Preeclampsia is a systemic pregnancy-associated disorder, which is characterized by the combined occurrence of persistent arterial hypertension and proteinuria after 20 weeks of gestation. The prevalence of preeclampsia during pregnancy is as high as 2% to 8% coming along with a high maternal and fetal morbidity and mortality. Because of the systemic character of the disease, maternal complications can affect different organs, including liver (coagulopathy and liver dysfunction) and brain (headache, visual disturbance, seizures, and coma). Abnormal placentaion with concomitant generalized maternal endothelial dysfunction is thought to be the principal cause of preeclampsia and its complications as a result of increased peripheral vascular resistance. Doppler studies of the uterine arteries have shown an abnormal high-resistance waveform (notch sign) as early as 12 to 16 weeks of gestation in women developing preeclampsia. Women with a persistent bilateral notch sign >24 weeks of gestation are at particular risk of developing general preeclampsia. The neurological manifestation of preeclampsia is probably caused by impaired cerebral vasoregulation leading to cerebral edema and (posterior) reversible encephalopathy syndrome. Cerebral autoregulation assessed from carotid compression was unaltered in mild preeclampsia, whereas during severe preeclampsia with neurological symptoms, dynamic properties of cerebral autoregulation (DCA) were strongly impaired. Such dynamic properties of autoregulation may be more sensitive to disturbances of cerebral autoregulatory mechanisms. It is not known whether disturbances of DCA occur earlier during pregnancy, particularly in women with abnormal placental hemodynamics and in those with subsequent preeclampsia.

This study investigates (1) whether DCA is altered in late midterm pregnant women, particularly in those with pathological bilateral notch sign of the uterine arteries and (2) whether changes in DCA at this stage of pregnancy could predict the occurrence of preeclampsia.

Patients and Methods
During a period of 2 years (January 2008 to December 2009) we recruited 72 pregnant women at 25 to 28 weeks of gestation. Most women were referred to Freiburg University Hospital for second trimester ultrasound (20–24 weeks of gestation), the remaining were referred directly to our study by their local consultant. The study was...
approved by the Local Ethics Committee, and all participants gave written informed consent. Exclusion criteria were age <18 or >45 years, insufficient temporal bone window for Doppler insonation, high-grade stenosis of brain-supplying arteries, disorders of the central nervous system, and the combination of pre-existing arterial hypertension with proteinuria at the time of study inclusion. This study was part of a larger project assessing the effect of various hemodynamic parameters in pregnancy.

At study inclusion, a standardized questionnaire was applied to all women. Every study participant underwent a neurological examination, extracranial duplexsonography, and uterine artery ultrasound to screen for the presence of a bilateral notch sign. Arterial blood pressure (ABP) at rest was measured manually with a blood pressure cuff at heart level. A urine sample was screened for proteinuria by urine dipstick analysis. During follow-up, study participants received a questionnaire to be completed by their local consultant at the regular control visit 6 weeks postpartum. Details on gestational age, prematurity, birth weight, birth length, and complications were gathered. The primary end point during follow-up was preeclampsia according to the criteria of the American College of Obstetricians and Gynecologists. In equivocal cases, treating physicians and patients were contacted directly to achieve more detailed information about the clinical course of the pregnancy. All clinical and follow-up data were obtained blinded for the results of the DCA measurements.

Measurements of cerebral hemodynamics were performed with the study participant in a supine position with 60° inclination of the upper body. Using a headband, cerebral blood flow velocity (CBFV) was captured simultaneously in one middle cerebral artery (MCA, M1 segment) and the posterior cerebral artery (PCA) on the opposite side (P1 segment) by insonation through the temporal bone window with 2-MHz transducers (Multidop-X4, DWL, Germany). Continuous noninvasive ABP and heart rate were recorded from the right index finger using a servo-controlled finger plethysmograph (Finapres 2300, Ohmeda) with the hand positioned at heart level. Absolute ABP values could not be calibrated to the upper arm cuff measurements with this device. End-tidal CO2 partial pressure was measured via infrared nasal capnography (Normocap, Datex, Finland). After stable baseline values were established, baseline values of all hemodynamic parameters were obtained, and afterward a data segment of 3.5 minutes was recorded with the woman breathing slowly without hyperventilation at a rate of 6/min (0.1 Hz) to elicit sinusoidal oscillations of ABP and CBFV. All parameters were recorded with a data-acquisition software package at a sampling rate of 100 Hz and were further analyzed with custom-written software.

Results

Seventy-two women were included in the study, of which 71 completed follow-up. DCA parameters could be analyzed in 70 cases for the MCA, and, because of a higher rate of artifacts, in 62 cases for the PCA. Baseline characteristics of pregnant women with and without subsequent preeclampsia are shown in Table 1. Women with subsequent preeclampsia had a higher body mass index, more often diabetes mellitus and (by trend) hypertension and a notch sign. Their newborns also had a lower birth weight.

General Hemodynamics

Hemodynamic baseline characteristics of pregnant and nonpregnant women are given in Table 2. Pregnant women showed a significantly higher blood pressure, higher heart rate, slightly increased PetCO2, as well as higher pulsatility and resistance index in MCA and PCA as compared with nonpregnant women. Among pregnant women, a significantly increased mean ABP could be found in those women who subsequently developed preeclampsia. In addition, pulsatility and resistance indices of MCA were slightly, but not significantly, lower in pregnant women who subsequently developed pre-eclampsia (Table 2).

DCA at Baseline

The DCA parameter phase was significantly higher in pregnant versus nonpregnant women both in the MCA and in the PCA, whereas the parameter gain showed no significant difference (Table 2). No differences in DCA parameters were observed between women with and without altered uteroplacental perfusion (positive bilateral notch sign), either in the MCA or in the PCA. Univariate linear regression of autoregulation parameters with various clinical characteristics at baseline did not yield significant results except from a reduced phase in pregnant women with a history of preeclampsia in a previous pregnancy. Clinical and autoregulation data on this subgroup are given in Table 3.
During follow-up, 9 pregnant women (13%) developed preeclampsia, being severe in 5 cases, including 1 case where mild neurological symptoms occurred. DCA parameters (gain and phase) did not significantly differ in women with or without the end point preeclampsia (Table 2; Figure 2). In the single woman with preeclampsia and neurological signs, normal autoregulation parameters were found at baseline (Table 4).

Logistic regression analysis showed no significant association of the end point preeclampsia with gain, phase, mean CBFV, and pulsatility index at baseline (Table 5). Also, neither of these parameters was associated with the duration of pregnancy and birth weight of the newborn.

Factors significantly associated with the end point preeclampsia were increased body mass index >29 kg/m² (odds ratio, 9.1; 95% confidence interval, 2.1–50.0; \( P = 0.004 \)), bilateral notch of the uterine arteries (odds ratio, 4.3; 95% confidence interval, 1.0–19.4; \( P = 0.048 \)), hypertension (odds ratio, 8.3; 95% confidence interval, 0.9–100.0; \( P = 0.046 \)), and diabetes mellitus (odds ratio, 11.6; 95% confidence interval, 2.2–63.5; \( P = 0.004 \)).

Discussion

This study shows that (1) DCA according to the parameter phase works slightly but significantly faster during late midterm pregnancy both in the MCA and in the PCA, whereas dampening characteristics (parameter gain) remain unaltered compared with nonpregnant women. (2) DCA is intact regardless of impaired uteroplacental perfusion at 25 to 28 weeks of gestation, whereas women with a previous history of preeclampsia have a significantly poorer DCA. (3) Maternal DCA during late midterm pregnancy is not a useful risk predictor for preeclampsia. We observed slightly better dynamic autoregulation during late midterm pregnancy compared with nonpregnant women in the MCA and PCA. This finding was observed despite the unexpected fact that the studied pregnant women showed slightly higher Petco₂ levels than the control group (which itself should rather lead to lower dynamic autoregulation parameters). The finding of better autoregulation properties is in accordance with the data of cerebral autoregulation in pregnant versus nonpregnant rats: late-pregnant rats showed more effective static autoregulation in the MCA and PCA compared with the nonpregnant rats.14 Contrarily,
further results from animal models suggest that structural and hemodynamic cerebral changes during late pregnancy facilitate autoregulatory breakthrough and blood–brain barrier disruption when blood pressure is elevated during late pregnancy. Thus, only pregnant rats developed cerebral edema during acute hypertension, despite more effective autoregulation.

Previous studies on autoregulation and cerebrovascular reactivity in human pregnancy and preeclampsia showed divergent results. Women with mild preeclampsia, but no reported neurological symptoms, displayed normal cerebral autoregulation using a carotid compression maneuver. In contrast, women with preeclampsia with severe neurological symptoms had severely reduced DCA in the MCA. In the present study, women who reached the primary end point preeclampsia showed no significant alteration of DCA at 25 to 28 weeks of gestation. DCA is a sensitive mechanism indicating hemodynamic integrity of the cerebral vasculature. Alterations in DCA do not necessarily lead to immediate clinical symptoms while blood pressure being in the normal range. They can, however, predispose to cerebral hemodynamic disturbances and cerebral complications as, for example, observed for carotid artery obstruction. Given the present results, it rather seems that changes of DCA develop only at a later stage of preeclampsia, perhaps even shortly before onset of neurological symptoms and thereby contributing to the cerebral manifestation of the disease. In accordance with this, women who developed preeclampsia later during pregnancy showed normal vasomotor responses to carbon dioxide inhalation and during isometric hand-grip at 19 to 28 weeks of gestation. In contrast, symptomatic preeclamptic women during late pregnancy displayed reduced vasomotor responses to similar challenge tests compared with healthy pregnant women.

The pathogenesis of preeclampsia involves endothelial dysfunction and it might be questioned if impaired cerebral autoregulation might at all be an early feature of the disease. This is because cerebral autoregulation primarily involves myogenic, neurogenic, and metabolic mechanisms although it may

Table 3. Results in the Subgroup of Women With a History of Previous Preeclampsia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pregnant Women With History of Previous Preeclampsia</th>
<th>Pregnant Women Without History of Previous Preeclampsia</th>
<th>Level of Significance (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>n=6 33.5±3.4</td>
<td>n=65 31.5±5.3</td>
<td>0.363</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>n=6 25.8±3.6</td>
<td>n=65 25.6±6.4</td>
<td>0.942</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>n=6 0 (0)</td>
<td>n=65 4 (6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>n=6 1 (17)</td>
<td>n=65 7 (11)</td>
<td>0.526</td>
</tr>
<tr>
<td>Primigravida, n (%)</td>
<td>n=6 0 (0)</td>
<td>n=65 33 (51)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Pregnancy duration, d</td>
<td>n=6 257±21</td>
<td>n=65 271±15</td>
<td>0.035*</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>n=6 2393±492</td>
<td>n=61 3195±563</td>
<td>0.001*</td>
</tr>
<tr>
<td>Subsequent preeclampsia, n (%)</td>
<td>n=6 1 (17%)</td>
<td>n=65 14 (22%)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Notch, n (%)</td>
<td>n=6 5 (83%)</td>
<td>n=65 14 (22%)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Mean ABP, mmHg</td>
<td>n=6 89.6±10.2</td>
<td>n=65 91.8±9.7</td>
<td>0.603</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>n=6 81.6±12.4</td>
<td>n=65 81.6±15.4</td>
<td>1.000</td>
</tr>
<tr>
<td>Phase MCA, °</td>
<td>n=6 26.9±29.7</td>
<td>n=63 46.7±22.5</td>
<td>0.049*</td>
</tr>
<tr>
<td>Phase PCA, °</td>
<td>n=6 28.9±21.5</td>
<td>n=61 51.6±22.0</td>
<td>0.018*</td>
</tr>
<tr>
<td>Gain MCA, %/%</td>
<td>n=6 0.9±0.1</td>
<td>n=60 0.9±0.2</td>
<td>0.610</td>
</tr>
<tr>
<td>Gain PCA, %/%</td>
<td>n=6 0.7±0.1</td>
<td>n=57 0.9±0.2</td>
<td>0.094</td>
</tr>
</tbody>
</table>

*indicates significant P value. Data are given as mean±SD with the number (n) of eligible records. Age, BMI, mean ABP, duration of current pregnancy, weight of the newborn, development of preeclampsia in current pregnancy, and presence of uterine notch sign. ABP indicates arterial blood pressure; BMI, body mass index; MCA, middle cerebral artery; and PCA, posterior cerebral artery.
be modulated by endothelial factors.20 We cannot report impaired DCA to be predictive of subsequent preeclampsia in our human cohort. Even women with already disturbed uteroplacental perfusion did not exhibit altered DCA during late mid-term pregnancy. Probably, even the vulnerable dynamic characteristics of pressure autoregulation are not early impaired and thus not sensitive enough to detect early cerebrovascular dysfunction in these women. Slight alterations of general cerebral perfusion parameters may be found already before the onset of the third trimester: Women who developed preeclampsia later were reported to show an increased diastolic blood flow (lower pulsatility index and resistance index) during mid-term pregnancy compared with healthy pregnant women.17,21 However, we could not find an association of pulsatility or resistance indices with subsequent preeclampsia in our study. Known risk factors for preeclampsia are an increased body mass index, elevated blood pressure, and diabetes mellitus.22,23 In accordance with this, we observed a significant predicting effect of these factors in our study sample. Epidemiological data reveal that women with a history of preeclampsia have a higher body mass index, higher blood pressure, and an increased prevalence of insulin resistance, especially if preeclampsia occurred by 34 weeks of gestation or in >1 pregnancy.24,25 These features of the metabolic syndrome are known risk factors for cerebrovascular disease, and many studies have confirmed an increased morbidity and mortality because of vascular disease in women with a history of preeclampsia.26

Table 4. Results of Dynamic Cerebral Autoregulation in Pregnant Women With or Without Preeclampsia During Follow-Up and Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonpregnant Women (I)</th>
<th>Pregnant Women Without Preeclampsia (II)</th>
<th>Pregnant Women With Subsequent Preeclampsia (III)</th>
<th>Level of Significance (PValue)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>I vs II+III</td>
</tr>
<tr>
<td>Phase MCA, °</td>
<td>26</td>
<td>61</td>
<td>8</td>
<td>0.007*</td>
</tr>
<tr>
<td>Phase PCA, °</td>
<td>26</td>
<td>59</td>
<td>8</td>
<td>0.019*</td>
</tr>
<tr>
<td>Gain MCA, %/%</td>
<td>26</td>
<td>60</td>
<td>6</td>
<td>0.340</td>
</tr>
<tr>
<td>Gain PCA, %/%</td>
<td>26</td>
<td>57</td>
<td>6</td>
<td>0.998</td>
</tr>
</tbody>
</table>

*indicates significant P value. Data are given as mean±SD with the number (n) of eligible records. Phase was significantly higher in the PCA than in the MCA in controls (P=0.001) and in the whole group of pregnant women (P=0.002). For gain, a same trend was observed (P=0.022 in controls and P=0.032 in pregnant women). MCA indicates middle cerebral artery; and PCA, posterior cerebral artery.

Our finding of reduced phase values in women with a history of preeclampsia during a previous pregnancy suggests that changes in DCA who have probably developed during the previous preeclampsia seem to persist until a subsequent pregnancy or at least reoccur during a subsequent pregnancy. Mean absolute phase values of these 6 women were slightly lower than in nonpregnant controls. However, 2 of them had clearly pathological phase values in the MCA and PCA in the range of those we have observed during severe preeclampsia or with poorly compensated carotid artery occlusion.26,27 Temporal dynamics of cerebral autoregulation thus are variably and in some cases even severely impaired in these women. Interestingly, also visually evoked blood flow response of the PCA, that is, altered metabolic vasoregulation of the brain, has been found to be altered in women with a history of preeclampsia.28 In addition, endothelial dysfunction in women with previous preeclampsia (≥3 months postpartum) was demonstrated by brachial artery flow-mediated (endothelium dependent) vasodilatation.29 Long-term cerebral imaging after preeclampsia showed an increased number and severity of white matter lesions in former preeclamptic women.30 Furthermore, women with a history of preeclampsia have more atherosclerotic plaques in the carotid arteries, a higher intima-media thickness, and an increased risk of stroke later in life.31 We thus assume that persistent changes of DCA might be an explanation for this observation.

Table 5. Dynamic Autoregulation and Cerebral Hemodynamic Parameters and the Risk of Preeclampsia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase MCA, °</td>
<td>0.99</td>
<td>(0.96–1.02)</td>
<td>0.636</td>
</tr>
<tr>
<td>Phase PCA, °</td>
<td>0.99</td>
<td>(0.02–28.82)</td>
<td>0.993</td>
</tr>
<tr>
<td>Gain MCA, %/%</td>
<td>1.02</td>
<td>(0.95–1.02)</td>
<td>0.444</td>
</tr>
<tr>
<td>Gain PCA, %/%</td>
<td>0.05</td>
<td>(0.3–3.99)</td>
<td>0.207</td>
</tr>
<tr>
<td>CBVF MCA, cm/s</td>
<td>1.01</td>
<td>(0.94–1.08)</td>
<td>0.717</td>
</tr>
<tr>
<td>CBVF PCA, cm/s</td>
<td>1.05</td>
<td>(0.96–1.14)</td>
<td>0.264</td>
</tr>
<tr>
<td>PI MCA</td>
<td>0.01</td>
<td>(0.2–0.5)</td>
<td>0.101</td>
</tr>
<tr>
<td>PI PCA</td>
<td>0.50</td>
<td>(0.74–4.9)</td>
<td>0.779</td>
</tr>
</tbody>
</table>

Univariate logistic regression analysis of phase, gain, CBVF, and PI of MCA/PCA. Phase and gain were determined at 0.1 Hz during slow respiratory-induced hemodynamic oscillations. CBVF indicates cerebral blood flow velocity; CI, confidence interval; MCA, middle cerebral artery; PCA, posterior cerebral artery; and PI, pulsatility index.

Limitations
The presently studied women were mainly recruited within a tertiary obstetric center including a considerable proportion of women with bilateral notch sign and thus reflecting a high-risk population. Therefore, the frequency of outcome events was comparatively high. Still, the absolute number of outcome events (9 of 70 pregnant study participants) was low, clearly limiting the statistical power of this study. Also, only 5 of our study participants developed severe preeclampsia, with only 1 of them showing neurological symptoms and none developed eclampsia. To record a significant number of women developing severe preeclampsia or eclampsia in a prospective study, a much higher number of study participants are required. As pregnant women tend to be precautious, recruitment of large numbers of healthy pregnant women is difficult in a single-center approach. This limitation could best be overcome using a multicenter approach.

Perspectives
Although limited in statistical power, this study does not indicate that impairment of DCA is an early feature of preeclampsia.
DCA is thus not suitable as a strong early risk marker of pre-eclampsia. Future studies on DCA in preeclampsia should focus on pregnant women with already established preeclampsia but still absent neurological symptoms. In this context, DCA may be able to predict the probability of developing neurological symptoms with preeclampsia. As a second finding, this study found that a history of previous preeclampsia is associated with poorer DCA values in subsequent pregnancies. The time course of changes in DCA and their persistence in former preeclamptic women warrants further investigation and might improve consultation and follow-up after preeclampsia, particularly in the light of the increased risk of vascular disease in these women.

Disclosures

None.

References

Dynamic Cerebral Autoregulation in Pregnancy and the Risk of Preeclampsia
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