47)	0.54
Arterial Malondialdehyde ¥			
Abnormal FHR [n=24 O2/ 21 control]	4.65 (3.86-5.45)	4.15 (3.40-4.45)	0.07
Intermediary FHR [n=17 O2 / 27control]	4.20 (3.30-5.35)	4.20 (3.35-5.20)	0.96
SGA [n=6 O2 / 4 control]	5.15 (3.03-6.98)	4.55 (4.31-4.75)	0.73
Venous Malondialdehyde ¥			
Abnormal FHR [n=26 O2/ 23 control]	4.60 (3.99-5.43)	4.40 (3.95-5.00)	0.50
Intermediary FHR [n=19 O2 / 31control]	4.60 (3.95-5.40)	4.45 (3.75-5.20)	0.37
SGA [n=7 O2 / 5 control]	4.60 (3.68-6.86)	4.20 (3.43-5.03)	0.66
Episiotomy, fetal indication			
Abnormal FHR ¶ [n=32O2/ 26control]	**8 (25%)**	**17 (65%)**	**<0.01**
Intermediary FHR ¶[n=25O2 /34control]	9 (36%)	10 (29%)	0.59
SGA‡ [n=7 O2 / 5 control]	4 (57%)	4 (100%)	0.24
Assisted delivery, all indications‡			
Abnormal FHR [n=32 O2/ 26 control]	5 (16%)	5 (19%)	0.74
Intermediary FHR [n=25 O2 /34 control]	2 (8%)	4 (12%)	1.00
SGA [n=7 O2 / 5 control]	2 (29%)	1 (25%)	1.00

Table 5. Continued.

Outcome parameter Subgroup	Maternal hyperoxygenation	Conventional care	*P*
Assisted delivery, fetal indications ‡			
Abnormal FHR [n=32 O2/ 26 control]	3 (9%)	4 (15%)	0.69
Intermediary FHR [n=25 O2 /34 control]	1 (4%)	2 (6%)	1.00
SGA [n=7 O2 / 5 control]	0	0	-
Active second stage of labor in minutes ¥			
Abnormal FHR [n=32 O2/ 26 control]	26 (17-56)	21 (12-55)	0.14
Intermediary FHR [n=25 O2 /34 control]	42 (27-74)	36 (16-61)	0.54
SGA [n=7 O2 / 5 control]	59 (38-79)	24 (8-47)	0.052

Data are median (IQR), or n (%). Data are analyzed by ¥; Mann-Whitney U test, **¶;** χ^2 test, ‡**;**Fisher's exact test, or §; Independent t-test. O2=maternal hyperoxygenation group. pCO_2 = Partial carbon dioxide pressure

Maternal outcome

The median duration of oxygen admission was 12 minutes (range 0-75 minutes). In 19 women (33%) oxygen administration was stopped before the infant was born, mostly due to the discomfort of the facemask (n=17, 89%). In 36 women (63%) no side effects were reported.

Per-protocol analysis

We performed a per-protocol analysis which excluded 13 women from the intervention group who had oxygen administration for <5 minutes. No women in the control group received additional oxygen. In addition, we excluded 20 women who had been included despite the presence of exclusion criteria. In the per-protocol analysis, maternal hyperoxygenation had a significant positive effect on FHR classification in the abnormal FHR subgroup (*P*=0.045). All other results of the per-protocol analyses were similar to the intention-to-treat analyses (Supplementary Tables 1-2).

Post-hoc analysis

In a post-hoc analysis, we calculated the Pearsons' and Spearman's correlation coefficient to explore the relation between the duration of oxygen administration and arterial cord blood parameters. No significant correlation was found between duration of oxygen administration and arterial pH, base excess, pCO_2, or MDA.

Sensitivity analysis

For our primary outcome, we had 39% missing data due to women who delivered within the time-frame of interest. First, we ran an analysis to compare the women with and without missing FHR time-frames (i.e. missing data for the primary outcome). We found multiparity (*P*<0.001), and assisted delivery (*P*=0.02) to be significantly higher in the missing group All other parameters (including FHR at baseline) were equal between these groups. Secondly, we performed a sensitivity analysis using ordinal regression

analysis correcting for multiparity and assisted delivery as possible confounders for missingness. In line with the results from the primary analyses, the sensitivity analysis showed a significant positive effect of maternal hyperoxygenation on FHR classification with an OR of 6.4 (95% CI 1.9-22.2). Furthermore, in this sensitivity analysis, a significant positive effect of maternal hyperoxygenation on FHR was shown in the subgroup of patients with abnormal FHR (OR 6.2, 95% CI 1.05-36.5). The subgroups of intermediary FHR and SGA showed the same non-significant trend of a positive effect of maternal hyperoxygenation on FHR as seen in the complete-case analyses (OR 5.6 95% CI 0.8-38.6 and OR 5.2 95% CI 0.3-102.3, respectively).

COMMENT

Principal findings

This study shows that maternal hyperoxygenation has a positive effect on FHR pattern in case of fetal distress during the second stage of labor, as compared to conventional care.

We found no adverse effects regarding neonatal outcome, mode of delivery, or formation of MDA. We did find fewer episiotomies on fetal indication following maternal hyperoxygenation in the subgroup with abnormal FHR pattern.

Results and clinical implications

The positive effect of maternal hyperoxygenation on FHR cannot be explained by the use of cointerventions, which was comparable in both groups. There is a relatively high frequency of deterioration of FHR pattern in both groups. However, this is not uncommon in women at the onset of the second stage of labor. The analyses of FHR pattern in the subgroups showed no significant differences in the complete-case analyses. This may be explained by small sample sizes due to the number of missing values (39% for FHR pattern analysis), which was higher than the accommodated 20%. To correct for possible confounders of missingness, we ran a sensitivity analysis which showed a similar significant positive effect as the complete-case analysis.

An important concern regarding the use of maternal oxygen administration during labor is a potential decrease in umbilical cord pH.[2,15] Although our study was not powered for this outcome, there are no indications in our results to confirm this effect. Moreover, in the intermediary FHR subgroup, pCO_2 was significantly lower in hyperoxygenated women than in conventionally treated women.

Thorp et al. found that the duration of prophylactic oxygen therapy was inversely correlated with arterial cord pH.[15] This relation was not found in our study with distressed fetuses.

A Cochrane review from 2012 on maternal oxygen administration for fetal distress identified two RCT on the prophylactic use of oxygen.[1,15,36] Since then, one RCT has been performed that included patients with suspected fetal distress. In this study by Raghuraman et al.,[17] women were included during labor with >6cm cervical dilation and type II FHR tracings. Patients were randomized to receive either maternal hyperoxygenation until birth or to the control group, breathing room air. The primary outcome was umbilical artery lactate. In line with our results, they found all umbilical artery blood gas components to be similar in both groups. Their results did not report results on FHR, Apgar score, and free oxygen radical activity.

We found 5-minute Apgar score <7 almost three times more frequent in the control group, albeit not significant. There were no previous studies investigating Apgar score after maternal hyperoxygenation. In the abnormal FHR subgroup, significantly fewer episiotomies on fetal indication were performed, and a similar trend was seen in the total group. These findings correspond with results from Haydon et al, which show that fetuses with the lowest initial oxygen saturations benefit the most from maternal hyperoxygenation.[9]

In this study, oxygen administration was stopped in 33% before the infant was born. We hypothesize that this high rate of discontinuation is partly due to the lack of evidence regarding the effect of maternal hyperoxygenation as an intrauterine resuscitation technique.

With the positive findings from this study, especially the positive effect on FHR and the decrease in episiotomy rate for fetal distress, we expect women to be more willing to continue oxygen supplementation.

Research implications

Based on our study results, we cannot subscribe to the theoretical increased risk of increased oxygen radical production.[2] Mean MDA values were not significantly different between the intervention and control group. However, the clinical implications of increased free oxygen radical activity in the neonate remain unclear. Furthermore, possible long-term effects of maternal hyperoxygenation were not taken into account in this study.

Strengths and limitations

This is the first RCT investigating the effect of maternal hyperoxygenation in the presence of fetal distress, only including women during the second stage of labor.[1] In addition, this study takes into account both the beneficial and harmful effects of maternal hyperoxygenation. However, practical and safety issues led to some limitations. Ideally, the primary outcome should have been neonatal morbidity. Achieving sufficient power to address this outcome measure would require a sample size of over 10,000 women.[2] Because some studies raised concerns about the potentially harmful effects of maternal hyperoxygenation, we chose not to expose such a large group of women and their fetuses

to this intervention before its safety has been further investigated. Hence we took FHR as the primary outcome of our study, which represents a surrogate endpoint, of fetal wellbeing. Currently, FHR is deemed the best available method to record changes in fetal condition during labor, despite its poor specificity.[21-24,27,37] We focused on analyzing features in the FHR pattern that are previously related to fetal acidosis. It is therefore unlikely to expect improvement in neonatal outcome if no beneficial effect on FHR can be shown.

Our intended time-frame after the start of the study protocol was 10 minutes after the start of the study in the control group.[26] In the intervention group, our time-frame of interest was the period between 5 and 15 minutes after maternal hyperoxygenation was initiated, since it will take 5 minutes for maternal pO2 to increase to a maximum.[26,35] To allow blinding and limit potential bias for the gynecologists who classified the FHR, we chose to equalize the time-frames for the intervention and the control group. Further investigations are needed to detect whether the amelioration in FHR pattern translates into improved fetal metabolic status and neonatal outcome.

Despite the widespread use of oxygen for intrauterine resuscitation, there is no guideline regarding the optimal dose or duration. The dose used in this study (100% oxygen at 10L/min), applied via a non-rebreathing facemask, is consistent with other studies.[11,15,17,38] Furthermore, the expected effect of 100% oxygen is greater than that of 40% oxygen.[9] Due to practical impossibilities and in line with other studies, we have chosen not to use a sham procedure in the control group.[11,15,17,38] This prohibited blinding of health care providers during labor, which could potentially cause bias for the outcomes episiotomy and assisted delivery. We aimed to minimize the influence of bias by blinding the FHR expert panel for treatment.

Due to the complex setting of the study, it was difficult to adhere to the protocol, despite intensive training of all study personnel. A total of 21 women were included despite having exclusion criteria. In addition, we included one woman more than we originally aimed for. Factors that may have contributed to this violation of the study protocol are the acute obstetric situation, strict exclusion criteria, and the use of envelopes for randomization. To investigate the effect of these patients on the study results, the per-protocol analysis was performed with and without exclusion of the incorrectly included women. This did not alter the results, nor did the results indicate safety hazards.

CONCLUSION

Maternal hyperoxygenation has a positive effect on the FHR pattern in the presence of fetal distress during the second stage of labor. There was no significant difference in mode of delivery or neonatal outcome, however, significantly fewer episiotomies on fetal indication were performed following maternal hyperoxygenation in the subgroup with

abnormal FHR pattern. A larger study powered for improvement in neonatal outcome is needed to propose strong recommendations for clinical practice.

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SUPPLEMENTARY TABLES

Supplementary Table 1. Changes in FHR according to FIGO classification following maternal hyperoxygenation versus conventional care in the per protocol analysis

	Deterioration FHR	Equal FHR	Improvement FHR	*P*
Total study population (n=50)				
Maternal hyperoxygenation (n=20)	**2 (9.5%)**	**16 (76.2%)**	**3 (14.3%)**	**0.02**
Conventional care (n=29)	**11 (37.9%)**	**18 (62.1%)**	**0**	
Abnormal FHR (n=23)				
Maternal hyperoxygenation (n=13)	**0**	**12 (85.7%)**	**2 (14.3%)**	**0.045**
Conventional care (n=9)	**3 (33.3%)**	**6 (66.7%)**	**0**	
Intermediary FHR (n=27)				
Maternal hyperoxygenation (n=7)	2 (28.6%)	4 (57.1%)	1 (14.3%)	0.22
Conventional care (n=20)	8 (40%)	12 (60%)	0	
SGA (n=5)				
Maternal hyperoxygenation (n=3)	0	2 (66.7%)	1 (33.3%)	0.33
Conventional care (n=2)	1 (50%)	1 (50%)	0	

Data are n (%). FHR= fetal heart rate. SGA = small for gestational age. The differences are analyzed with a χ^2 test since ordinal regression analysis was not possible because of too many cells with zero frequencies.

Supplementary Table 2. Neonatal outcome and mode of delivery following maternal hyperoxygenation or conventional care in the per protocol analysis

Outcome parameter	Maternal hyperoxygenation	Conventional care	*P*
Neonatal outcome			
1- minute Apgar score ¥ [n= 31 O2 / 53 control]	9 (9-9)	9 (9-9)	0.52
Neonates with 1-minute Apgar Score <5 ‡ [n=31 O2 / 53 control]	1 (3.2%)	4 (7.5%)	0.65
5-minute Apgar Score ¥ [n**=** 31 O2 / 53 control]	10 (10-10)	10 (9.5-10)	0.15
Neonates with 5-minute Apgar Score <7 ‡ [n=31 O2 / 53 control]	0	3 (5.7%)	0.29
pH arterial § [n=22 O2 / 47 control]	7.23±0.05	7.21±0.06	0.20
pH arterial <7. 05 ‡ [n=22 O2 / 47 control]	0	0	-
pH venous ¥ [n=**31** O2 / **53** control]	7.30 (7.27-7.34)	7.31 (7.27-7.35)	0.50
Base Excess arterial § [n=22 O2 / 4**5** control]	-4.73±2.55	-5.87±2.68	0.10
pCO_2 arterial § [n=22 O2 / 4**6** control]	55.4±5.4	56.4±7.2	0.56
Malondialdehyde arterial ¥ [n=2**5** O2 / 4**2** control]	4.45 (3.68-5.75)	4.05 (3.31-4.84)	0.13
Malondialdehyde venous § [n=2**6** O2 / 47 control]	4.82±1.40	4.34±1.22	0.13
NICU admissions ‡ [n=31 O2 / 53 control]	0	2 (3.8%)	0.53
Mode of delivery outcome			
Episiotomy, all indications ¶ [n=31 O2 / 53 control]	18 (58.1%)	28 (52.8%)	0.64
Episiotomy, fetal indication ¶ [n=31 O2 / 53 control]	10 (32.3%)	22 (41.5%)	0.40
Assisted delivery, all indications ¶ [n=31 O2 / 53 control]	4 (12.9%)	10 (18.9%)	0.48
Assisted delivery, fetal indication ¶ [n=31 O2 / 53 control]	1 (3.2%)	5 (9.4%)	0.41
Active second stage of labor in minutes § [n=31 O2 / 53 control]	46.9±28.7	37.6±30.3	0.17

Data are mean±SD, median (IQR), or n (%). Data are analyzed by ¥; Mann-Whitney U test, **¶;** χ^2 test, ‡ Fisher's exact test, or §; Independent t-test. pCO_2= Partial carbon dioxide pressure

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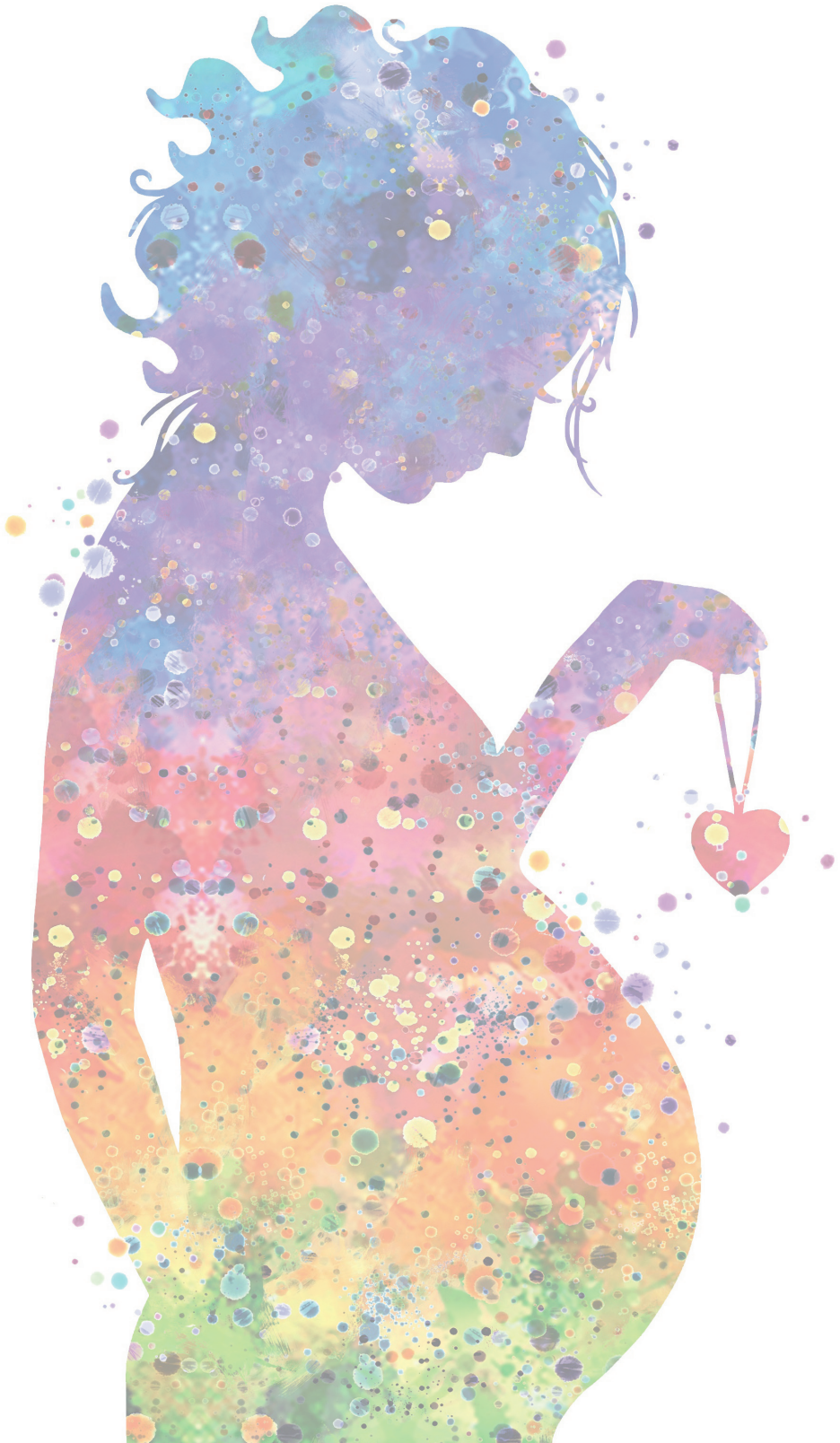

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A randomized controlled trial studying the effect of maternal hyperoxygenation on fetal heart rate in case of fetal distress

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ABSTRACT

Objective

To investigate the effect of maternal hyperoxygenation on fetal heart rate (FHR) when applied for suspected fetal distress during the second stage of term labor.

Approach

A single-center randomized controlled trial was conducted in a tertiary care hospital in The Netherlands. Participants were included during the second stage of labor in case of an intermediary or abnormal FHR pattern. Patients were randomized to receive either 100% oxygen at 10L/min until delivery, or conventional care without additional oxygen. The primary outcome was the change in FHR pattern before and after the onset of the study, measured as the change in depth and duration of FHR decelerations. Secondary outcome measures were features based on phase-rectified signal averaging (PRSA), baseline assignability, and deceleration characteristics of the FHR pattern.

Main results

Between March 2016 and April 2018, 117 women were included. The FHR pattern could be analyzed for 71 participants, the other 46 women delivered before the end of the post time-frame. A 2.3% reduction in depth and duration of FHR decelerations was found after maternal hyperoxygenation, compared to a 10% increase in the control group (p=0.24). Maternal hyperoxygenation had a significantly positive effect on PRSA metrics, with a decrease in PRSA-acceleration capacity (p=0.03) and PRSA-deceleration capacity (p=0.02) in the intervention group compared to the control group.

Significance

The difference in depth and duration of decelerations after the start of the study was not significantly different between both study groups. A statistically significant positive effect on PRSA-deceleration capacity and PRSA-acceleration capacity was found after maternal hyperoxygenation, which might be associated with a positive effect on neonatal outcome.

Trial registration

The study was registered in the EudraCT database (2015-001654-15) on April 3rd, 2015 and in the Dutch Trial Register (NTR5461) on October 20th, 2015. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2015-001654-15 and http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5461. Date of initial participant enrollment: March 2nd, 2016.

INTRODUCTION

During labor, contractions cause alterations in intrauterine pressure and may thereby lead to intermittent interruption of uterine and umbilical blood flow.[1,2] This may decrease oxygen delivery to the fetus, leading to reduced fetal oxygenation, and eventually to fetal hypoxia and acidosis.[1,2] Timely clinical interventions, such as intrauterine resuscitation, may avoid these detrimental effects.[3,4]

In some countries, maternal hyperoxygenation is commonly used to improve fetal oxygenation status through increased oxygen delivery to the placenta.[3–8]Indeed, Vasicka et al. showed increased partial oxygen pressure (pO_2) levels in all placental and fetal compartments already after five minutes.[9] However, concerns are raised about potential side effects of maternal hyperoxygenation, such as an increase in free oxygen radicals and a decrease in arterial cord pH.[10–13] Unfortunately, the number of clinical studies on the effects of maternal hyperoxygenation in case of fetal distress is limited and their results are inconclusive.[14–20] Hence, several reviews have urged for a randomized controlled trial (RCT) to study the effects of maternal hyperoxygenation during the second stage of labor in the presence of fetal distress.[3,5,7]

Therefore, we conducted a RCT, the INTEREST O2 study, in which maternal hyperoxygenation was compared to conventional care in case of suspected fetal distress during the second stage of labor.[21] The maternal and neonatal outcomes from this study have been published previously.[22] No harmful side-effects of maternal hyperoxygenation were observed, especially no reduction in Apgar Score or arterial umbilical cord blood pH and no increase in free oxygen radical activity. Moreover, a significantly positive effect on change in International Federation of Gynecology and Obstetrics (FIGO) classification was found following maternal hyperoxygenation.[22] Although such visual FHR analysis is one of the most used methods to evaluate FHR, it is known to have a large intra- and inter-observer variability.[23,24] Recent advances in computerized analysis of FHR could provide additional insights in the physiological changes caused by maternal hyperoxygenation.

The detailed analyses of FHR features presented in this paper are based on the link between FHR and the autonomic nervous system (ANS) in response to reduced fetal oxygenation.[1,25] FHR decelerations are a well-known fetal adaptation to hypoxia to reduce myocardial work and oxygen requirements.[2,26] We will evaluate the depth and duration of FHR decelerations as these are related broadly to the severity of the fetal hypoxia.[2,27]

Furthermore, changes in fetal well-being can also be measured using phase-rectified signal averaging (PRSA). This innovative method of FHR analysis can quantify the acceleration and deceleration capacity of FHR, thereby providing insights into the compensatory activation of the ANS in case of fetal distress.[25,28]

Finally, we will also evaluate other important FHR features mentioned in literature as being related to unfavorable neonatal outcomes, namely periods with unstable baseline, decelerations in combination with tachycardia or bradycardia, and decelerations with loss of internal variability.[2,27,36,37,28–35]

METHODS

Study design

The INTEREST O2 study, a single-center RCT, was conducted at a tertiary care teaching hospital in the Netherlands. The study protocol has been published previously.[21] Women, aged ≥18 years, with a term non-anomalous singleton in cephalic presentation and intended vaginal delivery, were considered eligible for this study. Exclusion criteria were mainly based on the risk of increased free oxygen radical activity: maternal fever during labor with the need of antibiotic therapy, the use of tobacco, recreational drugs, or alcohol during pregnancy, pulmonary disease requiring medication, pre-existing cardiac disease, diabetes, hyperthyroidism, anemia (hemoglobin <10.5 g/dL) or recent use of any of the following medications: anti-hypertensives, magnesium sulfate, corticosteroids, amiodarone, adriamycin, bleomycin, actinomycin, menadione, opioids, promazine, thioridazine, or chloroquine. Eligible subjects were only randomized in the study if they presented with suspected fetal distress during the second stage of labor. Suspected fetal distress was defined as an intermediary or abnormal FHR pattern according to the modified FIGO classification, see Figure 1.[27,38]

	Baseline heart frequency	FHR variability and reactivity	FHR decelerations
***Normal* FHR**	• 110–150 bpm	• Accelerations • 5–25 bpm	• Early uniform decelerations • Uncomplicated variable decelerations (loss of < 60 beats)
***Intermediary* FHR**	• 100–110 bpm • 150–170 bpm • Short bradycardia episode, defined as: < 100 bpm for > 3 minutes < 80 bpm for > 2 minutes	• Saltatory pattern (> 25 bpm) • < 5 bpm for > 40 minutes	• Uncomplicated variable decelerations (loss of > 60 beats)
A combination of two or several intermediary observations will result in an abnormal FHR classification			
***Abnormal* FHR**	• > 170 bpm • Persistent bradycardia < 100 bpm for > 10 minutes < 80 bpm for > 3 minutes (without an increasing tendency)	• < 5 bpm for > 60 minutes • Sinusoidal pattern	• Complicated variable decelerations with a duration of > 60 seconds • Repeated late uniform decelerations
***Pre-terminal* FHR**	• Total lack of variability (< 2 bpm) and reactivity with or without decelerations or bradycardia		

Figure 1. Classification of FHR according to modified FIGO criteria
Bpm = beats per minute. FHR = fetal heart rate.

Intervention and randomization

All women eligible to be included in this study received antepartum oral and written information about the study when they visited the outpatient clinic or when they were admitted to the delivery ward. After informed consent was obtained, two sealed opaque envelopes with treatment allocation were assigned per patient during the first stage of labor, one in case of future intermediary FHR and one in case of future abnormal FHR. The allocation sequence was computer-generated with the use of random blocks of four or six patients. Stratification was applied for intermediary or abnormal FHR.

Only in case of suspected fetal distress during the second stage of labor, women were randomized in the study by opening the appropriate envelope (i.e. intermediary or abnormal FHR). Unopened envelopes were reused.

Patients were randomized to receive either conventional care without additional oxygen (control group), or maternal hyperoxygenation with 100% oxygen at 10 L/min via a non-rebreathing mask until delivery (intervention group). Preferably, other intrauterine resuscitation techniques, such as maternal positioning, admission of tocolytic drugs, or adjustment of oxytocin dosage, were not initiated within the first 10 minutes after randomization. However, the obstetric staff could overrule the study protocol at any time if deemed necessary.

Primary outcome

The primary outcome was the change in FHR pattern after the onset of the study protocol, measured as the percentage change in the depth and duration of FHR deceleration in the intervention group compared to the control group. To be able to analyze decelerations of the FHR, visually or through computerized analysis, the baseline of the FHR needs to be identified. Subsequently, the depth and duration of FHR decelerations can be calculated.

The change in FHR was first analyzed per patient, each with a “pre-study” and “post-study” 10-min time-frame with respect to the start of the protocol as shown in Figure 2. The FHR time-frames of interest correspond to the 10 minutes before start of the study protocol (pre-study time-frame) and the period 5 to 15 minutes after the start of the study protocol (post-study time-frame). The difference between the pre and post scores was provided as a single score per parameter per patient. Results were subsequently compared between the intervention and the control group.

By definition, women who delivered within 15 minutes after the start of the study did not have complete time-sets of FHR in the post time-frame, therefore changes in FHR pattern could not be analyzed in these cases.

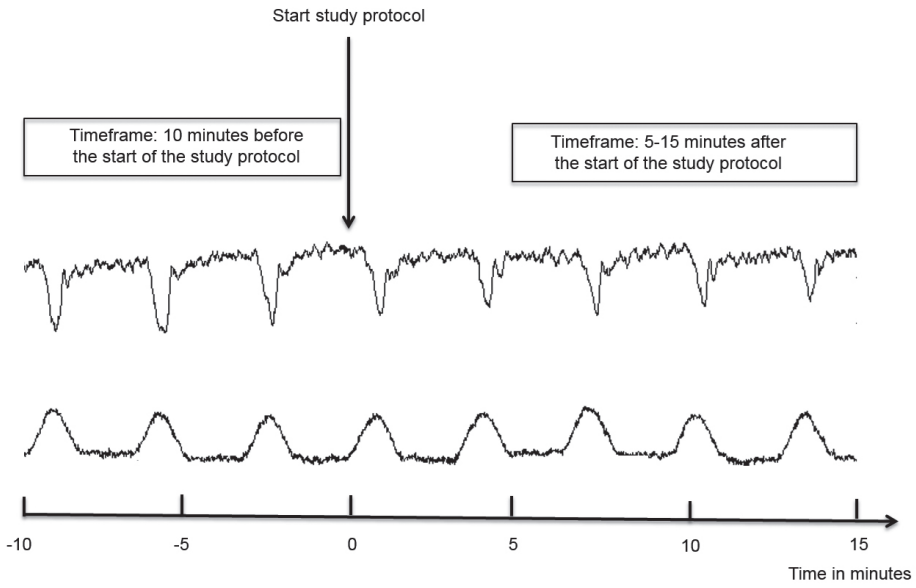


Figure 2. The 10-minute time-frames of interest, pre and post-initiation of the study protocol. Patients in the intervention group receive standard care with the start of oxygen administration immediately after time=0, while patients from the control group will continue to receive standard care without oxygen.

FHR-baseline assignment

The baseline of the FHR is defined by the FIGO as "the mean level of the most horizontal and least oscillatory FHR segment".[27] A FHR baseline can sometimes be unassignable, due to poor signal quality or when FHR is unstable.

To determine the baseline, two methods were used, namely *visual evaluation* and *computerized analysis*. Visual evaluation of the baseline was done by a team consisting of a consultant-obstetrician (NvO) and an obstetric resident (LB), both blinded for treatment allocation. Both clinicians independently visually analyzed whether a FHR baseline was assignable for each time-frame. For assigning the FHR baseline, they could use both the FHR pattern and the uterine contraction pattern. Any disagreement was resolved by consensus. In the event no baseline could be assigned in the 10-minute time-frame of interest, the time-frame of interest was extended with the 10 minutes preceding the original time-frame.

The *visual analysis* was then used to validate a preexisting *computerized* algorithm for baseline evaluation, henceforth referred to as the OxSys algorithm.[29,30,39] The uterine contraction pattern is not taken into account in the FHR baseline evaluation by this algorithm.

The results of the visual analysis by clinicians were used as the gold standard for baseline assignment when comparing the two methods. An interobserver agreement of >0.60[40] was set as a cut-off to determine whether the Oxsys algorithm will be used for assignment of baseline values for further calculations. In case of a lower interobserver agreement, baseline values determined from visual inspections will be used for further calculations.

Primary outcome of FHR decelerations: deceleration surface

An integral measure of the depth and duration of FHR decelerations was assessed by calculating the area under the curve with respect to the baseline (Figure 3). This so-called deceleration surface was determined for both the pre-study and post-study 10-minute window (Figure 2), also if the corresponding baseline was determined from a 20-minute window. FHR deceleration surface was not analyzed for FHR baseline values ≤110bpm, as this is by definition a bradycardia.

Per subject, the normalized percentage change in deceleration surface between the pre- and post-study window was calculated. Subsequently, these changes were compared between the intervention and control group.

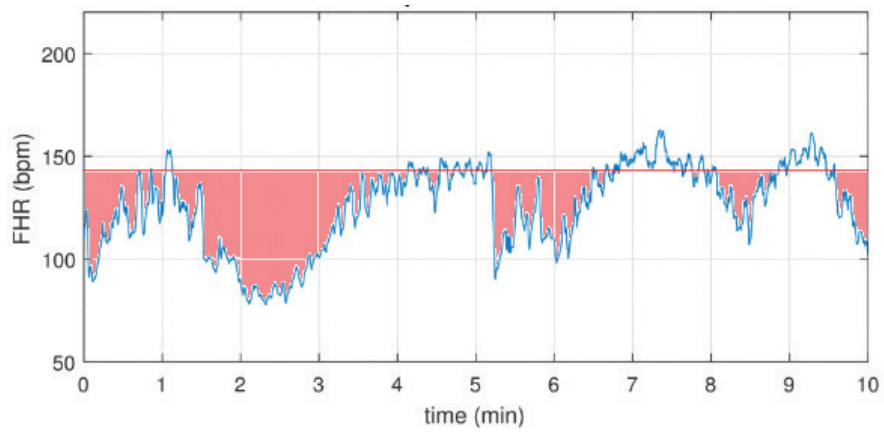


Figure 3. An example to showcase the deceleration surface (in pink), a single integrated measure to capture the depth and duration of FHR decelerations.

Secondary outcomes

Unstable baseline

The instability of FHR may indicate compromised fetal condition.[30] Therefore, all cases in which a baseline could not be assigned in the original 10-minute time-frame due to unstable FHR were compared between the intervention and the control group.

FHR variability: Phase-rectified signal averaging

PRSA is a non-traditional computerized measure to characterize heart rate variability (HRV).[41] More details about this signal processing technique can be found in the article by Bauer et al.[41] PRSA is based on two parameters, *T* determining the periods of average increase or decrease in the FHR (around the anchor points) that count as accelerations and decelerations respectively, and *L* that represents the period over which the data around the anchor points are averaged.[41] For these analyses, we used *T*= 20 anchor points (corresponds to 5 seconds) and *L*= 100 anchor points (corresponds to 25 seconds). The acceleration- and deceleration-related modulations identified through PRSA can be characterized by specific features to quantitatively study changes in autonomic regulation.[41,42] Specifically, the average acceleration capacity (PRSA-AAC) can be used to characterize the acceleration capacity of the fetal heart.[41] Similarly, the average deceleration capacity (PRSA-ADC) can be used to characterize the deceleration capacity of the fetal heart. [37,41,43] The PRSA-AAC and PRSA-ADC are calculated from 15 seconds of FHR.[43]

Characteristics of FHR decelerations

The following two aspects of FHR decelerations were analyzed visually by the same two clinicians (NvO and LB);

- Presence of decelerations with loss of internal variability (beat-to-beat variability < 5 bpm)
- Presence of decelerations in combination with tachycardia (defined as >160 bpm) or bradycardia (defined as < 110 bpm)

Disagreement was resolved by consensus.

Traditional heart rate variability metrics

In addition to the primary and secondary outcomes described in the study protocol,[21] we also analyzed the following traditional HRV metrics; short term variability (STV), standard deviation of the NN interval (SDNN), and the root mean squared successive differences of NN intervals (RMSSD). To calculate STV, the algorithm described by Dawes/Redman was used.[44]

Signal processing

During labor, the FHR was continuously recorded with either Doppler ultrasound or fetal scalp electrode using Philips Avalon FM30 (Philips Healthcare, Best, The Netherlands). To perform the computerized FHR analysis, the digital FHR tracings were extracted from the electronic patient file (HIX, ChipSoft, Amsterdam, The Netherlands), anonymized and subsequently analyzed offline using MATLAB 2018 software (MathWorks Inc., Natick, MA, USA). For all computerized analysis, the FHR data, acquired at a sampling rate of 4Hz, were preprocessed. First, to remove potential measurement artifacts, all FHR values above 250 and below 20 beats per minute (bpm), as well as those FHR values that differed by more than 25 bpm from the preceding value were filtered out and considered

to be a missing value. Next, only those time-frames that had less than 50% of missing data were retained for further analysis. Finally, all missing data were interpolated by employing shape-preserving, cubic spline interpolation.

Intention-to-treat and per-protocol analyses

The primary analyses were intention-to-treat. In some cases, oxygen may not have been applied according to the study protocol, due to practical concerns such as fast progression of labor. To anticipate for these cases, additional per-protocol analyses were performed. For the per-protocol analyses, all women receiving <5 minutes of oxygen were excluded, since it takes 5 minutes of maternal hyperoxygenation for maternal pO2 to increase to a maximum.[9] Furthermore, unjust inclusions were also excluded from the per-protocol analyses.

Sample size calculation

A sample size calculation was performed as described previously.[21,45] To provide a power of 90% at a two-sided significance level of 0.05, 96 women (48 in each group) were required. To accommodate for 20% missing data, 116 participants were planned to be included in the study.

Statistical analyses of outcome parameters

IBM SPSS Statistics software (version 25; IBM, Armonk, NY, USA) was used for all statistical analyses. In case of non-normally distributed outcomes, continuous variables were analyzed with a Mann-Whitney U test for differences between the intervention and control group and a Wilcoxon matched-pairs test for changes within the same participant. In case of normal distribution, continuous data were analyzed using independent samples t-tests (two-tailed) for differences between the intervention and control group, and paired t-tests were used for changes within the same participant. For categorical variables, the χ^2 test or Fisher's exact test was used depending on the expected number of observations per category. $P<0.05$ for a two-tailed test was considered significant. For calculation of the interobserver agreement of baseline assignability (i.e. whether a baseline can be assigned) between the visual analysis of the clinicians and the computerized analysis, Cohen's kappa was used.

All analyses were performed for the total study population (i.e. the combined group of intermediary and abnormal FHR), as well as for the subgroups of *intermediary FHR*, *abnormal FHR*, and *small for gestational age neonates* (birthweight <10th percentile).

When missing data exceeds the 20% accommodation window of the study design, additional or sensitivity statistical analyses will be performed to evaluate risk factor imbalances between treatment groups (violation of the randomization due to missingness) and evaluate the sensitivity of these potential imbalances.

To analyze whether possible risk factors of missingness were likely to have affected the primary outcome, the Mann-Whitney U statistic will be applied to the following parameters to compare women with and without missing FHR time-frames (i.e. missing data for FHR analyses): FIGO classification before start of the study, gestational age, birth weight, Apgar Score at one and five minutes, arterial umbilical cord gas parameters (pH, Base Excess, pCO_2 and Malondialdehyde) episiotomy on fetal indication, assisted delivery, maternal age, maternal body mass index, and multiparity. In the event of imbalances, a propensity score matching approach will be used to correct for the observed imbalances using a SAS algorithm for matching (PSMatch_Multi).

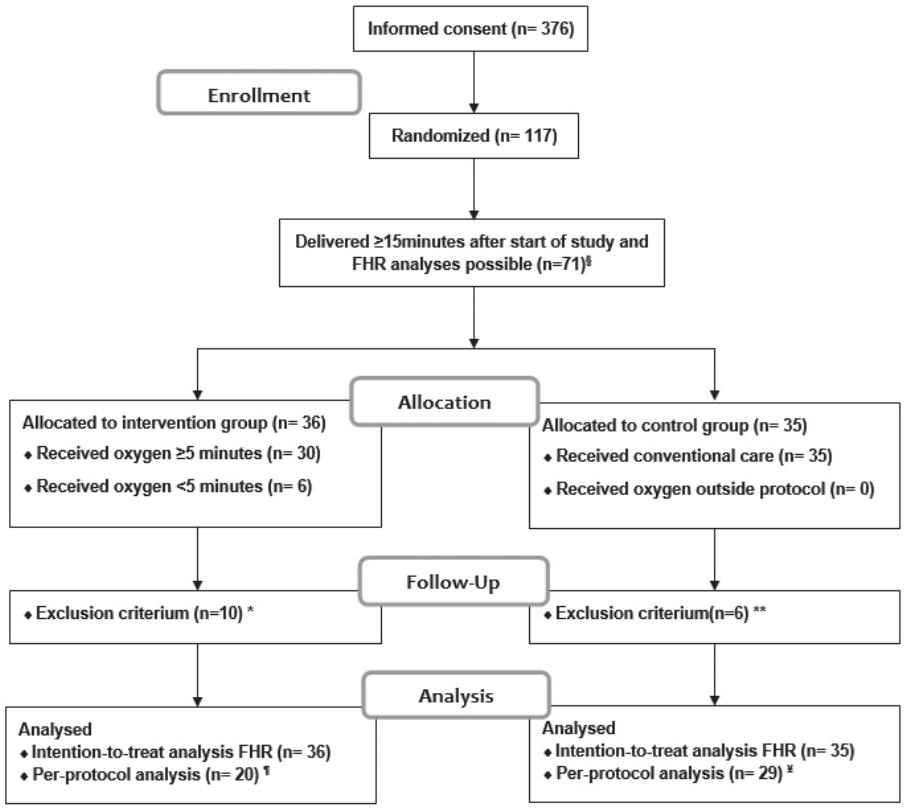
Ethical approval

We conducted this study in accordance with the Declaration of Helsinki. The Central Committee on Research Involving Human Subjects approved this study (protocol number NL53018.000.15). The trial was registered at the EudraCT database (2015-001654-15) and at the Dutch Trial Register (NTR5461).

RESULTS

Between March 2016 and April 2018, a total of 376 women gave informed consent for the study during outpatient visits or during the first stage of labor (CONSORT flow diagram, Figure 4). During the second stage of labor, 117 women were randomized due to an *intermediary* or *abnormal* FHR pattern. Of these, 57 women were assigned to the intervention group and 60 women were assigned to the control group. In total, 46 women delivered within 15 minutes after the start of the study. Hence, the complete FHR time-frames suitable for FHR analyses were available for the remaining 71 women (61%). Of these, 36 women (51%) originated from the intervention group and 35 women (49%) from the control group.

The baseline characteristics of the included women are presented in Table 1. Groups were comparable regarding baseline characteristics, including gravidity and parity. Within the first 10 minutes after randomization, 7 women (9.9%) received additional intrauterine resuscitation, two (5.6%) in the intervention group and five (14.3%) in the control group (p=0.26). These intrauterine resuscitation techniques included discontinuation of pushing, adjustment of the dosage of oxytocin infusion, and maternal repositioning.



§ A total of 21 women from the intervention group and 25 women from the control group gave birth within 15 minutes after start of the study and by definition these women did not have complete time-sets of FHR in the post timeframe, therefore change in FHR pattern could not be analyzed in these cases.
* Four women had signs of infection and were treated with antibiotics, two women smoked during pregnancy, one woman had diabetes, one woman delivered prematurely, one fetus had congenital abnormalities (cheilognathopalatoschisis), and there was one case of fetal bradycardia prior to the start of the study (FHR baseline of 105bpm).
** Three women had signs of infection and were treated with antibiotics, two women smoked during pregnancy, and one woman delivered at 42 weeks of gestation.
¶ In the intervention group, the six women with oxygen admission <5min and the 10 women with exclusion criteria were excluded in the per-protocol analysis.
¥ In the control group, the six women with exclusion criteria were excluded from the per-protocol analysis

Figure 4. Trial flow diagram.
A total of 117 patients were allocated to either the intervention or control group. For the fetal heart rate (FHR) analysis, 71 women were eligible based on the availability of complete FHR time-frames. Both an intention-to-treat and per-protocol analysis were performed. FHR = fetal heart rate

Table 1. Baseline characteristics of patients included in FHR analyses

	Intervention group n=36	Control group n=35	*P*
Maternal age (years)	31±3	32±4	0.42
Gestational age (days)	280±9	278±9	0.27
Gravidity >1	22 (39%)	32 (53%)	0.11
Parity ≥1	8 (22%)	11 (31%)	0.38
BMI (kg/m2)	23 (20-27)	24 (21-27)	0.10
Fetal sex male	21 (58%)	15 (43%)	0.19
Birth weight (grams)	3610±623	3431±489	0.18
SGA	6 (17%)	3 (9%)	0.48
Abnormal FHR pattern	20 (56%)	14 (40%)	0.19

Data are mean±SD, median (IQR) or n (%). BMI = body-mass index, SGA = small for gestational age, FHR= fetal heart rate

Analyses of the FHR

Baseline assignability

Comparing the baseline assignability of the *computerized analysis* with the gold standard of *visual analysis* (i.e. whether a baseline could be assigned or not), a poor interobserver agreement was found, with kappa values ranging between 0.13 and 0.60 (Supplementary Table 1). Since this interobserver variability of baseline assignability was ≤0.60, all further analyses were based on the baseline value as assigned by the clinicians. For 27 women, a 20-minute time-frame was needed to be able to determine a baseline (Supplementary Table 1).

Depth and duration of decelerations

In one subject, the FHR baseline was <110 bpm and was therefore excluded from deceleration surface analysis. The deceleration surface in the pre-study and post-study time-frames are presented in Table 2 for both the intervention and control group. Figure 5 shows an example of the changes in FHR traces provoked by maternal hyperoxygenation.

The change in depth and duration of decelerations between the pre-study and post-study time-frame are presented in Table 3. The difference was not significant (p=0.24) between the maternal hyperoxygenation group (-2.3%) and the control group (+10%).

Unstable baseline

The change in the number of unstable baselines was not significantly different (p=0.48) between the intervention (+9%) and control group (-6%, Supplementary Table 1).

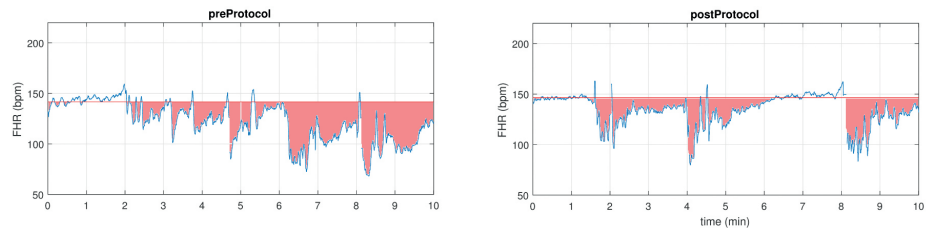


Figure 5. An example of the changes in the depth and duration of FHR decelerations after start of the study provoked by maternal hyperoxygenation in the intervention group (39% decrease in deceleration surface following maternal hyperoxygenation).

PRSA-based parameters

The PRSA values of the pre and post-study time-frames are presented in Table 2, whereas the differences after start of the study are presented in Table 3. The averaged PRSA measures are visualized in Figure 6.

Prior to the start of the study, the PRSA-ADC was similar between the intervention and the control group (p=0.23). After start of the study, the intervention group showed a 3% decrease of PRSA-ADC, compared to before the onset of the study. The control group showed an increase of 20% in PRSA-ADC after the onset of the study. This difference was statistically significant (p=0.02).

In the pre-study time-frame, PRSA-AAC was significantly higher in the intervention group than in the control group (7.01 vs 4.52, p<0.01). After the start of the study protocol, the intervention group showed a 4% decrease in PRSA-AAC between pre and post. The control group showed an increase in PRSA-AAC of 37% between pre and post. This difference was statistically significant (p=0.03).

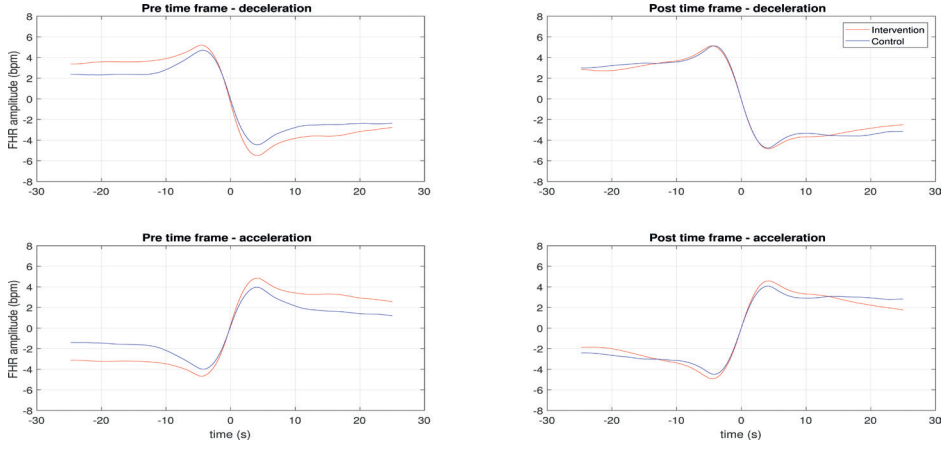


Figure 6. Averaged PRSA measures for the intervention and the control group.

Table 2. Measurements of FHR for the intervention and control group

	Pre-study time-frame			Post-study time-frame		
	Intervention N=36	**Control N=35**	***p-value***	**Intervention N=36**	**Control N=35**	***p-value***
Deceleration surface	17.42 [10.65 to 20.65]	11.23 [6.70 to 25.05]	0.28	13.97 [8.94 to 21.86]	17.84 [10.67 to 23.27]	0.16
PRSA – ADC (FHR/s)	-7.60 [-9.17 to -6.00]	-6.55 [-7.75 to -4.57]	0.23	-6.92 [-8.94 to -5.53]	-7.60 [-9.67 to 5.19]	0.57
PRSA – AAC (FHR/s)	7.01 [4.91 to 8.23]	4.52 [3.88 to 7.25]	0.005	5.99 [4.09 to 8.60]	6.30 [4.60 to 8.75]	0.71
STV (ms)	2.41 ± 1.06	2.07 ± 0.93	0.16	2.44 ± 1.33	2.38 ± 1.07	0.84
SDNN (ms)	88.83 [59.47 to 108.68]	78.49 [41.60 to 106.64]	0.22	91.16±51.31	96.91 ± 46.33	0.62
RMSSD (ms)	9.85 [6.42 to 12.36]	8.20 [5.99 to 11.49]	0.32	9.86 ± 4.96	9.57 ± 3.89	0.78

All calculations are based on the results of the adjusted algorithm. Data are mean± standard deviation or median [IQR].PRSA; Phase-rectified signal averaging. AAC; average acceleration capacity. ADC; average deceleration capacity. STV; short term variability. SDNN; standard deviation of the NN interval. RMSSD; root mean squared successive differences of NN intervals.

Table 3. Changes in computerized FHR before and after randomization

	Intervention (n=36)	**Control (n=35)**	**p**
Δ Deceleration surface in %	-2.31 [-39.46 to 68.30]	10.00 [-14.97 to 127.85]	0.24
Δ PRSA – ADC in %	-2.75 [-27.94 to 35.69]	19.75 [-9.24 to 67.11]	0.02
Δ PRSA – AAC in %	-3.93 [-39.56 to 30.75]	37.14 [-20.63 to 93.73]	0.03
Δ STV in %	-2.18 [-25.55 to 26.55]	13.11 [-24.56 to 53.25]	0.27
Δ SDNN in %	0.78 [-31.33 to 43.59]	11.25 [-9.15 to 61.29]	0.16
Δ RMSSD in %	-.06 [-27.75 to 32.87]	3.41 [-12.75 to 40.67]	0.33

Changes are presented as percentage difference (post time-frame minus pre time-frame with respect to pre time-frame). Data are median [IQR] PRSA; Phase-rectified signal averaging. AAC; average acceleration capacity. ADC; average deceleration capacity. STV; short term variability. SDNN; standard deviation of the NN interval. RMSSD; root mean squared successive differences of NN intervals.

Traditional heart rate variability metrics

The results of the analyses of STV, SDNN, and RMSSD in the pre- and post-study time-frames are presented in Tables 2, whereas the differences in these parameters after the start of the study are presented in Table 3. No significant differences were found in STV, SDNN, or RMSSD between the intervention and the control group.

Characterization of decelerations

The results of the analyses of the characteristics of FHR decelerations are presented in Supplementary Tables 2 and 3. No statistically significant differences were seen between the intervention and the control group in decelerations with loss of internal variability or in decelerations in combination with tachycardia (p=0.67 and p=0.11, respectively).

Subgroup analysis

The results of the analysis on the subgroups *intermediary FHR*, *abnormal FHR*, and *small for gestational age* neonates are presented in Table 4. The change in deceleration surface after start of the study protocol was not significant in either of the subgroups.

Table 4. Changes in computerized FHR before and after randomization, subgroup analyses

	Intervention	**Control**	**p**
Δ Deceleration surface in %			
Abnormal FHR [n= 33]	-7.09 [-47.90 to 25.23]	-0.38 [-30.89 to 90.71]	0.34
Intermediary FHR [n= 37]	67.66 [-18.58 to 103.03]	21.46 [-12.19 to 130.67]	0.94
SGA [n= 9]	-19.10 [-83.13 to 55.68]	-21.85 [-24.63 to 447.85]	0.55
Δ PRSA – ADC in %			
Abnormal FHR [n= 34]	-3.75 [-31.21 to 26.44]	29.92 [3.63 to 63.68]	0.06
Intermediary FHR [n= 37]	4.68 [-23.13 to 42.84]	17.08 [-11.32 to 70.70]	0.21
SGA [n= 9]	-20.96 [-70.43 to 14.38]	26.61 [7.92 to 66.41]	0.17
Δ PRSA – AAC in %			
Abnormal FHR [n= 34]	-5.06 [-34.26 to 23.46]	37.58 [4.34 to 108.98]	0.02
Intermediary FHR [n= 37]	-3.93 [-26.31 to 50.42]	30.33 [-28.93 to 92.46]	0.44
SGA [n= 9]	-38.85 [-69.71 to 81.07]	37.14 [-20.63 to 91.20]	0.38

Changes are presented as percentage difference (post time-frame minus pre time-frame with respect to pre time-frame). Data are median [IQR] PRSA; Phase-rectified signal averaging. AAC; average acceleration capacity. ADC; average deceleration capacity.

Per-protocol analysis

A per-protocol analysis was performed in which 6 women from the intervention group were excluded who received oxygen administration for <5 minutes. No women from the control group received supplementary oxygen. In addition, 16 women were excluded in the per-protocol analyses because they were included despite the presence of exclusion criteria. The per-protocol analysis therefore included a total of 49 patients of whom 20

women were allocated to receive oxygen and 29 women were allocated to the control group.(Figure 4).

All results of the per-protocol analyses were in line with the results of the intention-to-treat analyses (Table 5).

Table 5. Per-protocol analyses, changes in computerized FHR before and after randomization

	Intervention (n=21)	Control (n=29)	p
Δ Deceleration surface in %	-4.48 [-44.22 to 62.64]	9.19 [-14.02 to 128.91]	0.18
Δ PRSA – ADC in %	-0.46 [-31.21 to 26.44]	19.75 [-2.08 to 76.54]	0.02
Δ PRSA – AAC in %	-3.25 [-33.72 to 39.97]	41.20 [-17.81 to 99.10]	0.048

Changes are presented as percentage difference (post time-frame minus pre time-frame with respect to pre time-frame). Data are median [IQR] PRSA; Phase-rectified signal averaging. AAC; average acceleration capacity. ADC; average deceleration capacity.

Additional or sensitivity analyses

As the fraction of missing data exceeded the accommodated 20%, sensitivity analyses were performed. As shown in Table 2 and Supplementary Table 1, only parameter PRSA-AAC showed an imbalance between the intervention and the control group in the pre-study time-frame. Hence, a propensity score matched-pair analysis was performed for this parameter. Using a caliper of 1.3 (approximately 50% of the standard deviation and 10% of the range in PRSA-AAC pre-study values) 28 pairs were obtained.

Using a mixed effects model on the logarithmically transformed pre- and post-study differences, using the pair as random effect and the intervention as fixed effect, we obtain a p-value for the intervention equal to p=0.007, thus confirming the significant difference in the change of PRSA-AAC between the intervention and the control group after correcting for imbalances.

In the group with missing data for FHR analyses, multiparity (p<0.001) and assisted delivery (p=0.02) were significantly higher compared to the group without missing FHR time-frames, all other parameters did not differ between the two groups.

Both assisted delivery and multiparity were not associated with the difference in depth and duration of decelerations after start of the study (p=0.38 and 0.89, respectively).

DISCUSSION

Principal findings

In this study, the effect of maternal hyperoxygenation during the second stage of term labor was analyzed using specific FHR features that are associated with poor neonatal outcome. Differences in depth and duration of decelerations were seen between maternal hyperoxygenation (-2.3% deceleration surface) compared to the control group (+10% deceleration surface) in favor of maternal hyperoxygenation. These differences were not statistically significant (p=0.24). This may be (partly) due to the higher than accommodated fraction of missing data.

Heart rate variability metrics

The differences in STV, SDNN, and RMSSD were not statistically significant between the intervention and the control group. Caution should be applied when interpreting these parameters, due to the autocorrelation function and zero-order interpolation of the Philips Avalon FM30 monitoring system which calculates an *average* heart rate in beats per minute.[46] The device outputs the equally sampled FHR at 4Hz. When calculated at this low sampling rate, traditional HRV metrics such as STV, SDNN and RMSSD might remain unchanged in the event of fetal acidemia.[47–49]

In contrast to other measures of FHR variability, PRSA-based parameters can be used at a sampling rate of 4Hz to calculate both the variation in FHR as well as the speed of those changes.[41] Van Scheepen et al. showed that PRSA-metrics measured at 4Hz have a high correlation with signals measured with the use of fetal ECG (1000Hz), especially when T is larger than 15, which is the case in our study.[46] Moreover, by eliminating artifacts and signal perturbations in FHR, the PRSA-based approach can be used to separately quantify the acceleration and deceleration-related components in the underlying signal.[28,37,41] Fetal compensatory mechanisms to repetitive transient hypoxic stress during labor can therefore be measured using PRSA-based parameters, as the compensatory activation of the autonomic nervous system is reflected by an increase in PRSA-AAC and PRSA-ADC.[25,50]

The difference in PRSA-based parameters (i.e. the delta values) in the two study arms was found to be statistically significant. The PRSA-ADC showed a 3% reduction in the intervention group after start of maternal hyperoxygenation, whereas a 20% increase was found in the control group after start of the study (p=0.02). For PRSA-AAC, a 4% reduction was seen in the intervention group compared to a 37% increase in the control group (p=0.03). Since the primary outcome was the relative change, and the study was powered for this outcome, our study may lack power with the current number of participants to demonstrate a difference between treatment groups for the post study data.

Previously, several studies have reported on PRSA test characteristics to predict fetal acidemia.[25,28,37,50] Rivolta et al. presented an in-vivo sheep model, where fetuses were exposed to repetitive umbilical cord occlusions. Both PRSA-AAC and PRSA-ADC progressively increased with phases of acute hypoxic-acidemia.[50] In fact, Lobmaier et al. showed that antepartum measured PRSA-AAC is a better predictor of short-term perinatal outcome than short-term variability of FHR in severely growth-restricted fetuses.[37] Weyrich et al. and Georgieva et al. studied the prognostic value of PRSA-ADC in intrapartum FHR measurements.[25,28] Using ROC-analyses, they both showed that increasing values of PRSA-DC were related to low pH at birth, and that PRSA-ADC appears to predict acidemia more accurately than short-term variability.[25,28] Therefore, the significant difference in PRSA-based parameters in favor of hyperoxygenation found in our study may positively reflect on neonatal outcome.

Baseline assignment

Various computerized algorithms are developed to analyze FHR signals to overcome the subjectivity of visual FHR analysis.[51] Several of these computerized algorithms have a high agreement and reliability.[51]

As the time-frames of interest in our study are relatively short for baseline determination (10 minutes), we chose to implement the OxSys algorithm, which had previously been validated for short 15-minute segments of FHR during labor.[29] However, since the inter-observer agreement found in our study between the OxSys algorithm and *visual analysis* was poor (kappa ≤0.60), the baseline assignment by this computerized baseline algorithm could not be used.

This prompted us to evaluate whether the Omniview-SisPorto system (Speculum, Lisbon, Portugal),[52] which is based on the FIGO guidelines, was able to determine the FHR baseline in the 10-minute segments. Unfortunately, we experienced similar difficulties with this algorithm for detecting the baseline. The inability to assign the FHR baseline is a common problem of computerized FHR analysis in the intrapartum period, especially during the second stage of labor, due to greater signal instability and the frequent occurrence of signal loss and artifacts.[27,29,30,53] It is likely that the limited duration of the time-frames in our study has further reduced the applicability of the computerized algorithms. However, for the purpose of this study, it was considered unethical to withhold other intrauterine resuscitation techniques longer than 10-minutes in the event of suspected fetal distress. Therefore, we chose not the change the time-frames and based all further analyses on the baseline value as assigned by the clinicians. Our results underline the need for a more robust method to analyze shorter segments of FHR tracings.

Clinical and research implications

Up to now, mostly small, non-randomized studies have investigated the effect of maternal hyperoxygenation in the presence of fetal distress during the second stage of labor. Those studies showed a positive effect of maternal hyperoxygenation on FHR pattern and fetal scalp pH.[14,15,18,19,54,55] Only one other RCT studying maternal hyperoxygenation has been performed in patients with suspected fetal distress. In this study by Raghuraman et al. with a noninferiority design,[20] women with >6cm cervical dilatation (stage 1 and 2 of labor) and suspected fetal distress were randomized to breathing room air or to maternal hyperoxygenation until birth. They showed no significant difference in umbilical artery lactate between both groups, which was their primary outcome.

The primary outcome of the current study was the change of FHR pattern. This outcome was explicitly chosen as the primary outcome, rather than e.g. neonatal morbidity, as this would require a sample size of over 10,000 women.[5] Therefore, in the current study, FHR pattern was used as a surrogate marker with fewer patients needed because a non-reassuring pattern of FHR is considered to be indicative of potential fetal hypoxia.[56–59] We recognize that FHR monitoring has a high sensitivity but a relatively low specificity for fetal acidosis.[27,60] Therefore we also evaluated the change in FHR by using specific FHR features that are related to unfavorable neonatal outcome.[2,27,36,37,28–35]

The previously reported significant positive effects of maternal hyperoxygenation on the FIGO classification during the second stage of labor are concordant with our current results.[22] Furthermore, in our previous study, no negative side effects were found, especially no reduction in arterial umbilical cord blood pH or increase in free oxygen radical activity.[22] Moreover, in the group with abnormal FHR, a significant reduction was seen in the rate of episiotomies on fetal indication in the intervention group, likely due to the amelioration of the FHR pattern.

Although the difference in deceleration surface is not statistically significant in the current study, possibly due to the higher than accommodated fraction of missing data, the positive effect of maternal hyperoxygenation might be significant in a larger cohort. As maternal hyperoxygenation is shown to have no harmful side-effects and has a significantly positive effect on FIGO classification and PRSA-based parameters. Therefore, we recommend to study the effect of maternal hyperoxygenation in a large study powered for neonatal outcome.

Our results suggest that the use of maternal hyperoxygenation in case of suspected fetal distress does not have to be discouraged, which is in line with the guideline of the American College of Obstetrics and Gynecology.[4]

Strengths and limitations

This study is the first RCT investigating the effect of maternal hyperoxygenation on FHR in the presence of suspected fetal distress during the second stage of labor. By limiting co-interventions in the first 10 minutes after initiation of the study protocol, the pure effect of maternal hyperoxygenation on FHR could be studied more accurately. It was considered unethical to withhold additional interventions for a longer time, due to the risk of prolonged fetal hypoxia. Moreover, the obstetric staff could overrule the study protocol at any time if deemed necessary, which was done in seven women (9.9%).

By using several computerized methods to evaluate the effect of maternal hyperoxygenation on FHR, our analysis provides additional knowledge on the physiological changes caused by maternal hyperoxygenation. In contrast to visual analyses of FHR, these computerized analyses were not influenced by intra- and interobserver variability.

However, practical issues led to some limitations. In the sample size calculation, we accommodated for 20% missing data. Since 46 women (39%) gave birth before the end of the study time-frame, FHR analyses could only be performed in 71 women (61%). Therefore, we performed sensitivity analyses to address the potential bias caused by missing data. As the matched-pair analysis showed a similar result as the primary analysis, we believe the difference in PRSA-AAC prior to the start of the study does not influence the study results on which our conclusions are based.

Unfortunately, due to organizational challenges, it was not possible to blind patients and the medical care team to the treatment allocation. Yet, the risk of bias was minimized due to, on the one hand, a blinded visual analysis of FHR tracings by the investigators, and on the other hand, a computerized calculation of deceleration surface and PRSA-based parameters.

CONCLUSION

In patients with maternal hyperoxygenation during the second stage of labor in the presence of fetal distress, the difference in depth and duration of decelerations after the start of the study was not significantly different compared to the control group. However, a significantly positive effect on PRSA-ADC and PRSA-ACC was found after maternal hyperoxygenation. Since these effects may be associated with an improvement of neonatal outcome, we now deem it justified to initiate a study powered for neonatal outcome.

SUPPLEMENTARY TABLES

Supplementary Table 1. Baseline assignability of FHR for the intervention and control group

	Pre-study time-frame			**Post-study time-frame**		
	Intervention N=36	**Control N=35**	***p-value***	**Intervention N=36**	**Control N=35**	***p-value***
	Original OxSys algorithm					
Computerized assignability of baseline	30 (83%)	26 (74%)	0.35	23 (64%)	26 (74%)	0.34
Visual assignability of baseline	26 (72%)	30 (86%)	0.16	29 (81%)	28 (80%)	0.95
Agreement computerized and visual assignability baseline	Kappa= 0.21	Kappa= 0.13		Kappa= 0.60	Kappa = 0.19	
	Original OxSys algorithm with addition baseline <110bpm is unassignable					
	Intervention N=36	Control N=35	*p-value*	Intervention N=36	Control N=35	*p-value*
Computerized assignability of baseline	27 (75%)	26 (74%)	0.95	23 (64%)	23 (66%)	0.87
Visual assignability of baseline	26 (72%)	30 (86%)	0.16	29 (81%)	28 (80%)	0.95
Agreement computerized and visual assignability baseline	Kappa= 0.21	Kappa= 0.13		Kappa= 0.60	Kappa = 0.37	
	If needed, 20 minute time-frame ¶					
	Intervention N=36	Control N=35	*p-value*	Intervention N=36	Control N=35	*p-value*
Computerized assignability of baseline	32 (89%)	30 (86%)	0.74	28 (78%)	26 (74%)	0.73
Visual assignability of baseline	36 (100%)	35 (100%)	1.00	36 (100%)	35 (100%)	-
Agreement computerized and visual assignability baseline	Kappa = incalculable§	Kappa = incalculable§		Kappa= incalculable§	Kappa= incalculable§	

Data are or n (%).§ kappa cannot be calculated in the event of one parameter being 100%.
¶ In the event no baseline could be assigned in the original 10-minute time-frame of interest, the time-frame of interest was extended to 20 minutes, by including the 10 minutes preceding the original time-frame.

Supplementary Table 2. Decelerations with loss of internal variability

	Intervention	Control	P-value
Decrease after start of study	5 (14%)	3 (9%)	
No change after start of study	30 (83%)	29 (85%)	0.67
Increase after start of study	1 (3%)	2 (6%)	

Data are n (%).

Supplementary Table 3. Decelerations in combination with tachycardia or bradycardia

	Intervention	Control	P-value
Decrease after start of study	6 (17%)	3 (9%)	
No change after start of study	23 (64%)	29 (85%)	0.11
Increase after start of study	7 (19%)	2 (6%)	

Data are n (%).

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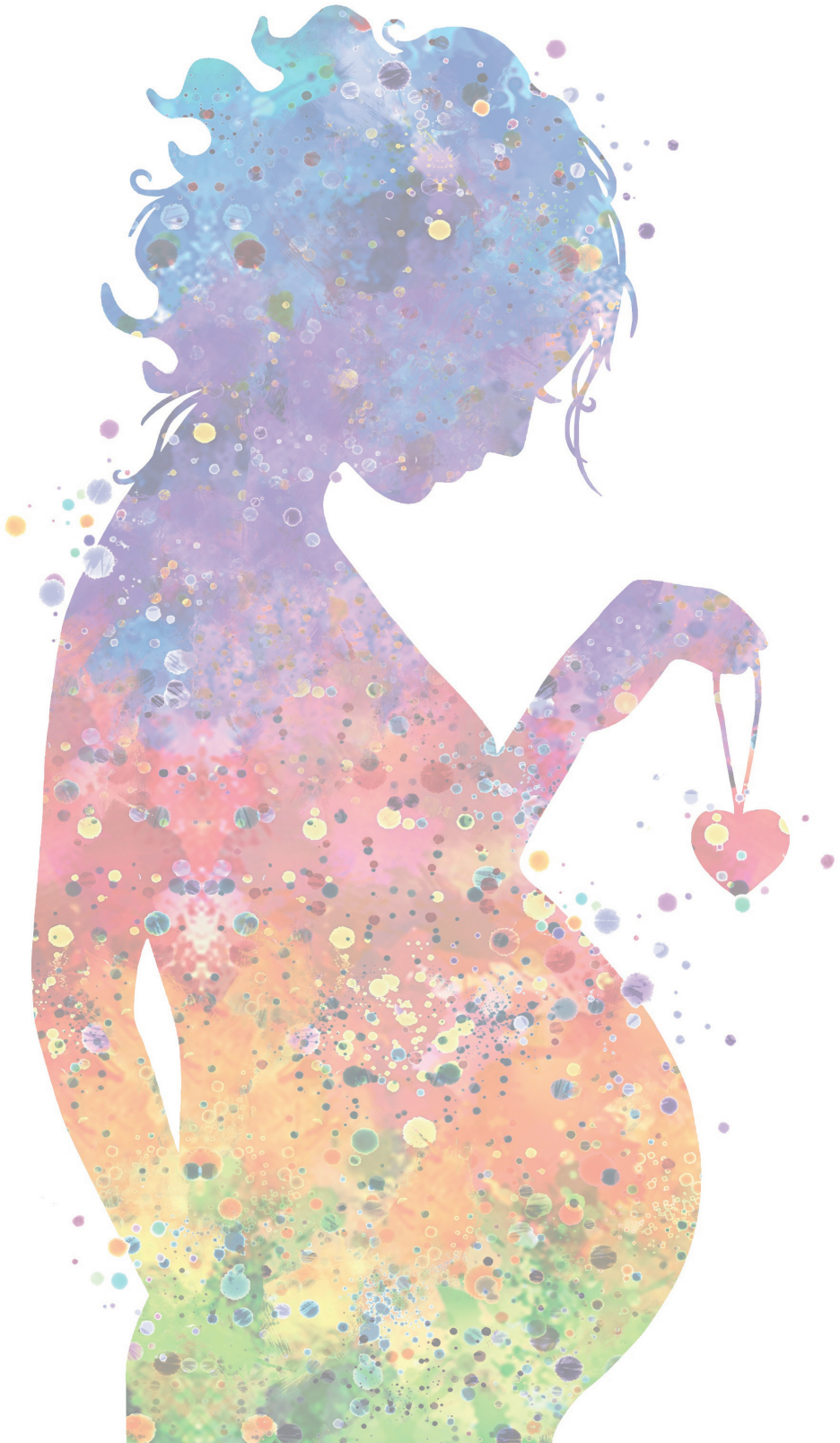

9

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Obstetric caregivers want pregnancy and delivery to be completed as safe as possible, since complications can have serious and lifelong consequences. In this thesis, several methods are addressed to help caregivers monitor and manage maternal and fetal complications during pregnancy and delivery. This thesis is subdivided into two parts, on the monitoring and management of maternal and fetal risks, respectively.

In this chapter, the main outcomes of the studies and its clinical implications are discussed and suggestions for future research are made.

MAIN FINDINGS

PART I – MONITORING AND MANAGEMENT OF THE MOTHER AT RISK OF HYPERTENSIVE PREGNANCY DISORDERS

Hypertensive pregnancy disorders (HPD) are associated with maternal, placental, fetal, and neonatal morbidity and mortality.[1–4] Therefore, adequate prediction of HPD is very important to enable early diagnosis and management. As current prediction models for HPD are limited in their predictive abilities, there is a need for new, more accurate methods. In part I of this thesis, we investigate whether two promising prediction methods, namely speckle tracking echocardiography (STE) and heart rate variability (HRV), are suitable to detect differences between women with (a history of) HPD and normotensive controls.

Is STE a suitable method to detect differences in cardiac function in pregnant women with HPD or women with a history of HPD compared to normotensive women?

Although the exact etiology of HPD is not fully known, several studies state that the primary derangement in HPD involves the cardiovascular system and abnormal placentation.[5–7] The inability of the maternal cardiovascular system to adequately adapt to pregnancy causes the maternal myocardium to subtly change in shape, size, and function.[5,8] The systematic review presented in **chapter 2** revealed that the STE parameter left ventricular (LV) global longitudinal strain (LV-GLS) is significantly decreased in pregnant women with HPD compared to normotensive pregnant women. A decrease in LV-GLS is associated with subclinical stages of multiple cardiac diseases.[9] Hence, a decreased LV-GLS in women with HPD may be an indicator of subclinical deterioration of the myocardium.

The other two directions of strain, LV global radial strain (LV-GRS) and LV global circumferential strain (LV-GRS), were found to be decreased in women with early-onset and severe preeclampsia, whereas no differences were found in women with late-onset

and mild preeclampsia. These two parameters might therefore be associated with a more severe course of HPD. However, little is known on the predictive value of abnormal strain during pregnancy. Possibly, STE results might show deterioration before the clinical onset of HPD and might therefore aid in the prediction and early diagnosis of HPD. Up till now, only one study investigated the prognostic value of STE in HPD, which showed that women with chronic hypertension and decreased LV-GLS mid-trimester had a significantly higher risk of developing superimposed preeclampsia.[10] STE therefore has tremendous clinical potential. Future studies are needed to further investigate the value of this diagnostic method during pregnancy.

Risk of cardiovascular disease after pregnancies complicated by HPD

Several large studies and meta-analyses have consistently demonstrated an increased risk of cardiovascular disease (CVD) in women with a history of HPD, especially after preeclampsia, compared to women with normotensive pregnancies.[11,12] Furthermore, the manifestation of CVD occurs earlier in women with a history of HPD compared to uncomplicated controls.[12] Hence, adequate follow-up of women with a history of HPD may allow early identification of CVD and provide opportunities for prevention and management of CVD.

Ideally, the CVD screening would focus on subclinical changes with a high predictive value of the actual development of the disease. Unfortunately, conventional echocardiographic features are unsuitable, as these parameters typically remain normal in the subclinical phase of cardiac disease.[9] In contrast, advanced techniques like STE can allow for earlier detection of these subtle myocardial changes.[13] The review provided in chapter 2 showed a decrease in cardiac function measured with STE, especially in LV-GLS, lasting up to 13 years after pregnancies complicated by HPD in women without clinical symptoms of heart disease. Possibly, these abnormal strain measurements after pregnancy may provide the desired differentiation in the risk of CVD within the high-risk group of women with a history of HPD. This could enable appropriate screening and management based on each women's personal risk profile.

Does HRV detect differences in the function of the autonomic nervous system in pregnant women with HPD or women with a history of HPD compared to normotensive women?

The autonomic nervous system (ANS) has a prominent role in the cardiovascular adaptations during pregnancy.[14–16] As HPD might originate from the inadequacy of such adaptations, differences in the functioning of the ANS – assessed by HRV – may be found between HPD and normotensive controls. Hence, in **chapter 3**, the differences in HRV were reviewed between pregnant women with HPD and normotensive pregnant women and between women with a history of HPD and women with a history of a normotensive pregnancy.

The results from the included studies showed a wide variety, possibly due to the heterogenicity of the data. Moreover, long-acting medication might influence HRV results, introducing an important confounding factor in many studies. Therefore, it is hard to draw firm conclusions based on available literature. However, a trend is seen towards an elevated sympathetic and a reduced parasympathetic tone in case of HPD. This imbalance of the ANS could contribute to the origin of HPD,[16,17] as illustrated in Figure 1. The increased sympathetic tone causes an increase in peripheral vascular resistance, leading to a higher heart rate and blood pressure. Moreover, the increase in sympathetic activity may expedite placental ischemic/reperfusion events, which subsequently leads to the release of abnormal soluble placental factors. These placental factors may cause endothelial dysfunction and vasoconstriction, which aggravates placental ischemia and leads to a higher blood pressure. The combination of these events could contribute to the development of HPD.[16,17]

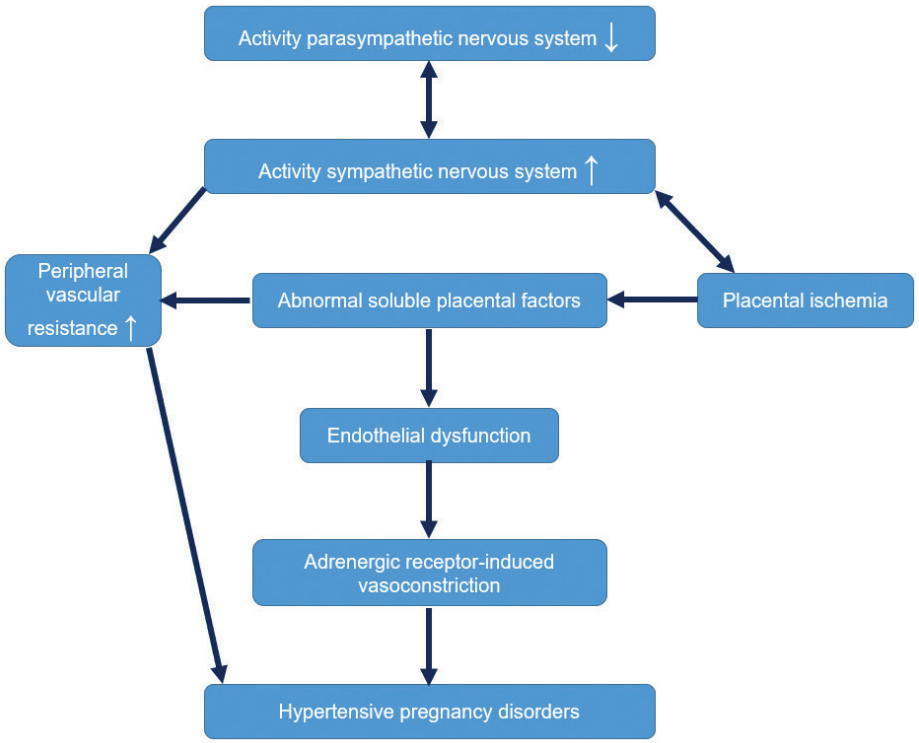

Figure 1. Schematic overview of how the autonomic imbalance is hypothesized to lead to HPD. Adapted from Moors et al.[18]

Changes in the sympathovagal balance, reflected in changes in HRV, might occur before the clinical onset of HPD. Thereby, these early changes might aid in the detection of HPD in preclinical stages. Three longitudinal studies demonstrated that in the first trimester, before the clinical onset of hypertension, the LF/HF ratio was significantly higher in high-risk women who developed gestational hypertension later in their pregnancy compared to the high-risk group that did not.[19–21] These results are promising and indicate the need for further longitudinal research.

However, before such future HRV studies are initiated, the confounding effect of certain medications should be clarified. As discussed above, the use of medication might influence HRV results, making it harder to interpret the results. Women with HPD are likely to receive routine medication such as antihypertensive drug therapy and, in severe cases, antenatally administered corticosteroids and magnesium sulfate. Unfortunately, little is known about how these medications affect maternal HRV. In contrast, several studies have demonstrated that corticosteroids and magnesium sulfate affect fetal HRV.[22–25] Given the mechanism of action of both drugs, it is likely that maternal HRV is also affected by its admission. Moreover, it is hypothesized that antihypertensive drugs may also affect maternal HRV.[17,26] Hence, it is important to quantify the effect of these medications on maternal HRV to improve the interpretation of HRV study results.

What is the effect of routine obstetric medication on maternal HRV?

To quantify the effect of routine obstetric medication on maternal HRV, we designed and initiated a longitudinal cohort study, known as the MAMA-hart study. A detailed description of the study protocol can be found in **chapter 4** of this thesis. Antenatally administered corticosteroids are chosen as the main focus of this study due to its frequent use and known effect on fetal HRV. HRV features will be compared between the epoch prior to medication admission and the epoch after medication admission, thereby quantifying the effect of medication on maternal HRV.

Participants are likely to also receive other obstetric medication as part of standard care, which is an unavoidable limitation in this study design. Although the administration of multiple drugs could confound the measurements, it also offers the opportunity to explore the effect of those medications on maternal HRV. This may contribute to also limit their confounding effect in future HRV studies.

All participants will wear a wrist-worn device that acquires continuous photoplethysmography (PPG) measurements, from which HRV features will be derived. Even though electrocardiography (ECG) is the more traditional method to measure HRV, the use of PPG measurement has several advantages over ECG. Firstly, the wrist-worn device that measures PPG is non-invasive, non-obstructive, and simple in its use. Secondly, continuous measurements with a wrist-worn device are less costly than continuous ECG measurements.[27]

Although ECG measurements offer a higher sampling rate of the heart rate than PPG, literature shows that if PPG is acquired with a sampling rate of ≥25 Hz, HRV measurements using PPG can be as reliable as those derived from ECG.[28] Hence, if HRV might turn out to be an effective method in prediction and early detection of HPD, the use of PPG measurement with a wrist-worn device might be better suited for clinical practice than ECG.

It is therefore expected that the results from the MAMA-hart study will reduce the confounding effect of routine obstetric medication in studies employing HRV. Thereby, future studies can more accurately distinguish changes in HRV associated with pregnancy complications, from those resulting from the use of medication. An improved understanding of possible HRV changes associated with pregnancy complications could in turn facilitate earlier diagnosis of those complications, allowing timely implementation of risk-mitigating interventions.

PART II – MONITORING AND MANAGEMENT OF THE FETUS AT RISK FOR FETAL DISTRESS

Monitoring and management of fetal distress during labor is complex. Obstetricians are challenged to, on the one hand, perform timely interventions to prevent fetal hypoxia and asphyxia, but, on the other hand, prevent unnecessary interventions due to their potential harm to both the mother and her child. Moreover, in case of suspected fetal distress, the healthcare team has to decide whether the risk of fetal hypoxia is so severe that immediate delivery of the baby is needed, or if fetal oxygenation can be restored with the use of intrauterine resuscitation techniques. To help with this decision, several methods can be used to monitor the fetal condition during labor.

In part II of this thesis, we first discuss which monitoring and management strategies are recommended in guidelines and used in clinical practice. Subsequently, we focus on the effect of one frequently debated intrauterine resuscitation technique: maternal hyperoxygenation.

Which methods are recommended in international guidelines regarding the monitoring and management of fetal distress during labor?

In **chapter 5** we compared recommendations regarding fetal monitoring and management of suspected fetal distress from the national guidelines of several Western countries. All of the obtained guidelines recommended the use of cardiotocography in high-risk population during delivery. Although it is deemed the best available method to monitor fetal condition during labor in high-risk population, it has some shortcomings, and additional information regarding the fetal condition might be desired. Two main methods can acquire such additional information, namely fetal scalp blood sampling (FSBS) and analysis of the ST segment of the fetal ECG (short ST analysis).

With respect to monitoring, all guidelines recommended the use of FSBS if additional testing is required. A Cochrane review reported an increase in instrumental deliveries and a decrease in neonatal acidosis following FSBS.[29]

In contrast to FSBS, the recommendations on the use of ST-analysis were conflicting, with three guidelines promoting this monitoring technique and three others advising against its use. This might be because, even though the use of ST-analysis significantly decreases the need for FSBS as well as the number of vaginal assisted deliveries,[30] the use of this technique does not cause significant decrease in other outcomes like cesarean sections, neonatal intensive care admissions, neonatal acidosis and perinatal deaths.[30] Previous studies have shown that ST-analysis is influenced by electrode placement and head orientation of the fetus.[31,32] This confounding effect may be partly corrected by using relative ST-analysis, in which the rise in T/QRS fragment is analyses as a percentage from the baseline.[33] To our knowledge, there are no trials comparing cardiotocography with FSBS to cardiotocography with (relative) ST-analysis. The variations in international guidelines regarding these techniques emphasize the need for such studies.

Five guidelines also contained recommendations on intrauterine resuscitation as a method for management of fetal distress. Their recommendations were consistent concerning the use of tocolytic drugs and discontinuation of oxytocin, which were advised in all guidelines. In contrast, the recommendations regarding maternal hyperoxygenation and amnioinfusion were contradictory.

How can these differences in international guidelines be explained? The main reason seems to be the lack of solid evidence. Hence, recommendations need to be made on limited available evidence, which may cause variation in the interpretation of the study results. The differences in international guidelines create ambiguity for health care professionals, which may lead to variations in clinical practice. Therefore, future research should focus on providing more clarity, especially with regard to maternal hyperoxygenation, amnioinfusion and ST-analysis.

Which fetal monitoring methods are used in Dutch clinical practice, and which intrauterine resuscitation techniques are utilized in case of suspected fetal distress?

To investigate how fetal distress is diagnosed and managed in the Netherlands, in 2015 a nationwide survey was conducted in all Dutch hospitals, the results of which are also presented in chapter 5. Cardiotocography was used in all hospitals to monitor the fetal condition. In addition, FSBS was available and used in 98% of Dutch hospitals. This was an increase compared to the 87% availability found in 2009.[34] In contrast, the use of ST-analysis decreased from 30% in 2012[35] to 23% in 2015.

The following intrauterine resuscitation techniques are commonly used in all Dutch hospitals; maternal repositioning, discontinuation of oxytocin, and the use of tocolytic drugs. The use of maternal hyperoxygenation and amnioinfusion is inconsistent in Dutch hospitals, thus reflecting conflicting international guidelines. This inconsistency also exposes the lack of recommendations regarding these two interventions in the Dutch guideline at the moment of this survey.

The results from this nationwide survey show that, even in a country as small as the Netherlands, a large practice variation is present in monitoring and management of fetal distress during labor. This is likely due to a lack of solid scientific evidence. Moreover, the lack of recommendations on certain aspects of monitoring and management of fetal distress in the Dutch national guideline, as well as the different interpretation of study results among delivery room staff, may extend this variation even more. This may be extremely confusing for a patient who gives birth to her first child in Dutch hospital A, moves to another city, and gives birth to her next child in Dutch hospital B.

What is the effect of intrauterine resuscitation by maternal hyperoxygenation during the second stage of term labor on neonatal and maternal outcome?

Maternal hyperoxygenation is one of the most debated intrauterine resuscitation techniques. Although it is frequently used, robust evidence regarding its effect is scarce and conflicting.[36,37] Consequently, the need for more research has been underlined in multiple reviews.[36,37]

Therefore, we designed and performed the INTEREST O2 study, which is the first randomized controlled trial (RCT) evaluating the effect of maternal hyperoxygenation in case of suspected fetal distress during the second stage of labor. A detailed description of the study protocol of this single center RCT can be found in **chapter 6.**

Patients were included in case of suspected fetal distress during the second stage of term labor, defined as either an intermediary or an abnormal FHR pattern according to the modified FIGO classification.[38] All participants were randomly allocated to receive either maternal hyperoxygenation with 100% oxygen or conventional care without additional oxygen.

The primary outcome of this study was the change in FHR, which may be topic of debate. One could argue that the primary outcome should have been neonatal morbidity. However, achieving sufficient power for the latter would require a very large sample size of over 10,000 women.[39] As the effect and potentially harmful side-effects of maternal hyperoxygenation were not properly investigated yet, we chose not to expose such a large group of women and their fetuses to this intervention. Hence, a change in FHR was used as a surrogate marker for neonatal outcome, with fewer patients needed. Currently,

FHR is deemed the best available method to monitor the fetal condition during labor, and a non-reassuring FHR pattern is considered to be indicative of potential fetal hypoxia.[29,40] One of the limitations of FHR monitoring is its low specificity for fetal acidosis.[38,41] Therefore, we also evaluated the change in FHR using specific FHR features that are related to unfavorable neonatal outcome.

Besides the change in FHR, several secondary outcomes were chosen to analyze the safety and potentially harmful side-effects of maternal hyperoxygenation.

In addition to the complete case analysis, additional subgroup analyses were performed on participants with *intermediary* FHR pattern and with *abnormal* FHR pattern, respectively. Moreover, a third subgroup was analyzed consisting of the patient group with *small for gestational age fetuses* (<10th percentile). With these subgroup analyses, we wanted to analyze more specifically whether one of the subgroups would potentially benefit more than others from maternal hyperoxygenation, as previous studies demonstrated that fetuses with the lowest initial oxygen saturation benefit the most from this intervention.[42,43]

The perinatal and maternal outcomes of the INTEREST O2 study are described in **chapter 7**. We found no statistically significant differences in Apgar Score, NICU admission, or umbilical cord blood gas. Furthermore, we measured malondialdehyde in umbilical cord blood as a marker to evaluate the potential harm of free oxygen radicals. In contrast to previous studies on the prophylactic use of maternal hyperoxygenation, the levels of malondialdehyde were not significantly different between both groups, implying that we could not observe harmful side effects on the fetus. This rejects the most important argument to discourage the use of this intrauterine resuscitation technique.

Besides the absence of harmful side-effects of maternal hyperoxygenation, a positive effect was seen on the number of episiotomies on fetal indication, as this intervention was carried out less often in mothers receiving extra oxygen, with a statistically significant decrease in the subgroup with abnormal FHR pattern. The reduction in this potentially harmful intervention might indicate a better fetal condition after maternal hyperoxygenation, as fewer fetuses were in such distress that an episiotomy was needed to immediately terminate the delivery.

Does maternal hyperoxygenation, applied in case of suspected fetal distress during the second stage of term labor, affect FHR?

In routine obstetric care, the FHR pattern is typically analyzed with the use of the FIGO classification.[38] Hence, we analyzed the change in FIGO classification following hyperoxygenation, as evaluated by clinicians.

The change in FHR could be analyzed for 71 participants (61%). The other 46 participants (39%) gave birth before the end of the time-frame of interest and, therefore, insufficient FHR data existed in the "post-study" time-frame to properly analyze the change in FHR. A significantly positive effect of maternal hyperoxygenation on change in FIGO classification was found. A similar beneficial effect was seen in all subgroup analyses, albeit not statistically significant. Even though this study was not powered for neonatal outcome, the positive effect seen on FIGO classification may positively reflect on neonatal outcome. Larger studies powered for neonatal outcome are needed to confirm this finding.

Although visual analysis of FHR, as used for the FIGO classification, is one of the most used methods to evaluate the FHR, it is known to have a large intra- and inter-observer variability.[44,45] Computerized analysis of FHR could improve intra- and interindividual reproducibility and could also provide additional insights in physiological changes by assessing FHR features that are not detected visually. Therefore, the effect of maternal hyperoxygenation has also been evaluated using detailed computerized analyses. These results are presented in **chapter 8.** The change in depth and duration of FHR decelerations was not statistically different between maternal hyperoxygenation (decrease of 2.3%) and conventional care (increase of 10%). This may be (partly) due to insufficient power due to the higher than accommodated fraction of missing data.

Besides FHR decelerations, fetal HRV is one of the most important markers to assess fetal wellbeing.[46] Phase-rectified signal averaging (PRSA) is an innovative non-traditional method to characterize HRV that, in contrast to traditional HRV metrics, can be used at the sampling rate of 4Hz, which is typically used at delivery wards.[47] A significantly positive effect of maternal hyperoxygenation was seen on PRSA-based parameters, with a decrease of both PRSA-acceleration capacity and PRSA-deceleration capacity in the intervention group and an increase of both these parameters in the control group. These significant differences in PRSA-based parameters indicate less compensatory activation of the ANS after maternal hyperoxygenation, which may positively reflect on neonatal outcome.

In conclusion, the INTEREST O2 study is the first RCT to study the effect of maternal hyperoxygenation on FHR in the second stage of labor. The difference in deceleration depth and duration was not significant, possibly due to the higher than accommodated

fraction of missing data. The change in FIGO classification and PRSA-based parameters did show a significantly positive effect of maternal hyperoxygenation, which may positively reflect on neonatal outcome. As this study shows a potentially beneficial effect of maternal hyperoxygenation, without any harmful side-effects, there is no need to ban this intervention from delivery rooms that are currently using this technique. Larger studies powered for neonatal outcome are needed to provide strong recommendations for the use of maternal hyperoxygenation in clinical practice. Given the results presented in this thesis, there are no longer impediments to withhold the conduction of such large trials.

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

The research presented in this thesis yields multiple opportunities to improve monitoring and management of both maternal and fetal risks during pregnancy and delivery.

Implications for maternal care

This thesis shows that STE is a suitable method to detect differences between pregnant women with HPD and normotensive controls. Its clinical implications may become more evident once the clinical and prognostic value of abnormal strain during pregnancy has been further evaluated. Likely, STE may become a key aspect in the future prediction and early detection of HPD. The significant differences observed in women with HPD may already exist before the clinical onset of HPD. If so, those parameters might be used for HPD risk stratification in addition to the currently used maternal medical history. Women with an increased risk of HPD based on their medical history (e.g. women with obesity, higher age, primigravida) could undergo STE, enabling a more precise and individual risk prediction. This might in turn facilitate a more personal management strategy and contribute to improved medical care for women at risk of HPD.

Besides the abnormalities that can be detected with STE during pregnancies complicated by HPD, this technique can also detect lasting myocardial changes in women with a history of early-onset preeclampsia before the clinical onset of CVD. STE has gained growing importance in several clinical settings over the last decade, confirming its added value in cardiac function analysis.[9] However, the clinical implications of these STE abnormalities after HPD are not yet known. Do women with a history of HPD have an even higher risk of CVD when they have decreased strain? Or do they have a higher risk of a specific cardiac conditions, like arterial hypertension and ischemic injury? Is there a drug therapy that should be advised for women who had early-onset preeclampsia and have abnormal STE parameters? Additional research is needed to answer these questions and establish which role STE might play in the cardiovascular follow-up after HPD. Possibly, abnormal strain measurements might help to differentiate the risk of

CVD within this high-risk group of women with a history of HPD, enabling appropriate screening and treatment based on each women's personal risk profile.

Similar to STE parameters, differences in HRV between women with (a history of) HPD and normotensive controls are also evaluated in this thesis. Even though some differences in the function of the ANS can be detected with the use of HRV, the large heterogenicity found in current literature combined with the confounding effect of long-acting medication, makes it hard to draw firm conclusions. This impedes the direct clinical applicability of this method. Does this mean that HRV is, thereby, unsuited for the prediction and early detection of HPD, making further research on this topic irrelevant? We believe not. Despite the limitation of confounding factors, there are still indications that HRV can detect a sympathovagal disbalance in HPD, possibly even before the clinical onset of HPD. Hence, when the 'noise' in the HRV signal caused by confounding factors is quantified and eliminated, HRV may still be a promising method for the prediction and early detection of HPD. Therefore, prior to future research on HRV differences between HPD and normotensive controls, the confounding effect of several medications should be clarified, enabling better interpretation of the results of HRV analyses and, subsequently, enable the use of this method in clinical practice.

To address this knowledge gap, we therefore designed the MAMA-hart study to quantify the effect of routine obstetric medication. The results of this study will enable future studies to eliminate the confounding effect of such medication. Thereby, future research can provide solid conclusions whether HRV can detect differences between HPD and normotensive controls, and, if so, whether longitudinal HRV measurements during pregnancy could aid in the prediction of HPD.

Implications for fetal care

This thesis also contains a comparison of the recommendation in international guidelines for monitoring and management of fetal distress, showing a large variation. Hence, even though the Netherlands and the United Kingdom have great similarities regarding medical care, a patient admitted at a British delivery ward might get a different treatment when fetal distress is suspected compared to a patient from a Dutch delivery ward. Due to the lack of solid evidence, it is difficult to say which of those two patients gets the 'best' medical care. If we don't know this answer as professionals, how can we promise our patients to provide the best possible care to make sure their baby is born as safely as possible? The observed variation underlines the need for high-quality research on this topic. Results from those high-quality studies can enable uniform, evidence-based recommendations, reducing the differences currently found at delivery wards in various Western countries as well as within the Netherlands itself.

Hence, we encourage to further evaluate the potentially beneficial effect of maternal hyperoxygenation as shown from the INTEREST O2 study results in a trial powered

for neonatal outcome. This will provide evidence whether this treatment should be implemented in delivery wards all around the world. Oxygen is a therapy that is available in almost all hospitals, is easy in use, and proven to have minimal side-effects. In the end, maternal hyperoxygenation might contribute to better management of fetal distress during labor, leading to a decrease in perinatal asphyxia with potentially life-long health consequences.

Before a new treatment like maternal hyperoxygenation can be implemented in clinical practice, its effect needs to be proven by of clinical research. Based on the available evidence, doctors try to provide the best care for their patients. Even though traditional RCTs are considered the gold standard to investigate clinical issues, their design may not always be feasible for all therapeutic problems. Other types of RCT design, like a stepped-wedge design, may in some cases be better suited to provide adequate evidence on the impact of interventions used in acute settings like the management of fetal distress. The design of a stepped-wedge study involves random and sequential crossover of clusters from control to the intervention until all clusters are exposed, thereby eliminating the need for individual randomization in the acute clinical setting.[48,49] As the Dutch national guideline currently advises to only use maternal hyperoxygenation in a study setting, an excellent opportunity is provided to set-up a large randomized trial with a stepped-wedge design in the Netherlands to evaluate the effect of this intervention on neonatal outcome. Moreover, the stepped-wedge design could also offer the possibility to study the clinical implementation of maternal hyperoxygenation at the delivery wards across the country. In the end, the high level evidence from such a trial can provide insights to improve perinatal care, thereby contributing to a reduction in neonatal morbidity and mortality.

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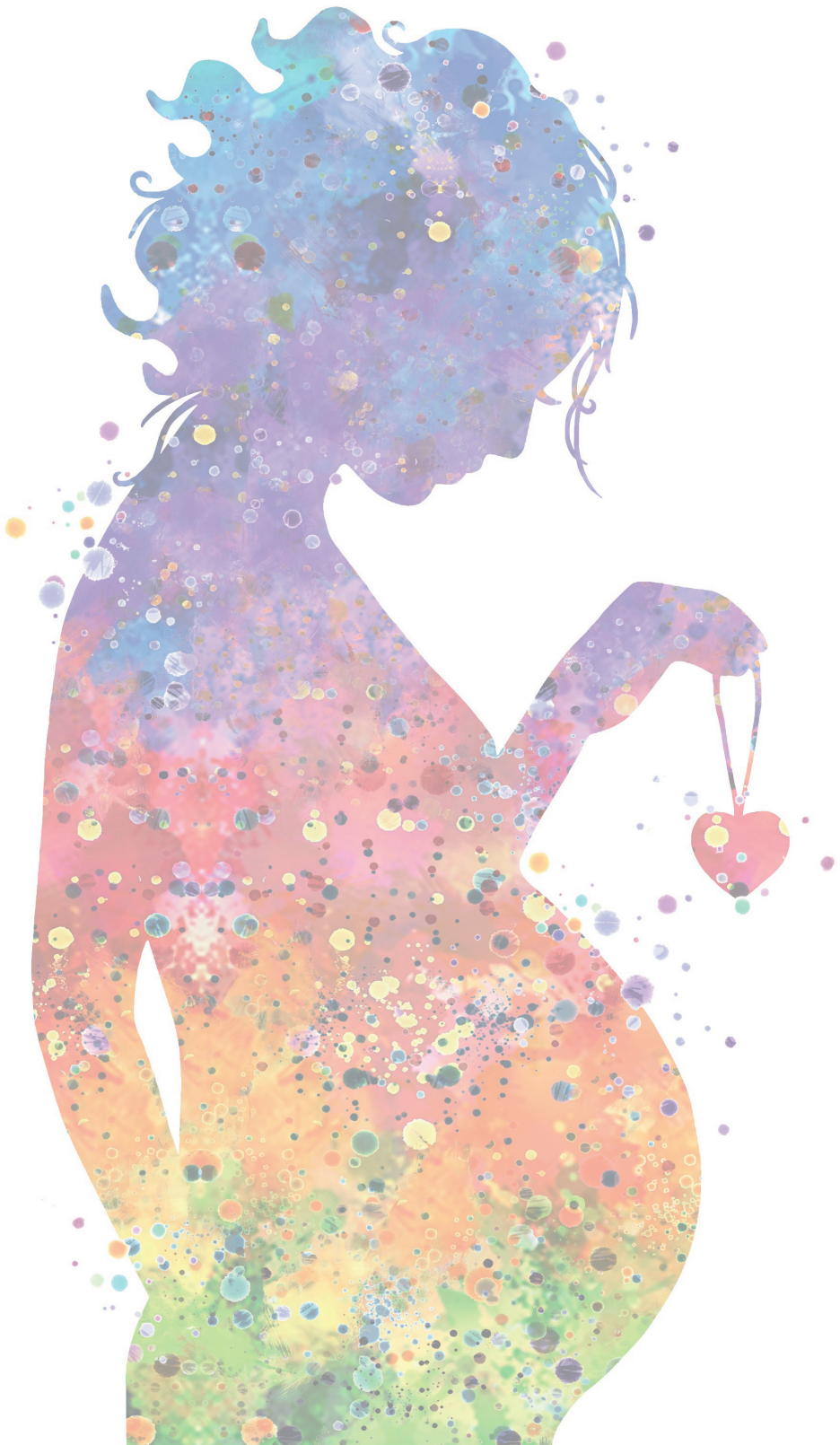

10

English summary

SUMMARY

Monitoring and management of mother and fetus at risk

Although most pregnancies and deliveries are uneventful, complications during pregnancy and childbirth can have serious and long-term consequences for both the mother and her baby. Monitoring can aid in early detection of those complications and enable appropriate management, thereby preventing adverse outcomes. Therefore, it is very important to adequately monitor and manage mothers and their fetuses.

This thesis describes the monitoring and management of maternal and fetal complications during pregnancy in two parts, respectively.

In **chapter 1,** a general introduction is provided on the physiological adaptations that occur in uncomplicated pregnancies, and on the monitoring and management of fetal and maternal pregnancy complications. Furthermore, the study objectives of this thesis are introduced.

Part I of this thesis concentrates on the monitoring and management of mothers at risk of hypertensive pregnancy disorders (HPD). As HPD are a major cause of maternal and fetal morbidity and mortality worldwide, accurate prediction of HPD followed by appropriate management can have major benefits for maternal, fetal, and neonatal health. Currently, risk prediction is mainly based on maternal history, which has limited predictive ability.[1,2] To improve the quality of prediction, numerous studies have evaluated the predictive abilities of various tests.[3] However, so far, none of those tests showed adequate performance.[3]

Therefore, there is a need for new methods for accurate prediction and early detection of HPD. In part I of this thesis, two promising prediction methods, namely speckle tracking echocardiography (STE) and heart rate variability (HRV), are evaluated on their ability to distinguish HPD from normotensive pregnancies.

STE is a relatively new diagnostic method that analyzes the motion of tissues in the heart by using acoustic reflections called speckles to measure strain. As HPD causes subtle changes in myocardial tissue, it is hypothesized that STE could aid in the prediction and early detection of HPD. Hence, in **chapter 2**, we performed a systematic review to study whether STE is a suitable method to detect differences in cardiac function in pregnant women with HPD compared to normotensive pregnant women. This review also studies possible STE differences between women with a history of a pregnancy complicated by HPD and women with a history of uncomplicated pregnancy. The databases of Medline (Pubmed), EMBASE, and Central were systematically searched and 200 articles were identified. These articles were screened, leaving 16 articles that met our inclusion criteria.

These 16 studies included 870 women with (a history of) HPD and 693 normotensive controls.

Of the three directions of strain, left ventricular (LV) global longitudinal strain was decreased the most in pregnant women with HPD, with a significant decrease in both preeclampsia and gestational hypertension. Also, LV global radial strain and LV global circumferential strain were found to be decreased in women with early-onset and severe preeclampsia compared to normotensive pregnant controls, whereas no differences were found in women with late-onset and mild preeclampsia.

Lasting myocardial changes were seen in women with a history of early-onset preeclampsia, with a significant decrease in all three directions of LV strain. In contrast, no significant alterations in strain were found between women with a history of late-onset preeclampsia compared to a history of uncomplicated pregnancy.

In addition to STE, heart rate variability (HRV) is another promising method to study the differences between normotensive and hypertensive pregnancies. HRV can be used as a proxy measure for autonomic nervous system (ANS) activity, and several studies state that HPD might be associated with a dysfunction of the ANS.[4,5]

In order to assess the value of HRV in detecting HPD, **Chapter 3** provides the results of a systematic review of previous studies comparing HRV in women with HPD or a history of a pregnancy complicated by HPD with normotensive controls. A systematic search was performed in the databases of Medline (Pubmed), EMBASE, and Central in which initially 523 articles were obtained. A total of 24 studies were found eligible and were included in this review, comprising 850 women with (a history of) HPD and 1205 normotensive controls.

The results of the included studies showed a wide variety, possibly due to the heterogenicity of the data. In frequency-domain features, the low frequency/high frequency-ratio (LF/HF-ratio) was increased in women with (moderate) preeclampsia compared to normotensive pregnant controls in four out of six studies. None of the included studies demonstrated a decrease in LF/HF ratio in patients with preeclampsia. Similar results were found for gestational hypertension and chronic hypertension.

In time-domain features, standard deviation of normal-to-normal interval (SDNN) and HRV triangular index, both indices reflecting overall HRV, were decreased in preeclampsia compared to normotensive pregnant controls. These results may be suggestive of a sympathetic overactivity of the autonomic nervous system, possibly associated with a parasympathetic withdrawal. However, due to the large diversity in the results of the included studies, caution should be applied when drawing these conclusions.

Unfortunately, the included studies reported very little on the medication used in their study population, causing a possibly important confounding factor in many studies. Women with pre-term HPD are likely to receive routine medication such as antenatally administered corticosteroids, however, little is known on how these medications affect maternal HRV.

Therefore, we designed a longitudinal cohort study, known as the MAMA-hart study, to study the effects of several routine obstetrical medications on maternal HRV, as presented in **chapter 4**. With the use of a wrist-worn device, continuous, long-term photoplethysmography (PPG) measurements will be obtained to derive HRV features. The study comprises two phases. In the *primary phase*, patients between 23+5 and 33+6 weeks of gestation with an indication to receive corticosteroids antenatally will be included, and PPG measurements will be obtained throughout the subjects' hospitalization. The study mainly focuses on the effect of antenatally administered corticosteroids, which are frequently used and are known to affect fetal HRV.[6,7] Yet, there is an evident knowledge gap regarding its effect on maternal HRV. In addition, we will also study Magnesium Sulphate, Nifedipine, Labetalol, and Methyldopa, as they are used routinely in obstetric care.

HRV features will be compared between the epoch prior to the medication admission and the epoch after medication is administered. By quantifying the effect of routinely used obstetric medication on maternal HRV, their confounding effect can be accounted for in studies employing maternal HRV. Hence, future studies will be enabled to distinguish changes in HRV associated with pregnancy complications like HPD and preterm labor from those resulting from the use of medication. This may aid in a better understanding of how dysfunction of the ANS might lead to pregnancy complications, possibly enabling earlier diagnosis and management of these complications.

During the *secondary phase* of the study, continuous PPG measurement will be acquired in the same patients from the primary phase during a 24-hour monitoring period at six weeks postpartum. The same wrist-worn device as used in the primary phase will be worn in free-living conditions at home during the *secondary phase*. This additional measurement offers a unique opportunity for comparison of cardiovascular parameters between the antepartum and postpartum periods, on which little literature exists.

Part I thus presents the results of our research on monitoring and management of mothers at risk during pregnancy. While showing that two promising methods can provide additional information on pregnancies complicated by HDP, we also identified a need for investigating the effects of routine obstetrical medications on maternal HRV.

Part II of this thesis focusses on the monitoring and management of fetal distress during labor, as the risk of compromised fetal oxygenation is increased during labor due to

reduced oxygen delivery caused by uterine contractions.[8] To monitor the fetal condition and oxygenation during labor, various methods can be used including a combined registration of FHR in relation to uterine contractions (i.e. cardiotocography), the analysis of the ST-segment of the fetal electrocardiogram (ST-analysis), fetal scalp blood sampling (FSBS), and fetal pulse oximetry.

When fetal distress is suspected, different intrauterine resuscitation techniques can be used to optimize the fetal condition, including maternal repositioning, discontinuation of oxytocin administration, administration of tocolytic drugs, amnioinfusion, iv fluid bolus, and maternal hyperoxygenation. However, evidence on the effect of these intrauterine resuscitation techniques is limited and sometimes conflicting.[9] This lack of robust evidence is likely to result in variation in clinical guidelines. Therefore, in **chapter 5,** the national guidelines of several Western countries were compared regarding their recommendations on fetal monitoring and management of fetal distress. Eight guidelines were obtained on monitoring of fetal distress during labor. All guidelines advised to use FSBS in addition to cardiotocography. The use of ST-analysis as part of fetal monitoring was recommended in three guidelines, while it was discouraged in three other guidelines. Two guidelines advised not to use fetal pulse oximetry, whereas the others did not mention this technique in their guidelines.

Five guidelines contained recommendations on the use of intrauterine resuscitation techniques. All guidelines recommended maternal repositioning, the discontinuation of oxytocin, and the use of tocolytic drugs. Regarding maternal hyperoxygenation, the guidelines were contradictory. In the United States of America and Canada, maternal hyperoxygenation is recommended in case of fetal distress, whereas the national guideline from the United Kingdom advises against this treatment due to the possible harmful side-effects and lack of solid evidence. The recommendations on the use of amnioinfusion and IV fluid bolus also varied between the different guidelines.

It seemed likely that the differences in recommendations would lead to variation in clinical practice. To test this hypothesis, a survey was conducted in all 86 Dutch hospitals on their diagnostic and therapeutic methods in case of suspected fetal distress. All hospitals use cardiotocography to monitor the fetal condition, and additional FSBS is available in 98% of Dutch hospitals. In 23% of the hospitals, ST-analysis is used to monitor the fetal condition. Whilst discontinuation of oxytocin infusion, administration of tocolytic drugs, and maternal repositioning are implemented in almost 100% of Dutch hospitals in case of suspected fetal distress, a large practice variation is shown in the use of maternal hyperoxygenation and amnioinfusion, in 58% and 33% of Dutch hospitals, respectively.

These differences in clinical practice and international recommendations may be attributed to the lack of solid evidence from clinical studies. With regard to maternal

hyperoxygenation, its effect in the presence of suspected fetal distress in women during the second stage of labor has not yet been evaluated in a randomized controlled trial (RCT). However, several small, non-randomized studies as well as a mathematical computer model showed an improvement in fetal heart rate (FHR) pattern and/or fetal scalp pH after applying this technique in case of fetal distress.[10–14] Supported by the results from these studies, we designed and conducted an RCT to study the effect of this intrauterine resuscitation technique during the second stage of labor, of which the study protocol is described in **chapter 6**. In this study, known as the INTEREST O2 study, patients with suspected fetal distress during the second stage of term labor will be randomized to receive either maternal hyperoxygenation with 100% oxygen at 10L/min applied by a non-rebreathing mask, or conventional care without additional oxygen. Suspected fetal distress is defined as an intermediary or abnormal FHR tracing according to the modified FIGO classification.[15]

The primary outcome of this study is the change in FHR pattern after the start of the study, measured as the change in depth and duration of FHR decelerations. This outcome represents a surrogate endpoint of fetal well-being, as a non-reassuring FHR pattern is considered to be indicative of potential fetal hypoxia.[16,17] Moreover, a study powered for neonatal morbidity would require a sample size of over 10,000 women.[18] Because some studies raised concerns about the potentially harmful effects of maternal hyperoxygenation, we chose not to expose such a large group of women and their fetuses to this intervention before its safety had been further investigated.

The secondary outcomes of the INTEREST O2 study include the change in FIGO classification, neonatal Apgar score, umbilical cord blood gas analyses, free oxygen radical activity, NICU admission, neonatal death, mode of delivery, and maternal side effects. Furthermore, detailed FHR analyses will be performed based on calculation of unstable baseline, phase-rectified signal averaging (PRSA)-based parameters, decelerations with loss of internal variability, and decelerations in combination with fetal bradycardia or tachycardia. All of these parameters have been previously related to poor neonatal outcome.[19–22]

The change in FHR will first be analyzed per patient and subsequently compared between the intervention and the control group. For each patient, the 10-minute epoch before start of the study will be compared to the epoch 5 to 15 minutes after the start of the study.

In addition to the intention-to-treat analyses, per-protocol analyses and subgroup analyses will be performed. Two subgroups consist of cases with either intermediate or abnormal FHR patterns (according to FIGO classification), while the third subgroup analysis comprises the group with small for gestational age neonates (birth weight <p10).

Perinatal and maternal outcomes of the INTEREST O2-study are described in **chapter 7**. A total of 117 women were included in the study. To evaluate potential harm from free oxygen radical activity, Malondialdehyde in umbilical cord blood was measured, but was not significantly different between the intervention and the control group. Most secondary clinical outcomes did not significantly differ between groups, e.g. Apgar score, umbilical cord blood gas analyses, and mode of delivery. However, in the subgroup with abnormal FHR tracings, there were fewer episiotomies on fetal indication in the intervention group (25%) compared to the control group (65%, p<0.01). This decrease in the intervention group is considered a favorable outcome, as episiotomies are considered a potentially harmful intervention.[23] Moreover, this reduction in episiotomies on fetal indication might indicate a better fetal condition in the intervention group, as fewer fetuses were in such distress that an episiotomy was indicated to immediately terminate the delivery.

Change in FHR could be analyzed for 71 participants (61%), as the other 46 women (39%) gave birth before the end of the time-frame of interest and therefore insufficient FHR tracing existed in the "post-study" time-frame to properly analyze the change in FHR. In this particular work, we studied the effect on FHR as the change in FIGO classification as evaluated by clinicians. Improvement of FIGO classification (e.g. abnormal to intermediary FIGO category) was seen over four times as often in the intervention group compared to the control group (13.9% vs. 2.9%). Furthermore, deterioration of FIGO classification was lower in the intervention group compared to the control group (8.3% vs. 34.3%). The change in FIGO classification in favor of maternal hyperoxygenation was statistically significant (OR 5.7, 95% CI 1.7-19.1). A similar trend was seen in the subgroup analyses, albeit not significant.

This study was powered for FHR, not for neonatal outcome. Yet, the positive effect of maternal hyperoxygenation on FIGO classification may positively reflect on neonatal outcome, however, larger studies powered for neonatal outcome are needed to confirm this finding.

The primary outcome of the INTEREST O2 study is the change in FHR pattern. Although visual analysis of the FHR, as used for the FIGO classification in chapter 7, is one of the most used methods to evaluate FHR, it is known to have a large intra- and inter-observer variability.[24,25] Therefore, we also performed a more detailed, computerized analysis of the change in FHR of the INTEREST O2 study, the results of which are presented in **chapter 8.** This detailed analysis provides additional knowledge of the physiological changes caused by maternal hyperoxygenation.

Differences were seen in the depth and duration of FHR decelerations between maternal hyperoxygenation (-2.3%) compared to the control group (+10%). These differences were not statistically significant (p=0.24), which may be (partly) due to the higher than

accommodated fraction of missing FHR data in the group of women that already gave birth before the end of the study time-frame.

The change in PRSA-average acceleration capacity (PRSA-AAC) and PRSA-deceleration capacity (PRSA-ADC) after the start of the study was statistically significant in favor of maternal hyperoxygenation (p=0.03 and p=0.02, respectively). These significant differences in PRSA-based parameters in favor of maternal hyperoxygenation indicate less compensatory activation of the autonomic nervous system after maternal hyperoxygenation, which may positively reflect on neonatal outcome.

No significant differences were found between the intervention and control group for the following FHR features; periods with unstable FHR baseline, decelerations with loss of internal variability, and decelerations in combination with tachycardia or bradycardia.

The results of the INTEREST O2 study show a significantly positive effect of maternal hyperoxygenation on FHR as evaluated with the use of FIGO classification and PRSA based parameters. The difference in deceleration depth and duration, however, was not significant. No harmful effects of maternal hyperoxygenation were demonstrated.

In **chapter 9**, the main findings of this thesis are discussed and subsequently, recommendations for future research are proposed.

The main conclusions of this thesis are:

1. Speckle tracking echocardiography is a suitable method to detect preclinical differences in cardiac function in pregnant women with HPD compared to normotensive pregnant women, especially with the use of LV global longitudinal strain. In women with a history of HPD, only the subgroup of early-onset preeclampsia showed lasting myocardial changes compared to women with a history of a normotensive pregnancy.
2. Some differences in autonomic nervous system functioning can be detected with the use of HRV in women with HPD, as a decreased overall HRV was found in preeclampsia, compared to normotensive pregnant controls. A trend is seen towards increased LF/HF-ratio in women with PE compared to normotensive pregnant controls.
3. The large heterogenicity in studies reporting on HRV, combined with the lack of knowledge on the possible confounding effect of routine obstetric medication, provide difficulty in the interpretation of current results from literature. Therefore, there is a need for a prospective study on the effect of routine obstetric medication on maternal HRV.
4. Major differences can be found in the recommendations of international guidelines regarding the monitoring and management of fetal distress during labor.

5. When fetal distress is suspected, the use of discontinuation of oxytocin and administration of tocolytics drugs are implemented in all Dutch hospitals. Maternal repositioning is used in 98% of Dutch hospitals, whereas maternal hyperoxygenation is applied 58% and amnioinfusion is used in 33% of hospitals.
6. Maternal hyperoxygenation in case of fetal distress during the second stage of term labor has a positive effect on FHR, with a significant positive effect on FIGO classification and PRSA-based FHR parameters. The depth and duration of decelerations also decreased after maternal hyperoxygenation, albeit not significant.
7. No harmful side effects of maternal hyperoxygenation on neonatal or maternal outcome, especially no increase in free oxygen radical activity or decrease in umbilical cord pH.

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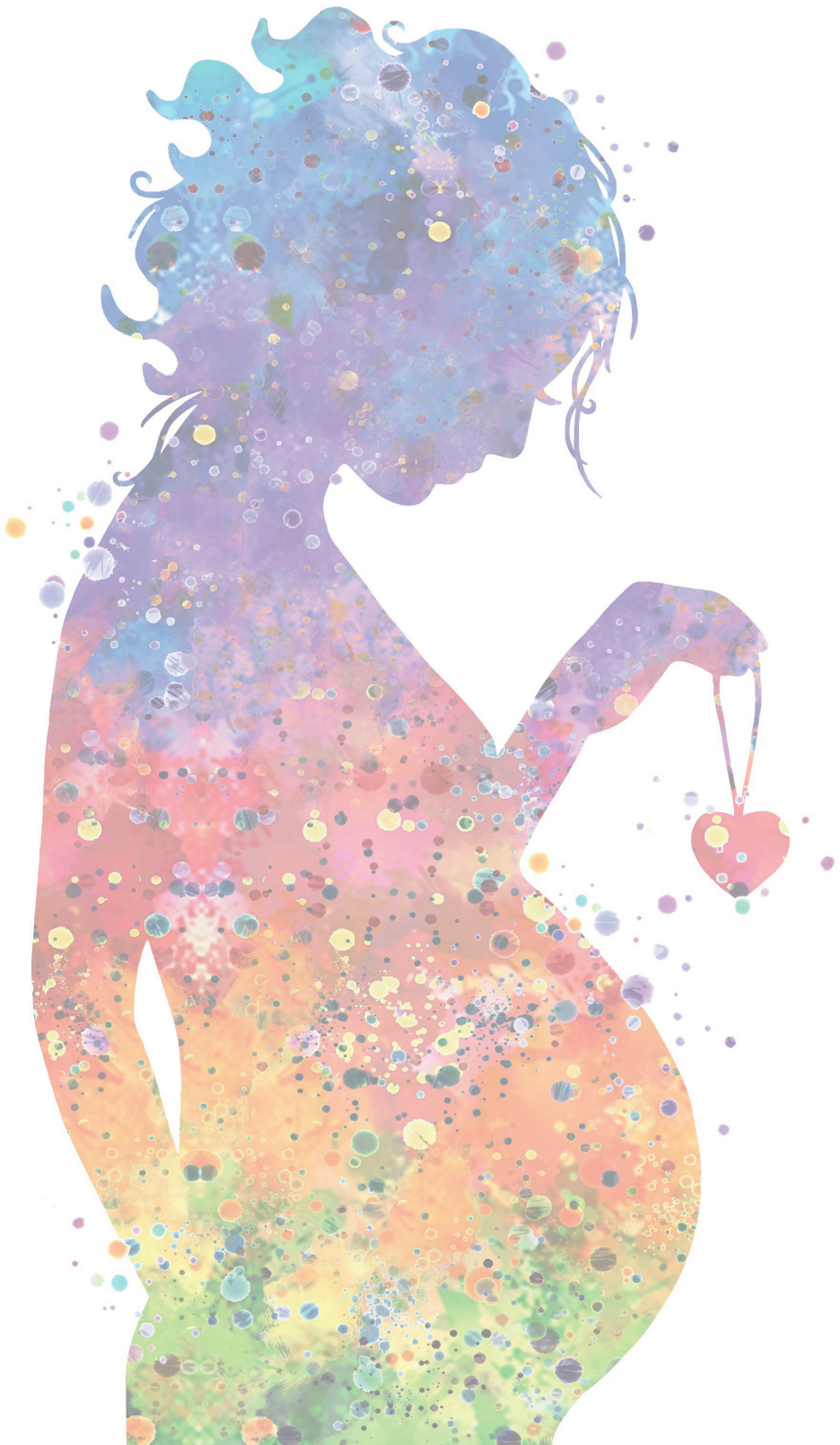

11

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Alhoewel de meeste zwangerschappen en bevallingen zonder problemen verlopen, kunnen complicaties tijdens de zwangerschap en bevalling ernstige en langdurige gevolgen hebben voor zowel moeders als hun baby's. Monitoring kan bijdragen aan het vroegtijdig opsporen van zulke complicaties, waardoor passende behandeling kan plaatsvinden. Hiermee kunnen nadelige gevolgen voorkomen worden. Het is daarom erg belangrijk om moeders en hun ongeboren kinderen adequaat te monitoren en behandelen.

Dit proefschrift beschrijft de monitoring en behandeling van respectievelijk maternale en foetale complicaties tijdens de zwangerschap in twee gedeeltes. In **hoofdstuk 1** wordt een algemene introductie gegeven over de fysiologische veranderingen die optreden tijdens een ongecompliceerde zwangerschap en over het monitoren en behandelen van foetale en maternale zwangerschapscomplicaties. Tevens worden de onderzoeksdoelstellingen van dit proefschrift geïntroduceerd.

Deel I van dit proefschrift gaat over de monitoring en behandeling van moeders met een risico op hypertensieve aandoeningen in de zwangerschap (HAZ). Aangezien HAZ belangrijke oorzaken zijn van wereldwijde maternale en foetale morbiditeit en mortaliteit kan het nauwkeurige voorspellen van HAZ, gevolgd door gepaste behandeling, grote voordelen hebben voor de maternale, foetale en neonatale gezondheid. Momenteel is de risicovoorspelling voornamelijk gebaseerd op de medische voorgeschiedenis van de moeder, wat een beperkte voorspellende waarde heeft.[1,2] Tal van studies hebben de voorspellende waarde van verschillende testen onderzocht om zo de kwaliteit van de risicovoorspelling te kunnen verbeteren.[3] Echter van geen van de tot nu toe onderzochte testmethodes zijn de testeigenschappen voldoende voor gebruik in de dagelijkse praktijk.[3]

Daarom is er vraag naar nieuwe methoden voor nauwkeurige voorspelling en vroege opsporing van HAZ. In deel I van dit proefschrift worden twee veelbelovende methodes voor risicovoorspelling, speckle-tracking echocardiografie (STE) en hartslagvariabiliteit, onderzocht ten aanzien van hun vermogen om HAZ te onderscheiden van normotensieve zwangerschappen.

STE is een relatief nieuwe vorm van diagnostiek die de beweging van weefsels in het hart analyseert door gebruik te maken van akoestische reflecties genaamd speckles om daarmee de parameter "strain" te kunnen meten. Aangezien HAZ subtiele veranderingen in het myocard weefsel veroorzaken, wordt verondersteld dat STE zou kunnen bijdragen aan het voorspellen en vroegtijdig vaststellen van HAZ. Daarom hebben we in **hoofdstuk 2** een systematische review uitgevoerd om te onderzoeken of STE een geschikte methode is om verschillen in cardiale functie te kunnen vaststellen tussen

zwangere vrouwen met HAZ en normotensieve zwangere vrouwen. In deze review wordt ook onderzocht of er verschillen in STE resultaten gezien worden tussen vrouwen met een voorgeschiedenis van HAZ en vrouwen met een voorgeschiedenis van een ongecompliceerde zwangerschap. De databases van Medline (Pubmed), EMBASE en Central werden systematisch doorzocht waarbij we aanvankelijk 200 artikelen vonden. Deze artikelen werden gescreend waarna er 16 geschikte artikelen overbleven met daarin in totaal 870 vrouwen met (een voorgeschiedenis van) HAZ en 693 normotensieve vrouwen.

Van de drie richtingen waarin strain gemeten wordt was linker ventrikel (LV) globale longitudinale strain het meest verminderd bij zwangere vrouwen met HAZ, met een significante afname bij zowel pre-eclampsie als zwangerschapshypertensie. Verder bleken LV globale radiale strain en LV globale circumferentiele strain verlaagd bij vrouwen met vroege en/of ernstige pre-eclampsie in vergelijking met normotensieve zwangere vrouwen, terwijl bij vrouwen met late en/of milde pre-eclampsie geen verschillen werden gevonden in deze twee parameters.

Bij vrouwen met een vroege pre-eclampsie in de voorgeschiedenis werden blijvende veranderingen in het myocard weefsel gezien, met een significante afname van alle drie de richtingen van LV strain. Daarentegen werden geen significante verschillen gezien in strain tussen vrouwen met een voorgeschiedenis van late pre-eclampsie en vrouwen met een ongecompliceerde zwangerschap in de voorgeschiedenis.

Naast STE is hartslagvariabiliteit een andere veelbelovende methode om de verschillen tussen normotensieve en hypertensieve zwangerschappen te onderzoeken. Verschillende studies stellen dat HAZ mogelijk geassocieerd is met disfunctie van het autonome zenuwstelsel,[4,5] en dat hartslagvariabiliteit kan gebruikt worden als maatstaf voor het functioneren van het autonome zenuwstelsel.

Om te onderzoeken in welke mate hartslagvariabiliteit geschikt is om HAZ op te sporen werd er een systematische review uitgevoerd waarvan de resultaten beschreven zijn in **hoofdstuk 3**. Studies die hartslagvariabiliteit vergeleken tussen vrouwen met (een voorgeschiedenis van) HAZ en normotensieve vrouwen werden onderzocht. De databases van Medline (Pubmed), EMBASE en Central werden systematisch doorzocht, waarbij aanvankelijk 523 artikelen werden verkregen. Na een verdere selectie werden 24 studies opgenomen in deze review die voldeden aan de inclusiecriteria met daarin in totaal 850 vrouwen met (een voorgeschiedenis van) HAZ en 1205 normotensieve vrouwen ter controle.

De resultaten van de geïncludeerde studies lieten grote variatie zien, mogelijk door de heterogeniteit van de data. Bij de frequentie-domein parameters werd een toename gezien in de ratio tussen de laagfrequente en hoogfrequente component

van hartslagvariabiliteit (LF/HF-ratio) bij vrouwen met (matig ernstige) pre-eclampsie vergeleken met normotensieve zwangere vrouwen (vier van de zes studies). In geen enkele studie werd een afname van LF/HF-ratio gezien bij vrouwen met pre-eclampsie. Vergelijkbare resultaten werden gezien voor zwangerschapshypertensie en chronische hypertensie.

Wat betreft de tijd-domein parameters waren beide parameters die de totale mate van hartslagvariabiliteit weergeven, SDNN en hartslagvariabiliteit index, verlaagd bij vrouwen met pre-eclampsie vergeleken met normotensieve controles. Deze resultaten wijzen op een overactiviteit van het sympathische zenuwstelsel, wat mogelijk geassocieerd is met een verlaging van de parasympatische activiteit. Echter is voorzichtigheid geboden bij het trekken van deze conclusies door de grote spreiding in de resultaten van de onderzochte studies.

Helaas werd er in de onderzochte studies weinig beschreven over de medicatie die gebruikt werd in de studiepopulatie. Dit kan mogelijk een verstorend effect hebben op de studieresultaten. Het is gebruikelijk dat vrouwen met vroege HAZ bepaalde medicatie krijgen zoals antenataal toegediende corticosteroïden. Er is echter weinig bekend over het effect van dit type medicatie op maternale hartslagvariabiliteit. Daarom hebben we een longitudinale cohort studie opgezet, de MAMA-hart studie, om het effect van verschillende routinematige verloskundige medicamenten op maternale hartslagvariabiliteit te onderzoeken. Het studieprotocol is beschreven in **hoofdstuk 4**. Door gebruik te maken van een apparaat dat om de pols wordt gedragen zullen continue, langdurige fotoplethysmografie (PPG) metingen verricht worden waarmee hartslagvariabiliteit parameters van afgeleid kunnen worden.

De studie bestaat uit twee fases. In de *primaire fase* zullen patiënten worden geïncludeerd met een zwangerschapsduur tussen de 23+5 weken en 33+6 weken die een indicatie hebben voor de toediening van antenatale corticosteroïden. Gedurende de gehele ziekenhuisopname zullen PPG metingen verricht worden. De studie richt zich voornamelijk op het effect van antenataal toegediende corticosteroïden, die veelvuldig gebruikt worden en waarvan bekend is dat ze de foetale hartslagvariabiliteit beïnvloeden.[6,7] Toch is er een duidelijke kenniskloof over het effect van deze medicatie op maternale hartslagvariabiliteit. Daarnaast zullen we ook het effect onderzoeken van magnesiumsulfaat, nifedipine, labetalol en methyldopa, aangezien deze medicijnen ook routinematig gebruikt worden in de verloskundige zorg.

De parameters van hartslagvariabiliteit zullen vergeleken worden tussen de periode voorafgaand aan de medicatie toediening en de periode nadat de medicatie is toegediend. Door het effect te kwantificeren dat routinematig gebruikte verloskundige medicatie heeft op maternale hartslagvariabiliteit, kan dit voortaan worden meegenomen in de analyses van toekomstige studies over maternale hartslagvariabiliteit. Hierdoor wordt

het voor toekomstige studies mogelijk om onderscheid te maken tussen veranderingen in hartslagvariabiliteit die geassocieerd zijn met zwangerschapscomplicaties zoals HAZ en vroeggeboorte en veranderingen die veroorzaakt worden door het gebruik van medicatie. Dit kan bijdragen aan betere kennis over hoe disfunctie van het autonome zenuwstelsel kan leiden tot zwangerschapscomplicaties waardoor mogelijk eerdere diagnose en behandeling van deze complicaties bereikt kan worden.

Tijdens de *secundaire fase* van het onderzoek zullen continue PPG-metingen verkregen worden bij dezelfde patiënten uit de *primaire fase*, welke gedurende een 24-uurs durende monitoringsperiode zullen plaatsvinden zes weken na de bevalling. Hetzelfde om de pols gedragen apparaat dat wordt gebruikt in de *primaire fase* zal tijdens de *secundaire fase* in vrije leefomstandigheden thuis worden gedragen. Deze aanvullende meting biedt de unieke mogelijkheid om cardiovasculaire parameters te vergelijken tussen de periode voor en na de bevalling, waarover nog maar weinig bekend is.

Deel I presenteert de resultaten van ons onderzoek naar monitoring en behandeling van moeders die risico lopen tijdens de zwangerschap. Hoewel we aantoonden dat twee veelbelovende methoden aanvullende informatie kunnen verschaffen over zwangerschappen die gecompliceerd zijn door HAZ, hebben we ook vastgesteld dat er behoefte is aan extra onderzoek naar de effecten van routinematig gebruikte verloskundige medicatie op maternale hartslagvariabiliteit.

Deel II van dit proefschrift richt zich op het monitoren en behandelen van foetale nood tijdens de bevalling aangezien het risico op verlaagde foetale oxygenatie toeneemt tijdens de bevalling ten gevolge van verminderde zuurstoftoevoer wat veroorzaakt wordt door samentrekkingen van de baarmoeder.[8] Om de foetale conditie en oxygenatie tijdens de bevalling te kunnen monitoren kunnen verschillende methodes gebruikt worden waaronder een gecombineerde registratie van de foetale hartslag in relatie tot de contracties van de baarmoeder (cardiotocogram; CTG), de analyse van het ST-segment van het foetale elektrocardiogram (ST-analyse), microbloedonderzoek (MBO) en foetale pulsoxymetrie.

Wanneer er een verdenking is op foetale nood kunnen verschillende intra-uteriene resuscitatietechnieken worden gebruikt om de foetale conditie te verbeteren, waaronder houdingsveranderingen van de moeder, het stoppen van toediening van oxytocine, het toedienen van tocolytica, amnioninfusie, intraveneuze vloeistofbolus en maternale hyperoxygenatie. Het bewijs over het effect van deze intra-uteriene resuscitatietechnieken is echter beperkt en soms ook tegenstrijdig.[9] Het is aannemelijk dat dit gebrek aan robuust bewijs zal leiden tot variatie in klinische richtlijnen. Daarom werden in **hoofdstuk 5** de nationale richtlijnen van verschillende westerse landen vergeleken ten aanzien van hun aanbevelingen over foetale monitoring en behandeling bij verdenking op foetale nood tijdens de bevalling. Er werden acht richtlijnen verkregen

met betrekking tot het monitoren van de foetale conditie tijdens de bevalling. Al deze richtlijnen adviseerden om MBO's te verrichten in aanvulling op het CTG. Het gebruik van ST-analyse werd aanbevolen in drie richtlijnen, terwijl het in drie andere richtlijnen juist werd afgeraden. Twee richtlijnen raadden het gebruik van foetale pulsoximetrie af, terwijl de andere deze techniek niet benoemden in hun richtlijn.

Vijf richtlijnen bevatten aanbevelingen ten aanzien van het gebruik van intra-uteriene resuscitatietechnieken. Alle richtlijnen raadden het stopzetten van toediening van oxytocine aan, net als houdingsveranderingen van de moeder en het toedienen van tocolytica. Met betrekking tot maternale hyperoxygenatie waren de richtlijnen tegenstrijdig. In de Verenigde Staten en Canada wordt maternale hyperoxygenatie aanbevolen in geval van foetale nood, terwijl de nationale richtlijn uit het Verenigd Koninkrijk deze behandeling afraadt vanwege de mogelijke schadelijke bijwerkingen en het ontbreken van wetenschappelijk bewijs. De aanbevelingen over het gebruik van amnioninfusie en intraveneuze vloeistofbolus varieerden ook tussen de verschillende richtlijnen.

Het leek voor de hand liggend dat deze verschillen in aanbevelingen zouden leiden tot verschillen in het klinisch handelen op de werkvloer. Om deze hypothese te testen werd in alle 86 Nederlandse ziekenhuizen een enquête gehouden over de wijze van monitoring en behandeling bij verdenking op foetale nood. Alle ziekenhuizen gebruiken CTG om de foetale conditie te monitoren en in 98% van de Nederlandse ziekenhuizen is tevens MBO beschikbaar indien nodig. In 23% van de ziekenhuizen wordt ST-analyse gebruikt om de foetale conditie te monitoren. Bijna 100% van de Nederlandse ziekenhuizen past de volgende methoden toe in geval van verdenking op foetale nood: het stopzetten van oxytocine-infusie, toediening van tocolytica en houdingsveranderingen van de moeder. Er blijkt echter een grote spreiding te zijn in het toepassen van maternale hyperoxygenatie en amnioninfusie, wat in respectievelijk 58% en 33% van de Nederlandse ziekenhuizen wordt gebruikt.

Deze verschillen in de klinische praktijk en internationale richtlijnen zou verklaard kunnen worden door het gebrek aan goede klinische onderzoeken. Met betrekking tot maternale hyperoxygenatie is het effect van deze behandeling bij verdenking op foetale nood tijdens de uitdrijvingsfase van de bevalling nog nooit onderzocht in een gerandomiseerde studie (RCT). Verschillende kleine, niet-gerandomiseerde onderzoeken en een wiskundig computermodel lieten een verbetering zien in het foetale hartslagpatroon en/of MBO uitslag na toepassing van deze behandeling in het geval van foetale nood.[10–14] Naar aanleiding van de resultaten van deze studies hebben we een RCT opgezet en uitgevoerd om het effect van deze intra-uteriene resuscitatietechniek tijdens de uitdrijvingsfase van de bevalling te onderzoeken. Het studieprotocol hiervan wordt beschreven in **hoofdstuk 6**. In deze studie, genaamd de INTEREST O2 studie, zullen patiënten met verdenking op foetale nood tijdens de uitdrijvingsfase van de bevalling worden geïncludeerd. Zij

zullen via loting worden toegewezen voor het ontvangen van maternale hyperoxygenatie met 100% zuurstof op 10L/min, toegediend via een mond-neus masker, dan wel voor gebruikelijke zorg zonder additionele zuurstof. De diagnose 'verdenking foetale nood' werd gesteld o.b.v. een suboptimaal of abnormaal CTG volgens de gemodificeerde FIGO-criteria.[15]

De primaire uitkomstmaat van deze studie is de verandering in het foetale hartslagpatroon na aanvang van de studie, gemeten als de verandering in de diepte en duur van de decelaraties. Dit betreft een surrogaat eindpunt voor de foetale conditie, gezien een afwijkend hartslagpatroon wordt beschouwd als een indicatie voor potentiële foetale hypoxie.[16,17] Bovendien zou voor een onderzoek dat is gebaseerd op neonatale morbiditeit een studiepopulatie van meer dan 10.000 vrouwen nodig zijn.[18] Aangezien sommige studies bezorgdheid uitten over de mogelijk schadelijke bijwerkingen van maternale hyperoxygenatie, werd gekozen om zo'n grote groep vrouwen en hun baby's niet bloot te stellen aan deze interventie voordat de veiligheid ervan verder onderzocht was.

De secundaire uitkomstmaten van de INTEREST O2 studie bevatten verschillende perinatale en maternale uitkomsten: veranderingen in FIGO-classificatie, Apgar Score, navelstreng bloedgasanalyses, activiteit van vrije zuurstofradicalen, opnames op de neonatale intensive care unit (NICU), neonatale sterfte, wijze van bevallen en maternale bijwerkingen. Verder zullen gedetailleerde analyses van het foetale hartslagpatroon worden uitgevoerd. Deze analyses zijn gebaseerd op instabiele basislijn, PRSA-gebaseerde parameters, decelaraties met verlies van variabiliteit en decelaraties in combinatie met foetale bradycardie of tachycardie. Al deze parameters zijn gerelateerd aan een slechtere neonatale uitkomst.[19–22]

De veranderingen in het foetale hartslagpatroon worden eerst per patiënt geanalyseerd en vervolgens vergeleken tussen de interventie en de controlegroep. Voor elke patiënt wordt de periode van 10 minuten vóór aanvang van het onderzoek vergeleken met de periode 5 tot 15 minuten na aanvang van het onderzoek.

Naast de intention-to-treat-analyses zullen per-protocol analyses en subgroep analyses worden uitgevoerd. De eerste twee subgroepen bestaan uit patiënten met suboptimaal CTG danwel abnormaal CTG (volgens de FIGO-classificatie). De derde subgroep bestaat uit neonaten met een te laag geboortegewicht (geboortegewicht <p10).

De perinatale en maternale uitkomsten van de INTEREST O2-studie worden beschreven in **hoofdstuk 7**. Er namen 117 patiënten deel aan dit onderzoek. Om de mogelijk schadelijke effecten van vrije zuurstofradicalen te onderzoeken werd Malondialdehyde in navelstrengbloed gemeten. Dit toonde geen significante verschillen tussen de interventie en controlegroep. De volgende secundaire uitkomstmaten toonden geen significante

verschillen tussen beide groepen; Apgar Score, navelstreng bloedgasanalyses en wijze van bevallen. In de subgroep analyse van abnormaal CTG werden significant minder episiotomieën op foetale indicatie geplaatst in de interventie groep (25%) vergeleken met de controlegroep (65%, p<0.01). Deze afname in de interventiegroep wordt als een gunstig resultaat beschouwd, aangezien episiotomieën een potentieel schadelijke interventie zijn.[23] Bovendien zou deze vermindering kunnen wijzen op een betere foetale conditie in de interventiegroep, aangezien er minder vaak sprake was van dusdanige foetale nood dat een episiotomie geïndiceerd was om directe geboorte van het kind na te streven.

Verandering in het foetale hartslagpatroon kon voor 71 vrouwen (61%) worden geanalyseerd, aangezien de andere 46 vrouwen (39%) reeds bevallen was voor het einde van de onderzoeksperiode waardoor er onvoldoende hartslagpatroon bestond in de "post-studie" periode om het goed te kunnen analyseren. In dit artikel werd het effect op foetale hartslagpatroon onderzocht als de veranderingen in FIGO-classificatie, beoordeeld door clinici. Verbetering van de FIGO-classificatie (bijvoorbeeld van abnormaal naar suboptimaal) werd meer dan vier keer zo vaak gezien in de interventiegroep in vergelijking met de controlegroep (13.9% versus 2.9%). Bovendien werd verslechtering van de FIGO-classificatie minder vaak gezien in de interventiegroep dan in de controlegroep (8.3% versus 34.4%). Het verschil in FIGO-classificatie in het voordeel van maternale hyperoxygenatie was statistisch significant (OR 5.7, 95% BI 1,7-19,1). Er werd een gelijke trend gezien in de subgroep analyses, zij het niet significant.

De populatiegrootte van de INTEREST O2 studie was berekend op veranderingen in het foetale hartslagpatroon in plaats van neonatale uitkomst. Het positieve effect van maternale hyperoxygenatie op verandering in FIGO-classificatie zou kunnen wijzen op een positief effect op neonatale uitkomst. Er zijn echter grotere studies nodig om deze bevinding te bevestigen.

De primaire uitkomstmaat van de INTEREST O2 is verandering in foetaal hartslagpatroon. Hoewel visuele analyse van de foetale hartslag, zoals toegepast wordt voor de FIGO-classificatie in hoofdstuk 7, een van de meest gebruikte methodes is om het foetale hartslag patroon te beoordelen, heeft het een grote intra- en interobservatie variabiliteit.[24,25] Daarom hebben we tevens een meer gedetailleerde computer analyse van het foetale hartslagpatroon in de INTEREST O2 uitgevoerd, waarvan de resultaten staan weergegeven in **hoofdstuk 8**. Deze gedetailleerde analyse geeft aanvullende informatie over de fysiologische veranderingen die veroorzaakt worden door maternale hyperoxygenatie.

Er werden verschillen gezien in duur en diepte van decelerations tussen maternale hyperoxygenatie (-2.3%) en de controlegroep (+10%). Deze verschillen waren niet

significant (p=0.24), wat te wijten kan zijn aan het hogere percentage van ontbrekende gegevens dan waar vooraf van werd uitgegaan.

De verandering in PRSA- acceleratie capaciteit (PRSA-AAC) en PRSA-deceleratie capaciteit (PRSA-ADC) na de start van de studie was statistisch significant verschillend in het voordeel van maternale hyperoxygenatie (p=0,03 en p=0,02, respectievelijk). Deze significante verschillen in op PRSA gebaseerde parameters in het voordeel van maternale hyperoxygenatie duiden op minder compensatoire activering van het autonome zenuwstelsel na maternale hyperoxygenatie. Dit zou kunnen wijzen op een positief effect op neonatale uitkomst.

Er werden geen significante verschillen gevonden tussen de interventie- en controlegroep voor de volgende foetale hartslagkenmerken: perioden met instabiele basislijn, decelerations met verlies van variabiliteit en decelerations in combinatie met tachycardie of bradycardie.

De resultaten van de INTEREST O2 studie laten een significant positief effect zien van maternale hyperoxygenatie op het foetale hartslagpatroon wat betreft veranderingen in FIGO-classificatie en op PRSA gebaseerde parameters. Het verschil in duur en diepte van decelerations was echter niet significant. Er werden geen schadelijke effecten van maternale hyperoxygenatie gevonden.

In **hoofdstuk 9** worden de belangrijkste bevindingen van dit proefschrift besproken waarna aanbevelingen worden gedaan voor toekomstig onderzoek.

De belangrijkste conclusies van dit proefschrift zijn:

1. Speckle tracking echografie is een geschikte methode om preklinische veranderingen in hartfunctie op te sporen bij zwangere vrouwen met HAZ in vergelijking met normotensieve zwangere vrouwen, met name bij gebruik van LV globale longitudinale strain. Bij vrouwen met een voorgeschiedenis van HAZ werden alleen in de subgroep van vroege pre-eclampsie blijvende veranderingen in hartfunctie gevonden in vergelijking met vrouwen met een normotensieve zwangerschap in de voorgeschiedenis.
2. Bepaalde verschillen in het functioneren van het autonome zenuwstelsel kunnen worden vastgesteld met behulp van hartslagvariabiliteit in vrouwen met HAZ, zoals een verlaagde hartslagvariabiliteit bij pre-eclampsie vergeleken met normotensieve zwangere vrouwen. Er werd een trend gezien richting een verhoogde LF/HF-ratio bij vrouwen met pre-eclampsie vergeleken met normotensieve zwangere vrouwen.
3. De grote heterogeniciteit in de hartslagvariabiliteit studies en het gebrek aan kennis over het mogelijk verstorende effect van routinematige verloskundige medicatie zorgen ervoor dat de resultaten van hartslagvariabiliteit studies niet

goed geïnterpreteerd kunnen worden. Er is daarom behoefte aan een prospectieve studie die het effect van routinematige verloskundige medicatie op maternale hartslagvariabiliteit onderzoekt.

4. Er zijn grote verschillen in internationale richtlijnen wat betreft hun aanbevelingen over de monitoring en behandeling van foetale nood tijdens de bevalling.
5. Bij verdenking op foetale nood wordt in alle Nederlandse ziekenhuizen gebruik gemaakt van het stoppen van oxytocine en toediening van tocolytica. Het herpositioneren van de moeder wordt toegepast in 98% van de Nederlandse ziekenhuizen. Maternale hyperoxygenatie en amnioninfusie worden toegepast in respectievelijk 58% en 33% van de ziekenhuizen.
6. Het toepassen van maternale hyperoxygenatie bij verdenking op foetale nood tijdens de uitdrijvingsfase van de bevalling heeft een positief effect op het foetale hartslagpatroon, met een significant positief effect op verandering in FIGO-classificatie en op PRSA gebaseerde parameters. De duur en diepte van decelaraties nam ook af door maternale hyperoxygenatie, zij het niet significant.
7. Maternale hyperoxygenatie heeft geen schadelijke bijwerkingen op neonatale of maternale uitkomst, met name geen toename van vrije zuurstofradicalen activiteit of afname van de pH van navelstrengbloed.

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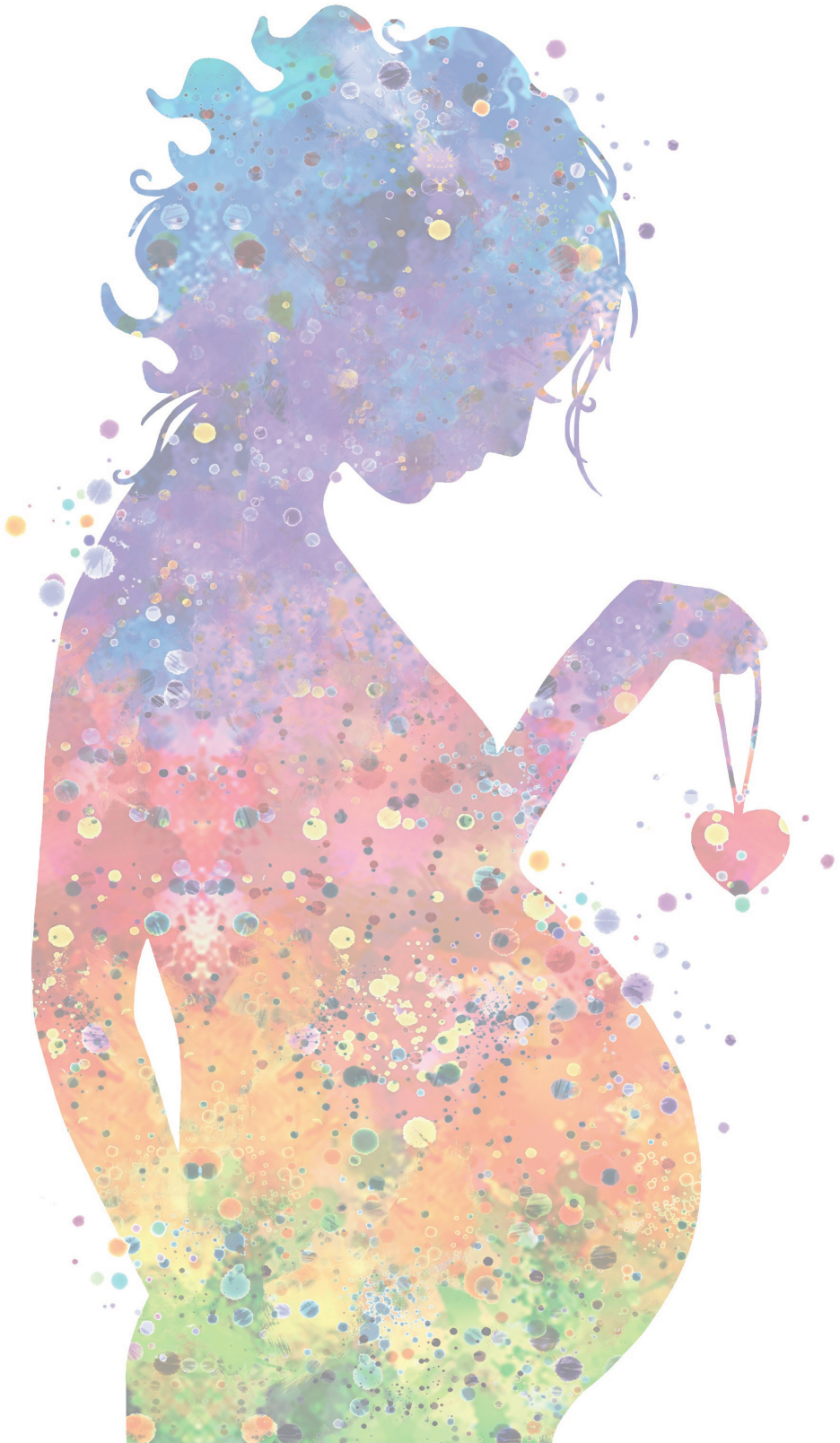

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APPENDICES

List of abbreviations

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LIST OF ABBREVIATIONS

ACOG	**American College of Obstetricians and Gynecologists**
AGA	Appropriate for gestational age
ANS	Autonomic nervous system
BMI	Body-mass index
BPM	Beats per minute
CH	Chronic Hypertension
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CS	Cesarean section
CTG	Cardiotocography
CVD	Cardiovascular disease
DNPH	2,4-Dinitrophenylhydrazine;
ECG	Electrocardiography
EO-PE	Early-onset preeclampsia
FHR	Fetal heart rate
fHRV	Fetal heart rate variability
FIGO	International Federation of Gynecology and Obstetrics
FSBS	Fetal scalp blood sampling
GDPR	General Data Protection Regulation
GH	Gestational hypertension
HF	High Frequency (power)
HPD	Hypertensive pregnancy disorders
HPLC-MS/MS	High-performance liquid chromatography–tandem mass spectrometry
HR	Heart rate
HRV	Heart rate variability
LF	Low frequency (power)
Ln	Natural logarithm
LO-PE	Late-onset preeclampsia
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LV-GCS	Left ventricular global circumferential strain
LV-GLS	Left ventricular global longitudinal strain
LV-GRS	Left ventricular global radial strain
MDA	Malondialdehyde
$MgSO_4$	Magnesium sulfate
mHR	Maternal heart rate
mHRV	Maternal heart rate variability
m/z	Mass-to-charge ratio

NICU	Neonatal intensive care unit
NN	Normal-to-normal
NOS	Newcastle-Ottawa scale
N.u.	Normalized units
NVOG	Dutch Society of Obstetricians and Gynecologists (Nederlandse Vereniging voor Obstetrie en Gynaecologie)
OCU	Obstetric care unit
OR	Odds ratio
pCO_2	Partial carbon dioxide pressure
pO_2	Partial oxygen pressure
PDL	Philips Data Logger
PE	Preeclampsia
pHa	pH in arterial blood gas
pO_2	Partial oxygen pressure
PPG	Photoplethysmography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist
PRSA	Phase-rectified signal averaging
PRSA-AAC	Phase-rectified signal averaging accelerative capacity
PRSA-ADC	Phase-rectified signal averaging decelerative capacity
PTB	Preterm birth
RCOG	Royal College of Obstetricians and Gynecologists
RCT	Randomized controlled trial
RMSSD	Root mean square of successive differences
SAE	Serious adverse event
SDANN	Standard deviation of the averages of NN intervals
SDNN	Standard deviation of all NN intervals
SGA	Small for gestational age
SOGC	Society of Obstetricians and Gynaecologists of Canada
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SpO_2	Oxygen saturation
SR	Strain rate
STAN	ST-analysis
STE	Speckle tracking echocardiography
SUSAR	Suspected unexpected serious adverse reaction
UCBG	Umbilical cord blood gas
USA	United States of America

LIST OF PUBLICATIONS

S Moors, NHM van Oostrum, C Rabotti, X Long, MEMH Westerhuis, HMC Kemps, SG Oei, JOEH van Laar. Speckle tracking echocardiography in hypertensive pregnancy disorders: a systematic review. *Obstetrical & Gynecological Survey 2020 Aug;75(8):497-509.*

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J Burd, J Quist-Nelson, **S Moors**, N Raghuraman, H Aly, V Berghella. Effect of intrapartum oxygen on the rate of cesarean delivery: a meta-analysis. *Submitted for publication in American Journal of Obstetrics & Gynecology*

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CONFERENCE PRESENTATIONS

S Moors, Extra zuurstof tijdens de bevalling, gunstig of gevaarlijk? Refereeravond Gynaecology and Obstetrics, Máxima MC, 12 November 2019, Veldhoven, the Netherlands,

S Moors. Extra zuurstof tijdens de bevalling, gunstig of gevaarlijk? Wetenschapsavond Máxima MC, 28 March 2019, Veldhoven, the Netherlands

S Moors. Intrauterine resuscitation during term labor by maternal hyperoxygenation. European Congress on Intrapartum Care, 14-16 March 2019, Turin, Italy.

S Moors, Summary of fetal monitoring research in Máxima Medical Center. Pre-congress Intrapartum Fetal Monitoring Networking Meeting, European Congress on Intrapartum Care, 14-16 March 2019, Turin, Italy.

CONFERENCE POSTERS

S Moors, NHM van Oostrum, MEMH Westerhuis, SG Oei, JOEH van Laar. Speckle tracking echocardiography in hypertensive pregnancy disorders: a systematic review. e/MTIC Symposium 'Technology meets Value-Based Health Care', 11 October 2019, Eindhoven, the Netherlands

S Moors, LM Bullens, PJ van Runnard Heimel, JP Dieleman, MB van der Hout- van der Jagt, SG Oei. Effect of intrauterine resuscitation by maternal hyperoxygenation during the second stage of term labour on free oxygen radicals; a randomised controlled trial. Birth symposium, 15-17 November 2018, Venice, Italy

S Moors, LM Bullens, PJ van Runnard Heimel, JP Dieleman, MB van der Hout- van der Jagt, SG Oei. Effect of intrauterine resuscitation by maternal hyperoxygenation during the second stage of term labour on neonatal outcome and mode of delivery; a randomised controlled trial. Birth symposium, 15-17 November 2018, Venice, Italy

DANKWOORD

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CURRICULUM VITAE

Suzanne Moors werd geboren op 25 maart 1992 in Geldrop. Zij groeide op in Eindhoven en in 2010 behaalde zij haar VWO-diploma aan het Augustinianum college te Eindhoven. Hierna is zij Geneeskunde gaan studeren aan de Universiteit van Maastricht. Tijdens haar buitenlandse keuze co-schap heeft zij stage gelopen bij de afdeling General Medicine van het Whakatane hospital in Whakatane, Nieuw-Zeeland. Tijdens haar reguliere Gynaecologie co-schap in het Máxima MC te Veldhoven werd haar interesse voor dit vakgebied 'geboren' en is zij begonnen met wetenschappelijk onderzoek onder leiding van prof. dr. Oei in de FUNdamentele Perinatologie onderzoeksgroep. Het laatste jaar van de opleiding Geneeskunde was zij semi-arts op de afdeling Gynaecologie en Obstetrie in het Máxima MC, waarbij ze meehielp met het opzetten van de INTEREST O2 studie. Na het behalen van haar artsenexamen in juli 2016, startte ze met werken als fertiliteitsarts en later als arts-assistent niet in opleiding op de afdeling Gynaecologie en Obstetrie van het Zuyderland MC. Per oktober 2017 is ze gaan werken als arts-assistent niet in opleiding op de afdeling Gynaecologie en Obstetrie van het Máxima MC. Tevens bleef zij naast haar werkzaamheden in de kliniek betrokken bij wetenschappelijk onderzoek. Van januari 2019 tot en met maart 2020 heeft zij voltijd aan haar promotietraject gewerkt. Sinds april 2020 is zij werkzaam als arts-assistent niet in opleiding tot specialist op de afdeling Gynaecologie en Obstetrie van het Elisabeth Tweesteden Ziekenhuis te Tilburg.

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