Neurovascular Coupling in Pregnancy and the Risk of Preeclampsia

Wibke G. Janzarik, MD; Renata Ehmann, MD; Elena Ehlers, MD; Arthur Allignol, PhD; Sebastian Mayer, MD; Boris Gabriel, MD; Cornelius Weiller, MD; Heinrich Prömpeler, MD; Matthias Reinhard, MD

Background and Purpose—This study investigated whether a short testing of neurovascular coupling during midterm pregnancy could identify women at risk for subsequent preeclampsia.

Methods—Transcranial Doppler sonography of the posterior cerebral artery during a brief visual stimulation was analyzed in 68 women at midterm pregnancy, the primary clinical end point was preeclampsia.

Results—Women with bilateral notching of the uterine arteries showed an exaggerated visually evoked blood flow increase and longer time-to-peak. Neurovascular coupling was not significantly associated with the occurrence of preeclampsia.

Conclusions—Neurovascular coupling was altered in women with impaired uteroplacental vasoregulation but not a significant predictor of preeclampsia. (Stroke. 2014;45:2792-2794.)

Key Word: preeclampsia

Preeclampsia is defined as persistent arterial hypertension and proteinuria after 2 weeks of gestation. It occurs in 2% to 8% of all pregnancies and entails a lifelong increased risk of stroke. An early diastolic high-resistance Doppler waveform (notching) of both uterine arteries beyond 24 weeks of gestation identifies women at increased risk of preeclampsia.

Neurovascular coupling (NVC) describes an adaptive mechanism of functional hyperemia in metabolically active brain regions and is altered in former preeclamptic women. Dynamic cerebral autoregulation is disturbed during preeclampsia but intact at midterm pregnancy. This study investigated whether a brief testing of NVC at midterm pregnancy could identify women with subsequent preeclampsia.

Patients and Methods
Seventy-two pregnant women at 25 to 28 weeks of gestation were recruited at Freiburg University Hospital from January 2008 to December 2009. The study was approved by the Local Ethics Committee, and all participants gave written informed consent. Exclusion criteria were preexisting arterial hypertension with proteinuria, age <18 or >45 years, high-grade stenosis of brain-supplying arteries, or central nervous system disease. A standardized questionnaire was completed, and women were screened for bilateral notching of the uterine arteries.

For assessment of NVC, continuous cerebral blood flow velocities of the left posterior cerebral artery (P2 segment) were captured with 2-MHz transducers (Multidop-X4, DWL, Germany) focused through the temporal bone window. Study participants were placed in supine position with the upper body 60° inflected. Continuous noninvasive arterial blood pressure and heart rate were recorded using a finger plethysmograph (Finapres 2300, Ohmeda, USA) with the hand positioned at heart level. Endtidal CO₂, partial pressure was measured by infrared nasal capnography (Normocap, Datex, Finland).

Visual stimulation consisted of 10 cycles of repetitive checkerboard pattern for 10 seconds at 1 Hz alternating with rest for 10 seconds. Hemodynamic parameters were captured at a sampling rate of 100 Hz and analyzed with a custom-written software. For each cycle of visual stimulation, we analyzed the averaged maximum visually evoked mean blood flow (VEBF) increase in the posterior cerebral artery compared with the prestimulus baseline (30 seconds), and the time-to-peak (TTP) of VEBF defined as the latency between start of visual stimulation to the maximum VEBF response. NVC was analyzed blinded to the further course of the pregnancy.

For follow-up, a questionnaire was completed 6 weeks after partum. Primary end point was preeclampsia according to the criteria of the American College of Obstetricians and Gynecologists. Secondary end points were duration of pregnancy and birth weight.

Associations between clinical parameters, hemodynamic baseline characteristics, NVC, and preeclampsia were assessed using univariate logistic regressions or Spearman coefficient for duration of pregnancy and birth weight. Association between NVC and risk factors (age, body mass index, hypertension >140/90 mm Hg, diabetes mellitus, and notch of uterine arteries) was also assessed in multivariate linear regression models. Results are considered significant at the 5% level. Statistical analyses were performed with R statistical software (version 2.15.1).

Results
Seventy-two women were included into the study, of which 71 completed follow-up. Preeclampsia developed in 9 women (13%), of whom 1 woman had mild neurological symptoms. Clinical risk factors of preeclampsia were a high body mass index, diabetes mellitus, and notch of uterine arteries. Pregnancy duration of women with subsequent
Preeclampsia tended to be shorter, and birth weight of their newborns lower. Clinical data are given in Table 1.

Hemodynamic parameters including NVC could be analyzed in 68 cases, comprising 18 women with bilateral notching of the uterine arteries. With regard to notching of the uterine arteries, there were no significant differences in basal hemodynamic characteristics. Women with subsequent preeclampsia had slightly higher mean arterial blood pressure values at baseline, which was not statistically significant.

Multivariate linear regression analysis including vascular risk factors showed a significant association of positive notching with exaggerated VEBF response and longer TTP in the posterior cerebral artery, whereas an increased body mass index associated with reduced VEBF (Table 2; Figure [A]). Women with a history of preeclampsia had significantly higher TTP ($P=0.043$).

Measurement of the initial VEBF response in the posterior cerebral artery was not associated with subsequent preeclampsia. Stimulation time in our study was not long enough to perform more complex analyses of NVC, which have shown alterations in women with gestational diabetes mellitus. We found a significant association of increased body mass index with lower VEBF.

### Discussion

At 24 to 28 weeks of gestation, we found an exaggerated cerebral blood flow increase on visual stimulation in women with impaired uteroplacental vasoregulation. The complex mechanism of NVC is influenced by endothelial function, smooth muscle function, and astrocyte–neuronal interactions. One important mediator of fast initial vasodilatation is nitric oxide. Placental endothelial nitric oxide synthase is upregulated in women with notching of the uterine arteries, and altered nitric oxide bioavailability might play a role during the development of preeclampsia.

The number of notch-negative women developing preeclampsia in our study was higher than expected, probably because of higher incidence of patients with preexisting medical conditions at our tertiary center. Still, the relatively low absolute number of preeclamptic patients in our study limits the statistical power.

Table 1. Clinical Characteristics at Study Inclusion and Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Preeclampsia (n=9)</th>
<th>No Preeclampsia (n=62)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>31.4±4.9</td>
<td>31.7±5.3</td>
<td>0.901</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.9±7.6</td>
<td>24.7±5.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2 (22)</td>
<td>2 (3)</td>
<td>0.075</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>5 (56)</td>
<td>4 (6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous preeclampsia, n (%)</td>
<td>1 (11)</td>
<td>5 (8)</td>
<td>0.571</td>
</tr>
<tr>
<td>Bilateral notching, n (%)</td>
<td>5 (26)</td>
<td>4 (8)</td>
<td>0.051</td>
</tr>
<tr>
<td>Pregnancy duration, d</td>
<td>264±22</td>
<td>271±15</td>
<td>0.274</td>
</tr>
<tr>
<td>Birth weight, g*</td>
<td>2734±565</td>
<td>3184±577*</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Data of univariate analysis are given as mean±SD or as absolute number (n) with frequency. Preeclampsia: subsequent preeclampsia.

*Data of birth weight was unknown in 4 cases.

Table 2. Multivariate Linear Regression Analysis of Neurovascular Coupling With Age, Vascular Risk Factors, and Notching of Uterine Arteries

<table>
<thead>
<tr>
<th></th>
<th>VEBF (n=68)</th>
<th>TTP (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate</td>
<td>$P$ Value</td>
<td>Estimate</td>
</tr>
<tr>
<td>Age &lt;19 or &gt;40 y</td>
<td>−5.24</td>
<td>0.060</td>
</tr>
<tr>
<td>Body mass index &gt;29 kg/m²</td>
<td>−3.48</td>
<td>0.038</td>
</tr>
<tr>
<td>Hypertension &gt;140/90 mm Hg</td>
<td>1.82</td>
<td>0.534</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>−1.04</td>
<td>0.636</td>
</tr>
<tr>
<td>Bilateral notching</td>
<td>4.05</td>
<td>0.008</td>
</tr>
</tbody>
</table>

TTP indicates time-to-peak of VEBF; and VEBF, maximum visually evoked blood flow increase.

Discussion

At 24 to 28 weeks of gestation, we found an exaggerated cerebral blood flow increase on visual stimulation in women with impaired uteroplacental vasoregulation. The complex mechanism of NVC is influenced by endothelial function, smooth muscle function, and astrocyte–neuronal interactions. One important mediator of fast initial vasodilatation is nitric oxide. Placental endothelial nitric oxide synthase is upregulated in women with notching of the uterine arteries, and altered nitric oxide bioavailability might play a role during the development of preeclampsia.

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Figure. A, Neurovascular coupling with regard to bilateral notching of the uterine arteries. Box- and whisker plots show exaggerated visually evoked mean blood flow (VEBF) response and increased time-to-peak (TTP) in the posterior cerebral artery (multivariate $P$ values, see Table 2). B, Neurovascular coupling with regard to the primary end point preeclampsia. Box- and whisker plots for parameters of neurovascular coupling show no significant difference in patients with and without subsequent preeclampsia ($P=0.547$ and $P=0.234$, respectively). VEBF, averaged maximum visually evoked blood flow increase in the posterior cerebral artery; and TTP, latency between start of visual stimulation to VEBF. Boxes denote the median, the lower and upper quartile, and whiskers denote the full range.
increase, whereas VEBF response in women with notching of the uterine arteries was exaggerated. These divergent results explain the low overall predictive value of the VEBF response with regard to the primary end point preeclampsia.

In women with a history of preeclampsia, dampening of VEBF response after visual stimulation has been demonstrated. In the present study, we found significantly increased TTP at midterm pregnancy in women with a history of preeclampsia. With respect to the lifelong increased risk for stroke, it will be crucial to understand the pathophysiological changes of cerebral hemodynamics during and after preeclampsia.

In conclusion, this study showed altered NVC at midterm pregnancy if uteroplacental vasoregulation was impaired. On its own, NVC was not sufficient for early prediction of preeclampsia.

Disclosures

None.

References

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