Non-invasive hemodynamic measurements early in pregnancy
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Summary and discussion
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Preeclampsia is a syndrome occurring by definition in the second half of pregnancy and resolves shortly after delivery. Two clinical symptoms, hypertension and proteinuria, define the disorder. It is a major cause of maternal and fetal morbidity and mortality. The exact underlying pathogenesis is unclear and preeclampsia is at present unpredictable in onset and progression and incurable except by termination of the pregnancy. It is often associated with fetal growth restriction, although fetal growth restriction can also occur without maternal hypertension. Prevention of preeclampsia would have significant impact on maternal and prenatal outcome worldwide. Prevention not only requires knowledge of pathophysiologic mechanisms of the disease, but also availability of methods of early detection, and means for intervention and correction of pathophysiologic changes. Signs and symptoms of preeclampsia mostly become apparent at a relatively late stage in pregnancy i.e. the late second, or third trimester. However, the origin of the underlying cause of the pathophysiologic mechanisms is thought to occur much earlier in pregnancy. For that reason, it seems logical to search for indicators of this disorder present in the first trimester of pregnancy.

Invasive measurements in untreated preeclamptic patients gave better insight in the hemodynamic expression of severe disease. Through extensive research in normal pregnancy, a better understanding of the profound changes in the maternal cardiovascular system has been obtained. Most of these changes occur already in early pregnancy, around 5-8 weeks of gestation. There is a large difference in hemodynamic characteristics between preeclamptic and normotensive pregnant women. Also pregnancies complicated by intrauterine fetal growth restriction showed differences in hemodynamic characteristics compared to healthy pregnant women at term.

Knowledge about cardiovascular changes before the development of preeclampsia or fetal growth restriction is only fragmentary. Studies show that hemodynamics differ from normal early in pregnancies that will become complicated, although there is no consensus regarding the exact nature and quantity of these differences.

Vascular resistance is observed to be increased in preeclampsia. Vascular tone is largely determined by the activity of the sympathetic nervous. By direct microneurography sympathetic activity has been studied in preeclamptic patients. It is found to be higher in preeclampsia, and returns to normal after delivery. In early pregnancy measurement of sympathetic activity by direct microneurography has not been performed. The increased sympathetic activity, observed in preeclampsia, may already be present before the clinical presentation of the disorder, before the blood pressure and vascular resistance start to rise.

There are two methods to test the function of the autonomic nervous system non-invasively. Analysis of spontaneous heart rate and blood pressure variability by spectral
analysis, from continuous recordings of heart rate and blood pressure, or cardiovascular reflex tests, where blood-pressure and heart rate responses to a variety of physiological stresses are analysed. These test methods give information about the parasympathetic and/or sympathetic nervous system.

The main focus of this thesis was to investigate if differences in hemodynamic adaptation to pregnancy could be observed in the first half of pregnancy between women who eventually developed preeclampsia or fetal growth restriction and women with a healthy pregnancy. We restricted our study to non-invasive measurement techniques since this would enable large scale use of tests. The intention was to develop a screening strategy, which could be applied to a large number of pregnant women.

Our first aim was to evaluate if differences in autonomic cardiovascular control could be observed in early pregnancy between women who develop preeclampsia and women with a healthy pregnancy and if non-invasive cardiovascular reflex tests or spectral analysis could be used for detection of such differences.

In Chapter 2 we present an overview of the literature regarding non-invasive tests for autonomic cardiovascular control in women with normal pregnancy and women with preeclampsia.

Medline was searched, using the following keywords: pregnancy, preeclampsia, autonomic nervous system. The reference lists of the retrieved articles were scanned for relevant articles, which had not been found by Medline. A total of 36 articles concerning autonomic cardiovascular control in human pregnancy by non-invasive test methods, were found and reviewed.

The test methods reviewed were fast fourier power spectrum analysis, orthostatic stress test, Valsalva’s maneuver, isometric handgrip test, cold pressor test and the deep breathing test. These tests give information on different parts or the integrity of the pathway for autonomic cardiovascular control. Each test method is described and a summary of test results is presented in women with healthy pregnancy and women with preeclampsia. Per test-method, the consistency between data from different studies was considered. Results were defined inconsistent if less than 75 % of the studies had comparable results in direction and magnitude. Small differences were observed between normal pregnancy and preeclampsia by individual studies using non-invasive methods but the consistency between available data was insufficient to discriminate between normal pregnancy and preeclampsia. Elevated sympathetic activity in women with preeclampsia in comparison with normal pregnancy was only demonstrated by two studies using direct microneurography. Nevertheless, these studies also did not observe a difference in hemodynamic and sympathetic activity response to isometric exercise,
cold pressor test or Valsalva’s manoeuvre between normal pregnant and preeclamptic women.\textsuperscript{12, 13} This difference in outcome might be caused by a variety of methodological factors of the non-invasive studies. First, most studies are cross-sectional or, if longitudinal, compare data in pregnancy with post-partum values. Only few studies performed measurements before the onset of disease and none did so before pregnancy. Second, the non-invasive studies are not easy to compare due to differences in definition of disease and performance of test methods. Third, the evaluated non-invasive tests involve the complete baro-reflex arc with afferent, central and efferent pathways, and not only the efferent pathway as neurography does. The observed increased resting sympathetic activity by direct microneurography \textsuperscript{12, 13} might be caused by a disturbance of central control or a change in afferent sensitivity, resulting in a higher efferent activity. The lack of differences in non-invasive tests between preeclampsia and normal pregnancy might presume an intact reflex response and efferent pathway, whereas within the system set points could have been altered. Alternatively, sympathetic activity to resistance vessels in skeletal muscle may not be a proper reflection of autonomic cardiovascular control in pregnancy.

If the increased efferent sympathetic activity, as observed by microneurography in preeclampsia, is not representative for the overall sympathetic vasomotor tone or is due to disturbed central command, then it could be concluded that non-invasive methods will not contribute to discriminate preeclampsia from normal pregnancy let alone predict preeclampsia.

We speculated that methodological confounders could explain the discrepancy between results, and consequently a longitudinal study design, with a very rigorous measurement protocol and sensitive measurement technique starting before pregnancy, might demonstrate differences between women with normal pregnancy or preeclampsia. Based on this hypothesis we performed the longitudinal study, which is described in Chapter 3.

In Chapter 3, we performed a longitudinal study that was designed to demonstrate differences in autonomic cardiovascular control between normal pregnant women and women who eventually develop preeclampsia by using non-invasive techniques. Multiparous women with a history of preeclampsia and primigravid women were studied serially. Measurements were performed before, during and after pregnancy. Measurements during pregnancy were performed at 6, 8, 10, 12, 16, 20 and 32 weeks. Outcome of pregnancy was classified after delivery as normal pregnancy or preeclampsia. Preeclampsia was defined according to the definition of the ISSHP. \textsuperscript{1} No women developed preeclampsia before the last registration during pregnancy. Heart rate and blood pressure were recorded from continuous finger pulse wave registration by Portapres (TNO, Amsterdam). There are basically two methods to test the function of the autonomic nervous system non-invasively. By analysis of spontaneous heart rate and blood pressure variability from continuous recordings of heart rate and blood pressure, or by
cardiovascular reflex tests, where blood-pressure and heart rate responses to a variety of physiological stresses are analysed. After a short pilot study we selected two cardiovascular reflex tests, the orthostatic stress test (standing up from sitting position) and spectral analysis during rest and paced breathing, both in supine and sitting position. Other tests (head-up tilting table, hand-grip test, ice water immersion) appeared too large a burden for the study participants to be used repeatedly.

There was no difference in heart rate and blood pressure variability with spectral analysis at different positions or breathing frequencies between the pregnant and the pre-pregnant state, nor between normal pregnant women and women who later developed preeclampsia. Baroreflex sensitivity decreased towards the end of pregnancy compared to the pre-pregnant state but there was no difference between healthy pregnant women and women who developed preeclampsia. Mean arterial pressure was significantly higher before and during pregnancy (ANOVA, p = 0.001) in women who developed preeclampsia. These women also showed a significantly larger negative phase difference during supine rest at low frequency from 8 weeks onward (ANOVA p = 0.003).

The negative phase difference at 0.1 Hz indicates that systolic blood pressure changes occur before the heart period changes. A larger phase difference indicates a larger influence of the slower sympathetic system. This larger phase difference in preeclampsia thus represents a larger contribution of the sympathetic system, which increases its activity towards the 3rd trimester. We observed a larger phase difference at rest, but not during stimulation by the sitting position. Although resting sympathetic activity seems to be increased in preeclampsia, the sympathetic response to stimuli is similar compared to normal pregnancy. Women who developed preeclampsia were observed to have a significantly larger initial blood pressure drop to orthostatic stress before and in the first half of pregnancy (ANOVA, p = 0.002). Although control blood pressure values were higher in the preeclamptic women, this can not entirely explain the larger initial blood pressure response. In the first 3 seconds after standing up, arterial blood pressure shows an increase due to the muscular compression of the vessels of the legs and an increase in abdominal pressure, causing a shift of blood towards the heart. This causes a reflex release of vasoconstrictor tone and a fall in blood pressure, followed by a sympathetically mediated vasoconstriction whereby blood pressure recovers and sometimes overshoots. During the fall in blood pressure, mean arterial pressure is mainly preserved due to the pooled blood volume in the lungs. When resting sympathetic activity is higher, the sensitivity to a decrease in vasoconstrictor tone will be increased. This increased sensitivity combined with a lower pooled blood volume, might explain the larger blood pressure drop, observed in women, who developed preeclampsia.

Our findings provide evidence for an increased resting sympathetic activity and decreased circulating volume, already present before and early in pregnancy, in women who will later develop preeclampsia.
Our second aim was to evaluate if cardiovascular parameters, either solitary or in conjunction with uterine artery Doppler assessment, could enable early selection of women at risk for the development of preeclampsia or fetal growth restriction.

In Chapter 4 we describe data from the same cohort as presented in chapter 3. Systolic and diastolic blood pressure, heart rate, cardiac output, total peripheral resistance, phase difference of systolic blood pressure and beat-to-beat interval were measured serially before, during and after pregnancy. At 20 weeks uterine artery Doppler measurements were performed. Outcome was classified as preeclampsia or gestational hypertension with or without fetal growth restriction, fetal growth restriction without preeclampsia or gestational hypertension and normal pregnancy. The study was designed as a pilot study to determine if hemodynamic parameters in conjunction with uterine artery Doppler could have predictive value and at which gestational age prediction was most accurate.

We observed differences for systolic blood pressure, cardiac output, phase difference and total peripheral vascular resistance, in early pregnancy, between groups. We performed a two-step discriminant analysis. The values of systolic blood pressure, cardiac output, phase difference and body mass index in the four outcome groups in the first trimester were used in the first discriminant analysis. In the second step the probability of normal group classification from the first step was used in conjunction with uterine Doppler (Pulsatility index and bilateral notch) and systolic blood pressure at 20 weeks gestational age. This second step procedure allowed selection of 93% of women with an abnormal outcome, while specificity was 100%. The estimated 95% lower confidence limit, based on study cohort number, was 65% for sensitivity and 87% for specificity.

With our data we confirmed the presence of hemodynamic changes shortly after the beginning of pregnancy. The study supports our hypothesis that hemodynamic changes differ from normal pregnancy in women whose pregnancies eventually are complicated by preeclampsia, gestational hypertension or fetal growth restriction. Although confirmation in a larger population is necessary, early selection of women at risk seems possible with our non-invasive tests.

For the above mentioned studies we used a non-invasive measurement device, the Portapres (TNO, Amsterdam). This device registers the arterial pulse waveform beat-to-beat at the finger. Out of this waveform, cardiovascular parameters can be analyzed by dedicated software (Beatfast, Modelflow). The method is based on the methodology of Penaz and the physical criteria of Wesseling and enables continuous, non-invasive measurement of heart rate, blood pressure, cardiac output and systemic resistance. The possible pressure gradients over the arm are corrected by the return to flow method. This method has been validated extensively in non-pregnant subjects, but not in pregnant women.
We therefore performed two studies for validation of this device during pregnancy, one regarding blood pressure and one regarding cardiac stroke volume and cardiac output.

In **Chapter 5** we describe a cross-sectional study where we compare Portapres with and without return to flow correction, against standard anaeroid sphygmomanometry according to Riva-Rocci-Korotkoff, in normal pregnant women, at each trimester, and preeclamptic pregnant women. Study protocol followed protocols from the Association for the Advancement of Medical Instrumentation (AAMI) and British Hypertension Society (BHS) and data were analyzed according to their recommendations. According to the grading criteria of the British Hypertension Society, Portapres with Return to flow correction achieved a B grading for comparison of diastolic blood pressure and a C grading for the comparison of systolic blood pressure. Portapres without return to flow correction achieved a D grading for both diastolic and systolic blood pressure comparison. The criteria of the Association for the Advancement of Medical Instrumentation (mean pressure difference no more than 5 mmHg, and SD no more than 8 mmHg) were reached for both diastolic and systolic blood pressure measurements with Return to Flow. However, these results represent the overall performance taken all pregnant women. In different trimesters or preeclamptics alone, performance differs and does not always meet the criteria set by the Association for the Advancement of Medical Instrumentation. Further evaluation is mandatory because of the small separate groups for each trimester.

In **Chapter 6** we compared cardiac output estimation, analysed by Modelflow, out of continuous finger arterial pressure waveform with the commonly used Doppler echocardiography. There are indications that aorta characteristic elements as aortic compliance and diameter, which are incorporated in the algorithm of Modelflow, change under influence of pregnancy. An increase in aorta compliance in pregnancy might cause an underestimation of stroke volume measured by Modelflow. Therefore, measurements of these aorta characteristics were incorporated in the study protocol. In primigravid women estimation of stroke volume and aortic characteristics were performed serially during first, second and thirth trimester of pregnancy and after delivery. Stroke volume was assessed by Doppler echocardiography and continues finger pulse wave registration. Aortic compliance was estimated by Pulse wave velocity and aortic diameter by echocardiography. Pulse wave velocity was significantly lower during pregnancy, compared to the non pregnant state 5 months after delivery, indicating an increased aortic compliance during pregnancy. There was no significant change of compliance during pregnancy, between trimesters. The differences between pulse wave velocity during pregnancy, compared to non pregnant values remained after correction for differences in mean arterial pressure. Aortic diameter, either systolic or diastolic showed no differences during and after pregnancy. Results on stroke volume measurements revealed, as
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expected, an underestimation of stroke volume during pregnancy and an overestimation after pregnancy. Pulse wave velocity and systolic blood pressure are related to aortic compliance and for both differences between pregnant and non pregnant state were observed. These parameters were entered in the algorithm for adjustment of Modelflow. Comparison of echocardiography and modelflow resulted in a measurement error for 30-40%. Similar variations have been described for Doppler echocardiography compared to thermodilution. 32 33 34 Because of these measurement errors, neither Doppler echocardiography nor Modelflow, is useful for routine clinical care, but both could be considered useful research instruments. Advantage of Modelflow above echocardiography is it capability for continuous measurements, the reliability for longitudinal measurements and the convenience of application.

General discussion

We confirmed our hypothesis that early in pregnancy hemodynamic and cardiovascular adaptation differences can be detected by non-invasive measurement methods between women who will have a normal pregnancy and women whose pregnancy eventually becomes complicated by preeclampsia or fetal growth restriction. We observed these differences already in early pregnancy. By combining different hemodynamic parameters with patient characteristics, selection of 93% of women with an abnormal outcome with a specificity of 100% was possible within our study population. Our measurements were performed by Portapres, a non-invasive device convenient to apply, that provides continues beat-to-beat measurements. In comparison to the commonly used measurement devices in clinical practice, Portapres showed similar variance in measurements in pregnant women.

Our findings give opportunities for early identification of women at risk for preeclampsia or fetal growth restriction. Much research has been performed in order to find a diagnostic test for preeclampsia. Many biochemical markers have been proposed to predict women likely to develop preeclampsia. Markers were chosen on the basis of specific patho-physiological abnormalities to be associated with preeclampsia, like those of placental dysfunction, endothelial and coagulation activation, and systemic inflammation. However, data show that predictive accuracy of these markers are inconsistent and insufficient for routine clinical practice. 35 36 Systolic blood pressure, diastolic blood pressure or an increase in systolic- or diastolic blood pressure predicted poorly for preeclampsia. Mean arterial pressure in the second trimester of 90 mmHG or more showed a positive likelihood ratio of 3.5 (95% CI 2.0 to 5.0) and a negative likelihood ratio of 0.46 (0.16-0.75). In a high risk population a diastolic blood pressure of 75 mmHg or more best predicted preeclampsia. 36 Abnormal uterine artery Doppler findings in the second trimester are associated with a six fold increase rate of preeclampsia. Neverthe-
less, out of a review of 27 studies, uterine artery Doppler assessment showed to be of limited value as a screening test for preeclampsia. Of the different Doppler indices, an increased pulsatility index with notching in the second trimester best predicted overall preeclampsia in low-risk and high-risk patients. An increased pulsatility index or bilateral notching best predicted severe preeclampsia. An increased pulsatility index alone or in combination with notching best predicted severe fetal growth restriction in low risk patients, whereas in high risk patients the best predictor was an increased resistance index. Other Doppler indices showed low to moderate predictive value. Both preeclampsia and intrauterine fetal growth restriction have relatively low prevalence. Therefore, a clinically useful test should have a high positive likelihood ratio (>10) and a low negative likelihood ratio (< 0.1). In predicting preeclampsia, an increased pulsatility index combined with notching showed a positive likelihood ratio of 21.0 (95% CI 5.5-80.5) and a negative likelihood ratio of 0.82 (0.72-0.93) among high risk patients and a positive likelihood ratio of 7.5 (5.4-10.2) and negative likelihood ratio 0.59 (0.47 -0.71) among low risk patients. For predicting overall fetal growth restriction a positive likelihood ratio of 9.1 (5.0-16.7) with a negative likelihood ratio of 0.89 (0.85-0.93) was found. For predicting severe fetal growth restriction positive likelihood ratio was 14.6 (7.8-26.3) with a negative likelihood ratio of 0.78 (0.68-0.87) among low risk patients. This relatively high negative likelihood ratio makes this test unreliable for common clinical practice. Different physiological tests, like the roll-over-test, that have been evaluated for prediction of preeclampsia had test characteristics that were insufficient for clinical use. 3

In our model we used a combination of cardiovascular and patient characteristics in conjunction with uterine artery Doppler measurement. Due to the two step model, false positive rate could be reduced. We are aware that our results depend to a large extent on the high rate of abnormal outcome in the multiparous group with previous complications. The power in the primiparous group was limited. Differences between nulliparous and multiparous women can not be excluded. Because in multiparous women the obstetric history is an effective risk selection parameter and the incidence of preeclampsia and fetal growth restriction is higher in nulliparous women, these women will benefit most from an effective screening strategy. Therefore, it is clear that our method should be evaluated in a larger population of nulliparous women.

No cure exists for fetal growth restriction and the only effective treatment of preeclampsia is termination of pregnancy. Prevention would have significant impact on maternal and prenatal outcome worldwide. The development of preventive strategies not only requires knowledge of pathophysiolologic mechanisms of the disease, but also availability of methods of early detection, and means for intervention and correction of pathophysiolologic changes. However, presently the only strategies with some effect are low dose
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aspirin in high risk women and calcium suppletion in women with low calcium intake.\textsuperscript{5} \textsuperscript{39} \textsuperscript{40} Next to the application of preventive strategies, early prediction could also be usefull for targeting obstetric care at those most likely to benefit.

Differences between healthy pregnant women and women, who will develop preeclampsia, were observed early in pregnancy, long before the clinical onset of disease. This implicates that interventions aimed at prevention of preeclampsia should start early in pregnancy. Our test method is non-invasive and application is easy. This makes further evaluation feasible and could make the test method suitable for screening if the test characteristics can be reproduced in a larger study.
Reference List


