The ophthalmic artery resistive index as a predictor of choriocapillaris ischemia in multivariate logistic models

Índice de resistência da artéria oftálmica como preditor de isquemias focais da coriocapilar em modelos logísticos multivariados

Alexandre Simões Barbosa[1], **Andre Aguiar de Oliveira**[1], **Antônio Carlos Vieira Cabral**[2]

[1] Department of Ophthalmology, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brasil.
[2] Department of Gynecology and Obstetrics, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brasil.

How to cite:
Barbosa AS, Oliveira AA, Cabral AC. The ophthalmic artery resistive index as a predictor of choriocapillaris ischemia in multivariate logistic models. Rev Bras Oftalmol. 2023;82;e0030.

doi:
https://doi.org/10.37039/1982.8551.20230030

Keywords:
Choroid; Retina; Ultrasonography, doppler; Pre-eclampsia; Endothelium; Ischemia

Descritores:
Corioide; Retina; Ulttrassonografia doppler; Pré-eclâmpsia; Endotélio; Isquemia

Received on:
Jan 23, 2023

Accepted on:
Jan 23, 2023

Corresponding author:
Alexandre Simões Barbosa
Rua Padre Rolim, 769/803 – Santa Efigênia
CEP: 30330090 – Belo Horizonte, MG, Brasil
E-mail: alexandre.oftalmo@gmail.com

Institution:
Hospital São Geraldo, Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brasil.

Conflict of interest:
the authors declare no conflict of interest.

Financial support:
The study was supported by CAPES-DGO113/00, FAPEMIG-DGO 9671/05 and FAPEMIG-DGO CDS-APQ 296/08.

Ethics committee:
Comitê de Ética em Pesquisa UFMG (ETIC078/05)

ABSTRACT

Objective: Vascular findings in preeclampsia are usually attributed to increased vascular tone. Recently, however, important studies have improved the understanding of the main pathophysiological events in this condition, especially vascular brain remodeling, impaired autoregulation, and damage of the blood-brain barrier, which are well recognized features of cerebral overperfusion.

Methods: In this study, the association between choriocapillaris ischemia with ophthalmic artery blood flow parameters on orbital Doppler ultrasound is reported for the first time using multivariate logistic models. Multivariate logistic models with ophthalmic artery blood flow parameters, as well as major clinical and laboratory predictive variables were established for choriocapillaris ischemia and choriocapillaris ischemia with retinal detachment.

Results: In a series of 165 patients, 46 (28%) presented choriocapillaris ischemia; among them, 20 (12%) presented associated retinal detachment. The ophthalmic artery resistive index was the main predictor for choriocapillaris ischemia and choriocapillaris ischemia with retinal detachment in multivariate logistic models. Ophthalmic artery resistance lower than 0.56 was associated with a significantly high incidence of both outcomes.

Conclusion: This study supports that the branching pattern of choroidal arterioles and the lobular organization of choriocapillaris are the major morphological aspects underlying endothelial damage and lobular ischemia in the context of choroidal overperfusion. Overperfused lobules bordering areas of choriocapillaris ischemia produce a perfusion pressure gradient, with lobular reperfusion, leakage from reperfused choriocapillaris, and retinal detachment. Ophthalmic artery-resistive index lower than 0.56 is proposed as a major predictor of the overperfusion-related choriocapillaris ischemia and choriocapillaris ischemia with retinal detachment in preeclampsia.

RESUMO

Objetivo: Os achados vasculares na pré-eclâmpsia são usualmente atribuídos ao aumento do tônus vascular. Recentemente, no entanto, importantes estudos têm melhorado a compreensão dos principais eventos fisiopatológicos nessa condição, especialmente o remodelamento vascular cerebral, a perda de autorregulação e a ruptura da barreira hematoencefálica, características bem reconhecidas de hiperperfusão cerebral.

Métodos: Neste estudo, a associação entre a isquemia da coriocapilar e parâmetros de fluxo sanguíneo da artéria oftálmica no Doppler orbitário é relatada pela primeira vez por meio de modelos logísticos multivariados. Modelos logísticos multivariados com parâmetros de fluxo sanguíneo de artéria oftálmica, assim como os principais preditores clínicos e laboratoriais, foram estabelecidos para isquemia da coriocapilar e coriocapilar associada a descolamento de retina.

Resultados: Em uma série de 165 pacientes, 46 (28%) apresentaram isquemia da coriocapilar; dentre eles, 20 (12%) apresentaram descolamento de retina associado. O índice de resistência da artéria oftálmica foi o principal preditor para isquemia da coriocapilar e isquemia da coriocapilar associada a descolamento de retina em modelos logísticos multivariados, e índice de resistência da artéria oftálmica menor que 0,56 foi associado a uma incidência significativamente elevada de ambos os desfechos.

Conclusão: Este estudo sustenta que o padrão de ramificação das arteríolas coroidianas e a organização lobular da coriocapilar são os principais aspectos morfológicos subjacentes ao dano endotelial e à isquemia lobular no contexto do hiperfluxo coroidiano. O hiperfluxo de lóbulos adjacentes às áreas de isquemia da coriocapilar estabelece um gradiente de pressão de perfusão, o que produz reperfusão lobular, extravasamento a partir de coriocapilares reperfundidos e descolamento da retina. O índice de resistência da artéria oftálmica inferior a 0,56 é proposto como um importante preditor de isquemia da coriocapilar e isquemia da coriocapilar associada a descolamento de retina relacionados ao hiperfluxo na pré-eclâmpsia.

INTRODUCTION

Preeclampsia is a multisystem progressive condition characterized by endothelial damage, coagulation cascade activation, shifting of blood volume from peripheral to central territories, and end-organ damage. Clinically, preeclampsia is suggested in presence of significant increase in blood pressure (≥160mmHg systolic, ≥110mmHg diastolic, or >126mmHg mean) after the 20th week of gestation, associated with clinical or laboratory evidence of end-organ damage. Ischemia and overperfusion are well-recognized underlying features in preeclampsia, and the vascular pathophysiology encompassing both events remains a subject of debate. Mean blood pressure at admission (MBPA), mean blood pressure elevation (MBPE) after the 20th week of gestational age, as well as laboratory evidence of glomerular damage (24-hour urine protein test) and endothelial damage (LDH) are major criteria of severity in preeclampsia. However, these clinical and laboratory criteria are insufficient to establish the risk of preeclampsia progression and its vascular complications.

The full spectrum of ophthalmologic findings in preeclampsia was formerly attributed to retinal vasospasm, recognized as a main vascular event in severe preeclampsia and the hallmark of systemic vasospasm.[1,2] The relevance attributed to retinal vasospasm in the vascular pathophysiology of preeclampsia was supported by authors who proposed that such finding would be considered a formal indication for delivery. However, the presence of retinal arteriolar narrowing, as well as retinal hemorrhages and cotton wool spots, the main findings of hypertensive retinopathy, had lost relevance in favor of choriocapillaris ischemia (CCI) and retinal detachment (RD). These findings provide evidence of hypertensive choroidopathy, which are primarily determined by high blood pressure in a structure where conditions of vasospasm are impaired.

Choriocapillaris ischemia, a leading ophthalmologic finding in preeclampsia, occurs as white or yellow-white subretinal spots of well-defined margins, with a mean diameter of 800µm, coincident with choriocapillaris lobule diameter. Choriocapillaris ischemia presents as multiple spots located in posterior pole and midperiphery, often associated with multifocal or diffuse RD.[3] In fluorescent angiography, CCI in preeclampsia appears as areas of choroidal filling delay, followed by hyper-fluorescence and leakage of dye into the subretinal space and retinal RD.[4] On OCT, choroidal thickening is a well-established finding in severe preeclampsia, whereas filling defects of the choriocapillaris are observed on OCTA.[2,5]

Blood flow parameters in the ophthalmic artery (OA) mirror the behavior of choroidal perfusion. Ophthalmic artery-resistive index (OARI) and pulsatility index (OAPI), which are measures of vascular resistance, are the main parameters to assess distal vascular resistance. Among them, OARI, which assumes values between zero and one, has been the main parameter to assess vascular resistance in OA and short posterior ciliary arteries (SPCA). Ophthalmic artery-resistive index and OAPI, in addition to ophthalmic artery mean velocity (OAMV), provide a reliable estimation of choroidal flow volume. The study of blood flow parameters with orbital Doppler ultrasound (ODU) was first reported in preeclampsia by Hata et al., who obtained lower OAPI in preeclampsia compared to normal pregnancy, as well as in severe preeclampsia compared to mild preeclampsia.[6,7] The association between CCI and RD with lower OARI was first presented by Barbosa et al.[8]

METHODS

The study included 165 patients admitted to the *Hospital das Clínicas* of the *Universidade Federal de Minas Gerais* (UFMG), a reference center for the diagnosis and treatment of high-risk pregnancy and preeclampsia, from January 2002 to May 2006. Inclusion criteria were diagnosis of preeclampsia, according to the Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy,[9] and prenatal examinations with reliable clinical and laboratory data. Exclusion criteria were occurrence of seizures, headache, and clinical evidence of preeclampsia-related encephalopathy before ODU; labor onset and uterine contractions; antiphospholipid antibodies; disseminated intravascular coagulation; hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; current and previous kidney and heart disease; gestational diabetes and diabetes mellitus, and glaucoma. The study was approved by the Research Ethics Committee of UFMG. All patients participated voluntarily, according to the terms of the Declaration of Helsinki.

Orbital Doppler ultrasound was performed immediately after hospital admission by the same examiner, who received no information regarding clinical data or medical history**.** A Medison 8800 color Doppler equipment was employed, coupled to a 7.5 MHz linear transducer applied to closed eyes covered with methylcellulose gel, with patients in the supine position. Ophthalmic artery was studied in its temporal segment, 14 to 20mm from the posterior scleral wall. Blood flow parameters were obtained in the arterial axis, proximal to ciliary branching,

from regular spectral curves of the right eye, with proper angle correction. For the present study, OARI and OAMV measurements were recorded. Immediately after the ODU, an indirect binocular ophthalmoscopy was performed using a Keeler ophthalmoscope with a 20-diopter aspherical Volk lens, after installation of 1% tropicamide drops. Until 48 hours after the ODU, patients were submitted to a posterior segment biomicroscopy with a Haag-Streit slit lamp and a 90-diopter aspherical Volk lens, and findings of posterior pole and midperiphery were documented with color retinography, obtained with a Topcon 50 VT or 50 Xi retinal scanner.

The normality of distribution of predictive variables was assessed with the Anderson-Darling test. Comparisons between groups of patients with and without CCI in relation to the predictive variables OARI, OAMV, MBPA, MBPE, LDH, and 24-hour urine protein test were performed with Mann–Whitney test. The power of discrimination of each predictor variable in relation to the presence of CCI was evaluated with the estimate of area under the Receiver Operating Characteristic (ROC) curve (A_E) and their confidence intervals (A_{CI}). The cut-off points of ROC curves were obtained through the intercept of sensitivity and specificity curves for each predictor variable, in function of the occurrence of CCI. Each categorized variable assumed the value of one or zero, for higher and lower risks of CCI, respectively.

Three groups of logistic models were constructed: a) a binary logistic regression for CCI (y=1 if CCI present, y=0 if CCI absent); b) a binary logistic regression for CCI superimposed by RD (CCI-RD; (y=1 if CCI associated with RD, y=0 if CCI and RD absent); and c) an ordinal logistic regression for CCI-RD, CCI (y=2 and y=1 respectively, and y=0 if CCI and RD absent). Logistic models were established with variables categorized in function of the cut-off point of each ROC curve and then with categorized OARI fixed as a factor, and further continuous variables as covariates. Binary CCI, binary CCI-RD and ordinal CCI/CCI-RD models were established as pairs of OARI-unfactored and OARI-factored models, which were presented in their complete form, with the full set of variables, and then in their ultimate form, only with significant variables.

Estimates of β coefficients, estimates and confidence intervals of odd ratios (OR_E and OR_{CI}), Wald statistics, G statistics, general measures of fit (Pearson, Deviance and Hosmer-Lemeshow), general measures of association (Sommers, Goodman-Kruskal Gamma and Kendall's Tau-a) were obtained for each model. Binary OARI-factored models were evaluated with A_E and A_{CI} and individual component analysis (changes in β coefficients, Pearson and Deviance, respectively Δβ, ΔPearson and ΔDeviance). All the analyses were obtained using SPSS 15 and Minitab 15 softwares. The present study was approved by the Ethics Committee of the Universidade Federal de Minas Gerais (ETIC078/05).

RESULTS

Ophthalmologic findings

Among the 165 patients in the series, CCI was identified in 46 (28%), from which 20 (43%) had associated RD. Among patients with RD, it was multifocal in 16 (80%) and diffuse in 4 (20%), respectively, at admission. Diffuse RD was characteristically bullous, with prominent shifting of the subretinal fluid, involving posterior pole and midperiphery, and including macula. Subretinal fluid was significantly opaque, producing white-yellowish subretinal inferior demarcation lines. Ten patients (62%) with multifocal RD at admission progressed to diffuse RD. Among four patients (20%) with flat diffuse RD at admission, two progressed to diffuse, bullous RD. All patients with multifocal or diffuse RD presented CCI. All patients with CCI or CCI-RD presented bilateral and symmetric findings. Retinal arteriolar narrowing in the posterior pole was identified in 34 (21%) patients in this series and was associated with significant retinal edema, characterized by increased striations in retinal nerve fiber layer. Images of CCI and CCI-RD are shown in figure 1. The association between retinal arteriolar narrowing and retinal edema suggest a bias in the evaluation of retinal vasospasm based on ophthalmoscopic findings. Analyses of retinal arteriolar narrowing with ODU, as well as clinical and laboratory predictors, were not performed in this study.

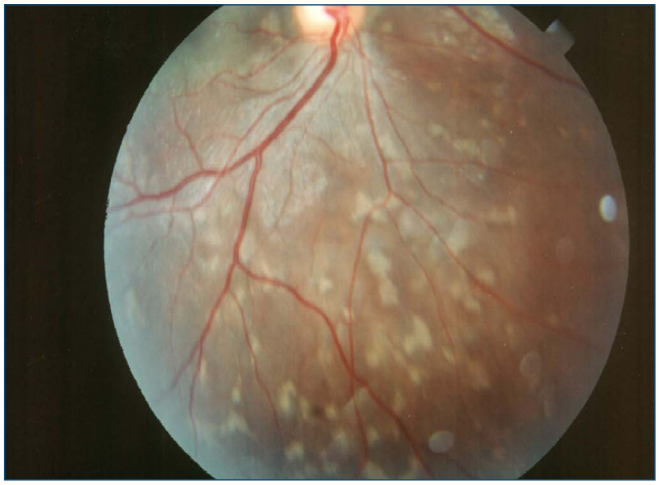


Figure 1. Retinography of a patient with severe preeclampsia presenting subretinal spots consistent with choriocapillaris ischemia associated with flat retinal detachment.

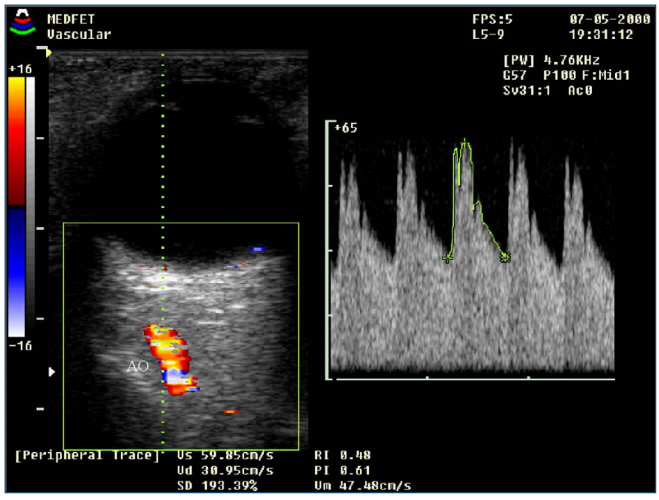
Differences in the predictor variables in function of the occurrence of choriocapillaris ischemia

Patients with and without CCI presented similar age (22.8±7.4 and 23.7±5.5 years old; p=0.556), as well as gestational age (32.6±8.4 and 33.7±7.8 weeks; p=0.338). Significant differences were obtained between patients with and without CCI, in relation to OARI (0.53±0.004 and 0.59±0.06, p<0.0001), OAMV (40.52±4.44 and 36.93±4.19 cm/s, p<0.0001), MBPA (145,00±15.57 and 128.10±13.17 mmHg, p<0.0001), as well as all other predictor variables. No association was obtained between OARI and maternal or gestational ages (p=0.445 and p=0.239, respectively), as well as between OARI and MBPA (p=0.078). A_E and A_{CI} obtained from ROC curves were greater than 0.50 for all variables, and remarkably high for OARI (A_E 0.825±0,330; A_{CI} 0.761 to 0.890) and MBPA (A_E 0.813±0,034; A_{CI} 0.746 to 0.879). Values of sensitivity, specificity, and likelihood ratios were remarkably high for OARI (CP 0.56; S 0.706; E 0.826; LR 4.057) and MBPA (CP 137.50; S 0.717; E 0.748; LR 2.845). The OA spectral curve, obtained with ODU, is presented in Figure 2. The differences in the predictor variables in function of the presence of CCI are presented in Table 1. Parameters of areas under ROC curves and measures of sensitivity, specificity, and likelihood ratios are presented in Table 1.

Table 1. Predictor variables

Distribution of predictors					
Predictor	Mean CCI-	Mean CCI+	SD CCI-	SD CCI+	p-value
OARI	0.59	0.53	0.006	0.004	<0.001
OAMV	36.93	40.52	3.34	4.44	<0.001
MBPA	128.10	145.00	13.17	15.57	<0.001
MBPE	35.24	49.26	15.42	15.76	<0.001
LDH	701	1070	607.4	649.4	<0.001
UPT	1.95	3.08	2.44	2.47	<0.001
Parameters of areas under ROC curves					
Predictor	A_E	A_{SD}	A_{LL}	A_{UL}	p-value
OARI	0.825	0.330	0.761	0.890	<0.001
OAMV	0.714	0.044	0.627	0.801	<0.001
MBPA	0.813	0,034	0.746	0.879	<0.001
MBPE	0.754	0.042	0.627	0.836	<0.001
LDH	0,700	0.044	0.612	0.787	<0.001
UPT	0.642	0.050	0.544	0.739	0.005
Parameters of cut-off point accuracy					
Predictor	CP	Se	Sp	1-Sp	LR
OARI	0.56	0.706	0.826	0.174	4.057
OAMV	38.75	0.696	0.689	0.311	2.238
MBPA	137.50	0.717	0.748	0.252	2.845
MBPE	42.50	0.694	0.697	0.303	2.224
LDH	705.50	0.674	0.681	0.319	2.130
UPT	2.10	0.609	0.664	0.336	1.812

CCI: choriocapillaris ischemia; SD: standard deviation; OARI: ophthalmic artery resistive index; OAMV: ophthalmic artery mean velocity; MBPA: mean blood pressure at admission; MBPE: mean blood pressure elevation; LHD: lactate dehydrogenase; UPT: urine protein test; ROC: Receiver Operating Characteristic; A_E and A_{SD}: area under Receiver Operating Characteristic curve estimate and standard deviation; A_{LL} and A_{UL} upper and lower limits of Receiver Operating Characteristic curve confidence intervals; CP: cut-off point; Se: sensitivity; Sp: specificity; LH: likelihood ratio.



Vs: systolic velocity; Vd: diastolic velocity; SD: systolic velocity and diastolic velocity ratio; RI: resistive index; PI: pulsatility index; Vm: mean velocity.

Figure 2. Ocular Doppler ultrasound presenting the main ophthalmic artery blood flow parameters: peak systolic velocity, final diastolic velocity, systolic velocity and diastolic velocity ratio, resistive index, pulsatility index, and mean velocity.

Logistic models and convergence parameters

In the final binary OARI-unfactored model of CCI was composed by OARI (β=1.96, p<0.0001 and OR_E =7,10; OR_{IC} 2.86-17.61) and MBPA (β=1.66; p<0.0001; OR_E =5.29; OR_{IC} 2.25-12.47). The final OARI-factored model of CCI was composed by OARI (β=1.56; p=0.002, and OR_E =4.80; OR_{IC} 1,77-12.99), MBPA (β=0.65; p<0.00, OR_E =1.92, OR_{IC} 1.39-2.64), and OAMV (β=0.48; p=0.055, OR_E =1.634, OR_{IC} 0.98-2.69). G statistics was significant in both final OARI-unfactored (G=55.27, p-value<0.0001) and OARI-factored models (G=62.823, p-value<0.0001). Metrics obtained in the binary model of CCI are presented in Table 2.

The final OARI-unfactored model was established with OARI (β=2.79, Z=2.64; p=0.008) and MBPA (β=2.79; p=0.008 and β=2.32, p<0.003), although associated with an unreliable high superior limit of OR_{CI} for both variables (OR_E =16.41, OR_{IC} 2.05-131.36 and OR_E =10.25, OR_{IC} 2.18-48.27). Similarly to the final OARI-unfactored model for CCI, the final OARI-factored model for CCI-RD was composed by OARI (β=2.60; p=0.029; OR_E=2.31, OR_{CI} 1.05-5.06), MBPA (β=1.09, p<0.0001; OR_E=2.31, OR_{CI} 1.05-5.06) and OAMV (β=0.78; p=0.049; OR_E=2.18, OR_{IC} 1.00-4.76). As observed, a more consistent model was obtained, with reliable OR_{CI}. G statistics was significant in both final OARI-unfactored (G=40.070, p-value<0.0001) and OARI-factored models (G=54.048, p-value<0.0001). The metrics obtained in the binary model of CCI-RD are presented in Table 3.

As both binary models, the final OARI-unfactored model was established with OARI (β=2.00, p<0.0001 and

Table 2. Binary models for choriocapillaris ischemia

Predictor	Coefficient	p-value	OR_E	OR_{LL}	OR_{UL}
Full binary OARI-unfactored CCI model					
OARI	1.52	0.010	4.62	1.44	14.82
OAMV	0.63	0.178	1.88	0.75	4.70
MBPA	1.60	0.008	4.99	1.53	16.28
MBPE	0.11	0.847	1.12	0.35	3.60
LDH	0.77	0.100	2.18	0.86	5.52
UPT	-0.33	0.511	0.72	0.27	1.93
Full binary OARI-factored CCI model					
OARI	1.35	0.018	3.87	1.26	11.83
OAMV	0.49	0.053	1.64	0.99	2.72
MBPA	0.64	0.015	1.91	1.13	3.21
MBPE	0.03	0.866	1.04	0.67	1.61
LDH	0.07	0.329	1.07	0.93	1.24
UPT	0.00	0.991	1.00	0.83	1.20
Final binary OARI-unfactored CCI model					
OARI	1.96	<0.0001	7.10	2.86	17.61
MBP	1.66	<0.0001	5.29	2.25	12.47
Final binary OARI-factored CCI model					
OARI	1.56	0.002	4.80	1.77	12.99
OAMV	0.48	0.057	1.63	0.98	2.69
MBPA	0.65	0.001	1.92	1.39	2.64

OARI: ophthalmic artery resistive index; CCI: choriocapillaris ischemia; OARI: ophthalmic artery-resistive index; OR_E: estimate confidence interval; OR_{LL}: lower limits of odds ratio confidence interval OR_{UL}: upper limits of odds ratio confidence interval; OAMV: ophthalmic artery mean velocity; MBPA: mean blood pressure at admission; MBPE: mean blood pressure elevation; LHD: lactate dehydrogenase; UPT: urine protein test.

Table 3. Binary models for choriocapillaris ischemia and retinal detachment

Predictor	Coefficient	p-value	OR_E	OR_{LL}	OR_{UL}
Full binary OARI-unfactored CCI-RD model					
OARI	2.70	0.019	15.01	1.56	144.65
OAMV	0.37	0.559	1.46	0.41	5.15
MBPA	1.94	0.043	7.01	1.06	46.19
MBPE	0.40	0.632	1.50	0.29	7.81
LDH	0.18	0.766	1.20	0.36	3.99
UPT	-0.44	0.481	0.64	0.19	2.21
Full binary OARI-factored CCI-RD model					
OARI	2.53	0.052	12.62	0.98	162.31
OAMV	0.83	0.037	2.31	1.05	5.05
MBPA	1.07	0.013	2.92	1.25	6.81
MBPE	0.13	0.686	1.14	0.60	2.20
LDH	0.12	0.193	1.14	0.94	1.38
UPT	-0.09	0.498	0.91	0.68	1.20
Final binary OARI-unfactored CCI-RD model					
OARI	2.79	0.008	16.41	2.05	131.36
MBP	2.32	0.003	10.25	2.18	48.27
Final binary OARI-factored CCI-RD model					
OARI	2.60	0.029	13.48	1.31	138.80
MBPA	1.09	0.001	2.98	1.72	5.18
OAMV	0.78	0.049	2.18	1.00	4.76

CCI-RD: choriocapillaris ischemia and retinal detachment; OARI: ophthalmic artery- resistive index; OR_E: estimate confidence interval; OR_{LL}: lower limits of odds ratio confidence interval OR_{UL}: upper limits of odds ratio confidence interval; OAMV: ophthalmic artery mean velocity; MBPA: mean blood pressure at admission; MBPE: mean blood pressure elevation; LHD: lactate dehydrogenase; UPT: urine protein test.

OR_E =7,43, OR_{IC} 3.02-18.27) and MBPA (β=1.70, p<0.0001; OR_E =5.49, OR_{IC} 2.40-12.56. Similarly, in the final ordinal OARI-factored model for CCI-RD, the Wald statistic and OR measures were significant for the OARI (β=1.45; p=0.004, OR_E=4.27, OR_{IC} 1.59-11.47), as well as for MBPA and OAMV (β=0.78, p<0.001, OR_E =2.18, OR_{IC} 1.60-2.97, and β=0.58; p=0.017, OR_E =1.79, OR_{IC} 1.11-2.90). G statistics was significant in final ordinal OARI-unfactored (G=57.741, p-value<0.0001) and final OARI-factored models (G=74.415, p-value<0.0001). The metrics obtained in the ordinal models are presented in Table 4.

Table 4. Ordinal models for choriocapillaris ischemia and retinal detachment

Predictor	Coefficient	p-value	OR_E	OR_{LL}	OR_{UL}
Full ordinal OARI-unfactored CCI-RD model					
OARI	1.61	0.005	5.04	1.61	15.77
OAMV	0.64	0.147	1.91	0.80	4.59
MBPA	1.74	0.003	5.84	1.85	18.47
MBPE	0.09	0.866	1.10	0.36	3.32
LDH	0.69	0.373	0.66	0.83	4.81
UPT	-0.42	0.122	2.00	0.26	1.65
Full ordinal OARI-factored CCI-RD model					
OARI	1.22	0.030	3.39	1.13	10.21
OAMV	0.61	0.012	1.85	1.15	3.00
MBPA	0.81	0.002	2.27	1.37	3.76
MBPE	0.19	0.928	1.02	0.67	1.55
LDH	0.10	0.105	1.12	0.98	1.27
UPT	-0.04	0.601	1.95	0.80	1.14
Final ordinal OARI-unfactored CCI-RD model					
OARI	2.00	<0.0001	7.43	3.02	18.27
MBPA	1.70	<0.0001	5.49	2.40	12.56
Final ordinal OARI-factored CCI-RD model					
OARI	1.45	0.004	4.27	1.59	11.47
MBPA	0.58	0.017	1.79	1.11	2.90
OAMV	0.78	<0.001	2.18	1.60	2.97

CCI-RD: choriocapillaris ischemia and retinal detachment; OARI: ophthalmic artery-resistive index; OR_E: estimate confidence interval; OR_{LL}: lower limits of odds ratio confidence interval OR_{UL}: upper limits of odds ratio confidence interval; OAMV: ophthalmic artery mean velocity; MBPA: mean blood pressure at admission; MBPE: mean blood pressure elevation; LHD: lactate dehydrogenase; UPT: urine protein test.

General measures of fit

General measures of fit included Pearson, deviance and Hosmer-Lemeshow statistics for each binary model, and Pearson and deviance for each ordinal model. Except for Pearson and deviance for the full OARI-unfactored binary models (p-values <0.05), all metrics were consistent with a good fit of all other OARI-unfactored and OARI-factored binary models (p-values >0.05). Similarly, OARI-unfactored and OARI-factored ordinal models presented metrics of Pearson and deviance also consistent with a good fit (p-values >0.05). Both full and final binary and ordinal OARI-factored models for CCI-RD presented general measures of fit close to one.

General measures of association

Measures of Somers' D, Goodman-Kruskal Gamma, Kendall's Tau-a statistics in binary CCI, binary CCI-RD, and ordinal CCI-RD were similar (p-values >0.05). A significant increase in the ratio of concordant and discordant

pairs was obtained between the full and the final binary OARI-unfactored model of CCI-RD (7.89 and 20.93), as well as between the full and the final ordinal OARI-factored models of CCI-RD (6.49 and 12.79). A significant high ratio of concordant and discordant pairs was also obtained in both full and final binary OARI-factored models of CCI-RD (14.49 and 12.46). In the other models, the ratios of concordant and discordant pairs were close to six.

Assessment of logistic model accuracy with ROC curves

Binary final OARI-factored and OARI-unfactored models were analyzed according to their discrimination accuracy between patients with and without CCI and CCI-DR**.** Impressive high measures of A_E were obtained in OARI-factored models for CCI (A_E 0.855, A_{IC} 0.771-0.899) and for CCI-RD (A_E 0.901 and A_{IC} 0.838-0.964) in both models, with similar A_{IC}. Similar A_E and A_{IC} were obtained with and without the inclusion of OAMV in both models. As ROC curves are inappropriate for assessing ordinal logistic model accuracy, they were restricted to binary models.

Analysis of covariate patterns with Individual component analysis

Scatterplots of Δβ, ΔPearson and Δdeviance were obtained for the final binary OARI-factored models CCI and CCI-RD, in function of the estimated probability (E_p). In the scatterplots for $\Delta\beta/E_p$, the CCI model presented high clustering of points around 0.5 E_p, whereas no clustering was obtained in the CCI-RD model. The top values of $0.26\Delta\beta/E_p$ and $1.37\Delta\beta/E_p$ and seven and nine points higher than $0.15\Delta\beta/E_p$ were obtained in CCI and CCI-RD models, respectively. The top values of ΔPearson/E_p and Δdeviance/E_p were 22 and 6.5 in the CCI and 27 and 7.4 for CCI-DR. Measures of ΔPearson/E_p higher than six were obtained in five points and two points, whereas Δdeviance/E_p higher than four were obtained in five and three points, respectively. Scatterplots of $\Delta\beta/E_p$, ΔPearson/E_p and Δdeviance/E_p for CCI and CCI-RD are shown in Figures 1 and 3.

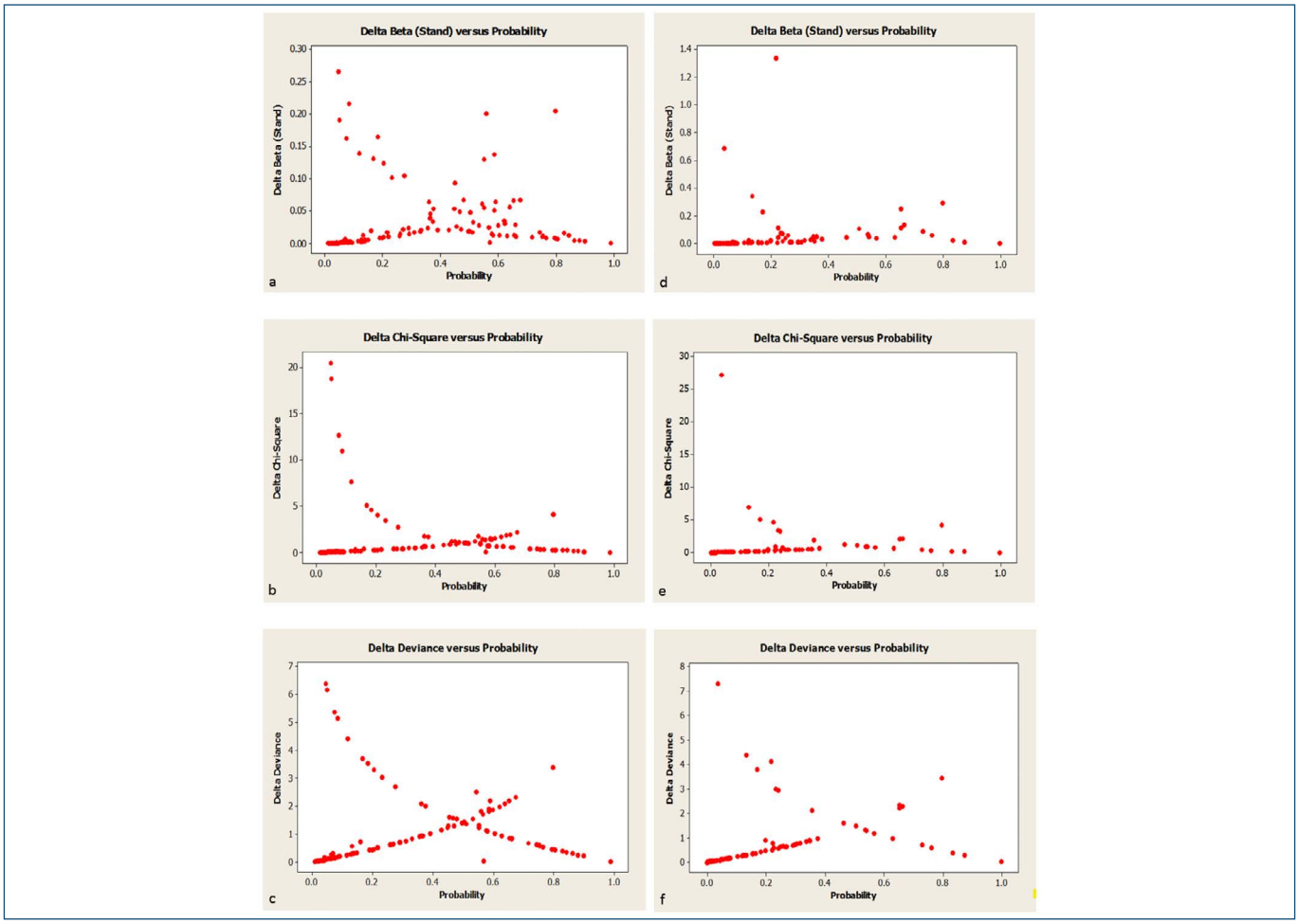


Figure 3. Scatterplots of individual component analysis for binary ophthalmic artery-resistive index-factored models. (A) Choriocapillaris ischemia Δβ/Ep; (B) choriocapillaris ischemia ΔPearson/Ep; (C) choriocapillaris ischemia Δdeviance/Ep; (D) choriocapillaris ischemia and retinal detachment Δβ/Ep; (E) choriocapillaris ischemia and retinal detachment ΔPearson/Ep; (F) choriocapillaris ischemia and retinal detachment Δdeviance/Ep.

DISCUSSION

This study presents high frequencies of CCI and CCI-RD in a series of severe preeclampsia. Choriocapillaris ischemia is a well-recognized finding in severe preeclampsia, reported in up to 20% in distinct series, and attributed to thrombotic occlusion of choroidal arterioles or choriocapillaris.[10-12] Choriocapillaris ischemia was recognized later than RD in the literature, and the association between CCI and RD has been under considered.[2,12] RD in preeclampsia is characteristically multifocal or diffuse and associated with CCI in the posterior pole and midperiphery.[1,3,13] The opaque subretinal fluid identified in this series supports the high permeability of both choriocapillaris and RPE in preeclampsia. Experimental studies demonstrated that CCI is produced by injection of latex microspheres in the vortex veins of rabbits.[14] The occurrence of RD superimposed on CCI occurred when choriocapillaris embolization was followed by shift of blood flow volume and choroidal overperfusion from thoracic aorta compression.[15,16] Angiographic studies in patients with preeclampsia demonstrated that CCI was associated with filling defects in early stages and leakage of dye to the subretinal space in late stages of the fluorescein angiogram.[17] Significant choroidal thickening was obtained in OCT and OCT-A in severe preeclampsia, consistent with choroidal overperfusion.[8,18] The association between CCI and RD with lower OARI was first presented by Barbosa et al.[8]

The analysis of the relevance of main predictors to the occurrence of CCI and CCI-RD was performed with logistic regression. This technique occupies a prominent position among multivariate models due to its high applicability, flexibility, and robustness.[20,21] However, in most studies using logistic regression, the description of model construction, behavior of coefficients, estimate, and confidence intervals of odd ratios, as well as metrics of stability and accuracy have been undervalued, which questions the validity of model inferences.[20-22] These analyses were performed in this study, which provided solid evidence that OARI and MBPA are the major predictors of CCI and CCI-RD in severe preeclampsia. The higher frequency of such findings with OARI <0,56 and MBPA >137.5mmHg demonstrated that CCI and CCI-RD are primarily related with choroidal overperfusion. With the aim to properly understand the conclusions of this study, a revision of the strategy should be performed.

In this series, variables were first introduced in their categorized forms, in reference to the cut-off points of ROC curves, to better summarize model variable distributions. The concept of the ROC curve, originated from signal detection theory, is based on the recognition of signal in presence of noise.[20,23] The main parameters obtained from ROC curves, A_E and A_{CI}, provide general accuracy measures of predictors, whereas sensitivity, specificity, and likelihood ratios of cut-off points provide information for clinical decision based on parameter data.[23] Due to the high A_E and A_{CI} obtained from the OARI ROC curve, as well as the impressive likelihood ratio of 4 related to the cut-off point of 0.56, OARI was established as a factor. Predictors were introduced in their categorized forms in OARI-unfactored models, and as continuous, transformed variables in OARI-factored models to better assess their relevance in the context of reduced vascular resistance.[20] Among predictive variables, OARI and MBPA presented the highest odds ratios, and the cut-off point of OARI was associated with an impressive high likelihood ratio, significantly above which was obtained for MBPA. These data support that OARI is the predictor that better summarizes the risk of CCI and CCI-RD.

Based on its unique performance in outcome discrimination, OARI was established as a factor in logistic model progression. Ophthalmic artery-resistive index-factorized models provided a better characterization of the additional relevant variables related to the outcome and allowed for the inclusion of OAMV as a significant, although secondary, predictor.[20,24] These findings suggest that, although vasodilation is the primary vascular event related to CCI and CCI-RD, the occurrence of vascular overflow, well documented by the combination of low OARI with high values of MBPA and OAMV, is the final event related to these outcomes. The higher performance of the ordinal model over the binary models supports overperfusion thresholds for the occurrence of CCI and CCI-RD. The ordinal OARI-factored model was established as the broader model comprising choroidal overperfusion spectrum.

The relevance of OARI and MBPA were highlighted in OARI-factored and OARI-unfactored models. OAMV was established as a significant predictor only in OARI-factored models. In binary CCI and CCI-RD, as well as ordinal CCI/CCI-RD models, the OR_E and upper limits of OR_{CI} for predictors were lower in OARI-factored than OARI-unfactored models, which is consistent with higher model stability of OARI-factored models. OARI-factored CCI model presented higher OR_E and OR_{CI} balance than unfactored models. Even in binary CCI-RD models, in which the upper limits of OR_{CI} for OARI and MBPA were unpredictably high, consistently lower measures were obtained in OARI-factored models.

Model validation encompasses structural and residual components. The structural component, which is

expressed by equation coefficients, describes the mathematical function that characterizes the relations between the set of predictors and the outcomes. Wald statistics, G statistics and OR are related to the structural component. Wald statistics directly assess the significance of each coefficient in the model.[20] Odd ratios, which correspond to the natural logarithm base raised to the slope β exponent (eβ), providing an indirect assessment of coefficients.[20] OR_{CI} provides robust metrics of model convergence, in which an unpredictable high upper OR_{CI} limit suggests model instability.

In this series, general measures of fit, Wald, and G statistics support good fit of both binary models, as well as the ordinal model. However, the behavior of OR_{CI} in the binary CCI-RD model indicates impaired convergence and poor fit. Although no significant difference in the measures of association was obtained among models, the ratio of concordant and discordant pairs supported a better fit of final binary models over full binary models. The final model, by summarizing the set of significant predictors, provides the better fit. The metrics of general measures of association support the better fit of final models over full models.

General measures of association provide metrics from the analysis of predicted rankings and true rankings that classify pairs of observations as concordant or discordant, in function of the relation between predictor values and outcome probability.[20,21] Measures of association suggest that final models, which encompass only significant predictors, provide higher concordance than full models. In summary, both groups of measures support the better fit of the OARI-factored final ordinal model among other models.

The residual component refers to differences between individual observations and variable distribution pattern predictors and are presented, and such analysis includes Pearson, deviance and Hosmer-Lemeshow statistics.[20,21] These metrics were consistent with a good fit of ordinal OARI-unfactored model and all OARI-factored binary models (p-values >0.05). No significant difference was obtained between full and final models. These findings are consistent with the adequacy of OARI-factored over OARI unfactored and ordinal over binary logistic models.

Similarly to the assessment of predictor accuracy in identifying an outcome, the assessment of binary logistic model accuracy in identifying the outcome can be performed with A_E and A_{CI}.[21] Although significant areas under ROC curves were obtained for CCI and CCI-RD binary models, impressive high A_E and A_{IC} obtained in CCI-RD was not related to high accuracy, but to model instability and lack of convergence. These metrics suggest that the binary model is insufficient to assess the occurrence of CCI-RD, and support, indirectly, that these outcomes should be evaluated with ordinal models.[5,24,25]

Unlike these general measures revised so far, the individual component analysis assesses the fit through the entire set of covariate patterns that compose the series.[21] Changes of βcoefficients, Pearson, and deviance in function of the E_P ($\Delta\beta/E_P$, $\Delta Pearson/E_P$ and $\Delta deviance/E_P$, respectively) are usually represented by scatterplots. Each point represents a particular covariate pattern obtained in one or more patients. Points in these scatterplots align in two major curves, one from the top left to the bottom right and another from the bottom left to the top right.[21] $\Delta\beta/E_P$ higher than 1 implies a significant contribution for β coefficients, whereas more than 6 and 4 outliers in $\Delta Pearson/P_E$ and $\Delta deviance/P_E$, respectively, identify covariate patterns significantly distinct from the model structure.[20,21]

In this series, the scatterplot $\Delta\beta/E_P$ presented a cluster around $0.5P_E$ in the binary CCI model, suggesting no significant contribution for β coefficients.[20,21] Conversely, in the binary CCI-RD model, $\Delta\beta/E_P$ presented no cluster around $0.5P_E$, but highly significant outliers at the top left, which are related to an inaccurately high β coefficient to the MBPA.[20,21] The higher number of outliers in $\Delta Pearson/E_P$ and $\Delta deviance/E_P$ in CCI-RD over CCI is consistent with a poorer fit in CCI-RD, as suggested by measures of convergence, fit and ROC curves. Furthermore, individual component analysis suggests that MBPA coefficients were overestimated, and a subgroup of patients with CCIF and CCIF-RD presented no significant increase of MBPA.[20,21] Individual component analysis supports OARI as the major predictor and ordinal OARI-factored as the most adequate model for the assessment of CCI and CCI-RD in severe preeclampsia.

Choroidal overperfusion can be achieved by blood flow parameters of the OA with ODU.[26] OA, the first division of the internal carotid artery, branches into ciliary trunks and then 16 to 20 SPCA, which penetrate the peridiscal posterior sclera to form the Haller-Zinn circle, as well as into the choroid to feed the choriocapillaris.[7,26,27] Choroidal arterioles present no autoregulation, due to the absence of pre-capillary circumferential muscular fibers.[27] Choriocapillaris present a mean diameter of 20-25μm, significantly larger than retinal capillaries (mean 7-8μm), and highly fenestrated endothelial cells, with rare pericytes.[27,28] The choriocapillaris organization is lobular, in

which a precapillary arteriole penetrates the center of the lobule and then branches radially at right angles on the choriocapillaris plane.[27]

These morphologic features imply a low vascular resistance in choroidal arterioles, as well as a lobular perfusion pressure primarily determined by blood pressure.[20,29,31] Due to the branching pattern of the OA, as well as the lack of autoregulation of choroidal arterioles, OA blood flow parameters mirror choroidal perfusion.[7] Low OARI and high OAMV, especially in the context of high blood pressure and volume centralization, are consistent with choroidal overperfusion.[32] The present study supports that, due to the unique morphological features of choroidal arteriole branching and lobular choriocapillaris, choroidal overperfusion is associated with endothelial damage and occlusion and probably occurs in its terminal segment, at the point of right angle branching at the emergence of choriocapillaris.

Main neurological manifestations of preeclampsia are well recognized in the spectrum of posterior reversible encephalopathy syndrome (PRES), which is pathophysiologically characterized by vascular brain remodeling, increased capillary density, brain overperfusion, damage of the blood-brain barrier, and parieto-occipital lobe edema.[4,33,34] In addition, systemic vasospasm, which is the determinant of systemic high blood pressure, produces a volume shift from peripheral to central territories and blood volume centralization. Damage of the blood-brain barrier in the context of high perfusion pressure impairs blood flow autoregulation and produces posterior overperfusion-related, vasogenic edema.[4,35]

The clinical spectrum related to PRES encompasses significant and persistent headache, blurred vision, seizure (eclampsia), and coma, as well as ischemic and hemorrhagic vascular events.[4,34] Indeed, although defined as reversible, PRES is the major cause of maternal death and permanent deficits in gestational period and immediate postpartum.[4] OARI has been proposed as a major predictor of PRES in severe preeclampsia, based on multivariate logistic models.[36] PRES must be considered in the differential diagnosis of blurred vision in preeclampsia.

Preeclampsia had been recognized as a model of vasospasm. The full spectrum of ophthalmoscopic findings had been attributed to retinal vasospasm and ischemia.[25]

After the first reports of ODU presenting lower vascular resistance in OA, overperfusion was recognized as the basic event in vascular pathophysiology in preeclampsia, even though experimental studies demonstrated that choroidal overperfusion is related to CCI and RD.[6,37,38] The present study is aligned with a novel concept of vascular pathophysiology in preeclampsia, in which central overperfusion is the main determinant of clinical manifestations. Recent studies have changed the focus from retinal vasospasm to choroidal overperfusion, which is consistent with main central vascular events in preeclampsia.

CONCLUSION

The present study demonstrates, using a multivariate logistic approach, that ophthalmic artery-resistive index is a major predictor of choriocapillaris ischemia superimposed by retinal detachment, although a significant improvement was obtained with the inclusion of mean blood pressure at admission and ophthalmic artery-resistive index. Although high blood pressure is a benchmark of severe preeclampsia, it is well documented that main complications are not related with significant increase in mean blood pressure. Therefore, the relevance of mean blood pressure has been questioned in recent guidelines. The study supports that choriocapillaris ischemia and choriocapillaris ischemia superimposed by retinal detachment are related to an overperfusion-related choroidopathy characterized by multilobular endothelial choriocapillaris and retinal pigment epithelial damage, followed by leakage of fluid from reperfusion of ischemic lobules. This vascular pathophysiology has been consistently underrecognized in the spectrum of choriocapillaris ischemia and retinal detachment. The unique vascular architecture of the choriocapillaris, especially the branching pattern of the choroidal arterioles at right angles from the center of the lobule, as well as the lack of blood flow autoregulation, implies a higher incidence of choriocapillaris ischemia and choriocapillaris ischemia superimposed by retinal detachment in the context of diffuse choroidal overperfusion. Our study provides a significant contribution for a better understanding of the spectrum of vascular pathophysiology in this condition.

AKNOWLEDGEMENTS

We would like to thank Professor Sueli Mingoti and Professor Roberto Quinino for their support in the elaboration of this study.

FINANCIAL SUPPORT

The study was supported by CAPES-DGO113/00, FAPEMIG-DGO 9671/05 and FAPEMIG-DGO CDS-APQ 296/08

REFERENCES

1. Cheney RC. The toxemias of pregnancy from an ophthalmic standpoint. JAMA. 1924;103:1383-9.
2. Hallum AV. Changes in retinal arterioles associated with the hypertensions of pregnancy. Arch Ophthal. 1947;37(4):472-90.
3. Fry WE. Extensive bilateral retinal detachment in eclampsia, with complete reattachment. Arch Ophthalmol. 1929: 1: 609-614.
4. Schwartz RB, Jones KM, Kalina P, Bajakian RL, Mantello MT, Garada B, et al. Hypertensive encephalopathy: findings on CT, MR imaging, and SPECT imaging in 14 cases. AJR Am J Roentgenol. 1992;159(2):379-83.
5. Mc Cullag HP. Regression models for ordinal data. J R Stat Soc Methodol. 1980; 42(2):109-42.
6. Hata T, Hata K, Moritake K. Maternal ophthalmic artery Doppler velocimetry in normotensive pregnancies and pregnancies complicated by hypertensive disorders. Am J Obstet Gynecol. 1997;177(1):174-8.
7. Hayreh SS. Arteries of the orbit in the human being. Br J Surg. 1963;50:938-53.
8. Barbosa AS, Cabral AC, Reis ZN. The association between retinal detachment in severe preeclampsia and blood now parameters in ophthalmic and central retinal arteries on ecodoppler. Hypertens Pregnancy. 2004;23:91.
9. 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.
10. Klien BA. Ischemic infarcts of the choroid (Elschinig spots). A cause of retinal separation in hypertensive disease with renal insufficiency. A clinical and histopathologic study. Am J Ophthalmol. 1968;66(6):1069-74.
11. Morse PH. Elschnig's spots and hypertensive choroidopathy. Am J Ophthalmol. 1968;66(5):844-52.
12. Saito Y, Tano Y. Retinal pigment epithelial lesions associated with choroidal ischemia in preeclampsia. Retina. 1998;18(2):103-8
13. Barbosa AS. Estudo da associação entre as manifestações oftalmológicas da pré-eclâmpsia grave e os parâmetros de fluxo sanguíneo das artérias oftálmica e central da retina ao ecodoppler ocular [tese]. Belo Horizonte: Universidade Federal de Minas Gerais; 2004
14. Collier RH. Experimental embolic ischemia of the choroid. Arch Ophthalmol. 1967;77(5):683-92.
15. Ernest JT. The effect of systolic hypertension on rhesus monkey eyes after ocular sympathectomy. Am J Ophthalmol. 1977;84(3):341-4.
16. Stern WH, Ernest JT. Microsphere occlusion of the choriocapillaris in rhesus monkeys. Am J Ophthalmol. 1974;78(3):438-48.
17. Fastenberg DM, Fetkenhour CL, Choromokos E, Shoch DE. Choroidal vascular changes in toxemia of pregnancy. Am J Ophthalmol. 1980;89(3):362-8.
18. Garg A, Wapner RJ, Ananth CV, Dale E, Tsang SH, Lee W, Allikmets R, Bearelly S. Choroidal and retinal thickening in severe preeclampsia. Invest Ophthalmol Vis Sci. 2014;55(9):5723-9.
19. Lee CS, Choi EY, Lee M, Kim H, Chung H. Serous retinal detachment in preeclampsia and malignant hypertension. Eye (Lond). 2019;33(11):1707-14.
20. Hosmer DW. The Multiple Logistic Regression Model. In: Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression 3rd ed. Hoboken: John Wiley and Sons; 2013. Chap 2. p. 35-48
21. Hosmer DW. Assessing the fit of the model. In: Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression 3rd ed. Hoboken: John Wiley and Sons; 2013. Chap 5. p.133-226
22. Hosmer DW. Logistic Regression Models for Multinomial and Ordinal Outcomes. In: Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression 3rd ed. Hoboken: John Wiley and Sons; 2013. Chap 8: p. 269-312.
23. Obuchowski NA. Receiver operating characteristic curves and their use in radiology. Radiology. 2003;229(1):3-8.
24. Lall R, Campbell MJ, Walters SJ, Morgan K. A review of ordinal regression models applied on health-related quality of life assessments. Stat Methods Med Res. 2002;11(1):49-67.
25. Scott SC, Goldberg MS, Mayo NE. Statistical assessment of ordinal outcomes in comparative studies. J Clin Epidemiol. 1997;50(1):45-55.
26. Harris A, Kagemann L, Cioffi GA. Assessment of human ocular hemodynamics. Surv Ophthalmol. 1998;42(6):509-33.
27. Hogan MA. Choroid. In: Hogan MA, Alvarado JA, Weddel J. Histology of the human eye. Philadelphia: Saunders; 1971. Chap 8. p. 320-92.
28. Hogan MA. Retina. In: Hogan MAJ Alvarado JA, Weddel J. Histology of the human eye. Philadelphia: Saunders; 1971. Chap 9. p. 393-522.
29. Barbosa AS, Leite HV, Oliveira AA, Cabral AC. Ophthalmic artery resistive index in mild and severe preeclampsia. Hypertens Pregnancy. 2006;25:212.
30. Barbosa AS, Leite HV, Oliveira AA, Cabral AC. Longitudinal evaluation of preeclampsia progression using ophthalmic artery resistive index. Hypertens Pregnancy. 2006; 25:134.
31. Bill A. Some aspects of the ocular circulation. Friedenwald lecture. Invest Ophthalmol Vis Sci. 1985;26(4):410-24.
32. 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.
33. Ay H, Buonanno FS, Schaefer PW, Le DA, Wang B, Gonzalez RG, et al. Posterior leukoencephalopathy without severe hypertension: utility of diffusion-weighted MRI. Neurology. 1998;51(5):1369-76
34. Zeeman GG, Hatab MR, Twickler DM. Increased cerebral blood flow in preeclampsia with magnetic resonance imaging. Am J Obstet Gynecol. 2004;191(4):1425-9.
35. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med. 1996;334(8):494-500.
36. Barbosa AS, Pereira AK, Reis ZS, Lage EM, Leite HV, Cabral AC. Ophthalmic artery-resistive index and evidence of overperfusion-related encephalopathy in severe preeclampsia. Hypertension. 2010;55(1):189-93.
37. Hata T, Senoh D, Hata K, Kitao M. Ophthalmic artery velocimetry in pregnant women. Lancet. 1992;340(8812):182-3.
38. Hata T, Senoh D, Hata K, Kitao M. Ophthalmic artery velocimetry in preeclampsia. Gynecol Obstet Invest. 1995;40(1):32-5.