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ORIGINAL ARTICLE

Carotid Atherosclerosis in Pre- and Post-Menopausal Women with a History of Pregnancy-Induced Hypertension: Case-Control Study

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Abstract

Background: Cardiovascular disease mortality among women remains high. Observational studies are controversial about the participation of a history of gestational hypertensive disorder in cardiovascular risk.

Objective: To verify the association between carotid atherosclerosis in menopausal women who had pregnancy-induced hypertension.

Methods: Case-control study, with cases consisting of women with carotid atherosclerosis, defined as carotid intima-media thickness > 1 mm and/or presence of carotid plaques; the controls did not have these alterations. The significance level was set at 95%.

Results: A total of 504 women without previous cardiovascular disease were assessed, 126 cases and 378 controls. Of the total, 67% were hypertensive; 76% were dyslipidemic; and 16% were diabetic. Approximately 10% reported a history of hypertension during pregnancy. Women with carotid atherosclerosis had higher values of systolic blood pressure (134.18 mmHg vs. 128.59 mmHg, p = 0.008) and LDL-cholesterol (156.52 mg% vs. 139.97 mg%; p = 0.0005). No statistical difference was found regarding the presence of carotid atherosclerosis and history of hypertension during pregnancy (OR 1.672, 95% CI: 0.883-3.131).

Conclusion: The history of hypertension during pregnancy was not associated with subclinical carotid atherosclerosis in menopausal women. However, an association was observed between carotid atherosclerosis and classic risk factors, such as elevated systolic blood pressure and LDL-cholesterol levels. (Int J Cardiovasc Sci. 2018;31(4)359-366)

Keywords: Carotid Artery Diseases/physiopathology; Hypertension, Pregnancy-Induced; Women, Premenopause; Postmenopause; Case-Control Studies.

Introduction

Cardiovascular diseases (CVD) are the leading cause of death among women worldwide.[1,2] In the United States, they account for almost a third of all causes of death in the female gender,[3,4] and similar data are observed in Europe[5] and in Brazil.[6] Advances in CVD treatment in the last three decades have allowed a sustained decrease in mortality. However, socioeconomic and behavioral aspects have interrupted this process in recent years.[7] In 2014, there were 340,284 CVD deaths among Brazilian women, representing an increase of almost 20% in relation to those occurring 10 years earlier.[6] The cardiovascular risk stratification in the female population has failed to detect and prevent the disease. The exploration of new risk factors thus becomes essential to reduce such indices.

Pregnancy is an important moment to evaluate women's cardiovascular health, since the development of complications during this period may indicate an increase in future cardiovascular risk.[8] Several observational studies have shown a higher prevalence of atherosclerosis in women with a history of gestation-induced hypertension,[9-11] and some have observed an association between the number of cardiac events and

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the number of complicated pregnancies,[12] even after the normalization of blood pressure levels after childbirth.

Nonetheless, Romundstad et al.[13] questioned whether such an association would be a factor of ambiguity, because pre-gestational characteristics – especially obesity, hypertension and dyslipidemia – would attenuate the effect that the gestational hypertensive disorder has on the late cardiovascular outcome. Unfortunately, most studies have insufficient evidence, such as limited sample size and clinical follow-up.

Considering that atherosclerosis is a gradual process that starts in childhood, the aim of this study was to verify the association between carotid atherosclerosis in menopausal women who had pregnancy-induced hypertension.

Methods

A case-control study was carried out, with a population of women aged between 45 and 65 years, who had had menstrual irregularities or interruption in the last year. Women receiving hormone replacement therapy, those with chronic inflammatory conditions or any previously diagnosed conditions with high cardiovascular risk or heart disease were excluded from the analysis.

The sample was calculated based on the systematic review performed by Brown et al.,[14] using as reference a hypertension exposure during pregnancy of around 8% and Odds Ratio (OR) to increase the risk of atherosclerosis of 2.28. For a paired study with a one-tailed hypothesis test, we calculated at least 116 cases and 348 controls in order to obtain a 95% level of significance and 80% of test power with a ratio of one case for three controls. Controls were obtained from the same database, and were paired by age group.

All women underwent carotid ultrasound with the same examiner; the carotid intima-media thickness (CIMT) was quantified and the presence of carotid plaques was assessed. For image acquisition, a high-resolution device (EnVisor, Philips) was used with a 12.3 MHz linear transducer. The data were recorded for subsequent analysis using the QLAB-Intima Media Thickness (QLAB-IMT, Philips) software.

The presence of carotid atherosclerosis was defined when the CIMT was greater than 1 mm (mean values obtained in the analyzed segments of the right and left carotid arteries) and / or the presence of atheroma plaque. Atheroma plaque was defined as: (1) localized parietal structure with a thickness greater than 1.5 mm; (2) protrusion into vessel lumen > 0.5 mm or; (3) thickness > 1.5-fold the adjacent CIMT, according to the Mannheim Carotid Intima-Media Thickness and Plaque Consensus.[15]

The cases consisted of women who had carotid atherosclerosis and the controls, of women who did not have this alteration at the ultrasonographic assessment.

The independent variable was pregnancy-induced hypertension, considered as the self-reported information of blood pressure increase during pregnancy. According to Diehl et al.,[16] this information shows good accuracy (specificity of 96% and sensitivity of 79.6%) for the antecedents of pregnancy-induced hypertension, even 24.5 years after the pregnancy. Other variables were considered, namely: blood pressure, income, smoking, type 2 diabetes mellitus, family history of coronary artery disease (CAD), body mass index (BMI), number of pregnancies, preterm birth, low birth-weight offspring, fasting glycemia, total cholesterol (CT), high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol), triglycerides and ultrasensitive C-reactive protein (us-CRP).

The study was approved by the Research Ethics Committee of *Complexo Hospitalar Hospital Universitário Oswaldo Cruz/ Pronto-Socorro Cardiológico de Pernambuco* under CAAE number 55361416.0.0000.5192 and Opinion number 1,593,189 of June 16, 2016.

Statistical analysis

The results were expressed as percentages for categorical variables and as statistical measures such as means, standard deviation and medians, when indicated, for numerical variables. The association between the occurrence of carotid atherosclerosis and the categorical variables was performed using Pearson's chi-square test, whereas the non-paired Student's *t* test was used to compare carotid atherosclerosis in relation to numerical variables. Cox regression analysis was performed to evaluate the influence of covariates on carotid atherosclerosis development in the menopausal period. The strength of the association between the categorical variables was evaluated using the odds ratio (OR) with the respective confidence interval. The normality hypothesis verification was performed using the Kolmogorov-Smirnov test. The level of significance used in the statistical test decisions was 5% and the intervals had 95% of confidence. The Statistical Package for the Social Sciences (SPSS) version 21 was the statistical program used for the statistical calculations.

Results

A total of 504 women were studied, of which 126 had carotid atherosclerosis and 378 did not. The groups did not differ regarding age, ethnicity, marital status and literacy (Table 1). There was also no difference regarding the number of pregnancies, preterm birth and low birth-weight offspring (Table 2).

Carotid atherosclerosis showed a higher association with systemic arterial hypertension (OR 1.837, 95% CI 1.154-2.925, p = 0.01) and dyslipidemia (OR 1.971, 95% CI, 1.149-3.380, p = 0.01). There was a tendency to a higher prevalence of carotid atherosclerosis in women with metabolic syndrome (OR 1.442, 95% CI, 0.957-2.172, p = 0.08). Carotid atherosclerosis was also directly associated with higher systolic blood pressure (134.18 mmHg vs. 128.59 mmHg, p < 0.01), LDL-cholesterol (156.52 mg% vs. 139.97 mg%, p < 0.01) and TC levels (229.68 mg% vs. 214.31 mg%, p < 0.01). There was no difference in relation to diastolic blood pressure, BMI, waist circumference, hip circumference, glycemia, HDL-cholesterol, triglycerides or CRP levels (Tables 3 and 4).

Approximately 10% of the sample had a history of pregnancy-induced hypertension. No statistically significant difference was observed between carotid atherosclerosis in the menopausal period and history of pregnancy-induced hypertension (OR 1.631, 95% CI: 0.874-3.042, p = 0.12). When analyzing only the women with a history of pregnancy-induced hypertension and those with systemic arterial hypertension in the menopausal period, no statistical difference was observed either (OR 1.862, 95% CI: 0.955-3.628, p = 0.07).

When the mean CIMT was evaluated, no statistical association was observed with the history of pregnancy-induced hypertension (0.8516 ± 0.1491 vs. 0.8101 ± 0.1441,

Table 1 - Comparison of sociodemographic characteristics with carotid atherosclerosis in menopausal women

Characteristics	Total (504) n (%)	Carotid atherosclerosis		p value*
		No (378) n (%)	Yes (126) n (%)	
Age, years				
45-50	86 (17.1)	67 (17.7)	19 (15.1)	0.585
51-55	122 (24.2)	89 (23.5)	33 (26.2)	0.550
56-60	169 (33.5)	132 (34.9)	37 (29.4)	0.277
61-65	127 (25.2)	90 (23.8)	37 (29.4)	0.236
Ethnicity				
White	149 (29.6)	115 (30.4)	34 (27)	0.500
Black	83 (16.5)	65 (17.2)	18 (14.3)	0.491
Asian	8 (1.6)	6 (1.6)	2 (1.6)	1.000
Mixed-race	252 (50)	182 (48.1)	70 (55.6)	0.181
Native Brazilian	4 (0.8)	3 (0.8)	1 (0.8)	1.000
Marital status				
Single	216 (42.9)	158 (41.8)	58 (46)	0.408
Married	288 (57.1)	220 (58.2)	68 (54)	0.408
Literate				
No	76 (15.1)	56 (14.8)	20 (15.9)	0.775
Yes	428 (84.9)	322 (85.2)	106 (84.1)	0.775

** Chi-square test.*

Table 2 - Comparison of pregnancy-related characteristics with carotid atherosclerosis in menopausal women

Characteristics	Total (504) n (%)	Carotid atherosclerosis		p value*
		No (378) n (%)	Yes (126) n (%)	
Number of pregnancies				
None	38 (7.5)	27 (7.1)	11 (8.7)	0.561
One	42 (9)	36 (10.2)	6 (5.2)	0.132
Two	112 (24)	82 (23.3)	30 (26.1)	0.530
Three	114 (24.4)	86 (24.4)	28 (24.3)	1.000
Four	67 (14.3)	50 (14.2)	17 (14.8)	0.879
Five	41 (8.8)	29 (8.2)	12 (10.4)	0.453
Six	32 (6.9)	22 (6.3)	10 (8.7)	0.396
Pregnancy-induced hypertension				
No	454 (90.1)	345 (91.3)	109 (86.5)	0.124
Yes	50 (9.9)	33 (8.7)	17 (13.5)	0.124
Low birth-weight newborn				
No	475 (94.2)	358 (94.7)	117 (92.9)	0.507
Yes	29 (5.8)	20 (5.3)	9 (7.1)	0.507
Preterm birth				
No	454 (90.1)	340 (89.9)	114 (90.5)	1.000
Yes	50 (9.9)	38 (10.1)	12 (9.5)	1.000

** Teste do qui quadrado.*

p = 0.06). Also, no statistical difference was observed when only the presence of carotid plaques was compared with a history of pregnancy-induced hypertension (OR 1,332, 95% CI: 0.668-2.655, p = 0.41).

In the logistic regression model, only systemic arterial hypertension (B = 0.108, p = 0.01) and dyslipidemia (B = 0.122, p = 0.01) showed statistical significance with carotid atherosclerosis in the menopausal period (Table 5).

Discussion

In our study, carotid atherosclerosis was associated with systemic arterial hypertension and dyslipidemia, but not with a history of pregnancy-induced hypertension, although the CIMT and the presence of carotid plaques were analyzed separately. These results indicate that pregnancy-induced hypertension is not associated with subclinical atherosclerosis.

Increased CIMT and the presence of carotid plaques have been described as independent cardiovascular risk predictors.[17-20] However, most studies attempting to associate a history of pregnancy-induced hypertension and carotid atherosclerosis are conflicting, since they did not use standardized CIMT and carotid plaque measurements.

Our data add information to the literature due to the large number of assessed patients. All ultrasonographic assessments were performed by the same examiner, blinded for the variable history of pregnancy-induced hypertension, eliminating measurement bias. The latest recommendations for CIMT and carotid plaque measurements were followed.[15]

The physiological behavior of CIMT was described by Akhter et al.,[21] who, after analyzing 57 healthy women, showed that CIMT remains practically stable during pregnancy, but decreases one year after delivery. Blaauw

Table 3 - Comparison of clinical characteristics, life habits and family history with carotid atherosclerosis in menopausal women

Classic risk factors	Total (504) n (%)	Carotid atherosclerosis		p value*
		No (378) n (%)	Yes (126) n (%)	
Systemic arterial hypertension	341 (67.7)	244 (64.6)	97 (77)	0.011
Diabetes mellitus	84 (16.7)	61 (16.1)	23 (18.3)	0.583
Dyslipidemia	387 (76.8)	280 (74.1)	107 (84.9)	0.014
BMI – obesity	166 (32.9)	122 (32.3)	44 (34.9)	0.586
Central obesity	481 (95.4)	366 (96.8)	115 (91.3)	0.014
Metabolic syndrome	270 (53.6)	194 (51.3)	76 (60.3)	0.081
Sedentary life style	146 (29)	105 (27.8)	41 (32.5)	0.310
Consumption of ≥ 5 servings of fruit/day	133 (26.4)	99 (26.2)	34 (27)	0.907
Passive smoking < 6 months	398 (79)	300 (79.4)	98 (77.8)	0.706
Family history of CAD	85 (16.9)	60 (15.9)	25 (19.8)	0.336

** Test of the chi square. BMI: body mass index; CAD: coronary artery disease.*

Table 4 - Comparison of classic cardiovascular risk factors with carotid atherosclerosis in menopausal women

Dependent variables	Total	Carotid atherosclerosis		p value*
		No	Yes	
Age	56.23 (± 5.40)	56.25 (± 5.334)	56.63 (± 5.089)	0.477
SBP	130.40 (± 20.29)	128.59 (± 19.87)	134.18 (± 21.54)	0.008
DBP	84.03 (± 11.51)	83.30 (± 11.30)	84.50 (± 13.07)	0.322
BMI	28.45 (± 5.05)	28.29 (± 4.94)	28.79 (± 5.07)	0.328
Abdominal circumference	92.11 (± 11.51)	91.73 (± 11.29)	91.82 (± 11.34)	0.945
Brachial circumference	28.72 (± 4.47)	28.73 (± 4.58)	28.56 (± 4.57)	0.714
Hip circumference	103.11 (± 12.06)	103.09 (11.86)	102.39 (± 12.18)	0.571
Glycemia	102.41 (± 42.16)	100.00 (± 36.03)	107.72 (± 48.67)	0.060
Total cholesterol	219.43 (± 43.42)	214.31 (± 42.48)	229.68 (± 47.44)	0.001
HDL-cholesterol	51.80 (± 11.11)	52.36 (± 11.02)	51.91 (± 12.39)	0.709
LDL-cholesterol	143.85 (± 40.84)	139.97 (± 40.38)	156.52 (± 42.59)	0.0005
Triglycerides	141.46 (± 81.19)	134.26 (± 74.68)	149.41 (± 85.32)	0.058
us-CRP	0.34 (± 0.54)	0.32 (± 0.52)	0.34 (± 0.47)	0.773

** Unpaired Student's t test. SBP: systemic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; us-CRP: ultra-sensitive C-reactive protein.*

Table 5 - Logistic regression of variables with p < 0.20 in the univariate analysis with carotid atherosclerosis

Variables	B	p value*
LDL	0.002	0.0005
Glycemia	0.001	0.0005
Diastolic blood pressure	- 0.006	0.003
Systolic blood pressure	0.005	0.002

LDL: low-density lipoprotein-cholesterol.

et al.[22] believe that the effects of pregnancy, mediated by metabolic and immunological responses, could take up to more than one year to return to basal levels.

When comparing the CIMT of women who developed hypertension during pregnancy and those who had uneventful pregnancies, the literature data show to be similar to those found in our study. Akhter et al.[23] did not detect a statistically significant difference during pregnancy and up to one year postpartum when evaluating 55 women. Blaauw et al.[22] also found no differences 5 years after the pregnancy. Moreover, when women between 40 and 50 years of age were assessed, there was no statistical difference regarding CIMT between those who had hypertension during pregnancy and those with uneventful pregnancies.[24]

Nevertheless, several observational studies have shown an association between gestational hypertensive disorder and cardiovascular clinical outcomes. Haukkama et al.,[25] when assessing 141 women, identified an almost three-fold higher cardiovascular risk in those with a history of gestational hypertension disorder. In the study by Kessous et al.,[26] the previous history of gestational hypertensive disorder was associated with a greater number of hospitalizations secondary to atherosclerosis 11 years after the pregnancy complicated by hypertensive disorder, even after statistical adjustment for maternal age, parity, diabetes and obesity. Canoy et al.[27] identified in a large cohort that pregnancy-induced hypertension increased the risk of CVD in women in the menopausal period.

Similarly, studies with longer follow-up periods also showed an increase in severe cardiac complications in women with a history of pregnancy-induced hypertension. As verified by Arnadottir et al., women who had hypertensive complications during pregnancy had a higher risk of death due to ischemic heart disease and cerebrovascular diseases after 30 years, in addition to a shorter time of survival.[28]

One of the explanations for not finding an association between carotid atherosclerosis and a history of pregnancy-induced hypertension would be the method used to measure CIMT. That would be caused by the fact that CIMT measured in the common carotid artery would not be a good parameter for the determination of cardiovascular outcomes, as it estimates the total thickness of the intima and media layers. Some authors have shown that only the increase in the intima layer in association with the reduction in the media layer would be important to increase cardiovascular risk.[21,23,24] In our study, we did not analyze the measurements of the intima and media layers separately.

In agreement with the literature,[19,29] we have identified an association between carotid atherosclerosis and traditional cardiovascular risk factors, such as systemic arterial hypertension and hypercholesterolemia. A possible explanation is that both atherosclerosis and gestational hypertension share several common metabolic abnormalities, such as obesity, insulin resistance, dyslipidemia and hypertension itself, as well as the favoring of endothelial dysfunction.[30]

According to Brandão et al.,[31] endothelial dysfunction precedes the clinical manifestations of a gestation complicated by hypertension and, therefore, it would accelerate the atherogenic process.[32]

According to McDonald et al.,[33] the persistence of classic risk factors is the foundation of carotid atherosclerosis development, since even after two decades, women with a history of pregnancy-induced hypertension still had more cardiovascular risk factors than those with uncomplicated pregnancies. In our study, women with a history of pregnancy-induced hypertension had a higher prevalence of obesity and chronic hypertension (data not shown in the tables).

Although our population consists of outpatients from the public health care system, the sociodemographic characteristics did not differ from those of the general population. Moreover, it was not possible to evaluate information prior to the pregnancy, due to the proposal of the original study.

Conclusion

Carotid atherosclerosis was positively associated with some classic cardiovascular risk factors, such as increased systolic blood pressure and higher levels of LDL-cholesterol. A history of pregnancy-induced hypertension was not associated with carotid atherosclerosis in a group

of menopausal and asymptomatic women, from the cardiovascular point of view. More studies are needed to understand the atherosclerosis process in women with a history of pregnancy-induced hypertension.

Author contributions

Conception and design of the research: Gomes RAF, Barros IML. Acquisition of data: Gomes RAF, Barros IML. Analysis and interpretation of the data: Gomes RAF, Barros IML. Statistical analysis: Gomes RAF, Barros IML. Writing of the manuscript: Gomes RAF. Critical revision of the manuscript for intellectual content: Barros IML, Ferreira MNL, Costa LOBF.

Potential Conflict of Interest

This manuscript is part of the master of the Graduate Program in Health Sciences of the University of Pernambuco by Rafael Alessandro Ferreira.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Complexo Hospitalar Hospital Universitário Oswaldo Cruz/Pronto-Socorro Cardiológico de Pernambuco* under the protocol number 55361416.0.0000.5192 (CAAE) and number 1.593.189 of June 16, 2016. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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