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Original article

Maternal cerebral centralization of blood flow in pregnant women with specific gestational hypertension



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ABSTRACT

Objectives: To evaluate the occurrence of maternal brain centralization in pregnant women with specific gestational hypertension; to establish normal values of the ratio of the uterine artery with (mean and standard deviation) ophthalmic artery; to compare the ratio of uterine to the ophthalmic artery with normal and abnormal groups; and to establish the Receiver Operator Curve (ROC) for diagnosis of patients with specific hypertensive disease of pregnancy.

Methods: To achieve the proposed objectives a case-control study was carried out where the sample consisted of 178 pregnant patients divided into two groups. The control group included pregnant 83 pregnant normotensive women; a case group included 95 patients with clinical and laboratory diagnoses of specific gestational hypertension.

Results: Patients with preeclampsia had lower values than the patients who had eclampsia. The Doppler parameters that were statistically significant were those of the ratio of uterine artery with the ophthalmic artery (AU/AO) and vice versa. A comparison between the normal curve systole-diastole and the respective cut-off point was performed. A ROC is shown in the cut-off considering the systolic velocity, the diastolic velocity, the systole/diastole relation, and the index of resistance of the ophthalmic artery.

Conclusion: The maternal centralization in high risk pregnancies was observed when specific gestational hypertension is real. The normal curve has a mean and standard deviation of the relative Doppler of the uterine artery to the ophthalmic artery systolic/diastolic ratio was 0.43 ± 0.16 for normal pregnant patients. Comparing the group of patients with normal pathological group of patients there was a statistically significant difference between them

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considering the relation of Doppler uterine artery with ophthalmic artery. The cut-off point was more sensitive, verified by ROC, which defines maternal brain centralization in patients with specific gestational hypertension as 0.57 for the Doppler systolic/diastolic ratio of the uterine artery compared with the ophthalmic artery, with 78% sensitivity and 13% false positive.

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Centralização cerebral do fluxo sanguíneo materno em grávidas com hipertensão gestacional específica

R E S U M O

Palavras-chave:

Artéria oftálmica
Artéria braquial
Artéria uterina
Sonografia Doppler
Pré-eclâmpsia
Eclâmpsia

Objetivos: Avaliar a ocorrência de centralização no cérebro materno em grávidas com hipertensão gestacional específica; estabelecer os valores normais (média e desvio padrão) da razão artéria uterina/artéria oftálmica; comparar a razão artéria uterina/artéria oftálmica entre grupos normal e enfermo; estabelecer a curva ROC para o diagnóstico de pacientes com doença hipertensiva específica da gravidez.

Métodos: Estudo de caso-controle em uma amostra de 178 pacientes gestantes, divididas em dois grupos. O grupo controle consistiu em 83 grávidas normotensas; o grupo de casos consistiu em 95 pacientes com diagnóstico clínico e laboratorial de hipertensão gestacional específica.

Resultados: Pacientes com pré-eclâmpsia apresentaram valores mais baixos versus pacientes que sofreram eclâmpsia. Os parâmetros da sonografia Doppler estatisticamente significativos foram os referentes à relação artéria uterina/artéria oftálmica (AU/AO) e vice versa. Foi traçada uma curva de normalidade para sístole-diástole de comparação com os respectivos pontos de corte. A curva ROC exhibe os pontos de corte, respectivamente, para velocidade sistólica, velocidade diastólica, razão sístole/diástole e índice de resistência da artéria oftálmica.

Conclusão: Foi observada centralização materna em gestações de alto risco em casos de hipertensão gestacional específica. Na curva normal, a média $\pm$ desvio-padrão da relação sistólica/diastólica entre artéria uterina e artéria oftálmica foi de $0,43 \pm 0,16$ (Doppler) para pacientes grávidas normais. Comparando-se o grupo de pacientes normais com o grupo de pacientes enfermas, houve diferença estatisticamente significativa entre grupos, considerando o estudo Doppler para a razão artéria uterina/artéria oftálmica. O ponto de corte mais sensível, verificado pela curva ROC, definindo centralização cerebral materna em pacientes com hipertensão gestacional específica, foi de 0,57 para a razão sístole/diástole da artéria uterina versus artéria oftálmica (Doppler), com 78% de sensibilidade e 13% de resultados falso-positivos.

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Introduction

Preeclampsia (PE) and eclampsia (E) are important causes of maternal and perinatal morbidity and mortality worldwide. They are complicated by other specific gestational hypertension in about 2–8% of pregnancies.^{1–3}

According to the National Monitoring Report on the Millennium Development Goals by the World Health Organization, Brazil reported a drop of 43% in the proportion of deaths among women experiencing complications during pregnancy or childbirth from 1990 to 2013. This is in line with the reduction in maternal mortality worldwide. However, this rate will not achieve the proposed 35 maternal deaths per 100,000 births by 2015.^{3,4}

PE is a disease of unknown cause. Various theories have been proposed to explain its pathophysiology, two of which greatly support the vascular theory and immune theory, respectively. The vascular theory is based on the presence of “ischemia-perfusion defects” that lead to oxidative stress and vascular disease. According to the immune theory, PE is caused by poor maternal and paternal immune adaptation i.e., a maternal alloimmune reaction triggered by rejection of the fetal graft.^{5–7}

Effective prevention depends on the recognition of a latent and early stage of the disease that can be prevented or reversed and the availability of effective intervention methods. Clinical experience suggests that early detection and treatment of PE is beneficial to both the patient and fetus.^{2,5,8–11}

Knowledge of vascular changes during the pregnancy-puerperal cycle is critical for ensuring a better prognosis for both pregnant women and their fetuses, and obstetric Doppler examination is the gold standard technique for this analysis. Thus, the objective of this research was to evaluate the occurrence of maternal brain centralization in pregnant women with specific gestational hypertension, to establish normal values of the ratio of the uterine artery with ophthalmic artery, and to compare the ratio of uterine to the ophthalmic artery with normal and abnormal groups. Setting the cut-off point by ROC curve, with specific gestational hypertension and to establish the cut-off between normal and specific gestational hypertension.

Methods

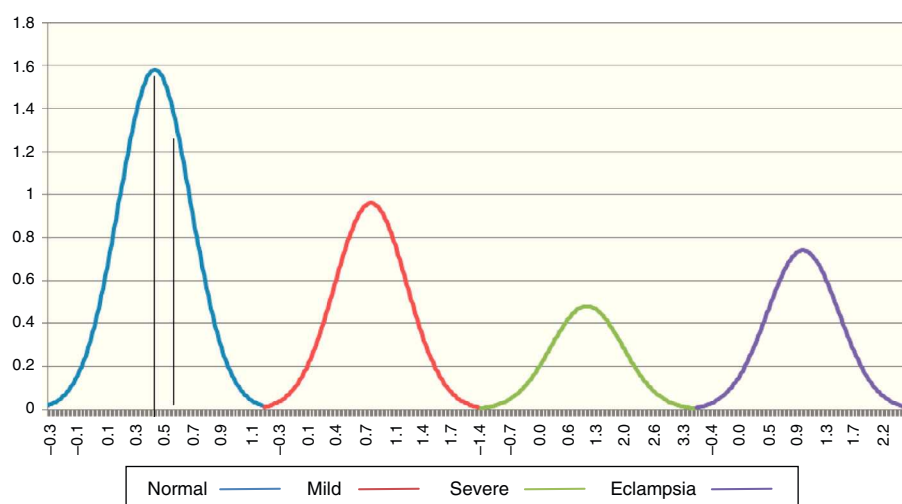
A case-control study involving assessment of the OA, and UA, was performed using Doppler ultrasound in pregnant women in the second and third quarter. Patients were recruited in 2013 from among pregnant women at low and high risk from the Department of Obstetrics and Gynecology, Hospital das Clínicas, Federal University of Goiás, Mother and Child Hospital, and Clinical Diagnostics Femina Clinic Fertile services.

The sample size comprised 178 pregnant women. The patients were divided into a control group of 83 normal

patients and 95 pathological patients with clinical and laboratory diagnoses of PE and E. The pathological group was further divided into three subgroups: patients with mild preeclampsia ($n = 31$), severe preeclampsia ($n = 60$), and eclampsia ($n = 4$). The sample size was obtained through calculation for a finite population, assuming that the collection sites showed a flow of approximately 2300 pregnant women from 1 month and with an error of 0.8%; a sample of 85.5 patients was required.

The inclusion criteria for both groups were women with spontaneous pregnancy and no comorbidities, no history of drug ingestion, normal blood pressure levels at the beginning of pregnancy, agreement to participate, and completion of written informed consent.

A further inclusion criterion in the PE and E groups was meeting the clinical and laboratory criteria for diagnosis of either PE or E, respectively. The criteria used for diagnosis of PE and E were those described in the National High Blood Pressure Education Program.¹² The criteria for PEL were one blood pressure measurement of $\geq 140/90$ mmHg out of at least two measurements performed after the 20th week of pregnancy, without hypertension (except cases of trophoblastic disease which may be associated with PE before 20 weeks) associated with proteinuria of 0.3–2.0 g in 24 h or 1+ on a random urine sample. PEG was considered to be present when blood pressure of $\geq 160/110$ mmHg was associated with any of the following signs, symptoms, or laboratory abnormalities:



VS-systolic velocity, VD- diastolic velocity, A-B – systole / diastole, IR - Resistance index

CUTTING POINT

Variable	CONSIDERED VALUE		CUTTING POINT
	SENSITIVITY	1 - Specificity	
VS (UD/AO)	0,78	0,96	0,06
VD (UD/AO)	0,78	0,96	0,09
A/B (UD/AO)	0,78	0,13	0,57
IR (UD/AO)	0,81	0,51	0,56

VS-systolic velocity, VD- diastolic velocity, A-B – systole / diastole, IR - Resistance index
UD/AO- artery uterine / ophthalmic artery

Fig. 1 – Normal curve adjusted with a cutting point of the systole/diastole relation of the relation uterine artery/ophthalmic artery in normal pregnant women, Goiânia, 2013–2014.

proteinuria of ≥ 2 g in 24 h, serum creatinine above 1, 2 mg/dL proteinuria; persistent headache and/or abdominal pain and/or visual disturbances; changes in habitual behavior (mood swings); anasarca; signs of microangiopathic anemia and/or elevation of liver enzymes and/or a low platelet count ($<100,000/\text{mm}^3$); and eclampsia. Eclampsia is defined by the expression of one or more tonic-clonic seizures generalized and/or coma in a pregnant woman with gestational hypertension or preeclampsia, with absence of neurological disorders.^{5,6,12-15}

Pregnant women who went into labor during Doppler ultrasound and those with other types of hypertension and comorbidities were excluded.

Imaging was performed with an ultrasound machine equipped with pulsed Doppler and color flow mapping and an electronic transducer (linear, 7.5 MHz; convex, 5.0 MHz) (Philips and Medison Accuvix). All examinations were performed by our own researcher who has experience in this type of examination, and a report with the results found was delivered to the patient.

For Doppler examination of the OA, the patients were placed in the supine position and a drop of gel was administered onto the right upper eyelid with the patient's eyes closed. The transducer was then transversely positioned on the eyelid. The transducer was moved in the craniocaudal direction without pressure, thus avoiding possible changes in local flow. The evaluation technique described by Diniz et al.¹⁶ was used.

After identifying the ophthalmic artery (OA), brachial artery (BA) and uterine artery (UA) were recorded for about six waves with a good standard, and the proposed index (velocity systolic, diastolic velocity, resistance index and systole-diastole relationship) was then measured. The images were analyzed in real time. The insonation angle between the ultrasound beam and the blood flow was maintained to the greatest extent possible between 30° and 60° . The filter was 50 Hz, pulse repetition frequency was 125 kHz, and volume-adjusted sample was 2–3 mm.

The OA was displayed next to the optic nerve. Flow measurement of the OA was performed nasal and superior to the optic nerve 10–15 mm posterior scleral wall position, Fig. 1. A 7-MHz linear transducer was used.¹⁶

The UA was assessed near the iliac vessels in its portion proximally. A 3.5-MHz convex transducer was used.

The following Doppler parameters were analyzed in the three vessels: the systolic velocity (SV), diastolic velocity (DV), resistance index, and systole/diastole ratio. The resistance index was calculated as follows: $(SV-DV)/SV$. Additionally, epidemiological variables such as number of pregnancies, parity, abortion, weight, height, body mass index (BMI), maternal age, and gestational age were studied.

Comparison of the homogeneity of the groups was performed by calculating the mean, standard deviation for cut-off values, and p normal course of epidemiological variables. The Kolmogorov-Smirnov test results showed that the data had a normal distribution. After removal of the variables, we used the Kruskal-Wallis test, Mann-Whitney test, Student's t test, and Fisher's exact test for validation of the associations found.

After determining the variables, a reference curve was plotted for the normal pregnancies to establish the cut-off point which determines maternal cerebral centralization. The ROC

Table 1 – Parameters of the variables in the epidemiological profile in accordance with the normal and abnormal groups (pre-eclampsia, eclampsia and pregnant women), in Goiânia 2013–2014.

Variable	Normal (control)		Pathological (case)		p
	n	Mean $\pm$ SD	n	Mean $\pm$ SD	
Gestation	78	1.71 ± 0.84	93	2.22 ± 1.65	0.019
Parturition	78	0.60 ± 0.76	93	1.12 ± 1.46	0.008
Abortion	78	0.09 ± 0.33	93	0.25 ± 0.65	0.070
BMI	81	26.88 ± 5.60	92	30.55 ± 5.12	<0.001
Age	82	29.87 ± 4.71	94	26.14 ± 6.17	<0.001
IG	79	34.67 ± 3.57	90	32.40 ± 3.37	<0.001

BMI, body mass index; IG, gestational age.

Test: Kruskal Wallis.

Table 2 – Analysis of Doppler parameters of the variables according to the normal group (control) and case (mild, severe and eclampsia), in Goiânia 2013–2014.

Variables	Normal (control)		Pathological (case)		p
	n	Mean $\pm$ SD	n	Mean $\pm$ SD	
UD/AO					
VS	83	2.35 ± 1.14	95	1.56 ± 1.20	<0.001
VD	83	5.90 ± 3.31	95	2.06 ± 1.88	<0.001
A/B	83	0.43 ± 0.16	95	1.00 ± 0.74	<0.001
IR	83	0.57 ± 0.16	95	0.84 ± 0.37	<0.001

VS, systolic velocity; VD, diastolic velocity; A/B, systole/diastole; IR, resistance index.

Test: logistic regression analysis.

curve, with power of discrimination between normal pregnant women and pregnant women with specific gestational hypertension, was made.

The study protocol was approved by the Regional Ethics Committee of the Maternal and Child Hospital (HMI/SES).

Results

A total of 178 patients took part in our study. The average age of patients in the group of normal pregnant patients was 29.8 ± 4.7 and patients with specific gestational hypertension it was 26.14 ± 6.17 . The mean gestational age of normal pregnant patients was 34.3 ± 3.5 weeks and patients with specific gestational hypertension it was 32.40 ± 3.37 . The average body mass index (BMI) of normal pregnant women was 26.8 ± 5.6 and for patients with specific gestational hypertension it was 30.55 ± 5.12 (Table 1).

In Table 2 through logistic regression analysis, the mean and standard deviation of the UD/AO in accordance with the normal group (control) and pathological (PEL, PEG, E) group were performed. The Doppler parameters that were statistically significant were those of AU/AO and vice versa.

The curve of the systole-diastole normally compared with the respective cut-off point is shown in Fig. 1.

Fig. 2 shows the ROC curve with the cut-off point, considering the systolic velocity, diastolic velocity, systolic/diastolic ratio and resistance index of the ophthalmic artery.

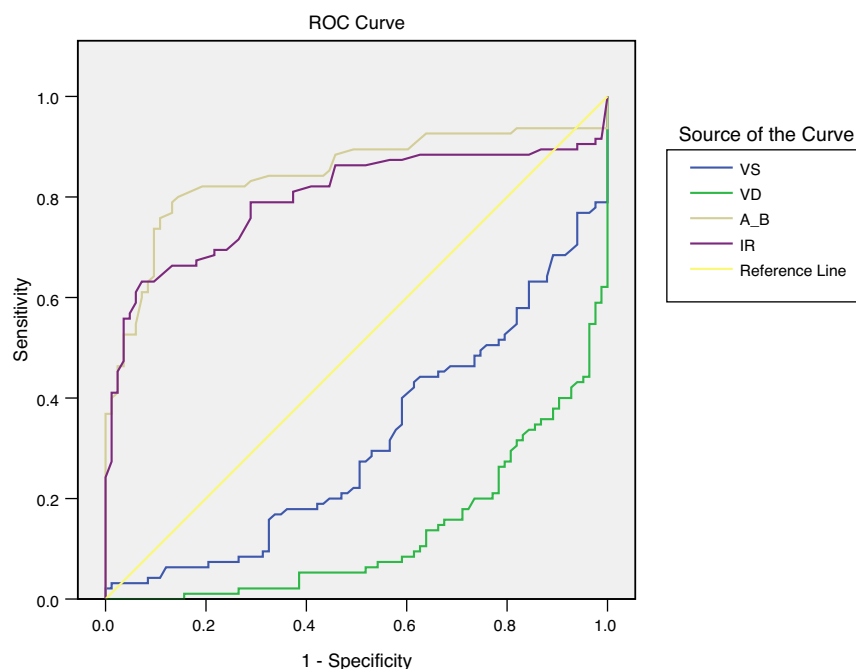


Fig. 2 – Receiver Operator Curve (ROC) for the systolic velocity, diastolic velocity, resistance index and systole/diastole relation, in pregnant women, Goiânia, 2013–2014.

Discussion

After an extensive literature review, we believe that the present study is the first to analyze the Doppler variables of two different vessel ratios (UA/OA) to screen for PE. This topic is of growing interest in the academic population.

Table 1 shows the epidemiological characteristics of groups of normal pregnant women and patients with these specific hypertensive diseases of pregnancy. The patients with specific gestational hypertension presented index higher than that of normal pregnant patients body mass. It was statistically significance for patients except during abortion.

Making the analysis of the relationship of the AU/OA, all parameters were significant. Patients with specific gestational hypertension showed the mean values of systolic/diastolic ratio greater than normal patients (Table 2).

Because of limitations in the prevention of PE, focus has been placed on identifying women at high risk of PE along with monitoring clinical and laboratory parameters to recognize the disease in its early stages. Many clinical and laboratory variables have been used to assess the severity of the disease, including high blood pressure and proteinuria associated with symptoms such as headache, epigastric pain, and visual disturbances. New variables that can help to identify severe cases of PE would have great practical applications, allowing physicians to more intensively treat pregnant women at higher risk.

All parameters were significant in the analysis of the UA/OA ratio. Patients with PEG had lower ratios than did patients with E. These data suggest that an increase in the UA/OA ratio in patients with PEG indicates a worsening of symptoms and potential development of E.

The results were similar when we evaluated the right and left UA. When the Doppler variables were reversed (i.e., UA/OA to OA/UA), the normal pregnant women and women with specific gestational hypertension showed the greatest statistical significance.

Maternal centralization of blood flow is best documented when analyzing the UA/OA ratio. This may be explained by changes in the UA in accordance with placentation. There is a real possibility of maternal centralization of blood flow in pregnancies at high risk of PE (Table 2).

The normal curve has a mean and standard deviation of the relative Doppler of the uterine artery to the ophthalmic artery systolic/diastolic ratio that was 0.43 ± 0.16 for normal pregnant women.

Comparing the group of patients with normal pathological group of patients there was a statistically significant difference between them considering the relation of Doppler uterine artery with ophthalmic artery.

The cut-off point by ROC curve, with power of discrimination between normal pregnant women and pregnant women with specific gestational hypertension, was 0.57 compared to the Doppler systolic/diastolic ratio of the uterine artery to the ophthalmic artery, with 78% sensitivity and 13% false positive.

Vascular endothelial injury, clinically characterized as endothelial dysfunction, has been widely demonstrated in patients with PE through Doppler flow meter measurement of the UA and OA.¹⁷ There is evidence that vasodilation in healthy patients generally reflects an increase in production of endothelial-derived relaxing factor, especially those dependent on nitric oxide, decreased vascular reactivity, and vasoconstrictor peptides such as endothelin, thromboxane, and angiotensin II.¹⁸ In patients with PE, placental ischemia

leads to a release of soluble substances in the maternal bloodstream, resulting in hyperactivity of these vasoconstrictive factors. This change can be detected even before hypertension becomes apparent.¹⁸

Lower values of flow mediated dilation and high resistance indices of the uterine arteries have been demonstrated in patients who subsequently developed PE, indicating that the test can be used to predict the clinical manifestations of PE.¹⁹⁻²² Endothelial dysfunction apparently precedes the clinical manifestations of PE.²⁰

The results of this study showed that the Doppler parameters of the relationship between the UA and OA in pregnant women with PE are significantly different from those of healthy pregnant women, indicating that the Doppler UA/OA ratio can be used to assess the severity of PE. However, confirmation of these findings in larger samples and more ethnically diverse populations is needed.

Conclusion

It is observed that the possibility of maternal centralization in high risk pregnancies such as specific gestational hypertension is real.

The normal curve that has a mean and standard deviation of the relative Doppler of the uterine artery to the ophthalmic artery systolic/diastolic ratio was 0.43 ± 0.16 for GN.

Comparing the group of patients with normal pathological group of patients there was a statistically significant difference between them considering the relation of Doppler uterine artery with ophthalmic artery.

The cut-off point by ROC curve, with power of discrimination between normal pregnant women and pregnant women with specific gestational hypertension, was 0.57 compared to the Doppler systolic/diastolic ratio of the uterine artery to the ophthalmic artery; the sensitivity was 78% and the false positive was of 13%.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Duley L. The global impact of pre-eclampsia and eclampsia. *Sem Perinatol.* 2009;33:130-7.
2. ACOG. Hypertension in pregnancy. The American College of Obstetricians and Gynecologists; 2013.
3. Antonios TF, Nama V, Wang D, Manyonda IT. Microvascular remodelling in preeclampsia: quantifying capillary rarefaction accurately and independently predicts preeclampsia. *Am J Hypertens.* 2013;26:1162-9.
4. WHO. Trends in maternal mortality 1990-2013. World Health Organization (WHO); 2013.
5. Steegers EAP, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. 2010;376:631-44.
6. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet.* 2005;365:785-99.
7. Amorim MMR, Souza ASR. Prevenção da pré-eclâmpsia baseada em evidências. *FEMINA.* 2009;37.
8. Fayyad AM, Harrington KF. Prediction and prevention of preeclampsia and IUGR. *Early Hum Dev.* 2005;81:865-76.
9. WHO. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva: WHO; 2011.
10. Lai J, Poon LC, Pinas A, Bakalis S, Nicolaides KH. Uterine artery Doppler at 30-33 weeks' gestation in the prediction of preeclampsia. *Fetal Diagn Ther.* 2013;33:156-63.
11. Brandão AHF, Lopes APBM, Cabral MA, Scala FD, Leite HV, Cabral ACV. Predição de pré-eclâmpsia: a realidade atual e as direções futuras- revisão. *FEMINA.* 2010;38:9.
12. NBPB National High Blood Pressure Education Program working group on high blood pressure in pregnancy. *Am J Obstet Gynecol.* 2000;183:S1-22.
13. Vasconcellos M, Almeida M, Kahhale S, Peraçoli J, Sass N, Ramos J. Projeto diretrizes hipertensão na gravidez. Federação Brasileira das Sociedades de Ginecologia e Obstetrícia. 2002.
14. Souza ASR, Noronha Neto C, Coutinho IC, Diniz CP, Lima MMS. Pré-eclâmpsia. *Femina.* 2006;34(7):499-507.
15. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol.* 2003;102:181-92.
16. Diniz AL, Moron AF, Santos MC, Sass N. Dopplervelocimetria colorida dos vasos orbitais: Técnicas de exame e anatomia vascular normal. *Radiol Bras.* 2004;37:287.
17. Matias DS, Costa RF, Matias BS, Claudio Lemos CL. Doppler velocimetry of the orbital vessels in pregnancies complicated by preeclampsia. *J Clin Ultrasound.* 2012;40:576-85.
18. Matsubara K, Matsubara Y, Hyodo S, Katayama T, Ito M. Role of nitric oxide and reactive oxygen species in the pathogenesis of preeclampsia. *J Obstet Gynaecol Res.* 2010;36:260-347.
19. Brandão AHF, Barbosa AS, Lopes APBM, Leite HV, Cabral ACV. Dopplerfluxometria de artérias oftálmicas e avaliação da função endotelial nas formas precoce e tardia da pré-eclâmpsia. *Radiol Bras.* 2012;45:20-3.
20. Savvidou MD, Noori M, Anderson JM, Hingorani AD, Nicolaides KH. Maternal endothelial function and serum concentrations of placental growth factor and soluble endoglin in women with abnormal placentation. *Ultrasound Obstet Gynecol.* 2008;32:871-6.
21. Parra-Cordero M, Rodrigo R, Barja P, et al. Prediction of early and late pre-eclampsia from maternal characteristics, uterine artery Doppler and markers of vasculogenesis during first trimester of pregnancy. *Ultrasound Obstet Gynecol.* 2013;41:538-44.
22. Brodzki J, Lanne T, Laurini R, Streven H, Wide-Svensson D, Marsal K. Vascular mechanical properties and endothelial function in pre-eclampsia with special reference to bilateral uterine artery notch. *Acta Obstet Gynecol Scand.* 2008;87:154-62.