Non-invasive hemodynamic measurements early in pregnancy
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General introduction and aims of this thesis
Preeclampsia is a major cause of maternal morbidity and mortality, perinatal death, preterm birth, and fetal growth restriction. It is a multisystem disorder of unknown cause. A common hypothesis is that inadequate remodelling of the uterine blood vessels that supply the placenta early in pregnancy, the spiral arteries, results in a systemic response that is associated with endothelial dysfunction and consequently increased systemic vascular resistance, enhanced platelet aggregation, and activation of the coagulation system. Preeclampsia presents as a maternal syndrome with a large variation in clinical expression and severity of disease. Obligatory symptoms for the clinical diagnosis are hypertension and proteinuria while associated renal, hepatic, neurological and clotting abnormalities can vary greatly in presence. Preterm preeclampsia is nearly always associated with placental dysfunction, resulting in fetal malnutrition, growth restriction, hypo-oxygenation, and acidosis. Preeclampsia by definition is a disorder of the second half of pregnancy that resolves shortly after delivery. Because the underlying pathogenesis is unclear, pre-eclampsia is at present unpredictable in onset and progression, and incurable except by termination of the pregnancy.

Hemodynamic characteristics
Hemodynamic characteristics of patients suffering from preeclampsia and fetal growth restriction have been described. From the results of Swan-Ganz measurements in untreated preeclamptic patients we know now that the hemodynamic expression of severe disease is characterised by a low cardiac index and low stroke volume index, a high systemic vascular resistance index and a reduced plasma volume. Pregnancies complicated by fetal growth restriction are characterised at term by low cardiac output combined with increased vascular resistance. However, the clinical expression usually does not become apparent before 32-36 weeks of gestational age, and could be preceded by a long latent phase.

It is well known that the maternal cardiovascular system undergoes profound changes during pregnancy and that most of these changes occur already in the first trimester of pregnancy. Cardiac output increases, initially because of increased heart rate, soon followed by an increased stroke volume. The largest increase from the non-pregnant state is already observed before 8 weeks of gestation. Cardiac output continues to increase until midpregnancy, and remains stable thereafter. Blood pressure decreases, reaching a minimum in midpregnancy. Peripheral vascular resistance is reduced throughout pregnancy and total circulating volume is supposed to increase to 40 % compared to non-pregnant subjects.

A number of observational studies point to hemodynamic differences, that may be present before or in early pregnancy in women predisposed to develop preeclampsia or fetal growth restriction. However, results are conflicting between studies and the magnitude of such differences is not clear.
Sympathetic activity

Vascular tone is largely determined by the activity of the sympathetic nervous system. Schobel et al\textsuperscript{12} were the first to measure postganglionic action potentials in sympathetic-nerve fibers innervating blood vessels in the skeletal muscle in patients with preeclampsia. Mean sympathetic activity during rest appeared to be three times higher in preeclamptic women compared to healthy pregnant women, and two times higher compared to the hypertensive non-pregnant women. After delivery, the preeclamptic women showed an almost parallel decrease of mean arterial pressure and sympathetic nerve activity. Although Schobel et al found a higher sympathetic nerve activity in preeclampsia, they observed no difference in hemodynamic and sympathetic nerve responses to Valsalva’s manoeuvre and cold pressure test. Data of Schobel et al were later confirmed by Greenwood et al\textsuperscript{13}, who performed a similar study in women with pregnancy induced hypertension. These data could indicate that the increase in systemic vascular resistance, at least partly, is mediated by a marked increase in sympathetic vasoconstrictor activity in hypertensive pregnancies.\textsuperscript{12,14} 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.

The association between the development of hypertension in pregnancy and alterations in autonomic cardiovascular control was already investigated before the observations of Schobel \textit{et al} and Greenwood \textit{et al} were published. For a review of these studies see chapter 2. Different methods for the clinical assessment of autonomic cardiovascular control in humans have been used. Most studies were performed with non-invasive methods. There are basically 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.\textsuperscript{15-19,20} These methods have the advantage of minimal risk for the mother and the conceptus and the possibility of repeated measurements during pregnancy.

Early prediction

Although numerous clinical, biophysical or biochemical tests have been proposed for the prediction and early detection of preeclampsia, their results have been inconsistent and contradictory.

The most frequently applied methods are risk factor assessment, standard blood pressure measurement\textsuperscript{1} and measurement of the Doppler wave form of the uterine artery\textsuperscript{21,22,23,24} Presently, no predictive method exists with characteristics that make application for routine use in clinical practice feasible.\textsuperscript{1,25,26,27,28}
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Aims of this thesis

The main focus of this thesis was to investigate if by non-invasive strategies differences in hemodynamic and autonomic cardiovascular adaptation to pregnancy could be observed early in pregnancy, between women who eventually developed preeclampsia or fetal growth restriction and women with a healthy pregnancy. The intention was to develop a screening strategy, which could be applied to a large number of pregnant women.

Outline of this thesis

Part 1
An overview is presented of the literature regarding non-invasive tests of the function of the autonomic nervous system. (Chapter 2). Secondly, we performed a longitudinal study measuring patients before and in the first half of pregnancy, to evaluate if a difference could be detected in autonomic cardiovascular control between women with a normal development of pregnancy and women, who developed preeclampsia later in pregnancy, using non-invasive measurement techniques. (Chapter 3)

Part 2
Within the same cohort as described in chapter 3, we measured cardiovascular parameters like blood pressure, cardiac output and peripheral vascular resistance using finger pulse contour analysis with Portapres. We evaluated if differences were already present before or in early pregnancy between women with normal pregnancy and women who eventually developed preeclampsia or fetal growth restriction. Secondly, we combined our findings with those described in chapter 3 concerning autonomic control and analysed if this could enable selection of women at risk for the development of preeclampsia or fetal growth restriction, either solitary or in conjunction with uterine artery Doppler assessment. (Chapter 4)

Part 3
For the studies of chapter 3 and 4 we used the measurement of finger pulse wave by Portapres. This device offers the advantage of continuous non-invasive measurement and convenience of application. Although it has been validated extensively in non-pregnant subjects, this was not done in pregnant subjects. We therefore compared blood pressure registration by Portapres with standard sphygmomanometry in pregnant subjects (Chapter 5) and cardiac output by finger arterial pressure waveform registration with Doppler echocardiography (Chapter 6).
Reference List

Introduction


