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CLINICAL ARTICLE

Endothelial dysfunction after pregnancy-induced hypertension

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ABSTRACT

Objective: To carry out long-term analysis of the presence of endothelial dysfunction after the development of pregnancy-induced hypertension (PIH). *Methods:* In a retrospective cohort study, data were analyzed from 60 women who delivered at a tertiary maternity hospital in Fortaleza, Ceara, Brazil, between 1992 and 2002. Thirty women had a history of PIH and 30 had no history of complications. Anthropometric and laboratory data were collected, and endothelial function was evaluated by flow-mediated dilatation of the brachial artery. Continuous variables were analyzed via Student *t* test, and Mann–Whitney test was used to compare means. Clinical and metabolic measures were categorized according to cardiovascular risk by cutoff points determined by national consensus; χ^2 and Fisher exact tests were used to compare the groups. Relative risk was calculated for variables that were statistically significant ($P < 0.05$). *Results:* Women with a history of PIH had higher body mass index ($P = 0.03$), systolic blood pressure ($P = 0.03$), low-density lipoprotein cholesterol ($P = 0.02$), and fasting glucose ($P = 0.02$) compared with women with no pregnancy complications. The frequency of endothelial dysfunction was 60% among all women, with a significant difference between the 2 groups ($P = 0.01$). *Conclusion:* Women with a history of PIH were found to have a higher frequency of long-term endothelial dysfunction.

1. Introduction

Among the morbid conditions that can compromise the normal course of pregnancy, pregnancy-induced hypertension (PIH) has great clinical significance and is considered a major cause of maternal and perinatal mortality [1,2].

Occurrence of PIH has been associated with an abnormal placentation process, which results in the release of anti-angiogenic factors into the mother's circulation leading to endothelial injury and maternal and fetal damage—situations currently included in category of "placental syndromes" [3,4]. The changes related to PIH do not seem to be resolved during pregnancy, resulting in clinical outcomes with long-term cardiometabolic effects that can change the female epidemiologic profile [5].

Endothelial dysfunction has been identified to be responsible for many of the clinical features of maternal pre-eclampsia syndrome and has been recognized as the main factor related to adverse cardiovascular risk among women with a history of this condition [6,7].

On the one hand, several theories present endothelial dysfunction as a predisposing factor for obstetric complications such as PIH and gestational loss, because impaired endothelial function can damage the physiologic process of placentation. On the other hand, other studies view endothelial dysfunction as a change caused by long-term pre-eclampsia, making women susceptible to chronic hypertension and cardiovascular disease (CVD) [8–11].

Because many studies have shown that an assessment of endothelial function is an important subclinical measure of future changes in cardiovascular events, the aim of the present study was to analyze the presence of endothelial dysfunction among women with a history of PIH after a long follow-up period [8,10,12].

2. Materials and methods

In a retrospective cohort study conducted at the Assis Chateaubriand Maternity Teaching Hospital (MEAC), Federal University of Ceara, Fortaleza, Ceara, Brazil, data were reviewed from women who gave birth between January 1, 1992, and December 31, 2002. The study was approved by the MEAC Ethics Committee under Norm No. 83/11; informed consent was obtained from all participants.

Women diagnosed with PIH documented in their medical records on discharge were included in the cohort group. The participants in the comparison group were women without a history of PIH who gave birth during the same period as the women in the cohort group, with equal numbers in each group.

The study sample was calculated on the basis of a 1:1 ratio in a 2-tailed analysis, a power of 80%, a significance level of 5%, and an

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expected reduction of 25% in dilation of brachial artery lumen during reactive hyperemia, in accordance with previous studies that have evaluated endothelial dysfunction among women with a history of preeclampsia [10]. In total, 44 patients (22 in each group) were required.

Potential participants were contacted by home visits and telephone using information in their medical records. For those who were contacted successfully, the purpose of the study was explained and an invitation was given to participate in the evaluation. If the women were not present for the visit and telephone contact was not possible, an invitation letter was left at the residence together with survey information and the contact number of the researchers. Interviews were used to collect medical data on current obstetric history, demographic data, history of current morbidities, lifestyle, and family history of CVD. Clinical evaluation was carried out via the collection of anthropometric and laboratory variables by trained investigators using a verification protocol defined in accordance with national consensus [13,14].

Endothelial function was verified by measuring flow-mediated dilatation (FMD) in the right brachial artery with the patient lying comfortably with abduction of the right arm and supination of the hand in order to expose the anteromedial side of the arm to the examiner. The test was conducted in a softly lit, silent room, after a rest of at least 20 minutes. A 10-MHz linear probe of a GE Healthcare Logiq P6 (General Electric Company, Hatfield, UK) ultrasound instrument was placed on the medial side of the arm, longitudinally and perpendicular to the skin, 5 cm above the antecubital crease, sounding the brachial artery and directly adjacent to the biceps muscle. Seven zones were identified corresponding to the 2 middle-adventitia interfaces, the 2 intimal regions, the 2 medium regions, and the luminal of the artery, confirming that the transducer was at the center of and perpendicular to the vessel [15]. The luminal diameter was measured in the center of the vessel at the time corresponding to end diastole; this was considered the basal diameter (D1) [16].

After verification of the basal diameter, the skin was marked with a pen at the position of the transducer when making the measurement. The sphygmomanometer's cuff was positioned on the ipsilateral forearm, the pressure was adjusted to 250 mm Hg, and this occlusion was maintained for 5 minutes. The post-occlusion diameter (D2) was measured, using the same standards described above, 60 seconds after removal of the cuff because this was considered to be the moment of maximum hyperemia. The FMD value was obtained from the following calculation: FMD (%) = [(D2 – D1)/D1] × 100. The FMD was considered normal when greater than or equal to 10% and abnormal when less than 10%, in accordance with the criteria of Celermarjer et al. [17].

In an attempt to decrease interobserver variations, all of the tests were performed by the same examiner who was blind to the patient's pregnancy history during the test; only 1 test was performed for each patient.

The data collected were tabulated and analyzed via Stata version 18.0 (StataCorp, College Station, Texas, USA). For the analysis, only patients with complete clinical evaluation at the end of the protocol (anthropometry, laboratory, and FMD analysis) were included. The mean ± SD of clinical and metabolic variables was calculated, and the Kolmogorov–Smirnov test was used to test the normality of the variables. Student *t* test was used to analyze the differences between the 2 groups for variables with normal distributions, and the Mann–Whitney test was used for data with non-normal distributions. Pearson χ^2 test or Fisher exact test was used for categorical data. A *P* value of less than 0.05 was considered significant.

The crude relative risk (RR) was calculated for variables that showed significance in the primary analysis ($P < 0.05$). Variables for which the 95% confidence interval (CI) did not include unity were included in a multiple logistic regression and presented as the adjusted RR and 95% CI. A logistic regression model was used to assess the dependent variable (FMD) as a function of the variables that were significant in the initial evaluation via a backward stepwise approach and the Wald statistic at a 5% significance level.

3. Results

The study included 60 women: 30 in the group with a history of PIH and 30 in the group without a history of PIH. Fig. 1 shows the identification and recruitment of women for the study. Among the 30 patients in the PIH group, 13 (43.3%) had severe pre-eclampsia, 9 (30.0%) had mild pre-eclampsia, 3 (10.0%) had chronic arterial hypertension (CAH), 2 (6.7%) had gestational hypertension, 2 (6.7%) had pre-eclampsia superimposed on CAH, and 1 (3.3%) had eclampsia in their index pregnancy.

Patient records were used to gather data on clinical and maternal obstetric characteristics in a follow-up period ranging between 10 and 20 years with a mean of 15.2 ± 3.5 years (Table 1). There was no significant difference in the follow-up period between the 2 groups ($P = 0.94$). The mean age of women at the index delivery was 26.2 ± 7.7 years. Overall, 76.7% of the study women were non-white. There was no significant difference in ethnicity between the 2 groups ($P = 0.76$).

The follow-up clinical and obstetric patient characteristics, and the anthropometric and metabolic variables obtained through physical assessment and laboratory tests are given in Table 2. The women's current age ranged from 28 to 61 years (mean 41.3 ± 8.8 years); there was no difference in age between the 2 groups.

In terms of the diagnosis of current conditions and/or treatments in progress, 40% of women reported at least 1 diagnosed disease (26.7% in the PIH group versus 53.3% in the no-PIH group, $P = 0.06$). CAH was the most frequent disease, being reported by 15 (25.0%) patients either in association with other pathologies or not. Diabetes mellitus type 2 (DM2) was the second most reported disease (8 cases; 13.3%). Statistical analysis showed that there was a significant difference in the diagnosis of CAH ($P = 0.001$) and type 2 diabetes ($P = 0.002$) between the 2 groups.

There were 3 cardiovascular events among women with a history of PIH and 0 among women with no history of PIH, but the difference was not significant. However, statistical differences were found in the risk factors for these events. There was a significant difference in the use of antihypertensive drugs: 10% in the no-PIH group were using antihypertensive drugs, compared with 36.7% in the PIH group ($P = 0.03$). Overall, the use of hypoglycemic agents was reported by 13.3% of the women.

Body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) ranged from 19.7 to 46.9 (mean 29.9 ± 4.9). There was a significant difference between the 2 groups ($P = 0.03$). Women in the PIH group had a higher mean systolic blood pressure (SBP) ($P = 0.03$). Similarly, LDL cholesterol and fasting glucose were higher in the group of women with a history of PIH (both $P = 0.02$). The percentage dilation of the brachial artery after reactive hyperemia ranged between 0% and 40% (mean 12.4% ± 7.9%). Dilation values were significantly lower in the group of women with a history of PIH than in the group without PIH (10.0% ± 6.8% versus 14.8% ± 8.3%, $P = 0.01$).

When categorized by the presence of endothelial dysfunction (FMD <10%), the PIH group showed a significantly higher frequency of dysfunction (RR, 4.12; 95% CI, 1.4–12.2). After smokers and users of anticoagulants (factors known to alter endothelial function) were excluded, the difference remained significant (RR, 4.74; 95% CI, 1.5–15.1; $P = 0.01$).

To verify the influence of the factors that differed significantly between the groups and might be associated with endothelial dysfunction (BMI, SBP, LDL cholesterol, and glucose), multiple logistic regression was carried out via a backward stepwise approach and the Wald statistic. None of BMI, SBP, LDL, and glucose contributed significantly to variations in the prevalence of alterations of FMD; in other words,