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ORIGINAL ARTICLE

Cerebral Hemodynamics Analysis by Doppler Ultrasound in Chronically Hypertensive Pregnant Women

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Abstract

Objective: To study the arterial blood flow of the carotid and vertebral systems during pregnancy in women with chronic hypertension via Doppler ultrasound and to compare the results with those obtained for normotensive pregnant women.

Design: A prospective cohort study.

Setting: Maternal care tertiary center; RJ - Brazil.

Population: 68 chronic hypertension pregnant women and 223 normotensive pregnant women.

Methods: Doppler ultrasound was used to evaluate Doppler velocimetry indices of the common carotid artery, internal carotid artery, and the vertebral artery. We studied the peak systolic velocity (PSV), resistance index (RI), pulsatility index (PI) and diameter of the arteries. A sample of 68 pregnant women with chronic hypertension was compared to a group of 223 normotensive pregnant women.

Main outcome measures: Doppler velocimetry indices.

Results: There were no significant differences between the studied parameters for normotensive pregnant women and those of pregnant women with chronic hypertension. Among the variables that influenced arterial blood flow, gestational age was the only variable that was statistically significant, showing an increase in diameter and a decrease in resistance index with advancing gestation.

Conclusions: Chronic hypertension does not alter the cerebral hemodynamics of pregnant women. However, protective brain microcirculation effects, such as hypertrophy, were not found in hypertensive pregnant women. The physiological changes of pregnancy may prevent or reverse these protective effects, which may predispose the brain to complications related to an acute increase in blood pressure.

Keywords

Pregnancy, Hypertension, Cerebrovascular circulation, Doppler ultrasound, Common carotid artery, Internal carotid artery, Vertebral artery

Introduction

The reported prevalence of hypertension varies around the world. According to the World Health Organization, the percentage of the population aged 18 years and over with high blood pressure (systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90) in 2014 was 26.4% in males and 20.4% in females [1]. Chronic hypertension is estimated to be present in 3% to 5% of pregnancies and is being encountered with increasing frequency. Chronic hypertension during pregnancy is associated with significantly elevated risks of maternal and perinatal morbidity and mortality, especially when preeclampsia is present [1,2]. In the general population, the risk of preeclampsia is 3% to 5%, yet among women with chronic hypertension, 17% to 25% develop superimposed preeclampsia [3-6].

Although cerebral circulation has a central role in the pathogenesis of neurological complications, our understanding of how pregnancy chronic hypertension affect this exclusive circulation is limited [2]. The carotid and vertebral arteries are extracranial cerebral vessels and have rarely been studied during pregnancy. They are of fundamental importance to a better understanding of

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cerebral circulation in pregnancy [2].

Chronic hypertension is associated with hypertrophy of cerebral arteries and it also undergo eutrophic remodeling, defined as a decrease in external and internal lumen diameter such that the cross-sectional area does not change. Both the hypertrophic and eutrophic remodeling of the great and small cerebral arteries attenuate the increased pressure in the microvessels, thus protecting the blood brain barrier. Based on this finding, we expected to find a difference between flows and diameters of the arteries evaluated, which was not confirmed [7,8]. Histological evidence suggests that the protective physiological changes that occur during a healthy pregnancy are able to reverse the hypertrophy and remodeling of cerebral vessels associated with chronic hypertension. This hypothesis would explain why pregnant women who develop hypertensive disease for the first time during pregnancy have so many neurological complications with high morbidity and mortality rates.

The purpose of this study was to perform a more complete evaluation of cerebral circulation in pregnant women with chronic hypertension by evaluating the blood flow within the common carotid artery (CCA), internal carotid artery (ICA) and vertebral artery (VA) using Doppler ultrasound. The values obtained were compared with the values previously established for normal pregnancies.

Methods

A total of 279 pregnant women were recruited. All women had a gestational age between 20 and 40 weeks, as confirmed by the date of last menstrual period and/or an ultrasound performed before 20 weeks. The normotensive group consisted of 223 pregnant women at 20 to 40 weeks' gestation, without comorbidities. The study group consists 68 pregnant women with chronic hypertension. The project was approved by the hospital's ethics committee, and all the women signed the informed consent.

Singleton pregnancies without major fetal malformations, chromosomal abnormalities, or other comorbidities were included in the study. Chronic hypertension was defined as increased blood pressure diagnosed before pregnancy or before 20 weeks of pregnancy, at levels above 140 × 90 mmHg. The exclusion criteria included the following: Presence of carotid or vertebral artery disease, such as atherosclerotic plaque, fibromuscular dysplasia, carotid or vertebral artery dissection, or Takayasu's disease; pregnant women using drugs other than antihypertensive agents that could interfere with blood flow; smokers; and women classified as having preeclampsia, even if the condition was superimposed on chronic hypertension. Preeclampsia was defined as the presence of proteinuria (≥ 0.3 g protein in a 24-hour sample or ≥ 1+ on the dipstick test), associated with hypertension (blood pressure higher than 140 × 90 mmHg) [9-11].

All patients had the blood flow velocities of the vertebral, common carotid and internal carotid arteries examined bilaterally by B-mode, color and spectral Doppler ultrasound. A linear transducer with a frequency range of 7.0 to 12.5 MHz (Medison Sonoace 8000 SE) was used. Before performing the Doppler exam, we measured the blood pressure of the pregnant woman with an appropriately sized cuff while she was sitting with her arm positioned at heart level.

The examination of the carotid arteries was performed with the patient in the supine position, with the head slightly extended and turned to the opposite side [6,9].

The ICA had a low-resistance, laminar, antegrade flow in the brain throughout the cardiac cycle and had a high end diastolic velocity (EDV). The CCA had an intermediate flow pattern resembling the flow of the internal carotid, with 80% of the flow going to the ICA and 20% to the external carotid artery (ECA).

The peak systolic velocity (PSV); pulsatility index (PI), which is calculated by the formula PSV - EDV/mean velocity; resistance index (RI), which is calculated by the formula PSV - EDV/PSV; and the vessel diameter were evaluated for these vessels.

For the vertebral arteries, the exam began by locating the CCA on the longitudinal plane. A gradual scanning of the transducer was performed sideways, showing the VA and vein running between the C2 and C6 transverse processes, which were identified by their acoustic shadow. Color Doppler showed the presence and direction of flow, and a spectral analysis showed low-resistance flow similar to that of the common carotid artery. A longitudinal plane with a magnified image was obtained to measure the vessel lumen diameter. The same parameters described for the common and internal carotid arteries were evaluated for the vertebral arteries.

The data were analyzed using the statistical analysis software S-Plus 8.0. All parameters were subjected to descriptive analysis and are expressed as the mean and standard deviation for each group. The Kolmogorov-Smirnov normality test was carried out for each variable for each vessel, bilaterally. A significance level of 5% was established for all analyses.

Our main goal was to compare and evaluate the differences between the flows and the diameters of the carotid and vertebral arteries of hypertensive pregnant patients with those of normotensive pregnant women. To compare the groups and exclude possible confounding factors, we performed a linear regression analysis in the group of normotensive women and a multiple regression analysis for the hypertensive women to ascertain which independent variables could influence

Table 1: Mean and the standard deviation of each parameter and for each vessel in the group of pregnant women with chronic hypertension.

Vessel	Chronic hypertension group n = 68 Mean (SD)			Normotensive group n = 223 Mean (SD)		
	PSV (cm/s)	RI	PI	PSV (cm/s)	RI	PI
RCCA	60.61 (± 20.5)	1.33 (± 0.66)	1.86 (± 0.44)	83.25 (± 14.92)	0.76 (± 0.06)	1.95 (± 0.44)
LCCA	56.32 (± 17.48)	0.72 (± 0.10)	1.64 (± 0.49)	83.55 (± 15.27)	0.75 (± 0.06)	1.92 (± 0.42)
RICA	56.32 (± 17.48)	0.72 (± 0.10)	1.64 (± 0.49)	52.77 (± 14.09)	0.60 (± 0.08)	1.10 (± 0.33)
LICA	38.48 (± 13.57)	0.72 (± 0.21)	1.47 (± 0.49)	53.75 (± 13.86)	0.58 (± 0.11)	1.05 (± 0.28)
RVA	29.02 (± 12.49)	0.63 (± 0.11)	1.48 (± 1.6)	39.45 (± 10.07)	0.65 (± 0.08)	1.24 (± 0.30)

RCCA: right common Carotid Artery; LCCA: left common carotid artery; RICA: right internal carotid artery; LICA: left internal carotid artery; RVA: right vertebral artery; LVA: left vertebral artery; PSV: peak systolic velocity; RI: resistance index; PI: pulsatility index.

our results. In the normotensive group, the independent variable used in the linear regression analysis was gestational age. In the group of pregnant women with chronic hypertension, the independent variables used in the multiple regression analysis were the following: gestational age, systolic blood pressure, diastolic blood pressure, and the use of more than one antihypertensive agent. These regressions generated residual values for each group that were free from the influence of confounding variables. We then applied Student's t-test to the residual values to compare the groups.

Results

Sixty-eight chronically hypertensive pregnant women were compared to two hundred and twenty-six healthy, normotensive pregnant women. The chronically hypertensive group had a mean age of 30.6 years (ranging from 17 to 40 years) and a mean gestational age of 31.1 weeks. The examination was successfully performed on all patients, and none were excluded. All 68 of the women were using an antihypertensive medication (methyldopa), and 15 patients used it in combination with another antihypertensive drug. The diastolic blood pressure was greater than or equal to 90 mmHg in 21 of these patients at the time of examination, and the systolic pressure was greater than or equal to 140 mmHg in 15 patients. The normotensive group consisted of pregnant women with a mean age of 27.3 years (ranging from 15 to 43 years) and with a mean gestational age of 29.5 weeks. The examination was successfully performed on all patients.

Mean and the standard deviation of PSV; RI and PI in the group of pregnant women with chronic hypertension for right common carotid artery (RCCA) are: 60.61 (± 20.5), 1.33 (± 0.66) and 1.86 (± 0.44); for left common carotid artery (LCCA) are: 56.32 (± 17.48), 0.72 (± 0.10) and 1.64 (± 0.49); for right internal carotid artery (RICA) are: 56.32 (± 17.48), 0.72 (± 0.10) and 1.64 (± 0.49); for left internal carotid artery (LICA) are: 38.48 (± 13.57), 0.72 (± 0.21) and 1.47 (± 0.49); for right vertebral artery (RVA) are: 29.02 (± 12.49), 0.63 (± 0.11) and 1.48 (± 1.6); and left vertebral artery (LVA) are: 33.46 (± 13.57), 0.65 (± 0.10) and 1.18 (± 0.35) respectively (Table 1).

Our ultimate goal was to compare the group of normotensive pregnant women with pregnant women with chronic hypertension to evaluate whether the different dependent variables (PSV, PI, RI and diameter) of the three vessels studied showed significant differences between the groups. To achieve the goal of our study, we evaluated whether the dependent variables were influenced by the independent variables. To make our groups comparable, a linear regression in the normotensive group and a multiple regression in the hypertensive group were performed so that both groups could be compared without the influence of the independent variables, which could cause confusion.

To determine if gestational age exerts an influence over blood flow in normotensive mothers, a simple linear regression performed for each of the vessels bilaterally found no significant differences between blood vessels of the right and left sides [7].

For the hypertensive group, a multiple regression analysis was performed to evaluate whether some of these variables influence the blood flow of this group. The following independent variables were studied: gestational age; systolic blood pressure ≥ 140 mmHg; diastolic blood pressure ≥ 90 mmHg; and use of more than one antihypertensive agent (all chronically hypertensive patients were taking methyldopa, but only a few patients were taking this antihypertensive agent in combination with another antihypertensive drug). Most variables did not have a statistically significant "p" value. Therefore, we assumed variables such as gestational age, blood pressure and use of more than one antihypertensive agent do not influence the flow velocities, resistance indices and diameters of arteries in chronically hypertensive pregnant women (Table 2).

The linear and multiple regressions for the normotensive and hypertensive groups generated residual values for each group. The Student's t-test was performed to compare the values in both groups, without the influence of the independent variables (Table 3).

Discussion

The current study allows us to better understand how the physiological changes of pregnancy affect cerebral hemodynamics in women with chronic hypertension who already have experienced previous changes

Table 2: Cross-sectional regression for the chronic hypertension group.

Vessels	GA p value	SBP ≥ 140 p value	DBP ≥ 90 p value
RCCA PSV	0.0309	0.1023	0.0368
RCCA RI	0.4236	0.7809	0.8781
RCCA PI	0.9833	0.1261	0.2568
RCCA DIAMETER	0.0504	0.8526	0.8261
RICA PSV	0.0013	0.3075	0.1874
RICA RI	0.6195	0.5400	0.9594
RICA PI	0.3872	0.1735	0.8674
RICA DIAMETER	0.2574	0.8498	0.7467
RVA PSV	0.9943	0.4278	0.7708
RVA RI	0.2197	0.1196	0.2266
RVA PI	0.3159	0.2020	0.2187
RVA DIAMETER	0.9260	0.3507	0.0119
LCCA PSV	0.5215	0.4881	0.4275
LCCA RI	0.2190	0.5076	0.5271
LCCA PI	0.2781	0.3989	0.5415
LCCA DIAMETER	0.3827	0.1146	0.6997
LICA PSV	0.0327	0.0473	0.2898
LICA RI	0.2369	0.5274	0.8873
LICA PI	0.3893	0.5004	0.8029
LICA DIAMETER	0.5522	0.4724	0.4494
LVA PSV	0.0771	0.0837	0.0818
LVA RI	0.0078	0.0568	0.4452
LVA PI	0.0234	0.9791	0.8614
LVA DIAMETER	0.5479	0.5054	0.8242

RCCA: right common Carotid Artery; LCCA: left common carotid artery; RICA: right internal carotid artery; LICA: left internal carotid artery; RVA: right vertebral artery; LVA: left vertebral artery; PSV: peak systolic velocity; RI: resistance index; PI: pulsatility index.

due to the underlying disease. It may be possible to understand why these women are more susceptible to complications than the general population. The prevalence and severity of these events may enable us to detect patients who are more susceptible to these episodes, and the prevention of these episodes will greatly reduce maternal mortality worldwide.

Pregnancy poses a unique challenge to the brain and its circulation differs from that of other organs. While other organs and systems undergo a substantial increase in blood flow, the cerebral circulation appears to remain relatively constant, even with large increases in plasma volume and cardiac output [12].

Current research in to the behavior of cerebral blood flow during pregnancy is preliminary and inconclusive. The vessels most studied are the ophthalmic artery, the middle cerebral artery, and, most recently and to a lesser degree, the ICA [12-14].

Previous Doppler ultrasound studies of the ophthalmic artery have revealed significant differences in blood flow between hypertension and preeclampsia: in chronic hypertension, there seems to be hypoperfusion and an increased RI; whereas in preeclampsia (PE), there are signs of vasodilation and increased flow velocities [13-16].

Table 3: Comparison of residual values of each group.

Vessels	Hypertensive residuals	Normotensive residuals	P
RCCA PSV	4.996004e-016	-1.433831e-016	1
RCCA RI	5.286776e-017	3.516121e-018	1
RCCA PI	-2.168404e-017	1.095287e-017	1
RCCA DIAMETER	-8.540177e-018	-1.991431e-017	1
RICA PSV	-3.006142e-016	-6.078844e-016	1
RICA RI	2.238353e-018	3.422773e-018	1
RICA PI	-3.469447e-018	2.178128e-019	1
RICA DIAMETER	1.521219e-018	4.560378e-016	1
RVA PSV	6.012285e-016	0	1
RVA RI	5.421011e-018	-4.667417e-020	1
RVA PI	-4.813858e-017	1.667824e-017	1
RVA DIAMETER	6.661338e-018	-1.632974-016	1
LCCA PSV	9.868649e-016	-4.460806e-016	1
LCCA RI	3.524518e-018	-1.089064e-018	1
LCCA PI	4.229421e-017	-1.493574e-018	1
LCCA DIAMETER	1.345725e-017	3.823548e-016	1
LICA PSV	2.018587e-016	6.372581e-017	1
LICA RI	-1.195625e-017	2.582638e-018	1
LICA PI	1.009294e-017	3.982863e-018	1
LICA DIAMETER	-4.794145e-017	2.668518e-016	1
LVA PSV	-1.387779e-016	-1.371443e-016	1
LVA RI	8.811294e-018	-2.178128e-019	1
LVA PI	1.233581e-017	2.165682e-017	1
LVA DIAMETER	-6.728624e-018	3.684148e-017	1

RCCA: right common Carotid Artery; LCCA: left common carotid artery; RICA: right internal carotid artery; LICA: left internal carotid artery; RVA: right vertebral artery; LVA: left vertebral artery; PSV: peak systolic velocity; RI: resistance index; PI: pulsatility index.

Another cerebral vessel studied to date is the middle cerebral artery (MCA) via transcranial Doppler (TCD). All resistance indices decrease during normal pregnancy, while cerebral blood flow increases [17,18]. In eclampsia, a significant decrease occurs in cerebral vascular resistance as perfusion pressure increases, leading to hyperperfusion [19,20].

Another study also concluded that women with preeclampsia have impaired dynamic cerebral vascular autoregulation. The fact that blood pressure does not correlate with autoregulation functionality may explain why cerebral complications such as eclampsia can occur without a sudden or excessive elevation in blood pressure [21].

Regarding the ICA, decreased resistance indices have been observed throughout gestation along with increased flow volume, which is attributed to cerebral vasodilation [22]. Another recent study also corroborated this hypothesis with its findings of increased flow volume, decreased resistance indices, and an increased ICA diameter [7].

Numerous studies by Cipolla, et al. (2008, 2011 & 2013) in rats have confirmed some aspects of this hypothesis. They established that chronic hypertension is associated with hypertrophy of the lumen of small and large cerebral arteries; these vessels also simultaneously undergo eutrophic remodeling, defined as a decrease in external and internal lumen diameter such that the cross-sectional area does not change. Both the hypertrophic and eutrophic remodeling of the great and small cerebral arteries attenuate the increased pressure in the microvessels, thus protecting the blood brain barrier. Based on this finding, we expected to find a difference between flows and diameters of the arteries evaluated, which was not confirmed [7,12].

Protective physiological changes that occur during a healthy pregnancy are able to reverse the hypertrophy and remodeling of cerebral vessels associated with chronic hypertension. Consistent with our findings, there were no differences between the group of normotensive pregnant women and those with chronic hypertension.

We noted that there were no significant differences in the flow velocities and diameters of the vessels when comparing the hypertensive and normotensive groups. This result may have occurred because we compared the residual values of each group without confounding factors, such as gestational age, medication use, and systolic and diastolic blood pressure levels. There are important vascular changes directly associated with gestational age; therefore, the 20-week interval of our sample should be recognized as a weakness of the study.

Chronic hypertension is associated with medial hypertrophy of large and small cerebral arteries. This response of the cerebrovascular smooth muscle in patients with chronically high blood pressure is considered an important protective factor. Several studies have shown that chronically hypertensive rats are less susceptible than normotensive rats are to blood-brain barrier disruption and stroke during acute hypertensive episodes [5,7,12].

The findings of hypertrophy and increased resistance were not observed in our group of pregnant women with chronic hypertension compared to normotensive pregnant women. One explanation for this result might be that the protective physiological changes observed in healthy pregnancies would be able to reverse the hypertrophy and remodeling of cerebral vessels observed in chronic hypertensive women.

This hypothesis would explain why pregnant women have so many neurological complications with high rates of morbidity and mortality if they develop hypertensive disease. A series of studies on rats showed that pregnancy both prevents and reverses hypertensive remodeling in the cerebral arteries. While the adaptation of cerebral circulation during pregnancy predicts relatively normal cerebral blood flow and blood brain barrier properties, in the face of significant cardiovascular changes, i.e., in pathological conditions, such adaptations seem to promote greater brain injury, including the development of edema during acute hypertensive episodes [12].

The physiological adaptations of a normal pregnancy may reverse protective adaptive changes found in chronic hypertension that protect the cerebral microcirculation from the deleterious effects of acute increases in blood pressure. These findings may reflect that pregnancy itself predisposes the brain to injuries caused by acute changes in blood pressure.

Conclusion

In conclusion, the results of this study indicate that there are no differences in the cerebral blood flow of the carotid and vertebral arteries between normotensive pregnant women and chronically hypertensive pregnant women. None of the following variables caused significant changes in the group of chronically hypertensive pregnant women: systolic blood pressure level, diastolic blood pressure level, gestational age and the use of more than one antihypertensive agent.

Disclosure

All authors disclosure any conflict of interest that could be perceived to bias their work, making known all financial support and any other personal connections.

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