Non-invasive hemodynamic measurements early in pregnancy
Rang, S.

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Serial hemodynamic measurement in normal pregnancy, preeclampsia and intrauterine growth restriction

Saskia Rang, MD a,
Gert A. van Montfrans, PhD b,
Hans Wolf, PhD a

a Department of Obstetrics & Gynecology,
b Department of Internal Medicine.
Academic Medical Center, Amsterdam,
The Netherlands

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Abstract

**Objective:** The study hypothesis was that hemodynamic measurements in conjunction with uterine artery Doppler could enable selection of women at risk for the development of preeclampsia or fetal growth restriction.

**Study design:** Systolic (SBP) and diastolic blood pressure (DBP), heart rate (RR), cardiac output (CO), total peripheral resistance (TPR), phase difference of SBP and RR interval were measured serially before, during and after pregnancy. At 20 weeks uterine artery Doppler measurement was performed. Outcome was classified as preeclampsia (PE) or gestational hypertension (GH) with or without fetal growth restriction (FGR), FGR without PE or GH, and normal pregnancy (NP). Differences between these groups were assessed by 1-way analysis of viriance and discriminant analysis.

**Results:** In early pregnancy, in comparison to NP (n=28), PE/GH had a higher SBP and phase difference of SBP-RR interval. CO was higher in PE/GH without FGR (n=5), but not in PE/GH with FGR (n=5). FGR, either with or without PE/GH (n=4), was associated with higher TPR. Conjunction with uterine Doppler allowed selection of 93% of women with an abnormal outcome with a specificity of 100%.

**Conclusion:** The study supports our hypothesis that in early pregnancy hemodynamic parameters differ from normal in women predisposed to develop preeclampsia or fetal growth restriction.
Introduction

Preeclampsia and intra uterine fetal growth restriction are common complications of pregnancy. Hemodynamic characteristics of these disorders have been described during the clinical phase.\textsuperscript{1-4} However, this clinical expression usually does not become apparent before 32-36 weeks of gestational age, and is preceded by a long latent phase.

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.\textsuperscript{5-9} However, results were conflicting between studies and the magnitude of such differences is not clear. We therefore performed a prospective longitudinal study beginning before pregnancy to evaluate whether cardiovascular differences are present in the pre-clinical phase in women who eventually develop preeclampsia or fetal growth restriction, compared to women with uncomplicated pregnancies.

In a previous study, we provided evidence for an increased resting sympathetic activity and found indications of a decreased circulating volume, already present in early pregnancy, in women who will develop preeclampsia, compared with women who will have a normal pregnancy.\textsuperscript{10} The objective in the present analysis of the same cohort was to evaluate if measurement of cardiovascular parameters by continuous finger arterial pressure waveform analysis 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.

Materials and Methods

Women who intended to become pregnant were recruited from the outpatient clinic and by advertisement. Women with a history of preeclampsia before 34 weeks in a previous pregnancy or women, who had never been pregnant, were eligible. All women had a normal blood pressure at time of enrollment, by conventional sphygmomanometry (diastolic blood pressure less than 90 mmHg, systolic blood pressure (SBP) less than 140 mmHg). All women had a regular menstrual cycle and none of them was taking oral contraceptives or other medication.

After written informed consent, all participants underwent identical study protocols. The study was approved by the Medical Ethical Committee of our hospital.

Measurements were started before pregnancy in the first (day 5 – 10) and second (day 18 - 25) half of the menstrual cycle. Not all participants completed two measurements before pregnancy. Because hemodynamic parameters are similar between first and second half of menstrual cycle, we either averaged both measurements or used the available single 1.\textsuperscript{11} In 7 women the second measurement before pregnancy could not be performed because of the onset of pregnancy. Once pregnant, further measurements were
performed at the gestational age of 6, 8, 12, 16, 20 and 32 weeks, with a maximum deviation of 4 days. Gestational age was confirmed by ultrasound measurement of the crown-rump length in the first trimester. All women had singleton pregnancies. Fifteen (range 11-19) weeks after delivery, 1 final measurement was performed. For each participant, visits were scheduled on the same time of day. Studies took place in a quiet room with an ambient temperature between 20 and 22°C. Participants were advised to refrain from caffeine or smoking from the night before the measurement. They were informed about all procedures and instructed to empty their bladder before the start of testing. They were asked not to move or speak during the procedure. Before the actual protocol was started, a test run was performed to accustom the participant to the procedure.

Continuous finger arterial pressure waveform registration

Non-invasive finger arterial pressure waveform registration by Portapres (TNO-TPD, Finapres Medical Systems, Amsterdam, The Netherlands) was used for continuous monitoring of heart rate, blood pressure, cardiac stroke volume, cardiac output and peripheral vascular resistance.

Portapres is a device for the continuous measurement of the finger arterial pressure, based on the volume clamp method of Penaz.\textsuperscript{12,13} Aortic pressure is estimated for each heart beat from the integral of the finger arterial pressure wave. Aortic input flow can be calculated by a model that combines the continuous aortic pressure estimates with estimation of aortic compliance and diameter. These 2 parameters have been derived from 45 human aortas in vitro and depend on sex and age.\textsuperscript{14} This approach is called the Modelflow method.\textsuperscript{15}

The accuracy of the device for blood pressure measurement has been validated for non-pregnant as well as pregnant subjects. By application of appropriate filtering of the signal and upper arm return-to-flow calibration the method meets the criteria set by the Association for the Advancement of Medical Instrumentation.\textsuperscript{16,17}

Stroke volume measurement has been validated extensively in non-pregnant subjects.\textsuperscript{18-22} We performed a longitudinal comparison of this method with stroke volume analysis by Doppler echocardiography during pregnancy and after delivery.\textsuperscript{23} Both methods showed a similar random variation of approximately 30%.\textsuperscript{23}

The registration was performed with an appropriate size finger cuff applied at the middle finger of the left hand. The cuffed finger was kept at heart level during the procedure by a sling to avoid hydrostatic pressure influences. At a stable signal, the pressure registration was corrected by the return-to-flow method.\textsuperscript{24,25} The physiocal, a dynamic servo set point adjuster, was switched off during the period of data collection to ascertain a continuous recording.\textsuperscript{26} Data collection was performed over a period of 10 minutes supine rest after a stable signal had been reached for at least 5 minutes. At gestational ages of 20 and 32 weeks, supine posture was changed to 30 ° left lateral tilt for all participants.
Serial hemodynamic measurements

Full-wave arterial pulse pressure signal was stored at a frequency of 200 Hz. Off-line beat-to-beat SBP, diastolic (DBP), mean arterial pressure and heart rate were extracted by Beatfast software (TNO/BMI). From the blood pressure waveform, stroke volume, cardiac output, and total peripheral vascular resistance were estimated by Modelflow software (TNO/BMI). Measurements were averaged over a stable period of 10 minutes in supine position.

The phase difference of systolic blood pressure and pulse interval was calculated by the Fast Fourier transform algorithm at the low frequency band (0.04–0.15 Hz). These values were presented in our previous study of this cohort regarding autonomic cardiovascular control. A more negative value of this parameter is associated with a dominance of the sympathetic system. Because our earlier analysis demonstrated that a more negative value in the first trimester was associated with later development of preeclampsia, we included this parameter in our present study.

Uterine artery Doppler
At 20 weeks uterine artery flow velocity waveforms were obtained using an ATL 3000 ultrasound machine (Phillips, Best, The Netherlands) with a 3.5/5-MHz curvilinear array. The transducer was placed in the lower lateral quadrant of the abdomen angled medially. Color flow pulsed Doppler imaging was used to identify the uterine artery at the point at which it crossed the external iliac artery. The range gate was placed over the entire diameter of the uterine artery approximately 1 cm distal to the crossover point. The quality of the flow velocity waveforms was maximized by using the smallest possible angle of insonation (range 15–50°) and accepting only those waveforms with a clear outline. Uterine artery waveforms were obtained from both sides in all the women studied. The pulsatility index (PI) was calculated from three identical consecutive waveforms using in-built software, and the average of both arteries was used for analysis. The presence or absence of a notch was noted in each of the waveforms in both uterine arteries. A notch was considered to be present when there was a clearly defined upturn of the flow velocity waveform at the beginning of diastole in all three waveforms in both arteries. One operator (S.R.) performed the majority of measurements.

Statistics
Classification of the women was based on the development of gestational hypertension (GH), preeclampsia (PE), or fetal growth restriction (FGR). GH was defined by a SBP higher than 140 mmHg or a DBP higher than 90 mmHg, measured at least twice with an interval of more than 6 hours after 20 weeks' gestational age in women with normal blood pressure before 20 weeks. PE was defined by GH with proteinuria more than 0.3 mg per 24 hours, according to the International Society for the Study of Hypertension in Pregnancy recommendation. FGR was defined as a newborn weight below the 10th percentile of its gestational age, adjusted for infant sex, maternal length, weight, parity and ethnic origin. The study group was stratified after delivery into 4 groups: women with PE or
GH without FGR, women with PE or GH with FGR and women with FGR without PE or GH. The remaining women were classified as having a normal pregnancy (NP). Data were analyzed by 1-way analysis of variance (ANOVA) to determine differences between measurement periods and outcome groups. Multiple post hoc comparisons were performed by Bonferroni t-test. Discriminant analysis, using systolic blood pressure, cardiac output, low frequency phase difference of SBP and pulse interval at each measurement session before or at 20 weeks, was used to classify participants to the outcome groups. Body mass index, calculated by body weight and length obtained before pregnancy, was added to the analysis because this allowed adjustment of cardiac output to body size. The efficacy of the test at the measurement sessions before or at 20 weeks was expressed by the percentage of women allocated to the correct outcome group and by sensitivity and specificity for discriminating the normal outcome group from the abnormal outcome groups. This enabled detection at which gestational age (before or at 20 weeks) the classification was most effective. Measurements at that gestational age were then used for selection of women with a predicted abnormal outcome. These women entered a second discriminant analysis using the probability for normal outcome in the first analysis and the average uterine artery Doppler pulsatility index, bilateral notch, and auscultatory SBP at 20 weeks.

Statistical calculations were performed with SPSS 12.0.2 (SPSS Inc.,Chicago, IL) The value of P ≤ .05 was considered statistically significant.

We estimated that 20% of the study population would develop preeclampsia or intrauterine growth restriction, resulting in a case-control ratio of 1:4. Forty women ( 8 cases ; 32 controls) would enable the detection of a difference of over 10% of a parameter with a standard deviation of 10% at alpha 0.05 and a power of 80% (beta 0.2) when tested two-sided. We assumed that 50% of the women, who were recruited, would become pregnant within one year and would complete all examinations. The study was designed as a pilot study to determine if hemodynamic parameters could have predictive value in conjunction with uterine artery Doppler and at which gestational age prediction was most effective.

Results

Eighty-two women were enrolled before pregnancy. Forty-seven became pregnant within 1 year. Five had a miscarriage before 12 weeks’ gestational age. Forty-two women completed the study, 21 with a history of preeclampsia and 21 during their first pregnancy.

Of the 42 women participating in the study, 5 were diagnosed with PE (n=2) or GH (n=3) without FGR, five with PE (n=4) or GH (n=1) with FGR and 4 with FGR without PE or GH (Table 1) . Groups did not differ significantly regarding age and body mass
Table 1. Study group characteristics specified for women with an uneventful pregnancy (normal), women who developed preeclampsia (PE) or gestational hypertension (GH) without fetal growth restriction (FGR), women with PE or GH with FGR, and women with a pregnancy complicated by FGR without PE or GH.

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 28)</th>
<th>PE/GH, no FGR (n = 5)</th>
<th>PE/GH and FGR (n = 5)</th>
<th>FGR, no PE/GH (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At intake</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>30 (24-39)</td>
<td>30 (26-30)</td>
<td>30 (24-34)</td>
<td>26 (22-32)</td>
</tr>
<tr>
<td>Primigravid</td>
<td>17 (61)</td>
<td>1 (25)</td>
<td>3 (38)</td>
<td>0 (-)</td>
</tr>
<tr>
<td>Race Caucasian</td>
<td>28 (100)</td>
<td>5 (100)</td>
<td>4 (80)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1 (4)</td>
<td>0 (-)</td>
<td>1 (20)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>114 (102-138)</td>
<td>120 (112-136)</td>
<td>122 (110-124)</td>
<td>109 (106-124)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76 (60-88)</td>
<td>84 (78-86)</td>
<td>80 (72-88)</td>
<td>75 (70-80)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24 (19-39)</td>
<td>25 (21-31)</td>
<td>27 (20-32)</td>
<td>21 (16-28)</td>
</tr>
<tr>
<td><strong>At 20 weeks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine artery Doppler PI</td>
<td>0.8 (0.6-1.1)</td>
<td>0.9 (0.7-1.3)</td>
<td>1.1 (0.7-1.8)*</td>
<td>1.1 (1.0-2.2)*</td>
</tr>
<tr>
<td>Uterine artery Doppler notch</td>
<td>0 (-)</td>
<td>0 (-)</td>
<td>4 (80)*</td>
<td>3 (75)*</td>
</tr>
<tr>
<td><strong>At delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal weight (g)</td>
<td>3460 (2550-4500)</td>
<td>2970 (2695-4000)</td>
<td>2090 (750-3010)*</td>
<td>2615 (1250-2875)*</td>
</tr>
<tr>
<td>GA delivery (weeks)</td>
<td>40 (36-42)</td>
<td>38 (36-40)</td>
<td>38 (28-41)*</td>
<td>39 (34-41)</td>
</tr>
</tbody>
</table>

Blood pressure measured by conventional sphygmomanometry (diastolic blood pressure at Korotkoff V) at intake before pregnancy. Values are presented as median with range between brackets or number with percentage between brackets. DBP, diastolic blood pressure; GA, gestational age. * P<.05, compared with normal

index. All women were Caucasian, except two (1 was of South-East Asian ethnicity, 1 West-African ethnicity).

Gestational age at delivery in the PE/GH with FGR group was significantly lower compared to NP (P = 0.005). Birth weight was significantly lower in both groups with FGR (with or without PE/GH) than in the PE/GH group without FGR or the normal group. (P=0.012 and P=.002) Seventeen of the 21 nulliparous women (81%) and 11 of the 21 multiparous women (52%) had a normal outcome.

The cardiovascular measurement data for the normal outcome group (n=28) are presented by box-plots in Figure 1. Whereas systolic blood pressure was unchanged during the first trimester and decreased thereafter with a minimum at 32 weeks, diastolic blood pressure decreased from the beginning of pregnancy and stabilized after 16 weeks. Heart rate, total peripheral resistance and stroke volume showed a statistically significant change already at 6 weeks’ gestational age. Whereas heart rate increased gradually until 32 weeks, stroke volume decreased slightly after 20 weeks. These changes resulted in a higher cardiac output during pregnancy, due to an increase of stroke volume in the first half and an increase in heart rate in the second half of pregnancy. Phase difference was only slightly larger at 32 weeks, compared to all other periods. Fifteen weeks after delivery systolic blood pressure, diastolic blood pressure and total peripheral resistance were significantly lower than before pregnancy, whereas stroke volume was significantly higher than before pregnancy.
Figure 2 presents the means with SE for all parameters in the 4 outcome groups. Differences between outcome groups were statistically significant (1-way ANOVA) for systolic blood pressure at 20 and 32 weeks, for diastolic blood pressure at 20 and 32 weeks, total peripheral resistance at 32 weeks, and phase difference at 8 and 12 weeks.

In early pregnancy differences could be observed between the groups. Women in the PE-group (with or without FGR) had higher blood pressure values, compared with NP and FGR groups. Cardiac output was highest in the PE/GH without FGR group and lowest in the groups with FGR. Total peripheral resistance was higher in the FGR groups either with or without PE/GH. Phase difference was larger in the PE/GH groups with or without FGR than in the NP or FGR without PE/GH groups.

The values of systolic blood pressure, cardiac output and phase difference, which were used in discriminant analysis A, in the 4 outcome groups, are presented in Table 2 (means with SD).

Results of discriminant analysis at the measurement periods before or at 20 weeks are presented in Table 3. The highest percentage of correct classification was observed at 8 weeks gestation. Therefore this classification result was used for the second discrimi-
Figure 2. Means with SE of systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiac output (CO), total peripheral resistance (TPR), low frequency phase difference of blood pressure, and heart beat interval (phase) in women with normal pregnancy outcome (normal), women who developed preeclampsia (PE) or gestational hypertension (GH) without fetal growth restriction (FGR), women with PE or GH with FGR, and women with a pregnancy complicated by FGR without PE or GH. Measurements were performed before pregnancy (PG), at a gestational age of 6, 8, 12, 16, 20 and 32 weeks and 15 weeks after delivery (PP)
nant analysis, including all participants with an abnormal result in the first discriminant analysis. The scatter plot of the first 2 discriminant functions for all outcome groups is presented in Figure 3. Table 4 demonstrates the classification results of first and second steps of the analysis. The overall sensitivity of the 2-step procedure for any abnormal outcome was 93% and specificity 100%, with an estimated 95% lower confidence limit of 65% and 87%. One woman with FGR (gestational age at delivery 39 weeks, birth weight 2875 grams) was classified as normal outcome.

**Table 2** Mean of SBP, cardiac output (CO), and low frequency phase difference of blood pressure and heart beat interval (phase) in women with normal pregnancy outcome (normal), women who developed preeclampsia (PE) or gestational hypertension (GH) without fetal growth restriction (FGR), women with PE or GH with FGR, and women with a pregnancy complicated by FGR without PE or GH.

<table>
<thead>
<tr>
<th>Measure</th>
<th>PG</th>
<th>6 w.</th>
<th>8 w.</th>
<th>12 w.</th>
<th>16 w.</th>
<th>20 w.</th>
<th>32 w.</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>Normal</td>
<td>111(9)</td>
<td>111(8)</td>
<td>109(8)</td>
<td>111(9)</td>
<td>105(9)</td>
<td>103(8)</td>
<td>99(9)</td>
</tr>
<tr>
<td></td>
<td>PE/GH, no FGR</td>
<td>115(6)</td>
<td>116(2)</td>
<td>112(10)</td>
<td>112(8)</td>
<td>109(13)</td>
<td>112(11)</td>
<td>113(11)</td>
</tr>
<tr>
<td></td>
<td>PE/GH, and FGR</td>
<td>109(11)</td>
<td>114(11)</td>
<td>112(13)</td>
<td>114(13)</td>
<td>107(16)</td>
<td>113(12)</td>
<td>125(25)</td>
</tr>
<tr>
<td></td>
<td>FGR, no PE/GH</td>
<td>110(10)</td>
<td>111(12)</td>
<td>108(10)</td>
<td>113(11)</td>
<td>111(12)</td>
<td>103(10)</td>
<td>101(9)</td>
</tr>
<tr>
<td>CO</td>
<td>Normal</td>
<td>6.0(1.4)</td>
<td>7.5(1.8)</td>
<td>7.5(1.9)</td>
<td>7.9(1.9)</td>
<td>7.9(1.6)</td>
<td>7.3(1.5)</td>
<td>7.1(1.3)</td>
</tr>
<tr>
<td></td>
<td>PE/GH, no FGR</td>
<td>6.6(1.4)</td>
<td>9.1(1.8)</td>
<td>8.2(2.0)</td>
<td>8.8(2.1)</td>
<td>8.3(1.8)</td>
<td>8.6(1.7)</td>
<td>8.4(1.6)</td>
</tr>
<tr>
<td></td>
<td>PE/GH, and FGR</td>
<td>5.6(0.9)</td>
<td>7.0(0.5)</td>
<td>6.7(0.9)</td>
<td>7.0(1.3)</td>
<td>7.0(0.9)</td>
<td>7.7(1.3)</td>
<td>7.0(1.6)</td>
</tr>
<tr>
<td></td>
<td>FGR, no PE/GH</td>
<td>5.2(1.0)</td>
<td>6.8(1.6)</td>
<td>7.1(1.0)</td>
<td>7.1(1.3)</td>
<td>7.8(1.1)</td>
<td>7.2(0.9)</td>
<td>7.0(1.3)</td>
</tr>
<tr>
<td>Phase</td>
<td>Normal</td>
<td>-60(14)</td>
<td>-60(17)</td>
<td>-64(16)</td>
<td>-61(20)</td>
<td>-58(20)</td>
<td>-65(29)</td>
<td>-76(18)</td>
</tr>
<tr>
<td></td>
<td>PE/GH, no FGR</td>
<td>-59(22)</td>
<td>-68(20)</td>
<td>-83(21)</td>
<td>-86(23)</td>
<td>-65(28)</td>
<td>-95(34)</td>
<td>-87(14)</td>
</tr>
<tr>
<td></td>
<td>PE/GH, and FGR</td>
<td>-70(8)</td>
<td>-66(15)</td>
<td>-73(10)</td>
<td>-70(14)</td>
<td>-69(29)</td>
<td>-66(29)</td>
<td>-92(39)</td>
</tr>
<tr>
<td></td>
<td>FGR, no PE/GH</td>
<td>-66(7)</td>
<td>-67(10)</td>
<td>-60(4)</td>
<td>-76(12)</td>
<td>-63(21)</td>
<td>-56(29)</td>
<td>-79(31)</td>
</tr>
</tbody>
</table>

Measurements were performed before pregnancy (PG) and at a gestational age of 6, 8, 12, 16, 20 and 32 weeks and 4 months after delivery (PP)

**Table 3** Classification by discriminant analysis using systolic arterial pressure, cardiac output, and low frequency blood pressure – heart beat interval phase difference registered by Portapres and body mass index (calculated by prepregnancy values) at a gestational age of 6, 8, 12, 16 and 20 weeks.

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Classified correctly,%</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before pregnancy</td>
<td>67</td>
<td>93</td>
<td>57</td>
</tr>
<tr>
<td>6 weeks</td>
<td>72</td>
<td>100</td>
<td>64</td>
</tr>
<tr>
<td>8 weeks</td>
<td>72</td>
<td>100</td>
<td>64</td>
</tr>
<tr>
<td>12 weeks</td>
<td>62</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>16 weeks</td>
<td>52</td>
<td>86</td>
<td>39</td>
</tr>
<tr>
<td>20 weeks</td>
<td>43</td>
<td>76</td>
<td>46</td>
</tr>
</tbody>
</table>

Sensitivity and specificity calculated for normal outcome vs other groups

**Comment**

Our data confirm the presence of hemodynamic changes shortly after the beginning of pregnancy. Second, our hypothesis that these changes are different in women whose pregnancies eventually are complicated by preeclampsia, gestational hypertension or
Serial hemodynamic measurements intra uterine growth retardation was supported. These observations may provide an opportunity for early identification of pregnancies at risk of developing preeclampsia, gestational hypertension or intra uterine growth retardation, although confirmation in

Figure 3. All-group scatter plots of discriminant functions at 8 weeks, using systolic arterial pressure, cardiac output, phase difference of blood pressure and heart beat interval registered by Portapres, and body mass index, and at 20 weeks, using probability for normal outcome at 8 weeks, mean uterine artery pulsatility index, bilateral uterine artery notch, and auscultatory systolic blood pressure.

Table 4 Combined classification results of the discriminant analysis at 8 and 20 weeks, differentiating between normal outcome, PE or GH without FGR, PE or GH with FGR and FGR without PE or GH.

<table>
<thead>
<tr>
<th>Observed outcome</th>
<th>Predicted Group Membership</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>PE/GH no FGR</td>
</tr>
<tr>
<td>8 weeks discriminant analysis</td>
<td>Normal 18 (64)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Normal</td>
<td>PE/GH no FGR</td>
<td>0</td>
</tr>
<tr>
<td>PE/GH and FGR</td>
<td>0</td>
<td>1 (20)</td>
</tr>
<tr>
<td>FGR, no PE/GH</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20 weeks discriminant analysis</td>
<td>Normal 10 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td>PE/GH, no FGR</td>
<td>0</td>
</tr>
<tr>
<td>PE/GH and FGR</td>
<td>0</td>
<td>1 (20)</td>
</tr>
<tr>
<td>FGR, no PE/GH</td>
<td>1 (25)</td>
<td>0</td>
</tr>
</tbody>
</table>

The 8 week discriminant analysis included all participants, using systolic arterial pressure, cardiac output, and low frequency blood pressure – heart beat interval phase difference registered by Portapres and body mass index (72% of participants correctly classified). The 20 week discriminant analysis included all nonnormal participants according to the 8 week discriminant analysis (n=24), using probability for normal outcome in the 8 week discriminant analysis, mean uterine artery pulsatility index, bilateral uterine artery notch, auscultatory SBP (83% of participants and 100% of normal outcome correctly classified).
a larger population is necessary. Early selection could be useful for targeting health care resources at a high risk group and future research regarding methods for prevention. Our end-point selection was based on the observation that GH and PE share common risk factors\(^3\) and the assumption that they are variations in severity of a similar complication of pregnancy. A common hypothesis is that abnormal placentation is at the origin of these conditions. The observation that birth weight in early preterm preeclampsia is associated with severity of maternal disease is in accordance with this hypothesis.\(^3\) However, in PE at term, FGR is often absent.\(^3\) Because FGR appears to be associated with the expression of PE/GH and because it has impact on perinatal outcome and on later infant health, we decided to divide women with PE/GH in a group with and a group without FGR. Based on earlier observations that FGR could be associated with a lower cardiac output,\(^3\) we assumed differences in cardiovascular measurement results between these groups.

Women who developed PE or GH without FGR had a higher systolic arterial pressure in early pregnancy than women with uneventful pregnancies, although in both groups blood pressure was normal by traditional standards. Similar observations have been made by Easterling et al.\(^5\) and Spaanderman et al.\(^8\), although these studies did not differentiate for FGR.

Earlier studies described a significantly higher cardiac output and slightly lower or normal peripheral resistance in the preclinical phase of preeclampsia, compared with healthy pregnancy.\(^5\) Bosio et al described a lowering of cardiac output and an increase of peripheral resistance when the clinical signs of preeclampsia appeared. This is in accordance with other studies that observed high systemic vascular resistance and low cardiac index by invasive measurements in women with severe preeclampsia.\(^1,2\) In our study, the PE/GH without FGR group was more comparable to the preeclampsia group in the study by Easterling et al, in which birth weight was not statistical different between the control and the preeclampsia group. In the study by Bosio et al, women with gestational hypertension had a larger cardiac output in the first half of pregnancy than women with preeclampsia. The gestational hypertension group had a normal birthweight, whereas birthweight was lower in the preeclampsia group. The association of cardiac output and birthweight was not explored in this study. Our data seem to indicate that in women with PE/GH without FGR blood pressure increase is more mediated by an increase of cardiac output, whereas in those with FGR, this is by an increase of peripheral resistance. Because none of the participating women developed preeclampsia before the last measurement at 32 weeks, we could not confirm a change of cardiovascular parameters thereafter. Table 5 summarizes the observed changes in pregnancy in the studies by Easterling et al, Bosio et al, and our study.

In women, whose pregnancies eventually were complicated by intrauterine growth restriction, either with or without PE/GH, we observed lower cardiac output combined with higher vascular resistance early in pregnancy, compared to normal pregnancy. For-
Serial hemodynamic measurements

Table 5. Outcome of different studies of mean arterial pressure (MAP), heart rate (HR), stroke volume (SV), cardiac output (CO), and total peripheral vascular resistance (TPR) during the preclinical phase of preeclampsia or gestational hypertension, compared to women with uncomplicated pregnancies.

<table>
<thead>
<tr>
<th>Study</th>
<th>MAP</th>
<th>HR</th>
<th>SV</th>
<th>CO</th>
<th>TPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easterling et al, 1990 ^5</td>
<td>↑</td>
<td>↑</td>
<td>=</td>
<td>↑</td>
<td>↓ ^a</td>
</tr>
<tr>
<td>Bosio et al, 1999 ^7</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>=</td>
</tr>
<tr>
<td>Rang, et al, with FGR</td>
<td>↑</td>
<td>=</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>without FGR</td>
<td>↑</td>
<td>=</td>
<td>↑</td>
<td>↑</td>
<td>=</td>
</tr>
</tbody>
</table>

Arrows indicate the difference, compared with findings in uncomplicated pregnancies. Equal sign indicates no difference, compared to uncomplicated pregnancies; upward arrow denotes an increase; downward arrow denotes a decrease; dash denotes not applicable. ^a Statistical significance only at 23 weeks and postpartum

merely published data demonstrated low nonpregnant plasma volume to be associated with recurrent fetal growth restriction ^9,35 or preeclampsia.^34 One study observed an association of high peripheral resistance with FGR in women with normal blood pressure.^36 Also at term, low cardiac output combined with increased vascular resistance has been observed in pregnancies complicated by intra uterine fetal growth restriction.^3,4 All formerly discussed longitudinal studies used Doppler echocardiography for assessment of stroke volume and cardiac output. In our study stroke volume was assessed by the analysis of the finger arterial pulse wave by Modelflow. Stroke volume estimation by Modelflow has been investigated extensively in a variety of situations in non-pregnant subjects.^15,18-20 In an earlier longitudinal study, we compared estimation of cardiac output analyzed out of finger arterial pulse wave by Modelflow with Doppler echocardiography during and after pregnancy. We observed an underestimation of approximately 10% by the former method during pregnancy because of changes in vascular characteristics in pregnancy.^23 After adjustment with an algorithm using systolic blood pressure, heart rate and pulse wave velocity, average measurement results were similar between both measurement techniques, and both methods showed a similar random variation.^23 We decided against adjustment in the present study because the observed systematic difference did not change during pregnancy, was proportionally small, and adjustment would not increase the efficacy of the discriminant analysis.

We did not use cardiac index instead of cardiac output for presentation of our data because use of this measure in pregnancy is controversial.^37 However, because ventricular ejection fraction is related to body mass index, we included this measure in our prediction model.^38 Body mass index was calculated by pre-gestational data to eliminate the effect of pregnancy on body weight.

A number of studies described an increase sympathetic activity in women with preeclampsia. ^39,40 In an earlier report regarding the present study population, we provided evidence for an increased resting sympathetic activity and decreased circulating volume, already present in early pregnancy, in women who will develop preeclampsia, compared with women who will have a normal pregnancy.^10 A larger phase difference between systolic blood pressure and pulse interval at the low frequency appeared to be associated
with later development of preeclampsia. Therefore we decided to include this parameter in the present study.

We observed in women with a normal outcome of pregnancy that blood pressure and total peripheral resistance decreased in the first half of pregnancy in 2 steps, with a first drop before 6 weeks and a second one at 16-20 weeks of gestation. (Figure 1) These changes could coincide with changes in uterine vascular resistance due to trophoblast invasion in the first half of pregnancy. This phenomenon develops in 2 stages. In the first trimester, the spiral arteries of the decidua are invaded, and in the second trimester, this invasion extends to the spiral arteries of the myometrium. This causes an increase in diameter of the spiral arteries and a decrease in local resistance.41;42 Because the spiral arteries do not open earlier than 12 weeks of gestation, this decrease in vascular resistance might be causally related with the second drop of vascular resistance and blood pressure that we observed in our data. A similar pattern was observed in the different subgroups, although at different levels.

Uterine artery Doppler at 18-24 weeks has been extensively researched for prediction of preeclampsia or fetal growth restriction.43 In general, predictive values are considered insufficient for use in routine antenatal care. Some studies demonstrate that in a high risk population positive and negative predicting values could be useful for clinical management.44;45 Combination of systolic blood pressure, cardiac output, and phase difference at 8 weeks enabled a fairly effective prediction of normal outcome of pregnancy with regard to fetal growth or maternal elevated blood pressure (sensitivity 100%, specificity 64%). The high false positive rate in the first discriminant analysis could be reduced by a 2-step model using uterine artery Doppler at 20 weeks in those women who had a prediction of abnormal outcome in the first analysis.

Our results depended to a large extent on the high rate of abnormal outcomes in the multiparous group with previous complications, whereas the power in the nulliparous group was limited. It is clear that our method should be evaluated in a larger population consisting of nulliparous women because differences between primiparous and multiparous women can not be excluded, and nulliparous women could benefit more from an effective screening strategy than multiparous women.

Conclusion

The study supports our hypothesis that hemodynamic differences are present in early pregnancy in women predisposed to develop preeclampsia or fetal growth restriction. These differences might be associated with the underlying cause for the development of these disorders and could be effective for selection of high-risk women early in pregnancy.
Serial hemodynamic measurements

References