ORIGINAL ARTICLE

Endothelial function and uterine perfusion in subsequent pregnancies complicated by preeclampsia

Função endotelial e perfusão uterina e em gestações subsequentemente complicadas por pré-eclâmpsia

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ABSTRACT

Introduction: the pathophysiology of preeclampsia (PE) is based on a deficiency in the process of placentation associated with systemic maternal endothelial dysfunction. The investigation on the occurrence of these phenomena before the onset of PE clinical manifestations can become a new diagnostic method for its prediction. **Objectives:** to compare the process of placentation and endothelial function in pregnant women at high-risk for PE development, correlating these findings with its further development. **Patients and methods:** 74 pregnant women underwent flow-mediated dilation (DFM) of the brachial artery and Doppler flowmetry of uterine arteries to assess endothelial function and placentation process, respectively. The examinations were performed between 16 and 20 weeks of gestation and patients were followed until the postpartum period. **Results:** 15 patients had pregnancies complicated by PE and 59 remained normotensive until the postpartum period. Patients who subsequently developed PE presented high values of pulsatility index in uterine arteries ($p < 0.001$), between 16 and 20 weeks gestation, however, the analysis of DFM did not show difference compared to patients who remained normotensive. **Conclusion:** The observed data suggest that deficiency in the placentation process chronologically precedes the clinical manifestations of PE, which does not occur with endothelial dysfunction.

Key words: Pre-Eclampsia; Pregnancy Complications; Endothelium; Hypertension, Pregnancy-Induced.

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RESUMO

Introdução: *a fisiopatologia da pré-eclâmpsia (PE) baseia-se em deficiência no processo de placentação, associada à disfunção endotelial sistêmica materna. A investigação da ocorrência desses fenômenos, antes do aparecimento das manifestações clínicas da PE, pode constituir-se em novo método propedêutico para sua predição.* ***Objetivos:*** *comparar o processo de placentação e a função endotelial de gestantes de alto risco para desenvolvimento de PE, correlacionando esses achados com o seu desenvolvimento posterior.* ***Pacientes e métodos:*** *74 gestantes foram submetidas ao exame de dilatação fluxomediada (DFM) da artéria braquial e dopplerfluxometria das artérias uterinas para avaliação da função endotelial e do processo de placentação, respectivamente. Os exames foram realizados entre 16 e 20 semanas de gestação e as pacientes foram acompanhadas até o puerpério.* ***Resultados:*** *15 pacientes tiveram a gestação complicada por PE e 59 mantiveram-se normotensas até o puerpério. Pacientes que subsequentemente desenvolveram PE apresentaram, entre 16 e 20 semanas de gestação, maiores valores no índice de pulsatilidade das artérias uterinas ($p < 0,001$), mas a análise da DFM não apresentou diferença em relação às pacientes que se mantiveram normotensas.* ***Conclusão:*** *os dados observados sugerem que a deficiência no*

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processo de placentação precede cronologicamente as manifestações clínicas de PE, o que não ocorre com a disfunção endotelial.

Palavras-chave: Pré-Eclâmpsia; Complicações na Gravidez; Endotélio; Hipertensão Induzida pela Gravidez.

INTRODUCTION

The hypertensive disorders of pregnancy are extremely feared clinical complications due to their high potential for mortality and morbidity. Pre-eclampsia (PE) complicates 5-7% of pregnancies considered of normal risk, and its incidence reaches up to 20% in pregnancies of high-risk development.[1-3]

The pathophysiological mechanisms underlying the PE clinical manifestations are the cause of intense scientific production. It is postulated today that the early impairment of placental differentiation provides a localized hypoxic environment with release of placental debris damaging the maternal vascular endothelium.[4-6] The generated endothelial dysfunction, in turn, further compromises placental perfusion, increasing the present hypoxia and creating a perpetuating pathophysiological mechanism that ends only with the total removal of the placenta. The endothelial lesion is the cause of the loss of control of arterial tone culminating with the rise of maternal systemic blood pressure. The renal endothelial lesion occurs subsequently leading to glomeruloendotheliosis and proteinuria.[7]

The clinical methods of assessing these pathophysiological processes are of great interest in the medical practice because they allow monitoring the evolution of PE or predicting the onset of clinical manifestations, given that they occur chronologically. The assessment of placental perfusion is done routinely by dopplerfluxometry of uterine arteries; the analysis of increased pulsatility index (PI-AUt) constitutes a more reliable parameter for predicting PE.[10,11] The brachial artery flux mediated dilation test (DFM) can be clinically used for the analysis of the endothelial function to measure arterial caliber variation that is secondary to the hypoxic stimulus.[12]

Considering the chronological occurrence of these pathophysiological events in relation to the clinical manifestations of PE, and having clinical tests available for their detection and evaluation, this study aimed to evaluate possible differences in IP-AUt and DFM values comparing pregnant women who developed PE with those who did not.

PATIENTS AND METHODS

Patients

A total of 74 patients were selected for this longitudinal study in the High-Risk Prenatal Service of the General Hospital, Federal University of Minas Gerais (HC-UFMG). Of these, 15 pregnant women developed PE up to two weeks after delivery and 59 did not. All patients selected for the study presented at least one of the following risk factors for developing PE: chronic systemic hypertension (17; 22.9%); pre-pregnancy diabetes mellitus (10; 13.5%); PE personal history in previous pregnancy (18; 24.3%); family history of PE (mother or sister) (14; 18.9%); high body mass index (defined as > 35 kg/m^2) (18; 24.3%).

The diagnosis of PE was performed according to the criteria defined by the National High Blood Pressure Education Program Working group on high blood pressure in pregnancy, 2000.[14] According to this classification, PE is defined as elevated blood pressure after 20 weeks of gestation (pressure levels ≥ 140/90 mmHg on two measurements with a six hour interval) accompanied by proteinuria (1+ or higher on the tape measured proteinuria or proteinuria 24> 0.3 g). The overlapping PE in patients with chronic hypertension was considered based on one of the following factors:

- a significant increase in systemic blood pressure (above 160x110 mmHg);
- massive proteinuria (more than 2.0 g in 24 hours);
- a significant increase in blood pressure levels after a period of good control;
- serum creatinine values above 1.2 mg/dL.

After regular prenatal medical consultations between 16^{+0} weeks and 19^{+6} weeks of gestation, the patients were invited to participate in this study. This study was approved by the Research Ethics Committee of the HC-UFMG. Patients selected to participate were informed about the study at the time of recruitment and signed the free and informed consent. After consenting, they were submitted to the brachial artery flux mediated dilation and dopplerfluxometry of uterine arteries exams.

Fluxomediated brachial artery dilation

The technique of evaluating the brachial artery flux mediated dilatation (DFM) was performed using the ultrasound device with color Doppler, SONOACE 8800®

– Medson Co, Ltd, with a linear probe of 4 to 8 mHz. Patients were put at rest for 15 minutes in the supine position; blood pressure was measured in all pregnant women, and the brachial artery was identified medially in the antecubital fossa of the dominant upper limb. The vessel image was obtained approximately at 5 cm in the upper limb from the elbow with a longitudinal cut (B mode) during the moment of least vessel distension corresponding to the cardiac diastole, and obtained from the rescue of images by the equipment's "cine loop". This was frozen to obtain the average of three measurements in the vessel caliber (D1). After this first measurement, the blood pressure cuff was positioned distally (forearm) to the brachial artery measurement site and inflated for 5 min to a pressure higher than 250 mmHg and subsequently slowly deflated. The average of three new measurements of vessel caliber was obtained with the technique described above after 1 min of cuff deflation (D2). The DFM value was obtained through the following formula: DFM (%) = [(D2 - D1)/D1] × 100, where D1 = basal diameter and D2 = post-occlusion diameter. All examinations were performed by the same HC-UFMG professional, who was trained and certified in ultrasonography.

Dopplerlfuxometry of uterine arteries

The color doppler of uterine arteries was performed by a trained examiner who was blinded to the clinical information of patients. The Medison 8800 high-resolution color doppler with a convex probe with 3.5 mHz frequency was used in the exams. The examinations were performed with the patient in the supine position, with an average duration of 5 min. The insonation of arteries was made in their proximal third, with a maximum angle of 60°. The IP calculation in the uterine arteries was obtained from a wave, similar to at least three other symmetrical waves found. The pro-diastolic notch was also observed. The average IP of uterine arteries was calculated using the simple arithmetic average of IP values in the left and right uterine arteries.

Statistical analysis

The continuous data normality was verified with the Shapiro-Wilk test. The Student t-test was used to compare variables with normal distribution between the groups of patients who developed PE or not. The Pearson chi-square test compared categorical variables and the Mann-Whitney T test compared continuous variables without normal distribution. The statistical significance was set at $p < 0.05$. The analyses were performed in the SPSS®19 Software (SPSS Inc., Chicago, IL, USA).

RESULTS

Out of the 74 women who participated in the study, 15 developed PE, six in the early form of presentation (clinical manifestations before 34 weeks of gestation) and nine in the late form (after 34 weeks).

The demographic data and test results of the two groups (development of PE versus no PE) are shown in Table 1.

Between the 16^{+0} and 19^{+6} weeks of gestation, the group of patients who developed later PE showed higher IP-AUt average compared to the group that did not develop PE ($p < 0.001$). However, there was no difference regarding the average value of DFM between the two groups.

DISCUSSION

In order to prevent or minimize the complications of PE, it is essential to have a better understanding of the pathophysiological mechanisms that culminate in the syndrome clinical manifestations. The maternal endothelial lesion has been demonstrated in patients with clinical diagnosis of PE, both in its early form (before 34 weeks of gestation) and in its late form (after 34 weeks).[15] The impaired uterine perfusion is known as an early event in the pathophysiology of PE, demonstrated since the first gestational trimester.[15-17]

This study brings an important contribution demonstrating that impaired placental perfusion can be detected by the dopplerfluxometry of uterine arteries predicting increased risk of developing PE in high-risk pregnancies that are followed-up.

This phenomenon has been demonstrated even at earlier gestational ages, at the end of the first trimester, as reported by Plasencia et al.[11] and Gomez et al.[18] Reduced DFM values at the end of the second trimester was verified[19] in order to predict the clinical manifestations of PE. The combination of dopplerfluxometry of uterine arteries and DFM was demonstrated by Savvidou et al.,[20] proving to differentiate women with later development of PE and CIUR, corroborating the pathophysiological association of both entities.

Table 1 - Clinical characteristics and ultrasonography exams in patients divided into the studied groups

	Patients without Pre-eclampsia (n = 59)	Patients with Pre-eclampsia (n = 15)	P value
Maternal age (years)	29.7 ± 6.4	30.1 ± 4.2	0.76**
Body Mass Index (kg/m²)[1]	24.9 ± 6.5	27.5 ± 6.7	0.20**
Obese	*17 (14%)*	*4 (22%)*	*0.24****
Non-obese	*42 (86%)*	*11 (78%)*	
Number of pregnancies (median, range)	2 (1 – 8)	3 (1 – 6)	0.14**
Primigravidae	*24 (41%)*	*7 (47%)*	*0.17****
> 1 pregnancy	*35 (59%)*	*8 (53%)*	
Etnia[2]			
Caucasian	*14 (24%)*	*4 (27%)*	*0.42****
African-American	*13 (22%)*	*3 (20%)*	
Others	*32 (54%)*	*8 (53%)*	
Gestational age when examined (weeks)	17.5 ± 1.3	17.0 ± 1.3	0.142*
Mean Arterial Pressure when examined (mmHg)	89.7 ± 8.5	94.0 ± 5.2	0.020*
Average IP of uterine arteries between 16 and 20 weeks	1.05 ± 0.23	1.39 ± 0.14	0.000*
Basal diameter of the Brachial Artery 16-20 weeks	3.37 ± 0.47	3.47 ± 0.48	0.489*
Flux-mediated brachial artery dialation (%) 16-20 weeks	5.66 ± 3.31	3.93 ± 3.05	0.067*

* Student's t-test, ** Mann-Whitney U test, *** Chi-square test.
[1] Obesity defined as body mass index greater than 30 kg/m².
[2] Ethnicity self-declared by the patient at the time of recruitment for the study.

In this study, no difference in DFM values between the two evaluated groups was observed, suggesting that in the evaluated gestational age, the endothelial lesion has not possibly occurred yet, being similar in women with or without subsequent development of PE. The possible explanations for this fact are based on the precept that the systemic endothelial lesion succeeds the deficiency of the placentation process in the chain of pathophysiological events that characterize PE.

In conclusion, these results demonstrate that a deficient placental perfusion chronologically precedes the systemic endothelial dysfunction in the PE development process.

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