

# Endothelial function and uterine perfusion and 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 pre-eclampsia (PE) is based on a deficiency in the placenta formation process, associated to systemic maternal endothelial dysfunction. The occurrence of these phenomena before the appearance of the clinical manifestations of PE should be investigated, considering that new propaedeutic methods are available for prediction. **Objective:** to compare placenta formation process and endothelial function of high-risk pregnant women and correlate them with the occurrence of PE. **Patients and methods:** 74 pregnant women were subjected to flow mediated dilation (FMD) of the brachial artery and Doppler flux of uterine arteries to assess the endothelial function and the placenta formation process, respectively, between the 16th and 20th gestation weeks and followed until the puerperal period. **Results:** 15 patients had their pregnancies complicated by PE while 59 remained normotensive until the puerperium. Patients who subsequently developed PE showed, between gestation weeks 16 and 20, high scores in the pulsatility index for uterine arteries ( $p < 0.001$ ), but the FDM analysis presented no difference in relation to the patients who continued normotensive. **Conclusion:** data suggest that deficiencies in the placenta formation process chronologically precedes the clinical manifestation of PE, which does not occur with endothelial dysfunction.

**Key words:** Pre-Eclampsia; Laser-Doppler Flowmetry; Endothelium, Vascular.

### RESUMO

**Introdução:** a fisiopatologia da pré-eclâmpsia (PE) baseia-se em deficiência no processo de placentação, associada à disfunção endotelial sistêmica materna. É preciso investigar a ocorrência desses fenômenos antes do aparecimento das manifestações clínicas da PE, considerando a disponibilidade de novos métodos propedêuticos de sua predição. **Objetivos:** comparar o processo de placentação e a função endotelial de gestantes de alto risco e os correlacionar com o desenvolvimento ou não da PE. **Pacientes e métodos:** 74 gestantes foram submetidas à dilatação fluxomediada (DFM) da artéria braquial e dopplerfluxometria de artérias uterinas para avaliação da função endotelial e do processo de placentação, respectivamente; entre 16 e 20 semanas de gestação e 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, elevados 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 sugerem que a deficiência no processo de placentação precede cronologicamente as manifestações clínicas de PE, o que não ocorre com a disfunção endotelial.

**Palavras-chave:** Pré-Eclâmpsia; Fluxometria por Laser-Doppler; Endotélio Vascular.

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## INTRODUCTION

Hypertensive disorders of pregnancy are extremely worrying clinical complications due to their high potential of lethality and morbidity. Preeclampsia (PE) complicates 5 to 7% of gestations considered of usual risk, with incidence rates of up to 20% in gestations considered of high risk for its development.<sup>1-3</sup>

The physiopathological mechanisms underlying the clinical manifestations of PE constitute a topic of great scientific interest nowadays. It is postulated that the early compromise of differentiation processes creates a local hypoxic environment, which releases placental residue that is harmful to the mother's vascular endothelium.<sup>4-6</sup> The endothelial dysfunction generated further compromises placental perfusion, increasing the hypoxia already in place, which is perpetuated and only solved by completely removing the placenta. Endothelial lesions are the cause of loss of control of the arterial tonus, which culminates in an elevation of the mother's blood pressure levels. Later, renal endothelial damage ensues, leading to glomerular endotheliosis and proteinuria.<sup>7,8,9</sup>

There is great interest in the development of clinical methods for evaluating these physiological processes and make following the progression of PE or predicting the appearance of its clinical manifestations possible, considering its chronological precedence. Evaluation of placental perfusion is done routinely through laser-Doppler flowmetry of the uterine arteries, and in its analysis an increased pulsatility index (UtA-PI) became the most reliable parameter to predict PE.<sup>10,11</sup> Analysis of endothelial functions can be made using flow-mediated dilation (FMD) of the brachial artery, which measures the variation in arterial caliber secondary to a hypoxic stimulus.<sup>12,13</sup>

The objective of this study, which considers the chronological precedence of the physiopathological events in relation to the clinical manifestations of PE and has clinical tests available for detecting and evaluating it, is to investigate differences in the UtA-PI and the FMD values of pregnant women who later developed or did not develop PE.

## PATIENTS AND METHODS

### Patients

Seventy-four pregnant women were selected in the high-risk prenatal care service at Hospital das Clínicas

(HC) da Universidade Federal de Minas Gerais for this longitudinal study. Of this total, 15 pregnancies were complicated by PE and 59 were not diagnosed with PE until two weeks after birth. All patients selected for the study showed at least one of the following risk factors for developing PE: chronic hypertension (17; 22.9%); pregestational diabetes mellitus (10; 13.5%); history of PE in a previous pregnancy (18; 24.3%); family history (mother or sister) of PE (14; 18.9%); high body mass index (defined as  $> 35 \text{ kg/m}^2$ ) (18; 24.3%).

PE diagnosis was made in accordance with the criteria defined by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy<sup>14</sup>, characterized by the elevation of arterial pressure after 20 weeks of gestation (blood pressure levels  $\geq 140 \times 90 \text{ mmHg}$  in two measurements with an interval of six hours), followed by proteinuria (1+ or more in the measurement of dipstick proteinuria or 24-hour proteinuria  $> 0.3\text{g}$ ). Superposition of PE for patients with chronic arterial hypertension was considered in the presence of the following factors: a) significant increase in blood pressure levels (above  $160 \times 110 \text{ mmHg}$ ); b) massive proteinuria (more than 2.0 grams in 24 hours); c) significant increase of blood pressure levels after effective control period; d) serum creatinine in amounts higher than 1.2 mg/dL.

After the regular prenatal medical appointments between 16<sup>+0</sup> and 19<sup>+6</sup> gestational weeks, patients were invited to participate in this research. The study was approved by the HC Research Ethics Committee. The women selected to participate in the study were informed of that at the moment of recruiting and signed the informed consent form. After that, they underwent flow-mediated dilation of the brachial artery and laser-Doppler flowmetry of the uterine arteries.

### Flow-mediated dilation of the brachial artery

Flow-mediated dilation (FMD) for evaluation of the brachial artery is a technique that uses ultrasonography equipment with color Doppler SONOACE 8800@ – MedsonCo, Ltd, with a linear probe of 4 to 8 mHz. The patients rested for 15 minutes in dorsal decubitus. Blood pressure of all pregnant women was measured and the brachial artery was identified medially in the antecubital fossa of the dominant upper limb. An image of the vessel was obtained at approximately 5 cm from the elbow and a longitudinal cut (B mode) was made at the moment the vessel was least distended,

which corresponds to the cardiac diastole. The image was obtained from the image retrieval system in the equipment's cine loop and frozen so as to obtain the average of three measures of the vessel's caliber (D1). After this first gauging, the sphygmomanometer inflatable cuff was positioned distally (in the forearm) in relation to the position of the brachial artery's measurement and inflated for five minutes until the pressure was higher than 250 mmHg, and then the pressure was slowly released. The average of three new measures of the vessel's caliber was obtained through the same technique described, after a minute of deflating the cuff (D2). The value of the FMD was obtained based on the following formula:  $DFM (\%) = [(D2 - D1)/D1] \times 100$ , in which D1 = basal diameter e D2 = diameter post-occlusion. The tests were carried out by the same HC staff, trained and certified in ultrasonography.

### Laser-Doppler flowmetry of the uterine arteries

Color Doppler of the uterine arteries was performed by a trained examiner, who was not aware of the patient's clinical information. The tests were made using a high-resolution color Doppler Medison 8800, with a 3.5 MHz frequency convex probe. Patients rested in dorsal decubitus for approximately five minutes. The insonation of the arteries was made in the proximal third, with a maximum angulation of 60°. The calculation of the uterine arteries' pulsatility index (PI) was made from a wave similar to at least three other symmetric waves found. The protodiastolic notch was also observed. The average PI of the uterine arteries was calculated through simple arithmetic mean between the PI values of left and right uterine arteries.

### Statistical analysis

The normality of the continuous data was verified using the Shapiro-Wilk test. Student's t-test was used to compare the variables with normal distribution between the groups of patients that developed PE or not. Pearson's Chi-squared test was used to compare categorical variables, and the Mann-Whitney U test to compare the continuous variables without normal distribution. Statistical significance was set at  $p < 0.05$ . The analyses were made in the SPSS<sup>®</sup>19 (SPSS Inc., Chicago, IL, USA) software.

## RESULTS

Of the 74 pregnant women, 15 developed PE, six of them in the early form (clinical manifestations before 34 gestational weeks) and nine in the late form (after 34 weeks).

Table 1 shows the demographic data and test results of the two groups (development of PE versus non-development of PE).

Between 16<sup>+0</sup> and 19<sup>+6</sup> gestational weeks, the group of patients that would later develop PE displayed a higher average in the UtA-PI when compared to the group that did not develop PE ( $p < 0.001$ ). There was no difference between the two groups regarding the FDM average values.

## DISCUSSION

With the aim of preventing or minimizing PE complications, it is essential to have a better understanding of the physiopathological mechanisms that result in the clinical manifestations of the syndrome. Endothelial lesions were found in patients with a clinical diagnosis of PE, in both its early (before 34 weeks of gestation) or late forms (after 34 weeks of gestation).<sup>15</sup> Compromised uterine perfusion is known to be an early event in the physiopathology of PE, displayed since the first gestational trimester.<sup>15-17</sup>

This study brings an important contribution by showing that in duly followed high-risk pregnancies, jeopardy of placental perfusion can be detected by laser-Doppler flowmetry of the uterine arteries, thereby predicting increased risk of developing PE.

This phenomenon was already demonstrated also in earlier gestational ages, at the end of the first gestational trimester.<sup>11,18</sup> Reduction of FDM values at the end of the second trimester has also been shown<sup>19</sup> with the aim of predicting clinical manifestations of PE. The association of laser-Doppler flowmetry of uterine arteries and FDM<sup>20</sup> can distinguish pregnant women with later development of PE and IUGR, which corroborates the physiopathological association between the two entities.<sup>21</sup>

This study has not shown any difference between the FDM values in the two groups evaluated, which suggests that, at the gestational age studied, it is possible that the endothelial lesion still has not occurred and is similar in pregnant women with or without development of PE. Possible explanations for this fact are based on the precept that systemic endothelial lesions ensue a deficiency of the placentation process in the chain of physiopathological events that characterize PE.

**Table 1** - Clinical characteristics and ultrasound examinations of patients divided into two groups

	Patients without preeclampsia (n=59)	Patients with preeclampsia (n=15)	P-value
Maternal age (years)	29,7 ± 6,4	30,1 ± 4,2	0,76**
Body Mass Index (kg/m <sup>2</sup> )	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 gestations (average, limits)	2 (1 – 8)	3 (1 – 6)	0,14**
First gestation	24 (41%)	7 (47%)	0,17***
> 1 gestation	35 (59%)	8 (53%)	
<b>Ethnicity<sup>2</sup></b>			
Gestational age when examined (weeks)	17,5 ± 1,3	17,0 ± 1,3	0,142*
Average blood pressure when examined (mmHg)	89,7 ± 8,5	94,0 ± 5,2	0,020*
Average uterine artery PI between 16 and 20 weeks	1,05 ± 0,23	1,39 ± 0,14	0,000*
Basal diameter of brachial artery 16-20 weeks	3,37 ± 0,47	3,47 ± 0,48	0,489*
Flow-mediated dilation of the brachial artery (%) 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 is defined as body mass index higher than 30 Kg/m<sup>2</sup>.

2- Ethnicity declared by patient when recruited for the study.

## CONCLUSION

Deficient placental perfusions chronologically precede systemic endothelial dysfunctions in the process of developing PE.

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