Original Article

Endothelial Function, Uterine Perfusion and Central Flow in Pregnancies Complicated by Preeclampsia

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Abstract

Background: The physiopathology of Preeclampsia (PE) is characterized by a deficiency in the process of placentation, systemic endothelial dysfunction and Central Nervous System (CNS) hyperflow. From a clinical point of view, it would be interesting to determine the occurrence of these phenomena before the onset of clinical manifestations of the disease, raising the possibility of new methods for predicting PE.

Objective: Compare the process of placentation, endothelial function and CNS hyperflow in pregnant women at high risk for the development of PE who subsequently developed or not the syndrome.

Methods: A total of 74 pregnant women underwent the Flow-Mediated Dilation (FMD) of the brachial artery, Doppler study of uterine and ophthalmic arteries for the assessment of endothelial function, process of placentation and central hyperflow, respectively. The examinations were performed between 24 and 28 weeks of gestation and were followed until the postpartum period for data collection.

Results: Fifteen patients had PE and 59 remained normotensive until the puerperium. Patients who subsequently developed PE had between 24 and 28 weeks of gestation, higher pulsatility index of uterine arteries and lower values of FMD (p < 0.001 and p = 0.001, respectively). However, there was no difference in the values obtained in the resistive index in the ophthalmic artery (p = 0.08).

Conclusion: The data obtained suggest that the deficiency in the process of placentation and endothelial dysfunction chronologically precede the clinical manifestations of PE, which does not occur with CNS hyperflow. (Arq Bras Cardiol 2012;99(4):931-935)

Keywords: Pre-Eclampsia / physiopathology; endothelium / abnormalities; pregnancy; high-risk; placentation; central nervous system / physiopathology.

Introduction

The hypertensive disorders of pregnancy account for a significant number of maternal and fetal deaths worldwide[1]. Particularly, Preeclampsia (PE) is a greatly feared clinical complication, due to its high potential for mortality and morbidity, complicating 5% to 7% of pregnancies considered to be low risk and of which incidence reaches up to 20% in high-risk pregnancies[2,3].

The physiopathological mechanisms that trigger the clinical symptoms of PE are not yet fully elucidated, and the syndrome etiology remains one of the great mysteries of Medicine[4,5]. The most widely accepted theory postulates that a defective process of trophoblastic invasion in the uterine spiral arteries creates a localized hypoxic environment, having as physiological response the release of several factors that are hazardous to the systemic vascular endothelium, including

reactive oxygen species (ROS)[6]. As these factors have a harmful effect on the mother's systemic arterial endothelium, the pregnant woman begins to show clinical manifestations of PE, the first one being the elevation in blood pressure levels. Subsequently, it is followed by kidney endothelial injury, leading to glomerular-endotheliosis and proteinuria[7].

When the arterial bed of the Central Nervous System (CNS) has the endothelium compromised, the barrier capacity to hyper blood flow is lost, resulting in cerebral edema. The increase in neuron cytoplasm pressure is responsible for tonic-clonic seizures that characterize eclampsia itself[8,9].

Methods of clinical evaluation of these physiopathological processes are of interest in medical practice, as they allow the monitoring of PE outcome or even predict the onset of its clinical manifestations, considering that they chronologically precede the manifestations. The assessment of placental perfusion is routinely done by Doppler study of uterine arteries, and during this his analysis, the increase in the Pulsatility Index of Uterine Arteries (PIUtA) has shown to be the most reliable in predicting PE[10,11].

For the analysis of endothelial function, the Flow-Mediated Dilation (FMD) assessment of the brachial artery can be used

clinically, which measures the alterations in arterial caliber secondary to a hypoxic stimulus[12]. The flow or perfusion of the CNS can be assessed indirectly by ophthalmic artery Doppler velocimetry and the Ophthalmic Artery Resistance Index (OARI) has been the most often used in studies as it best reflects central hemodynamic conditions[13].

Considering the antecedence of these chronological events in relation to clinical manifestations of PE and the availability of clinical tests for their detection and evaluation, the objective of this study is to evaluate possible differences in the values of PIUtA, FMD and OARI in a group of women who subsequently developed PE and a group of patients with pregnancies not complicated by PE.

Patients and methods

Patients

A total of 74 patients were recruited from the High-risk Prenatal Service of Hospital das Clinicas, Universidade Federal de Minas Gerais for this longitudinal study. Of this total, 15 pregnancies were complicated by PE and 59 pregnant women were not diagnosed with PE up to two weeks after delivery. All patients selected for the study had at least one of the following risk factors for the development of PE, according to the study by Duckitt[14]: chronic arterial hypertension (17, 22.9%), pre-gestational diabetes mellitus (according to criteria defined by the ADA in 2011[15]) (10, 13.5%), personal history of PE in previous pregnancies (18, 24.3%), family history of PE (mother or sister) (14, 18.9%), elevated body mass index (defined as >35 Kg/m²) (18; 24.3%).

Patients were considered as having CAH when they had been diagnosed as hypertensive before pregnancy, or when they had BP levels > 140x90 mmHg before the 20th week of gestation or those who remained hypertensive for at least 12 weeks after delivery. 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[16]. According to this classification, PE is defined as elevated blood pressure after 20 weeks of pregnancy (BP levels ≥ 140 x 90 mmHg in two measurements with an interval of 6 hours), accompanied by proteinuria (1 + or more at proteinuria tape or 24-hour proteinuria > 0.3 g/24h). The overlap of PE in patients with chronic arterial hypertension was considered, according to the ACOG report[17], modified in our service, when one of the following factors was present: (1) severe elevations in blood pressure (greater than 160 x 110 mmHg) (2) massive proteinuria (more than 2.0 grams in 24 hours), (3) pressure levels significantly increased after a period of good control, (4) serum creatinine values > 1.2 mg / dL.

After the regular prenatal consultation between 24^{+0} and 27^{+6} weeks of gestation, patients were invited to participate in this study. The study was approved by the Ethics and Research Committee of Hospital das Clínicas of 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. After consent, patients were submitted to FMD of the brachial artery and Doppler velocimetry of uterine and ophthalmic arteries. All three examinations were performed by the same professional from HC-UFMG, trained and certified in ultrasonography.

Flow-mediated dilation of the brachial artery

The evaluation technique of the FMD of the brachial artery was performed using a color Doppler ultrasonography equipment (SonoAce ® 8800 - MedsonCo, Ltd.), with a linear probe of 4-8 MHz. Patients were asked to rest for 15 minutes 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, which corresponds to the cardiac diastole, which 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 and insufflated for 5 minutes until a pressure higher than 250 mmHg was achieved, and then slowly 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 using the following formula: FMD (%) = [(D2 - D1) / D1] × 100, where D1 = basal diameter and D2 = post-occlusion diameter.

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 minutes. A complete assessment of the orbit vessels was obtained, and the ophthalmic artery and its branches were identified. The Doppler velocimetry of the ophthalmic artery was performed in its anterior branch, approximately 10 mm from the posterior 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.

Doppler velocimetry of uterine arteries

The Doppler velocimetry of uterine arteries is performed with a convex probe with 3.5 MHz frequency. The insonation of the arteries is performed in its proximal third, with a maximum angulation of 60°. The calculation of the pulsatility index (PI) of the uterine artery is 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.

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Statistical analysis

The normality of continuous data was verified using the Shapiro-Wilk's test. The Student's *t* test was used to compare normally distributed variables between groups of patients who developed PE and those who did not develop PE. Pearson's Chi-square test was used to compare categorical variables and Mann-Whitney *t* test was used to compare continuous variables without normal distribution. Statistical significance was set at as $p < 0.05$. Analyses were performed using the software SPSS ® 19 (SPSS Inc., Chicago, IL, USA).

Results

Of the 74 women who participated in the study, 15 developed PE, with 6 having the early form of presentation (clinical manifestations before 34 weeks of gestation) and 9 the late form (after 34 weeks).

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

Between 24^{+0} and 27^{+6} weeks of gestation, the group of patients who subsequently developed PE had a higher mean PIUtA, when compared to those who did not develop PE ($p < 0.001$). Patients who developed PE also had lower mean values of FMD ($p = 0.001$). However, there was no difference between the two groups regarding the mean value of OARI ($p = 0.08$) or of any other compared variable.

Discussion

Hypertensive disorders during pregnancy are a major cause of maternal and fetal morbidity and mortality. However, most deaths could be avoided by frequent and effective monitoring[18-20]. In order to prevent or lessen the complications of PE, we must first understand the physiopathological mechanisms responsible for the clinical manifestations of the syndrome.

The present study contributed by demonstrating that when high-risk pregnancies are monitored, an impairment of endothelial function can be detected by FMD in pregnancies subsequently complicated by PE, as well as placental perfusion deficiencies assessed by Doppler velocimetry of uterine arteries. This last phenomenon has been demonstrated, even in earlier gestational ages, at the end of the first trimester, in the studies performed by Plasencia et al.[11] and Gomez et al.[21]. A decrease in FMD values in the second trimester has been demonstrated by Takase et al.[22], in order to predict the clinical manifestations of PE. The combination of uterine artery Doppler velocimetry and FMD was demonstrated by Savvidou et al.[23], being able to differentiate pregnant women with subsequent development of PE and Intrauterine Growth Restriction (IUGR), which confirms the physiopathological association of the two entities.

In the present study, no difference was found regarding OARI values between the two groups, suggesting that at gestational age studied, perfusion or blood flow in the CNS is similar in women with or without subsequent development of PE. Possible explanations for this fact are based on the principle that the central hyperflow may occur after the blood pressure increase and glomerular endothelial injury, so that the clinical manifestations of PE precede the decrease in OARI in affected patients. A study carried out in our center has demonstrated a significant decrease in OARI at the moment when the PE was diagnosed[24], in both its early and late forms. New studies that evaluate the behavior of OARI at the later gestational ages, such as the beginning of the third trimester, could validate the

Table 1 – Clinical characteristics and ultrasonographic data of patients in the two study groups

	Patients with no 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/m²)¹ **Obese** **Non-obese**	24.9 ± 6.5 **17 (14%)** **42 (86%)**	27.5 ± 6.7 **4 (22%)** **11 (78%)**	0.20** 0.24***
Number of pregnancies (median, range) **First pregnancy** **> 1 pregnancy**	2 (1 – 8) **24 (41%)** **35(59%)**	3 (1 – 6) **7(47%)** **8(53%)**	0.14** 0.17***
Ethnicity ² **Caucasians** **African-Americans** **Others**	**14 (24%)** **13 (22%)** **32 (54%)**	**4 (27%)** **3 (20%)** **8 (53%)**	0.42***
Gestational age at assessment (weeks)	25.8 ± 1.2	25.6 ± 0.8	0.59*
Mean arterial pressure at assessment (mmHg)	85.8 ± 7.41	91.3 ± 8.3	0.07*
Mean PI of uterine arteries between 24 and 28 weeks	0.84 ± 0.12	1.20 ± 0.16	< 0.0001*
Basal diameter of the brachial artery 24-28 weeks	3.36 ± 0.42	3.40 ± 0.49	0.81*
Flow-mediated dilation of the brachial artery (%) 24-28 weeks	8.42 ± 3.15	3.60 ± 2.38	0.001*
Ophthalmic artery resistance index 24-28 weeks	0.703 ± 0.032	0.681 ± 0.037	0.08*

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

hypothesis that central hyperperfusion appears only after the clinical manifestations of PE.

In conclusion, our results demonstrate that impaired placental perfusion and systemic endothelial dysfunction temporarily precede the clinical manifestations of PE, which does not occur with central hyperflow.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. World Health Organization (WHO). The World Health report 2005: make every mother and child count. Geneva; 2005.

2. Barton JR, Sibai BM. Prediction and prevention of recurrent preeclampsia. Obstet Gynecol. 2008;112(2 Pt 1):359-72.

3. Magee LA, Helewa M, Moutquin JM, von Dadelszen P; Hypertension Guideline Committee, Strategic Training Initiative in Research in the Reproductive Health Sciences (STIRRHS) Scholars. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. J Obstet Gynaecol Can. 2008;30(3 Suppl):S1-48.

4. Pennington KA, Schlitt JM, Jackson DL, Schulz LC, Schust DJ. Preeclampsia: multiple approaches for a multifactorial disease. Dis Model Mech. 2012;5(1):9-18.

5. Cudihy D, Lee RV. The pathophysiology of pre-eclampsia: current clinical concepts. J Obstet Gynaecol. 2009;29(7):576-82.

6. Roberts JM, Gammill HS. Preeclampsia: recent insights. Hypertension. 2005;46(6):1243-9.

7. Myatt L, Webster RP. Vascular biology of preeclampsia. J Thromb Haemost. 2009;7(3):375-84.

8. Young BC, Levine RJ, Karumanchi SA. Pathogenesis of preeclampsia. Annu Rev Pathol. 2010;5:173-92.

9. Diniz AL, Moron AF, dos Santos MC, Sass N, Pires CR, Debs CL. Ophthalmic artery Doppler as a measure of severe pre-eclampsia. Int J Gynaecol Obstet. 2008;100(3):216-20.

10. Onwudiwe N, Yu CK, Poon LC, Spiliopoulos I, Nicolaides KH. Prediction of pre-eclampsia by a combination of maternal history, uterine artery Doppler and mean arterial pressure. Ultrasound Obstet Gynecol. 2008;32(7):877-83.

11. Plasencia W, Maiz N, Poon L, Yu C, Nicolaides KH. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks and 21 + 0 to 24 + 6 weeks in the prediction of pre-eclampsia. Ultrasound Obstet Gynecol. 2008;32(2):138-46.

12. Harris RA, Nishiyama SK, Wray DW, Richardson RS. Ultrasound assessment of flow-mediated dilation. Hypertension. 2010;55(5):1075-85.

13. Barbosa AS, Pereira AK, Reis ZS, Lage EM, Leite HV, Cabral AC, et al. Ophthalmic artery-resistive index and evidence of overperfusion-related encephalopathy in severe preeclampsia. Hypertension. 2010;55(1):189-93.

14. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ. 2005;330(7491):565.

15. Standards of medical care in diabetes – 2011. Diabetes Care. 2011;34 (Suppl. 1):S11-61.

16. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000;183(1):S1-S22.

17. ACOG Committee on Practice Bulletins--Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol. 2002;99(1):159-67.

18. Campbell OM, Graham WJ, Lancet Maternal Survival Series steering group. Strategies for reducing maternal mortality: getting on with what works. Lancet. 2006;368(9543):1284-99.

19. Barton JR, Sibai BM. Prediction and prevention of recurrent preeclampsia. Obstet Gynecol. 2008;112(2 Pt 1):359-72.

20. Nicolaides KH. A model for a new pyramid of prenatal care based on the 11 to 13 weeks' assessment. Prenat Diagn. 2011;31(1):3-6.

21. Gomez O, Figueras F, Fernandez S, Bennasar M, Martinez JM, Puerto B, et al. Reference ranges for uterine artery mean pulsatility index at 11-41 weeks of gestation. Ultrasound Obstet Gynecol. 2008;32(2):128-32.

22. Takase B, Goto T, Hamabe A, Uehata A, Kuroda K, Satomura K, et al. Flow-mediated dilation in brachial artery in the second half of pregnancy and prediction of pre-eclampsia. J Hum Hypertens. 2003;17(10):697-704.

23. Savvidou MD, Hingorani AD, Tsikas D, Frölich JC, Vallance P, Nicolaides KH. Endothelial dysfunction and raised plasma concentrations of asymmetric dimethylarginine in pregnant women who subsequently develop pre-eclampsia. Lancet. 2003;361(9368):1511-7.

24. Brandão AH, Barbosa AS, Lopes AP, Leite HV, Cabral AC. Dopplerfluxometria de artérias oftálmicas e avaliação da função endotelial nas formas precoce e tardia da préeclâmpsia. Radiol Bras. 2012;45(1):20-3.