CHAPTER 3

CHANGES IN CEREBRAL AUTOREGULATION IN THE SECOND HALF OF PREGNANCY AND COMPARED TO NON-PREGNANT CONTROLS

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ABSTRACT

Objective: The mechanism by which pregnancy affects the cerebral circulation is unknown, but it has a central role in the development of neurological complications in preeclampsia, which is believed to be related to impaired autoregulation.

We evaluated the cerebral autoregulation in the second half of pregnancy, and compared this with a control group of healthy, fertile non-pregnant women.

Methods: In a prospective cohort analysis, cerebral blood flow velocity of the middle cerebral artery (determined by transcranial Doppler), blood pressure (noninvasive arterial volume clamping), and end-tidal carbon dioxide (EtCO₂) were simultaneously collected for 7 minutes. The autoregulation index (ARI) was calculated. ARI values of 0 and 9 indicated absent and perfect autoregulation, respectively. ANOVA and Pearson’s correlation coefficient were used, with p<0.05 considered significant.

Results: A total of 76 pregnant and 18 non-pregnant women were included. The ARI did not change during pregnancy, but pregnant women had a significantly higher ARI than non-pregnant controls (ARI 6.7 ± 0.9 vs. 5.3 ± 1.4, p<0.001). This remained significant after adjusting for EtCO₂ (p<0.001).

Conclusion: Cerebral autoregulation functionality is enhanced in the second half of pregnancy, when compared to non-pregnant fertile women, even after controlling for EtCO₂. The autoregulation did not change with advancing gestational age.
Chapter 3 - Cerebral autoregulation in pregnancy

3.1 Introduction

Pregnancy is characterized by major hemodynamic changes, which have been extensively studied in the systemic circulation. The adaptation of the cerebral circulation to pregnancy is unique. Several studies have examined maternal cerebral blood flow (CBF) during pregnancy using transcranial Doppler (TCD) and show a decrease in velocity in the middle cerebral artery during pregnancy with an increase in cerebral perfusion pressure and decrease in resistance index.\textsuperscript{1-4} The exact mechanism by which pregnancy affects the cerebral hemodynamics is unknown, but is likely multifactorial, including changes in carbon dioxide (PaCO\textsubscript{2}), hormones, cytokines and other circulating factors,\textsuperscript{5} and perivascular innervation.\textsuperscript{6}

The cerebral circulation has a central role in the development of neurological complications in preeclampsia, which is believed to be related to impaired autoregulation.\textsuperscript{7, 8} Cerebral autoregulation is a physiological process that maintains blood flow at an appropriate level despite changes in systemic blood pressure. The autoregulatory capacity can be assessed by using a combination of TCD and continuous non-invasive blood pressure measurement,\textsuperscript{9} and it is often expressed as the autoregulation Index (ARI), with 0 being absent and 9 perfect cerebral autoregulation.\textsuperscript{10} In normal pregnancy ARI appears in the high normal range when compared to non-pregnant subjects. Studies in preeclampsia indicate a lower ARI when compared to normotensive pregnancy.\textsuperscript{8} This suggests that the pregnant state in and of itself may enhance cerebral autoregulation. At what point during gestation enhancement of autoregulatory properties commences and how gestational age affects the autoregulation index is unknown. Studies reporting on non-pregnant subjects included both male and female participants in the age range of 20 to 56 years,\textsuperscript{11-13} and are therefore not comparable to a cohort of pregnant women.

The aim of this study therefore was to evaluate the cerebral autoregulation in the second half of pregnancy, and compare this with a control group of healthy, fertile non-pregnant women.

3.2 Materials and Methods

We conducted a prospective cohort study including non-laboring pregnant women without a history of cerebrovascular disease, and
with an estimated gestational age (EGA) >20 weeks. The non-pregnant control group consisted of healthy women of reproductive age, who had not been recently pregnant or nursing for at least one year. Recruitment of pregnant women took place when women visited the outpatient clinic for routine prenatal care or who were admitted for observation to rule out labor. Non-pregnant controls were recruited from the hospital staff.

One trained examiner (TRVV) performed all the measurements. The study was approved by the local Institutional Review Board at Baylor College of Medicine in Houston, Texas and North Austin Medical Center in Austin, Texas, and informed written consent was obtained from each participant prior to data collection.

Inclusion criteria for both groups included maternal age greater than 18 years, absence of chronic medical illnesses, and illicit drug abuse. Women were excluded if they had a history of cerebrovascular disease, used tobacco, had gestational diabetes, used vasoactive or diabetes medication or had a blood pressure (BP) greater than 140 mmHg systolic and/or 90 mmHg diastolic at any point during their pregnancy. Furthermore, we excluded any pregnant woman who was initially included but later developed preeclampsia (n=9). Additionally, non-pregnant controls were excluded if they gave birth less than one year before the measurement or if they were lactating.

Data were entered into a standardized database with the information being collected both from the medical record and from direct patient interview. The following maternal characteristics were based on self-report: race/ethnicity, height, current and pre-pregnancy weight, smoking and alcohol and illicit substance use. Gestational age was determined by menstrual dating. In cases of uncertain menstrual dates, ultrasound estimates of gestational age were used.

Women were studied in a semi-Fowlers position in a private room. Simultaneous transcranial Doppler (TCD) evaluation of both middle cerebral arteries (MCA) was carried out using 2 MHz pulsed, range gated transcranial Doppler probes (Spencer Technologies, Seattle, WA), held in place using a head frame. If only one MCA could be found, that one side was used in the analysis. At the time of the TCD examination, brachial systolic (SBP) and diastolic (DBP) blood pressure were measured.
Blood pressure was continuously measured non-invasively using finger arterial volume clamping (Finometer Pro, Finapres Medical Systems, Amsterdam, The Netherlands) with the servo-adjust switched off. This was subsequently calibrated with the brachial BP. The BP tracing also served to mark each cardiac cycle. End-tidal CO₂ (EtCO₂) was measured by infrared capnography with a nasal cannula (Nellcor Oximax N-85, Covidien, Mansfield, MA).

All data were recorded at 50 Hz, interpolated to 200 Hz and visually inspected during analysis to remove occasional large spikes. A median filter was used to remove small spikes and artifacts in the cerebral blood flow velocity (CBFV) signal. All signals were then low-pass filtered with a Butterworth filter with a cutoff frequency of 20 Hz. Mean BP, bilateral CBFV, EtCO₂ and heart rate were then calculated for each beat. The critical closing pressure (CrCP) and resistance-area product (RAP) were obtained using the first harmonic of BP and CBFV of each cardiac cycle. The resistance index (RI) was calculated as (systolic velocity-diastolic velocity)/systolic velocity. All time-series of beat-to-beat parameters were then resampled at 5 Hz.

Cerebral autoregulation was determined from the CBFV responses to spontaneous fluctuations in mean arterial BP as described previously. Segments consisting of 512 samples and 50% superposition, were transformed with the fast Fourier transform (FFT) algorithm (Welch method), to obtain the transfer function parameters coherence, gain and phase in the low frequency range (<0.1 Hz). The inverse FFT was then performed to estimate the impulse and step responses. The CBFV step response to a sudden change in ABP was compared to 10 template curves proposed by Tiecks et al. and the best fit curve corresponded to the ARI autoregulation index. Measurements were rejected if coherence did not reach 0.5 for any frequency <0.25 Hz.

Baseline cerebral hemodynamic parameters are reported as the average over a 7-minute baseline recording.

Data are reported as mean and standard deviation, or median and [range] as appropriate. Non-pregnant controls were compared to the pregnant participants with a gestational age of 20-30 weeks and 31-41 weeks at time of examination using ANOVA with Bonferroni’s post-hoc test or ANOVA on Ranks with Dunn’s post hoc test (both
comparisons versus the non-pregnant control group). Pearson’s correlation coefficient was used to investigate the relationship of the parameters of interest over gestational age, and multiple regression was used to control for EtCO\textsubscript{2}. Other analyses were performed using student t test or Mann-Whitney Rank Sum test. (Sigmastat 2004, Systat Software, Richmond, CA). p < 0.05 was used to indicate statistical significance.

3.3 Results
A total of 76 pregnant (26 at 20-30 weeks’ and 50 at 31-41 weeks’ gestation) and 18 non-pregnant women were included. Maternal demographics were similar for both groups, except for multiple pregnancies and time of delivery (Table 1). Those who delivered very preterm (EGA<32 weeks) were admitted for multiple gestation (n=6), cervical insufficiency (n=1) or preterm premature rupture of membranes (n=2). None of the women showed any sign of labor during the measurement.

Although the autoregulation index did not change during the course of pregnancy, pregnant women did demonstrate a significantly better functioning autoregulation when compared to non-pregnant controls (ARI 6.7 ± 0.9 and 6.6 ± 0.9 vs. 5.3 ± 1.4, p<0.001, Figure 1, table 2). Coherence was also lower in pregnancy (0.42 ± 0.13 and 0.41 ± 0.09 vs. 0.52 ± 0.09, p<0.001).

As expected, EtCO\textsubscript{2} was significant lower in the pregnant women. After adjusting for EtCO\textsubscript{2}, the ARI was still significantly different between the groups (p<0.001). BP and CBFV were lower in pregnant women between 20 and 30 weeks when compared to non-pregnant controls. CrCP and RAP were not different between the groups (Table 2, P-value ANOVA).

The ARI of the women having multiples was not different from those having a singleton pregnancy (ARI 7.1 ± 0.3 vs. 6.6 ± 0.9, p=0.20).
### Table 1) Demographic data.

BMI: Body mass index, for pregnant women: pre-gestational BMI; EGA: Estimated gestational age.
P-value: 1-way ANOVA or t-test or Mann-Whitney-U.
Data are mean ± SD, median (range) or number (%)

<table>
<thead>
<tr>
<th></th>
<th>EGA 20-30 weeks (n=26)</th>
<th>EGA 31-41 weeks (n=50)</th>
<th>Non-pregnant (n=18)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>28 ± 7</td>
<td>29 ± 7</td>
<td>31 ± 7</td>
<td>0.36</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29 ± 6</td>
<td>28 ± 7</td>
<td>25 ± 5</td>
<td>0.16</td>
</tr>
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<td>EGA at study (week³)</td>
<td>26⁰ ± 3⁰</td>
<td>36¹ ± 2²</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>EGA at delivery (week³)</td>
<td>37¹ (27¹-41⁰)</td>
<td>38⁰ (35⁰-41⁰)</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Multiple pregnancy (%)</td>
<td>5 (19%)</td>
<td>1 (2%)</td>
<td></td>
<td>0.016</td>
</tr>
</tbody>
</table>

**Figure 1) Autoregulation index with gestational age (●) and in non-pregnant women (＊)**
Gestational age was significantly correlated with blood pressure (p<0.001, coefficient: +0.66 mmHg/week) and RI (p=0.029, coefficient -0.002 /week). ARI or any of the other parameters were not correlated with gestational age (Table 2, P-value Pearson).

### 3.4 DISCUSSION

In this study, the autoregulation in the second half of pregnancy was examined and compared with observations in non-pregnant women of reproductive age. Our findings indicate that cerebral
autoregulation capacity is significantly enhanced in pregnant women, and is independent of gestational age in the second half of pregnancy.

The higher ARI seen in normal pregnancy was previously shown by our group, and hypothesized to be related to the relative hypocapnia seen in pregnancy. This is known to cause physiologic vasoconstriction, a reduction in cerebral blood flow, and enhanced autoregulatory capacity. However, the ARI is significantly higher in pregnancy, even after controlling for EtCO\textsubscript{2}. This enhanced cerebral autoregulation is in accordance with previous studies in both human and rats.

One explanation for the higher ARI might be the increasing concentrations of estrogen and progesterone during pregnancy, which has important protective effects on endothelial function and cerebrovascular health. Estrogens increase cerebrovascular reactivity and have a direct vasodilator effect on the microvasculature, by, at least in part, increased expression of endothelial nitric oxide (NO) synthase (NOS). However, studies evaluating the role of NO on the human cerebral autoregulation are sparse, and have shown conflicting results, reporting impaired AR following NO inhibition, and no effect. Other factors that might be involved in the enhancement of autoregulatory capacity could be the renin-angiotensin system (RAAS), perivascular innervation, vascular structure or cytokines, all known to be altered in preeclampsia.

Similar to previous studies, we also found a decrease in resistance index (RI) with advancing gestational age. While other studies also have shown a decrease in cerebral blood flow velocity (CBFV) as pregnancy advances, this was not confirmed by our data. We hypothesize that this decrease mainly takes place in the first half of pregnancy, and is therefore not noticed in our study, which focused on women in the second half of pregnancy.

The strengths of this study is the inclusion of both pregnant and non-pregnant women in their reproductive age years, who were all studied in an identical setting. This study also has some limitations, which merit discussion. Using TCD, only the CBFV can be obtained, and therefore relies on the assumption that changes in CBFV are directly proportional to changes in cerebral blood flow (CBF). Available literature shows that the MCA does not change in diameter despite
significant changes in CO$_2$\textsuperscript{25, 26} and that it maintains its diameter during pregnancy.\textsuperscript{27} The number of women studied in each group is unequal, with most women studied after 30 weeks of pregnancy, and patients before 20 weeks of gestation were not included. The women who were studied at EGA 20-30 weeks delivered significantly earlier and more often had a twin gestation.

The control group seems to have two outliers with very low ARI (ARI 1.6 and 2.8). Careful analysis of these subjects did not indicate erroneous measurements, and the individuals were therefore included in the analysis. However, if those would be excluded, the conclusion still holds true (ANOVA p<0.001). This cross-sectional study only included pregnant women in the second half of pregnancy. We can therefore not comment on the timing of the initiation of the enhancement of cerebral autoregulation, nor on the time postpartum when it returns to non-pregnant values.

In conclusion, this study demonstrates enhanced cerebral autoregulation functionality in the second half of pregnancy, when compared to non-pregnant fertile women, even after controlling for EtCO$_2$. The autoregulation did not change with advancing gestational age. The timing and the mechanism by which pregnancy enhances cerebral autoregulation functionality have yet to be explored.
References


