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Longitudinal evaluation of uterine perfusion, endothelial function and central blood flow in early onset pre-eclampsia

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ABSTRACT

Objectives: Physiopathological mechanisms that trigger clinical manifestations in pre-eclampsia (PE) remain unclear, and management is still a challenge. The identification of tools to predict the onset of the disease and prevent its complications is of great interest in medical practice. The present study aims to evaluate uterine perfusion, endothelial function and central nervous system blood flow in pregnant women with high-risk factors for PE, for comparison of the results between the group of patients who developed early onset PE and those who remained normotensive throughout pregnancy.

Study design: Sixty-two patients were recruited from our high-risk prenatal service, and followed throughout gestation. Patients were submitted to flow-mediated dilation, Dopplervelocimetry of uterine arteries and Dopplervelocimetry of ophthalmic arteries at three distinct moments of pregnancy: between 16 + 0 and 19 + 6 weeks, between 24 + 0 and 27 + 6 weeks and at hospital admission to delivery.

Main outcome measures: Pulsatility index of uterine arteries, flow-mediated dilation and ophthalmic arteries resistance index were evaluated and compared between the two groups of patients.

Results: Ten pregnancies were complicated by early onset PE, and these patients presented a significantly higher pulsatility index of uterine arteries between 16 + 0 and 19 + 6 weeks of gestation, compared with the normotensive group ($p = 0{,}016$). Both flow-mediated dilation and ophthalmic arteries resistance index values were lower in affected patients at 24 + 0 to 27 + 6 weeks ($p = 0{,}001$), and by the time of delivery ($p < 0{,}002$).

Conclusions: Those findings suggest that impaired placental perfusion, endothelial dysfunction and central hyperperfusion temporarily precede the clinical manifestations of early onset pre-eclampsia.

1. Introduction

Hypertensive disorders in pregnancy remain to be one of the most important obstetric complications, accounting for nearly 18% of all maternal deaths worldwide. Pre-eclampsia (PE) is a particularly feared clinical complication, due to its high potential for mortality and morbidity. It complicates up to 7% of 'low risk' pregnancies and it's incidence reaches up to 20% in high-risk pregnancies [1,2,3].

The physiopathological mechanisms that trigger the clinical symptoms of PE are not yet fully elucidated, and etiology of the syndrome remains unclear [4,5]. The most widely accepted theory postulates that a compromised process of trophoblast differentiation creates a localized hypoxic environment, leading to a physiological response that culminates with the release of several factors that are hazardous to the systemic vascular endothelium [6]. When kidney endothelial injury occurs, there is the appearance of glomerular-endotheliosis and proteinuria [7]. If the arterial bed of the Central Nervous System (CNS) has its endothelium compromised, the barrier capacity of regulating blood flow is lost, resulting in cerebral edema. The increase in neuron cytoplasm pressure is responsible for the seizures that characterize eclampsia [8,9].

Considering the precedence of these chronological events in relation to the clinical manifestations of PE and the availability of clinical tests for their detection and evaluation, it is reasonable to assume that they could represent a promising tool to predict the onset of preeclampsia and prevent its major complications. Placental perfusion is routinely assessed by dopplervelocimetrical study of uterine arteries, and an increase in the Pulsatility Index of Uterine Arteries (PI-UtA) has shown to be the most reliable predictor of PE, considering the Doppler parameters [10,11]. Endothelial function can be evaluated trough the Flow-Mediated Dilation (FMD) of the brachial artery [12], and perfusion of the CNS can be indirectly assessed by ophthalmic artery

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Dopplervelocimetry. Ophthalmic Artery Resistance Index (OARI) has shown to best reflect central hemodynamic conditions [13].

The objective of this study is to evaluate possible differences in the values of PI-UtA, FMD and OARI throughout gestation between a group of women who subsequently developed PE and a group of patients with fully healthy pregnancies.

2. Methods

Patients were recruited for this longitudinal study at the High-risk Prenatal Service of Hospital das Clínicas, Federal University of Minas Gerais (HC-UFMG). Inclusion criteria were the presence of risk factors for PE development [14] and gestational age between 16 + 0 and 19 + 6 at first prenatal appointment. Therefore, we included patients with history of PE in previous pregnancies, family history of PE, multiple pregnancies or primiparous women. Patients with chronic arterial hypertension, pre-gestational diabetes or other conditions linked with endothelial dysfunction were also included.

After the regular prenatal consultation between 16 + 0 and 19 + 6 weeks of gestation, patients were invited to participate in this study. The study was approved by the Ethics and Research Committee of HC-UFMG. The patients selected to participate in the study were informed about it at the time of recruitment and signed the Free and Informed Consent Term.

Patients were submitted to Dopplervelocimetry of uterine artery, FMD of the brachial artery and Dopplervelocimetry of ophthalmic arteries at three distinct moments of pregnancy: between 16 + 0 and 19 + 6 weeks, between 24 + 0 and 27 + 6 weeks and right before delivery. All three examinations were performed by the same professional from HC-UFMG, trained and certified in ultrasonography.

The diagnosis of PE was performed according to the criteria set by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000 [15]. According to this protocol, PE is defined as elevated blood pressure after 20 weeks of pregnancy (BP ≥ 140 × 90 mmHg in two measurements with an interval of 6 h), accompanied by proteinuria (1 + or more at proteinuria tape or 24-h proteinuria > 0.3 g/24 h). Classification criteria adopted was gestational age at diagnosis, and PE was categorized as early onset if established before 34 weeks of gestation.

2.1. Doppler velocimetry of uterine arteries

The Doppler velocimetry of uterine arteries was performed with a convex probe with 3.5 MHz frequency. The arteries were insonated in their proximal third, with a maximum angulation of 60°. The calculation of the pulsatility index (PI) of the uterine artery was made from a wave similar to at least other three symmetrical waves. The presence of protodiastolic notch was also observed. The mean PI of uterine arteries was calculated using the simple arithmetic mean between the PI values of the left and right arteries.

2.2. Flow-mediated dilation of the brachial artery

The evaluation technique of the FMD of the brachial artery was performed using color Doppler ultrasonography equipment (SonoAce ® 8800 – MedsonCo, Ltd.), with a linear probe of 4–8 MHz. Patients were asked to rest for 15 min in the supine position and BP was measured. The brachial artery was identified medially in the antecubital fossa of the dominant upper limb. An image of the vessel was obtained at approximately five centimeters from the elbow, using the longitudinal mode (B) during the time of the least vessel distension. That corresponds to the cardiac diastole, and was obtained by rescue of images by the machine cine loop. The image was frozen for determination of the mean of three measurements of vessel caliber (D1).

After this first measurement, the sphygmomanometer cuff was placed distally (on the forearm) to the site of measurement of the brachial artery. It was insufflated for 5 min until a pressure higher than 250 mmHg was achieved, and then deflated. The mean of three new measurements of vessel caliber was obtained by the technique described above, one minute after cuff deflation (D2). The value of the FMD was obtained by the following formula: FMD (%) = [(D2 − D1)/D1] × 100, where D1 = basal diameter and D2 = post-occlusion diameter.

2.3. Doppler velocimetry of ophthalmic arteries

Orbital color Doppler was obtained by a trained examiner who was blinded to patient clinical information. The examinations were performed using a high-resolution color Doppler (Medison 8800) with a linear transducer of 7.5 MHz, applied to closed eyes covered with methylcellulose gel. The examinations were performed with the patient in the supine position, with an average duration of 5 min. A complete assessment of the orbit vessels was obtained, and the ophthalmic artery and its branches were identified. The Dopplervelocimetry of the ophthalmic artery was performed in its anterior branch, approximately 10 mm from the posterior wall of the sclera, at nasal location relative to the optic nerve. The OARI was obtained from the right eye of patients after one cycle of at least three similar consecutive waves.

2.4. Statistical analysis

Normality test was performed with Shapiro-Wilk test for continuous data. T-Student's test was used to compare data with normal distribution between groups of patients who did and did not develop pre-eclampsia. The chi-square Pearson test was applied to compare categorical variables between the two groups. Mann-Whitney's test was performed to compare continuous non-normally distributed data. We applied Wilcoxon test to compare data within each of the groups. Differences were considered significant when $p < 0,05$.

Analyses were performed through the Software *Statistical Package for Social Sciences – SPSS®19* (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 62 patients were recruited and completed all ultrasound evaluations proposed for the follow up. Patient distribution according to risk factors presented at enrollment is shown in Table 1.

Ten pregnancies (16%) were complicated by early onset PE (clinical manifestations before 34 weeks of gestation), according to the established criteria [16,17], and 52 (84%) pregnant women remained normotensive and were not diagnosed with any other gestational disorder up to two weeks after delivery. The group of patients who developed PE and the control group did not differ on age, body mass index, number of gestations and gestational age at evaluations.

All patients diagnosed with PE presented features of severe illness (blood pressure of 160 × 110 mmHg or higher, proteinuria of 3 g in 24-h or higher, oliguria, neurologic or visual symptoms, epigastric or right upper quadrant pain, pulmonary edema, thrombocytopenia, impaired liver function, high serum creatinine, fetal growth restriction and/or

Table 1
Patient distribution according to risk factors presented.

Risk factor	Number of patients (%)
Chronic arterial hypertension	12 (19.4)
Pregestational diabetes	9 (14.5)
PE in previous pregnancy	18 (29)
Primiparous	11 (17.7)
Family history of PE (mother or sister)	5 (8.1)
Body mass index > 35 kg/m^2	4 (6.5)
Multiple gestation	2 (3.2)
History of thromboembolism	1 (1.6)
Total	62 (100)