CHAPTER 2

GLOBAL CHANGES IN MATERNAL POSTERIOR AND ANTERIOR CEREBRAL ARTERY HEMODYNAMICS DURING PREGNANCY AND POSTPARTUM – A LONGITUDINAL STUDY

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Cerebral hemodynamics in normal and complicated pregnancy

Abstract

Purpose: To longitudinally define the normal range of the blood velocity (and derived parameters) in the maternal anterior (ACA) and posterior cerebral arteries (PCA) during normal pregnancy and postpartum period.

Methods: Transcranial Doppler ultrasound (TCD) was used to determine the systolic, diastolic and mean blood velocities in the ACA and PCA during normal gestation. The resistance (RI), was calculated. Data were analyzed using multilevel modeling, incorporating random effects models, to construct mean and percentile curves.

Results: The 355 measurements performed on 59 patients showed decreased systolic and mean velocity in the ACA, and increased diastolic velocity in the PCA during normal pregnancy. RI in both vessels reached a maximum level in the second trimester, followed by a third trimester decrease, and a subsequent increase during the postpartum period.

Conclusion: This study provides normative data for ACA and PCA velocity and derived parameters in pregnancy and the postpartum period. The changes in velocity suggest a redistribution of cerebral blood flow from the anterior to the posterior cerebral circulation.
2.1 **Introduction**

The changes in central hemodynamics during pregnancy have been quite extensively studied and characterized, both with non-invasive and invasive techniques. However, for practical and logistic reasons (both MRI and CT are expensive and time consuming) changes in maternal cerebral hemodynamics have been less well studied. With the introduction of transcranial Doppler (TCD), intracranial cerebral blood vessels have become much more accessible and it is now possible to reliably and reproducibly study the cerebral blood flow velocity (CBFV) in the main intracranial vessels.

To date, several cross-sectional, and longitudinal studies have examined maternal cerebral blood flow (CBF) during pregnancy utilizing various techniques (Doppler ultrasound, MRI) and blood vessels (middle cerebral, posterior cerebral, internal carotid). Most show a decrease in velocity (and flow with MRI) in the middle cerebral artery during pregnancy with an increase in cerebral perfusion pressure. Belfort et al. published normative MCA data for pregnancy and defined 5th and 95th percentiles for systolic, diastolic and mean velocity, as well as resistance index and cerebral perfusion pressure. Using these normative data the same investigators studied women with preeclampsia and showed that CPP is increased in this condition, and that cerebral autoregulation in the MCA distribution is at risk, especially in women with concomitant headache.

Very few investigators have studied the changes of normal pregnancy (or preeclampsia) in the other major intracranial arteries (anterior and posterior cerebral arteries) and available data is generally derived from MRI studies of flow. This is most likely due to the increased difficulty in technique to reliably obtain a signal from these vessels. There is, however, good reason to study these vessels because, physiologically speaking, the posterior circulation is believed to be more vulnerable to dysfunctional cerebral autoregulation because of its relative lack of sympathetic innervation. Indeed, eclampsia is hypothesized to be a cause of posterior reversible encephalopathy syndrome (PRES).

To date, there are few studies that have examined the posterior cerebral artery (PCA) in pregnancy, and those that are available have usually involved patients in the third trimester. One
longitudinal study by Zeeman used MRI to determine flow in the posterior cerebral artery in normal pregnancy, but velocity data were not reported. Even less is known about the anterior cerebral artery (ACA) in normal or abnormal pregnancy. To our knowledge, no normative data detailing changes in velocity in these vessels have been published. This situation limits our understanding of normal pregnancy, and also prevents us from comparing the data derived from patients with disease states with the expected norms.

Our primary objective was therefore to longitudinally define the normal range of the blood velocity (and selected derived parameters and ratios) in the maternal anterior and posterior cerebral arteries during normal pregnancy and postpartum.

2.2 Materials and methods

We conducted a prospective cohort study of normotensive, healthy pregnant patients who underwent prenatal care at our institution. Approval from our institutional review board was obtained prior to data collection, and informed consent was obtained from all participants.

We included only normotensive, non-smoking, low-risk pregnant women without cerebrovascular abnormalities, or anemia. Medication use was limited to only prenatal vitamins.

The patients were approached for enrollment during routine prenatal visits, and enrolled as early in the pregnancy as possible. Examinations were performed at the time of enrollment and then every 4 weeks thereafter during their pregnancy. The patients also returned for two examinations in the postpartum period (at 6 and 12 weeks). Patients were asked to refrain from coffee and tea in the 2 hours before their examination.

Using a standard data collection sheet, demographic characteristics, obstetrical, and neonatal outcome data were abstracted from patient interviews and available medical records. In patients who were uncertain of their last menstrual period, estimated gestational age was determined by early (first trimester) ultrasound and normal growth was confirmed by subsequent ultrasound examinations. Subjects who developed maternal pregnancy related complications (e.g. preeclampsia) were excluded from the study.
Maternal vital signs including end-tidal CO\(_2\) (EtCO\(_2\)), urine protein, heart rate, systolic (SBP), diastolic (DBP), and mean arterial (MAP) pressures were obtained at time of each transcranial Doppler (TCD) examination. Maternal TCD examinations of the ACA and PCA were carried out using a 2 MHz pulsed, range-gated TCD probe (Medasonics Cerebrovascular Diagnostic System; Fremont, CA) with a 10 mm sample volume. The transducer was positioned at the temporal window to insonate the ACA and the PCA. Peak systolic (PSV), mean (MV), and diastolic (DV) velocities were obtained bilaterally where possible and averaged, and unilaterally if both arteries could not be insonated. A minimum of six waveforms were averaged for each parameter. Inter and intra observer variability were routinely evaluated by two examiners performing two examinations each on the same patient. Variability is known to be less than 10\%. Resistance (RI) indices were calculated as: \(RI = \frac{PSV - DV}{PSV}\)

Multilevel modeling, incorporating random effects models, was used to construct mean and percentile curves\(^{17}\). All dependent variables were logarithmically transformed in order to normalize their distribution. A linearizing function of gestational age (GA) was obtained from the best fitting fractional polynomial\(^{17}\). The model consisted of a fixed component (intercept and linearizing function of GA) and a random component (random effect of intercept and random effect for GA). For all parameters, residual diagnostic was performed and -2 log likelihoods and the likelihood ratio test were used to assess model fit\(^{18}\). The 5\(^{th}\) and 95\(^{th}\) percentile were calculated by subtracting and adding 1.645×SDtot from the mean. Formulas for the GA specific means and standard deviations (SDtot) are presented in the Appendix. All data analysis was performed using SAS statistical software (version 9.3, Cary, NC).

### 2.3 Results

A total of 355 measurements was performed on 59 patients undergoing a median of 6 [2-11] examinations and these were all included in the analysis. All had a singleton pregnancy and were normotensive (MAP <105 mmHg) during all visits, and none had a history of (pregnancy induced) hypertension. The mean age during their first study was 28.8 ± 5.3 years and the median [range] for
parity was 0 [0-3]. As demonstrated in Figure 1, ACA systolic velocity decreased during pregnancy from 80 cm/s (5th-95th centile: 63-100 cm/s) at 12 weeks to 67 cm/s (5th-95th centile: 54-84 cm/s) at 40 weeks. The linear trend slope was -0.00683 cm/sec/day (P<0.0001). Mean velocity also decreased during gestation (slope -0.00435 cm/sec/day, P < 0.0001), while diastolic velocity did not show a significant trend. Concurrently, RI showed a peak during the second trimester, and decreased towards term. (P <0.0001)

Figure 1) Anterior cerebral artery (ACA) hemodynamic parameters during pregnancy and postpartum (pp). A: systolic velocity; B: diastolic velocity; C: mean velocity; D: resistance index. (Mean, 5th and 95th centile)

Figure 2) Posterior cerebral artery (PCA) hemodynamic parameters during pregnancy and postpartum (pp). A: systolic velocity; B: diastolic velocity; C: mean velocity; D: resistance index. (Mean, 5th and 95th centile)
As shown in Figure 2, the velocity in the PCA progressively increased throughout the pregnancy. However, only diastolic velocity reached significance (slope +0.00456 cm/sec/day, \( P=0.006 \)). PCA RI showed the same pattern as ACA, with a decrease in from the second trimester (\( P<0.0001 \)).

Consistent with normal pregnancy physiology, maternal blood pressure gradually increased, and \( \text{EtCO}_2 \) decreased during the course of the pregnancy. (Data not shown)

With respect to the postpartum period, as demonstrated in Figures 1 and 2 both ACA and PCA demonstrated an increase in velocity. Due to the smaller number of observations in this group (\( n=57 \), vs 286 antepartum), only ACA systolic velocity (\( +0.01112 \text{ cm/sec/day} \), \( P=0.019 \)) reached significance.

### 2.4 Discussion

This study shows the normal range of blood velocity in the PCA and ACA during pregnancy, and in the postpartum period. Interestingly, we found that similar to velocity changes in the MCA,\(^5\) there is a decrease in the ACA systolic and mean velocity during normal pregnancy, while the diastolic PCA velocity increased. The MCA changes were hypothesized being due to increased vascular distenbility. Resistance index (RI) in both vessels demonstrated a peak during the second trimester of pregnancy, followed by a third trimester decrease, with subsequent increase postpartum. The magnitude of the third trimester decrease in RI was lower for the PCA than the ACA, which is consistent with the increased velocity seen in that vessel.

The exact mechanism of the observed changes in different directions for both arteries is not known. It might be caused by a combination of changes in carbon dioxide, hormones, cytokines and other circulating factors\(^{19}\) and perivascular innervations\(^{20}\) and the vessels’ dissimilar sensitivity to these shifts.

Pregnancy causes respiratory alkalosis and hypocapnia. As expected, we also found a decrease in \( \text{EtCO}_2 \) during pregnancy when compared to the postpartum period. A decrease in \( \text{EtCO}_2 \) is known to increase cerebrovascular resistance and decrease CBFV due to
constriction of the smaller arteries.\textsuperscript{21, 22} The ACA did show a decrease in systolic and mean velocity during pregnancy. However, RI, often interpreted as indicator of cerebrovascular resistance, decreased in the second half of pregnancy and the diastolic velocity PCA increased. This may indicate that EtCO$_2$ is not a main determinant of cerebrovascular changes in pregnancy.

Estrogen has a vasodilatory effect on the microvasculature\textsuperscript{23} through endothelial nitric oxide synthase.\textsuperscript{24} Indeed, studies have demonstrated that CBF declines with the onset of menopause, and increases with hormone replacement therapy.\textsuperscript{25, 26} By studying the effect of ovarian suppression and stimulation, a significant correlation between increased estrogen levels and increased blood flow velocity in the internal carotid artery has been shown with a concomitant decrease in cerebrovascular resistance.\textsuperscript{27} We did find a decreased RI in both the ACA and PCA, which increased postpartum. With respect to velocity, the PCA showed signs of increased velocity, while ACA decreased.

Cipolla \textit{et al.} have shown gestation-induced changes in endothelial and neuronal nitric oxide synthase\textsuperscript{20} in Sprague-Dawley rats and significantly decreased nNOS expression in the anterior cortex versus posterior.\textsuperscript{19} This regional difference might explain the different slopes seen in our study.

Our data, combined with previously published longitudinal MCA data\textsuperscript{5} show reduced velocity in the MCA and ACA, and increased velocity in the PCA. Even though not all velocities changed significantly, extrapolating these data and assuming no change in vessel diameter (as shown by Zeeman \textit{et al.}\textsuperscript{7}), we suggest that during normal pregnancy there may be some degree of redistribution of cerebral blood flow from the MCA and ACA territory to that of the PCA. Studies, mainly performed in animals, have shown decreased sympathetic innervation of the posterior cerebral circulation (vertebrobasilar arteries) when compared with the anterior circulation (MCA and ACA, arising from internal carotid arteries)\textsuperscript{11}, and less effective autoregulation in pregnancy.\textsuperscript{19}

This redistribution may explain why the posterior circulation is most vulnerable in preeclampsia and eclampsia.\textsuperscript{28, 29} The differential changes in velocity in the ACA and PCA are interesting and suggest
that more research is needed to further elucidate the differences between the anterior and posterior circulations in pregnancy.

To the best of our knowledge, only one other study has examined PCA changes longitudinally in pregnancy, and we were unable to find any that report on longitudinal ACA changes. Zeeman and colleagues used velocity-encoded phase contrast magnetic resonance imaging in showing a decrease in PCA and MCA flow in late pregnancy (PCA at 36-38 weeks, MCA at 28-32 weeks). Flow in both arteries increased at 6 weeks postpartum when compared to the 14-16 weeks measurement. We however did not find a decrease in PCA velocity during pregnancy, but did note an increase postpartum. The gestational age specific ACA velocities in our study are similar to those reported by others in cross-sectional studies.13, 15

Our study has some limitations, which merit discussion. Our cohort’s ACA and PCA velocities progressively rose in the postpartum period, although only ACA systolic was significant. Given that we did not have pre-pregnancy data, we do not know whether this rise returned velocity to a normal pre-pregnancy level, or whether this represents a reset level following pregnancy. We also cannot comment on the timing of the return to baseline. We do not have information on the maternal hematocrit at the postpartum visits, and nor do we have data on whether or not the patients were breastfeeding, which suppresses estrogen levels. Therefore, both anemia and breastfeeding could have impacted our results. As mentioned earlier, a limitation of using TCD derived velocity to make predictions about cerebral blood flow is that a constant vessel diameter has to be assumed. Available literature shows that the MCA does not change diameter despite significant changes in CO2,30,31 and that it maintains its diameter during pregnancy.7, 13 The PCA diameter has also been shown to maintain its diameter during pregnancy.7 No data currently exist regarding the ACA diameter during different physiological circumstances.

This study provides the normal range in ACA and PCA velocity and derived resistance ratios, for pregnancy and the postpartum period. These nomograms may now be used to categorize and define abnormal velocity and cerebral hemodynamic status in patients with preeclampsia or other cerebrovascular abnormalities. The ability to now define the changes in cerebral hemodynamics in multiple
vessels at the same time will allow researchers a better opportunity to understand normal pregnancy physiology. Furthermore, when data from sick patients are plotted against the normative ranges, we may now be able to better define the pathologic changes in disease states that affect cerebral blood flow such as diabetes, preeclampsia and eclampsia.

2.5 Appendix
Assuming $Y_i$=dependent variable of interest at gestational age $\text{GA}_i$, mean and variance of the logarithmic transformed $Y_i$, $Z_i$ at a transformed time $X_i$ are

$$\mu_i = \mathbb{E}(Z_i) = \beta_{0i} + \beta_{1i}X_i,$$

$$\sigma^2_i = \text{Var}(Z_i) = \sigma^2\text{int} + \sigma^2\text{time}X_i^2 + 2\sigma\text{int, time}X_i + \sigma^2_e$$

where $\beta_{0i}$, $\beta_{1i}$ are the fixed parameter estimate and $\sigma^2\text{int}$, $\sigma^2\text{time}$. $2\sigma\text{int, time}$, $\sigma^2_e$ are the estimated variance components from the multilevel analysis. The time specific values for $Y_i$ with 90% coverage is

$$\exp(\mu_i \pm 1.645 \times \sigma_i)$$
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References


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