CHAPTER 7

CEREBRAL AUTOREGULATION IN PREGNANCIES COMPLICATED BY DIABETES AND OVERWEIGHT

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Diab Vasc Dis Res. 2015 Sep;12(5):377-80 (Published in short)
Abstract

Aim: The aim of this study was to estimate the impact of diabetes and obesity on cerebral autoregulation in pregnancy.

Methods: Cerebral autoregulation was evaluated in women with gestational diabetes (GDM), type 2 diabetes (DM2), and/or overweight (body mass index (BMI ≥ 25 kg.m⁻²), and compared to a cohort of euglycaemic pregnant women. The autoregulation index (ARI) was calculated using simultaneously recorded cerebral blood flow velocity in the middle cerebral artery and blood pressure. ARI values of 0 and 9 indicate absent and perfect autoregulation, respectively.

Results: ARI in women with either diabetes (n=33, 6.6±1.1), or overweight (n=21, 6.7±0.6), was not significantly different to that in control patients (n=23, 6.6 ± 0.8, P=0.96).

Conclusions: Cerebral autoregulation is not impaired in pregnant women who have non-vasculopathic diabetes or overweight. This suggests that the increased risk of preeclampsia in diabetic and overweight women is not associated with early impaired cerebral autoregulation.
7.1 Introduction

Preeclampsia (PE) is a multisystem disease, which complicates 2-8% of pregnancies.\(^1\) The exact pathogenesis is still unknown, but maternal obesity and insulin resistance are believed to be important contributing factors.\(^2\) While the risk of PE is increased with pre-gestational diabetes,\(^3\) the association between PE and gestational diabetes (GDM) is less pronounced, and studies are conflicting.\(^4, 5\)

This inconsistency is likely to be due to heterogeneity of the GDM population, with regard to the degree of impaired glucose metabolism, glycaemic control, and its time of onset during pregnancy. Further confounding the association is that women with GDM often have co-existing obesity, which in itself is an independent risk factor for preeclampsia.\(^6, 7\)

Patients with diabetes have increased cardiovascular complications, including stroke. These complications could arise due to endothelial dysfunction, which is common in early and otherwise uncomplicated type II diabetes (DM2).\(^8\)

Preeclampsia is associated with altered cerebral hemodynamics,\(^9, 10\) and represents a risk factor for cerebrovascular complications.\(^11, 12\)

Impaired cerebral autoregulation may explain the development of cerebral oedema, convulsions, or cerebral haemorrhage, even in the absence of significant hypertension.\(^13, 14\)

Cerebral autoregulation is a physiological process that maintains blood flow at an appropriate level despite changes in blood pressure. Studies on cerebral autoregulation in non-pregnant patients with DM2 have shown conflicting results, showing either impaired autoregulation\(^15, 16\) or no difference\(^17, 18\) compared with control subjects. Differences in disease duration, severity and complications may underlie these inconsistencies. Preliminary evidence indicates impaired cerebral autoregulation in PE when compared to normotensive controls.\(^9\)

The effect of diabetes in pregnancy on the autoregulatory capacity is not known. Based on the increased risks of preeclampsia and cerebrovascular complications in patients with pre-gestational diabetes, but a less pronounced relationship with GDM, we hypothesize that the cerebral autoregulation is impaired in DM2, but not in GDM. Consequently, the primary aim of this study was to estimate...
the impact of diabetes and obesity on cerebral autoregulation in pregnancy.

**7.2 Materials and Methods**

We conducted a prospective cohort study in non-labouring pregnant women without a history of cerebrovascular disease, and with an estimated gestational age (EGA) >20 weeks. Cases included women with gestational diabetes (GDM), type 2 diabetes (DM2) (cases), or overweight (prepregnancy body mass index (ppBMI ≥ 25 kg.m⁻²) who were otherwise healthy. The referent population included healthy normotensive pregnant women with a ppBMI < 25. All women were screened for glucose intolerance using the 1-hour 50 gr. glucose challenge. Study participants were recruited from the outpatient clinics at Texas Children’s Pavilion for Women in Houston and North Austin Maternal-Fetal Medicine in Austin, Texas during a routine prenatal care visit. One experienced examiner (TRVV) performed all of the measurements. The study was approved by the local Institutional Review Boards 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 comprised pregnancy and maternal age greater than 18 years. Women were excluded if they had chronic medical illnesses (other than diabetes), used antihypertensive medications, smoked, used illicit drugs, or if they developed preeclampsia during their pregnancy. Furthermore, in the control and study groups, we excluded anyone who developed gestational diabetes after enrolment. Women with diabetes were excluded if they had underlying proliferative vasculopathy (White’s classification D or higher). GDM was diagnosed according to ACOG guidelines. GDM patients were categorized into A1 (diet controlled), and A2 (medication controlled). Women diagnosed with diabetes prior to 16 weeks of gestation were classified as “pre-gestational.”

Data from both the medical record and from patient interview were entered into a standardized database (Access, Microsoft Corp. Seattle, WA). The following maternal characteristics were based on self-report: race/ethnicity, height, pre-pregnancy weight, smoking
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and alcohol and illicit substance use. Gestational age (EGA) was determined by menstrual dating. In cases of uncertain menstrual dates, first trimester ultrasound estimates of EGA were used.

Cerebral autoregulation was assessed by using a combination of transcranial Doppler (TCD) and continuous non-invasive blood pressure measurement, and is expressed as the Autoregulation Index (ARI), with 0 being absent and 9 perfect cerebral autoregulation.

At the time of the TCD examination, brachial systolic (SBP) and diastolic (DBP) blood pressure were measured. Patients 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 two 2 MHz pulsed, range gated 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.

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, after an acclimatization period of at least 5 minutes, when a stable waveform was achieved with the servo-adjust on. This was subsequently calibrated with the brachial BP. The BP tracing also served to mark each cardiac cycle. End-tidal CO$_2$ (EtCO$_2$) was measured 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 artefacts in the cerebral blood flow velocity CBFV signal. All signals were then low-pass filtered with a Butterworth filter with a cut-off frequency of 20 Hz. Mean BP, bilateral CBFV, EtCO$_2$ 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. All beat-to-beat time series of parameters were then interpolated with a 3rd order polynomial and resampled at 5 Hz.

Cerebral autoregulation was determined from the CBFV responses to spontaneous fluctuations in mean arterial BP as described previously. Auto- and cross-spectral estimates were obtained with
the fast Fourier transform (FFT), using data segments of 512 samples and 50% superposition (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.21 and the best fit curve corresponded to the ARI autoregulation index.21, 22 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.

All data sets were checked for normalcy of distribution (Kolmogorov-Smirnov test). Data are reported as mean and standard deviation, or median and [range] as appropriate. Analyses were performed using ANOVA with Bonferroni’s post-hoc test or ANOVA on Ranks with Dunn’s post hoc test (both comparisons versus the control group). (Sigmastat 2004, Systat Software, Richmond, CA). P < 0.05 was used to indicate statistical significance.

7.3 Results:

A total of 36 women with DM (GDMA1, GDMA2, and DM2, 12 in each group), 24 overweight women without DM (ppBMI > 25 kg.m\(^{-2}\)), and 24 control women (ppBMI<25 kg.m\(^{-2}\)) were enrolled.

One woman with GDMA1, 2 with DM2, 3 with overweight/obesity and 1 woman in the control group later developed PE and were excluded from the analysis.

Maternal demographics were similar for both groups, except for BMI and gestational age at delivery (Table 1). Patients with DM2 used either insulin (n=4), Glyburide (n=4), both insulin and Glyburide (n=1) or metformin (n=1) for glucose control. All patients with GDMA2 used Glyburide.

When compared with the control group, women with GDM, DM2, and high BMI did not have any significant ARI differences. There was also no difference noted between GDMA1, GDMA2 and DM2 (ARI 6.5 ± 1.5, 6.4 ± 1.0 and 6.9 ± 0.6, P=0.53). CBFV was lower in patients with DM2, however, this was not clinical significant. None of the other parameters in Table 2 were different between these three
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#### Diabetes Mellitus (n=33)
- Maternal age (years): 30 ± 6  
- Prepregnancy BMI (kg.m\(^2\)): 30.8 (20.0-58.6)†  
- EGA at study (week\(^{day}\)): 34\(^{6}\) (24\(^{5}\)-38\(^{3}\))  
- Twin pregnancy: 0
- EGA at delivery (week\(^{day}\)): 38\(^{0}\) (27\(^{3}\)-41\(^{0}\))†
- Birth weight (grams): 3280 ± 551

#### Overweight (BMI≥25) (n=21)
- Maternal age (years): 29 ± 5  
- Prepregnancy BMI (kg.m\(^2\)): 29.9 (25.1-39.2)†  
- EGA at study (week\(^{day}\)): 33\(^{5}\) (20\(^{3}\)-40\(^{1}\))  
- Twin pregnancy: 2 (10%)
- EGA at delivery (week\(^{day}\)): 39\(^{0}\) (32\(^{0}\)-41\(^{0}\))†
- Birth weight (grams): 3157 ± 613

#### Control (BMI<25) (n=23)
- Maternal age (years): 30 ± 7  
- Prepregnancy BMI (kg.m\(^2\)): 22.6 (18.2-24.5)  
- EGA at study (week\(^{day}\)): 35\(^{5}\) (24\(^{4}\)-40\(^{2}\))  
- Twin pregnancy: 1 (4%)
- EGA at delivery (week\(^{day}\)): 39\(^{1}\) (28\(^{0}\)-41\(^{1}\))  
- Birth weight (grams): 3072 ± 698

### Table 1) Demographic data.
EGA: Estimated gestational age; BMI: Body mass index. Data are mean ± SD, median (range) or number (%). Indicated P-values by ANOVA, ANOVA on ranks or Chi-square.†P < 0.05 vs. control (ANOVA on ranks with Dunn’s test).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diabetes Mellitus (n=33)</th>
<th>Overweight (BMI≥25) (n=21)</th>
<th>Control (BMI&lt;25) (n=23)</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARI</td>
<td>6.6 ± 1.1</td>
<td>6.7 ± 0.6</td>
<td>6.6 ± 0.8</td>
<td>0.88</td>
</tr>
<tr>
<td>Phase (rads)</td>
<td>1.27 ± 0.29</td>
<td>1.25 ± 0.29</td>
<td>1.27 ± 0.27</td>
<td>0.96</td>
</tr>
<tr>
<td>Coherence</td>
<td>0.39 ± 0.10</td>
<td>0.39 ± 0.11</td>
<td>0.44 ± 0.11</td>
<td>0.107</td>
</tr>
<tr>
<td>Gain (cm.s(^{-1}). mmHg(^{-1}))</td>
<td>0.69 ± 0.21</td>
<td>0.67 ± 0.21</td>
<td>0.78 ± 0.29</td>
<td>0.26</td>
</tr>
<tr>
<td>CBFV (cm.s(^{-1}))</td>
<td>61 ± 8</td>
<td>68 ± 8</td>
<td>64 ± 10</td>
<td>0.032</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>86 ± 11</td>
<td>82 ± 9</td>
<td>80 ± 10</td>
<td>0.062</td>
</tr>
<tr>
<td>EtCO(_2) (mmHg)</td>
<td>33 ± 2</td>
<td>33 ± 2</td>
<td>34 ± 2</td>
<td>0.14</td>
</tr>
<tr>
<td>CrCP (mmHg)</td>
<td>11.2 (0-30)</td>
<td>10.5 (0-32)</td>
<td>14.6 (0-31)</td>
<td>0.77</td>
</tr>
<tr>
<td>RAP (mmHg.s.cm(^{-1}))</td>
<td>1.2 (0.8-1.8)</td>
<td>1.2 (0.9-3.0)</td>
<td>1.1 (0.6-1.8)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

### Table 2) Hemodynamic data.
ARI: autoregulation index; CBFV: Cerebral blood flow velocity; MAP: Mean arterial pressure; EtCO\(_2\): End-tidal CO\(_2\); CrCP: Critical closing pressure; RAP: Resistance area product. Phase, coherence and gain are obtained in the low frequency range (<0.1 Hz). Data are mean ± SD, or median (range). Indicated P-values by ANOVA or ANOVA on ranks.
groups. Patients who later developed preeclampsia and who were excluded had an average ARI of 6.2 ± 1.5 (range 4.2 – 7.8), which was not significantly different from the control group (P=0.34) However, the study was not powered to find this difference.

**7.4 Discussion**

In this study, dynamic autoregulation in pregnancies complicated by diabetes was examined and compared to normotensive and euglycaemic pregnant controls with BMI < 25 kg.m$^{-2}$. The findings indicate that cerebral autoregulation is not impaired in women with (uncomplicated non-vasculopathic) diabetes in pregnancy. Furthermore, the functionality of autoregulation is equally effective in euglycaemic women with and without pre-pregnancy obesity.

GDM, DM2, and obesity all are associated with endothelial dysfunction and chronic inflammation. These abnormalities lead to atherosclerosis and contribute to the increased cerebrovascular mortality and morbidity seen in DM2 and obesity. A study on cerebral infarction in young adults found an odds ratio of 11.6 for diabetes.

The effect of diabetes and subsequent endothelial dysfunction on cerebral autoregulation is less clear. Two studies in non-pregnant DM2 patients with good glycaemic control and no major complications showed normal autoregulation. Others found affected dynamic autoregulation in DM2 with, and without microvascular disease. We did not find evidence suggesting affected dynamic cerebral autoregulation in our group of pregnant women with DM2, but comparison with the aforementioned studies is difficult due to differences in age, disease duration and severity, and gender. None of our patients had microvascular complications or autonomic neuropathy, which are thought to be associated with cerebral autoregulation impairment in DM. In pregnancy, these factors (characterized by baseline proteinuria and the White classification) are associated with the development of PE. None of the women in the current study had baseline proteinuria or class D diabetes or higher which might explain the lack of impaired autoregulation. Furthermore, interpretation of previous studies on GDM and adverse pregnancy outcomes has been complicated by the fact that these studies were
not differentiated according to disease severity. We studied both diet- and medication controlled GDM separately, but did not find a difference in autoregulation in either of these sub groups. As in the patients with DM2 in our study, we hypothesize that the excellent glycemic control (as shown by daily glucose monitoring), relatively mild hyperglycaemia and short disease duration allow for preserved cerebral autoregulation.

Another explanation for the absence of impaired autoregulation in the current study might be pregnancy in and of itself. The ARI found in all groups seems to be in the high normal range when compared to non-pregnant subjects. This might be the result of the relative hypocapnia seen in pregnancy which improves the autoregulatory capacity, and the hormonal changes of pregnancy which enhance endothelial function.

One of the strengths of this study is the inclusion of both women with diabetes and two groups of women without diabetes (ppBMI < 25 kg/m²). Interpretation of the effect of GDM in pregnancy is complicated because these women are often obese, a condition known to be associated with insulin resistance, endothelial dysfunction, a pro-inflammatory state, and preeclampsia.

This study has some limitations, which merit discussion. The incidence and severity of endothelial dysfunction in DM is related to the duration of the disease and the glycaemic control. Although the duration of diabetes differed amongst the patients, none demonstrated poorly controlled diabetes, as determined by their Maternal-Fetal Medicine specialist. However, glycosylated haemoglobin (HbA1c) is not routinely measured in such pregnant patients, and thus was not available to monitor glycaemic control. Patients with diabetic complications (vasculopathy) were excluded from our study, and clearly may have demonstrated a different response given the nature of the disease. Furthermore, we only studied autoregulation within the context of spontaneous fluctuations in blood pressure during rest, which is a mainly myogenic activity. Therefore, we cannot exclude the possibility of CBF changes induced by metabolic activity such as might be present in patients with impaired CO₂ cerebrovascular reactivity. Lastly, the women were studied at a wide range of gestational age, but with a comparable median gestational age. The effect of advancing
gestational age on ARI is not known, however, we did not find a correlation between gestational age and ARI (data not shown).

In conclusion, our findings suggest the presence of normal functioning dynamic cerebral autoregulation in normal weight and high BMI pregnant women with pre-gestational and gestational diabetes. This suggests that if such women are at an increased risk for preeclampsia based on their diabetic and/or high BMI status, it is unlikely to be associated with significant impairment in dynamic cerebral autoregulation prior to the development of the hypertensive state. Whether this holds true for patients with advanced diabetic complications remains to be determined by future studies.
REFERENCES


Cerebral hemodynamics in normal and complicated pregnancy


