CHAPTER 8

LOW MATERNAL MIDDLE CEREBRAL ARTERY DOPPLER RESISTANCE INDICES CAN PREDICT FUTURE DEVELOPMENT OF PREECLAMPSIA

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Cerebral hemodynamics in normal and complicated pregnancy

Abstract

Objective: To determine if decreased resistance (vasodilatation) in the maternal middle cerebral artery (MCA) in the second trimester can predict third-trimester development of preeclampsia.

Methods: Four-hundred and five low-risk gravidas had MCA transcranial Doppler (TCD) once in the second trimester. Maternal/neonatal outcomes were evaluated after delivery. Mean blood pressure, MCA velocities, resistance index (RI), pulsatility index (PI) and cerebral perfusion pressure (CPP) were compared between normotensive and preeclamptic cohorts.

Results: Seven subjects (1.7%) developed preeclampsia. An RI of < 0.54 and a PI of < 0.81 were clinically useful in predicting subsequent preeclampsia. Areas under the receiver–operating characteristics curves for RI and PI were 0.93 and 0.93, respectively, with optimal sensitivity and specificity of 86% and 93% for both variables. Positive and negative likelihood ratios were 11.8/0.15 (RI) and 12.3/0.15 (PI).

Conclusion: TCD indices of low maternal MCA resistance in the second trimester are predictive of the subsequent development of preeclampsia in a low-risk, ethnically homogeneous population.
8.1 Introduction

Hypertensive disorders are a major contributor to maternal mortality worldwide. The incidence of all hypertensive disorders in pregnancy may be as high as 17% in nulliparous women, with the incidence of preeclampsia reportedly between 2 and 7%.

Although the etiology of preeclampsia remains unclear, current thought is that it follows from the failure of second-wave trophoblastic invasion in the late first and early second trimesters. As a result of the failed replacement of the spiral artery muscularis, these arteries do not transform into low-resistance conduits and uteroplacental resistance fails to decrease. In order to improve placental perfusion, it may be hypothesized that there is compensatory production of vasodilator substances by the placenta. These circulating factors, as a secondary effect, dilate vessels in multiple organs, including aorta, myometrium and mesentery. Easterling et al. and others have reported increased cardiac output in the second and early third trimesters, consistent with the presence of circulating vasodilator and inotropic substances.

Transcranial Doppler (TCD) ultrasound and velocity-encoded phase-contrast magnetic resonance imaging (MRI) have been used to study cerebral hemodynamics in normal pregnancy as well as in women with preeclampsia, and normative data for pregnancy have been published. Riskin-Mashiah et al. showed that women destined to develop preeclampsia had lower middle cerebral artery (MCA) resistance index (RI) and pulsatility index (PI) weeks before the development of preeclampsia. In that study, TCD ultrasound was used in the late second and early third trimesters (19–28 weeks). In the current study we aimed to further research the hypothesis that Doppler RI values in the maternal MCA can be used to reliably predict the subsequent development of preeclampsia by using a much larger sample size and by studying patients in the second trimester.

8.2 Methods

The protocol was approved by the Institutional Review Board for Human Investigation at St. Mark’s Hospital in Salt Lake City, Utah. All patients gave written informed consent. Normal pregnant women undergoing routine second-trimester obstetric ultrasound
examination in a maternal-fetal medicine practice were consecutively recruited for this study over a 4-year time period, from 2005 to 2009. Sample-size calculation on the basis of our previous work evaluating MCA-RI values and on an estimated preeclampsia rate of 5% indicated an enrollment goal of approximately 300 subjects ($\alpha = 0.05$, $\beta = 0.20$). Limitations in study resources and staff influenced the duration of the enrollment period. Women with chronic illness (including chronic hypertension), fetal anomalies, multiple pregnancy, medications other than vitamins and thyroxine, more than a trace of proteinuria or blood pressure (BP) > 140/90 mmHg at the time of the ultrasound examination were excluded. Gestational age was documented by confirmed last menstrual period and/or first-trimester ultrasound dating.

All patients were sitting upright in a chair in a quiet examination room and did not talk or move during the examination. Measurement of MCA flow velocities was performed by one of three study sonographers trained by the principal investigator. While no interobserver or intraobserver error was calculated specifically for this study, we and others have previously reported that error for MCA measurements is less than 10%. A 2-MHz-pulsed, range-gated TCD probe (Nicolet Companion EME; Nicolet Vascular, Madison, WI, USA) was used to insonate the M1 portion (the initial 2-cm segment) of the MCA via the transtemporal approach. The depth of interrogation was adjusted to optimize the Doppler signal. The MCA velocity waveform was recorded on both sides of the head, if possible, and the averaged value was then used in the analysis. In those cases in which the MCA waveform could be obtained from only one side of the head (n=70, 17% of cases) this value was used. A minimum of six waveforms were averaged for each side. The systolic, diastolic and mean velocities of the waveform spectrum were recorded and saved as hard copy. Derived MCA values were calculated as follows:

\[
\text{PI} = \frac{(\text{Velocity}_{\text{systolic}} - \text{Velocity}_{\text{diastolic}})}{\text{Velocity}_{\text{mean}}}; \\
\text{RI} = \frac{(\text{Velocity}_{\text{systolic}} - \text{Velocity}_{\text{diastolic}})}{\text{Velocity}_{\text{systolic}}}; \\
\text{Cerebral perfusion pressure (CPP)} = \frac{\text{Velocity}_{\text{mean}}}{(\text{Velocity}_{\text{mean}} - \text{Velocity}_{\text{diastolic}})} \times (\text{Mean arterial pressure} - \text{BP}_{\text{diastolic}}),^{18,19}
\]
Resistance area product (RAP) = Mean arterial pressure/ Velocity\textsubscript{mean}\textsuperscript{21}
Cerebral flow index (CFI) = CPP/RAP\textsuperscript{22}
Critical closing pressure (CCP) = Mean arterial pressure - CPP

At the time of TCD examination, BP was measured at the brachial artery on both arms, and urine was checked for proteinuria using a dipstick. The mean arterial pressure (MAP) was calculated using the following formula: MAP = (BP\textsubscript{systolic} + (2 × BP\textsubscript{diastolic}))/3.

Maternal and neonatal outcomes were evaluated after delivery by chart review. Preeclampsia was defined as BP ≥ 140 mmHg systolic and/or > 90 mmHg diastolic, and proteinuria > 1+ on a dipstick (or > 300 mg by 24-h collection). BP elevation without proteinuria was considered to be gestational hypertension (GH). Both classifications required new onset of symptoms after 20 weeks of gestation in a woman with previously normal BP\textsuperscript{23}

All data were tested for normality of distribution by visual comparison of the frequency distribution histogram with a super-imposed normal curve, as well as by visual evaluation of a Q-Q plot comparing each distribution with the normal distribution. The groups (normotensive, hypertensive and preeclamptic) were compared using appropriate parametric (Student’s t-test) and non-parametric (Mann – Whitney U-test) tests. Multiple MCA flow characteristics and derived values were evaluated for their predictive ability by calculating the area under the curve (AUC) of the receiver – operating characteristics (ROC) curve. Multivariable prediction models combining potential predictors of preeclampsia were tested using binary logistic regression. Sensitivity and specificity were calculated, as well as likelihood ratios (LRs) and predictive values. All statistical tests were performed using SPSS 19 (SPSS Inc., Chicago, IL, USA). Data are reported as mean ± SE (or median and range), and statistical significance was set at a probability value of < 0.05.

8.3 Results
A total of 405 women met the inclusion criteria and had good-quality TCD waveform measurements. TCD measurements were made at a mean of 19.0 ± 1.3 weeks (range, 12–26 weeks). Seven (1.7%) subjects developed preeclampsia at an average of 37.3 ±
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal (n=383)</th>
<th>GH (n=15)</th>
<th>PE (n=7)</th>
<th>Normal vs GH (two-tailed significance)</th>
<th>Normal vs PE (two-tailed significance)</th>
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<tr>
<td>Age (years)</td>
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<td>BMI (kg/m²)</td>
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<td>Caucasian (%)</td>
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<td>100</td>
<td>100</td>
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<td>Gravidity</td>
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<td>1 (1–3)</td>
<td>2 (1–5)</td>
<td>0.023</td>
<td>NS</td>
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<td>GA at TCD (weeks)</td>
<td>19±1.3</td>
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<td>19±1.5</td>
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<td>GA at PE diagnosis (weeks)</td>
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<td>Diastolic BP (mmHg)</td>
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<td>MAP (mmHg)</td>
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<td>MCA diastolic velocity (cm/s)</td>
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<td>MCA-CrCP</td>
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<td>41±10</td>
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**Table 1** Characteristics at transcranial Doppler (TCD) examination

Values are given as percentage, mean ± SD or median (range). BMI, body mass index; BP, blood pressure; CFI, cerebral flow index; CPP, cerebral perfusion pressure; CrCP, critical closing pressure; GA, gestational age; GH, gestational hypertension; MAP, mean arterial pressure; MCA, maternal middle cerebral artery; N/A, not applicable; NS, non-significant; PE, preeclampsia; PI, pulsatility index; RAP, resistance area product; RI, resistance index.
2.8 weeks’ gestation. Demographic data were similar in the women who did and who did not develop preeclampsia (Table 1). All study subjects denied smoking. Most women were Caucasian (91% of the normotensive patients vs 100% of the preeclamptics, $P = 0.4$). MAP at the time of measurement was higher in the group destined to develop preeclampsia, as was the MCA diastolic velocity. RI and PI values were lower in the group destined to develop preeclampsia. Other measurements and derived values describing cerebrovascular flow and resistance were not significantly different at the time of measurement (Table 1). No correlation was found between RI/PI and arterial BP, maternal age or body mass index (BMI) at the time of measurement. Although RI and PI are known to decrease slightly during pregnancy\textsuperscript{24}, their correlation with gestational age in this study was very weak ($R = 0.03$).

MCA-RI and -PI were associated with ROC-AUC values of $0.93 \pm 0.04$ and $0.93 \pm 0.04$, respectively, in predicting subsequent preeclampsia (Figure 1), and cut-off values of $\text{RI} < 0.54$ and $\text{PI} < 0.81$
were found to be clinically useful. An RI of <0.54 in the MCA was associated with a positive LR for preeclampsia of 11.8, and a PI of < 0.81 in the same vessel was associated with a positive LR of 12.3. For both RI and PI the negative LR for preeclampsia was low (0.15). Sensitivity and specificity, positive and negative predictive values, and LRs (with 95% CI) are shown in Table 2. No other parameter measured was a strong predictor of preeclampsia and no other parameter contributed independently to any multivariable prediction model. No characteristic or derived index we evaluated was useful to predict GH. The RI/PI values for all study subjects are plotted in Figure 2.

**Figure 2** Scatter plot of second-trimester maternal middle cerebral artery (MCA) resistance index (RI) (a) and pulsatility index (PI) (b) for study subjects who remained normotensive (○) and for those who developed gestational hypertension (■) and preeclampsia (●). The mean value for preeclampsia cases is indicated (X). Normal ranges for RI and PI with median and 5th and 95th percentiles are shown. TCD, transcranial Doppler.
8.4 Discussion

This study suggests that TCD indices of low MCA resistance in the second trimester are predictive of the subsequent development of preeclampsia in a low-risk, ethnically homogeneous population. This supports previous studies showing a reduced RI and/or PI either before or after the clinical development of preeclampsia. The results are also consistent with studies that show preeclampsia to be characterized by a hyperdynamic state with elevated cardiac output and reduced peripheral resistance early in pregnancy. Our patients all developed relatively mild and late-onset preeclampsia, and our data support the suggestion of Valensise et al. that women likely to develop early-onset preeclampsia (<34 weeks) show elevated peripheral vascular resistance before the onset of hypertension and proteinuria, while those who will develop preeclampsia late in pregnancy have an initially low vascular resistance. Our results are consistent with this proposal: six of seven preeclamptic patients were diagnosed at or after 34 weeks' gestation.

It has been hypothesized that cerebrovascular autoregulation is altered in overtly preeclamptic women. In one study, low MCA-PI and -RI at a mean of 23 weeks predicted the subsequent development of preeclampsia. However, women who underwent two cerebral autoregulatory challenge tests at the time of examination (CO₂ inhalation and hand grip), all showed a normal vasodilatory response. Thus, it is unlikely that these resistance changes early in gestation represent pathologic cerebrovascular dysfunction, but rather more likely that they represent a physiologic compensatory response. This is supportive of the hypothesis that there is release of a circulating vasodilator substance(s) from the placenta before measurable loss of autoregulatory function and/or elevation in BP. In the present study, the mean values of RI (0.51) and PI (0.75) of women who went on to develop preeclampsia were within the normal range but notably low for 19 weeks of gestation (Figure 2). However, estimated CPP for these patients was very near the normal mean for all pregnant women, suggesting intact autoregulation and physiologic compensatory vasodilation. These data underlie the need for further studies to assess cerebrovascular autoregulation before and at the onset of preeclampsia.
In this study, as in our previous study, RI and PI were predictive of preeclampsia but not of gestational hypertension, suggesting that the pathogenesis of gestational hypertension and preeclampsia may differ, at least in the timeline. We have also previously shown that in pregnant women with mild chronic hypertension the baseline PI and RI are similar to those of normotensive pregnant women, despite having a higher baseline mean BP. This finding of normal PI and RI in early pregnancy in hypertensive women who do not go on to develop preeclampsia underlies the contention that the clinical syndrome of preeclampsia is not simply linked to elevated BP, but is more likely to be determined by a separate pathophysiological pathway.

In our dataset, MCA-RI and -PI were shown to predict preeclampsia better than any previously reported test (86% sensitivity, 93% specificity). Other Doppler-based tests reported to predict preeclampsia at an early gestational age rarely reach specificities above 90% and often require combination with other parameters to exceed 60% sensitivity. We hypothesize that a multivariate model including MCA-RI/PI and other values shown to be predictive of preeclampsia (such as BMI and uterine artery Doppler) may allow further improvement in the detection rate into a reliable, clinically useful, range.

This study was conducted in a low-risk, middle-class, almost exclusively Caucasian population, which limits the ability to generalize the findings across a broader population. A second limiting factor was the low incidence of preeclampsia (1.7%), which reflects the true low regional incidence, predominant ethnic group and socio-economic class represented (confirming that we did not select a mixed risk group or enriched group and that our sample was truly representative of the local population) and the strict definition of preeclampsia we applied (BP ≥ 140 mmHg systolic and/or > 90 mmHg diastolic, and proteinuria > 1+ on a dipstick or > 300 mg by 24-h collection). This low incidence of preeclampsia resulted in wide confidence limits and in a relatively low positive predictive value for preeclampsia using RI and PI (0.17, 0.19, respectively). Additionally, as only one woman developed severe preeclampsia and only one woman developed preeclampsia before 34 weeks of gestation, we could not perform subanalyses of severity and time of development...
of the disease. Thus, the preeclamptic and normal groups in our data were not homogeneous, and therefore the within-group variability of hemodynamic values was high. We were also unable to evaluate the predictive ability of the test at specific gestational ages. Clearly, this potential screening test needs to be further developed and tested in a much larger population(s) of ethnically diverse patients at a more uniform gestational age.

The applicability of this test to first-trimester screening is unclear. However, given the low-normal second-trimester RI (<15%; Figure 2) found in those who went on to develop preeclampsia, the hypothesis of abnormal placentation leading to vasodilatation may hold true in the first trimester. It is possible that low MCA-RI in the first trimester has similar predictive capacity. This study is underway, and earlier prediction of preeclampsia may offer a better opportunity for prophylactic intervention with medications such as aspirin or nitric oxide donors.

The strengths of this study were that we applied a strict definition of preeclampsia and that patients satisfied this definition after chart review. We did not rely on patient recall or discharge codes for the diagnosis of preeclampsia. We also excluded patients from the study if they had a condition or were using a medication that could affect cerebral hemodynamics.

Based on these data, we believe that TCD indices of low MCA resistance in the second trimester are predictive of impending preeclampsia. These results justify a larger trial to confirm the findings in a more ethnically diverse population and at an earlier gestational age. MCA resistance indices may provide an important prenatal screening test for preeclampsia.
CEREBRAL HEMODYNAMICS IN NORMAL AND COMPLICATED PREGNANCY

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