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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DOI: 10.5935/2238-3182.20150064

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.

RESUMO

Introdução: a fisiopatologia da pré-eclâmpsia (PE) baseia-se em deficiência no processo de placentação, associada à distinção 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 dopplerflowmetria 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. Pácientes 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
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/m²) (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. 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 16th weeks and 19th 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 exam.

Fluxmediated 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"
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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 verified19 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.

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).
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.

REFERENCES


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

<table>
<thead>
<tr>
<th></th>
<th>Patients without Pre-eclampsia (n = 59)</th>
<th>Patients with Pre-eclampsia (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>29.7 ± 6.4</td>
<td>30.1 ± 4.2</td>
<td>0.76**</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24.9 ± 6.5</td>
<td>27.5 ± 6.7</td>
<td>0.20**</td>
</tr>
<tr>
<td>Obese</td>
<td>17 (14%)</td>
<td>4 (22%)</td>
<td>0.24***</td>
</tr>
<tr>
<td>Non-obese</td>
<td>42 (86%)</td>
<td>11 (78%)</td>
<td></td>
</tr>
<tr>
<td>Number of pregnancies (median, range)</td>
<td>2 (1 – 8)</td>
<td>3 (1 – 6)</td>
<td>0.14**</td>
</tr>
<tr>
<td>Primigravidae</td>
<td>24 (41%)</td>
<td>7 (47%)</td>
<td>0.17***</td>
</tr>
<tr>
<td>&gt; 1 pregnancy</td>
<td>35 (59%)</td>
<td>8 (53%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>14 (24%)</td>
<td>4 (27%)</td>
<td>0.42***</td>
</tr>
<tr>
<td>African-American</td>
<td>13 (22%)</td>
<td>3 (20%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>32 (54%)</td>
<td>8 (53%)</td>
<td></td>
</tr>
<tr>
<td>Gestational age when examined (weeks)</td>
<td>17.5 ± 1.3</td>
<td>17.0 ± 1.3</td>
<td>0.14*</td>
</tr>
<tr>
<td>Mean Arterial Pressure when examined (mmHg)</td>
<td>89.7 ± 8.5</td>
<td>94.0 ± 5.2</td>
<td>0.020*</td>
</tr>
<tr>
<td>Average IP of uterine arteries between 16 and 20 weeks</td>
<td>1.05 ± 0.23</td>
<td>1.39 ± 0.14</td>
<td>0.00*</td>
</tr>
<tr>
<td>Basal diameter of the Brachial Artery 16-20 weeks</td>
<td>3.37 ± 0.47</td>
<td>3.47 ± 0.48</td>
<td>0.489*</td>
</tr>
<tr>
<td>Flux-mediated brachial artery dialation (%) 16-20 weeks</td>
<td>5.66 ± 3.31</td>
<td>3.93 ± 3.05</td>
<td>0.067*</td>
</tr>
</tbody>
</table>

* 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.
