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Case-control study on ocular changes and ophthalmic Doppler velocimetric indices among preeclamptic and normotensive pregnant women in Ibadan, Nigeria

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ABSTRACT

Objective To compare the ocular changes and Doppler velocimetric indices in preeclamptic and normotensive pregnant women.

Methods and analysis This was a case-control study of 71 preeclamptic women and 72 parity-matched normotensive pregnant women conducted at the University College Hospital, Ibadan, Nigeria. Demographic data were obtained using questionnaires. All participants had visual acuity assessment, funduscopy, intraocular pressure measurement and orbital Doppler ultrasonography. The differences in parameters between the two groups were tested using Student's t-test for quantitative variables and χ^2 tests for categorical variables.

Results There were no significant differences between cases and controls with respect to sociodemographic variables. The mean pulsatility index was 1.35±0.46 in cases and 2.1±0.4 in controls (p<0.001); the resistivity index was 0.7±0.18 in cases and 0.83±0.27 among the controls (p=0.01). A similar pattern was observed in the peak systolic velocity (p<0.001) and the peak ratio (p<0.001). There was no significant difference between the groups concerning end-diastolic velocity (p=0.535). Three preeclampsia patients (5.2%) had abnormalities on funduscopy compared with none of the controls. Preeclamptic women had significantly higher intraocular pressures in both eyes at baseline and at 24 hours post delivery.

Conclusion This study demonstrated lower Doppler velocimetry and impedance parameters and higher intraocular pressure among preeclampsia cases compared with controls. Abnormal funduscopic findings were observed in a few preeclamptic women and none among the controls. Ophthalmic artery Doppler parameters could be useful in identifying those women who are likely to suffer preeclampsia and its complications.

Key messages

What is already known about this subject?

- Preeclampsia is a multiorgan disorder that is associated with ocular complications, but the ocular parameters of affected patients are not routinely monitored.

What are the new findings?

- This study provided evidence of abnormal changes in Doppler velocimetry, impedance and intraocular pressure among women with preeclampsia compared with normotensive controls.

How might these results change the focus of research or clinical practice?

- Ophthalmic Doppler ultrasonography as well as funduscopy are useful adjuncts in the assessment of the well-being of women with preeclampsia.

INTRODUCTION

Preeclampsia is a multisystemic disorder of pregnancy characterised by abnormal vascular response to placentation with increased systemic vascular resistance, a hypercoagulable state and endothelial dysfunction.[1 2]

Preeclampsia is defined as elevated blood pressure ≥140/90 mm Hg taken on two consecutive occasions at least 6 hours apart and the presence of proteinuria after a gestational age of 20 weeks in a previously normotensive and non-proteinuric woman that resolves 6 weeks postpartum.[1 2] Preeclampsia before 32 weeks is said to be early-onset and is associated with increased morbidity.[1 2] The prevalence of preeclampsia is about 5% to 10% of all pregnancies, especially frequent in primigravid women.[1–4] Risk factors for preeclampsia include primigravidity, family history of preeclampsia, chronic renal disease, chronic hypertension, preceding history of preeclampsia, high body mass index or obesity, antiphospholipid syndrome, diabetes mellitus, extremes of age (<18 or >40), black race, twin gestation and presence of angiotensinogen gene.[1 2] However, the exact cause of preeclampsia is unknown.[1 2]

Preeclampsia can present with complications in the eye in 30% to 100% of patients.[5] Specifically, visual disturbance develops in 25% of women with severe preeclampsia, but blindness is rare and occurs at an incidence of 1% to 3% in eclampsia.[5] Visual symptoms in preeclampsia and eclampsia include: photopsia, visual field defects, sudden inability to focus, blurred or decreased vision and, in severe cases, complete blindness.[5–7]

The severity of the ocular changes observed depends on the severity of preeclampsia.[5 8] Retinal changes are likely to occur when diastolic blood pressure is more than 100 mm Hg and systolic blood pressure more than 150 mm Hg.[7 9] The three most common ocular complications are hypertensive retinopathy, exudative retinal detachment and cortical blindness.[7 8]

Hypertensive retinopathy, the most common manifestation of preeclampsia and eclampsia occurring in 60% of patients, clinically evaluated by funduscopy, may be associated with oedema, haemorrhages, exudates and cotton wool spots, leading to a decrease in the retinal artery to vein ratio.[10 11]

Another primary pathology in preeclampsia patients is retinal detachment, which may be localised but without rapid treatment may involve the entire retina, leading to loss of vision and blindness.[7 12 13] It has been shown that preeclamptic women complicated by HELLP (Haemolysis, Elevated Liver enzymes and Low Platelets) syndrome are seven times more likely to develop retinal detachment than those who do not develop HELLP.[14]

Furthermore, retinal pigment epithelium lesions called Elschnig spots may also occur in preeclamptic patients with choroidal infarcts.[15] Cortical blindness occurs in up to 15% of patients with preeclampsia and eclampsia from petechial haemorrhages and focal oedema in the occipital cortex.[8 16] Symptoms of headache, hyperreflexia and paresis may precede or be accompanied by cortical blindness.[8 17] Cerebral blood flow velocity is increased in pregnancy-induced hypertension, suggesting an increased resistance to flow.[18] Doppler studies of the orbital vessels give information on intracranial circulation due to the similarities in the embryology, anatomy, and function of orbital and intracranial vessels.[18–20]

Ocular ultrasonography has become an essential tool in the evaluation of ocular diseases.[21] While the B-mode ultrasound evaluates the anterior chamber and posterior segment, including the anchored retinal layer, the Doppler ultrasound mode evaluates blood flow in blood vessels in the eye.[19–21] Doppler ultrasonography detects changes in ocular blood flow resulting from changes in mean arterial blood pressure at the level of the eye and changes in intraocular pressure.[19 21] Also, ocular Doppler is an accurate and objective method of evaluating preeclampsia severity.[19–22]

There is a paucity of literature comparing the ocular changes among preeclamptic and normotensive pregnant Nigerian women.[22] This study compared the ocular changes in preeclamptic women with normotensive pregnant women to determine if there is a difference in the visual acuity, intraocular pressure, ophthalmoscopy findings and ophthalmic Doppler velocimetric findings between the two groups. In addition, this study also evaluated whether the ocular changes seen in preeclamptic women correlated with the severity of the disease.

MATERIALS AND METHODS

Study design, settings and population

This was a case-control study that compared the ocular changes among preeclamptic and normotensive pregnant women who were managed at the University College Hospital, Ibadan, between February and December 2015.

The University College Hospital, Ibadan, Nigeria, offers specialised maternity care for pregnant women, including management of preeclampsia and eclampsia, among others. The hospital has 850 beds and it is one of the leading tertiary public health institutions in sub-Saharan Africa with an annual delivery rate of between 1500 and 2000 and serves as a referral centre for other health institutions in Ibadan and the South Western Region of Nigeria.

Eligibility criteria

The inclusion criteria for cases were consenting pregnant women with a diagnosis of preeclampsia after a gestational age of 20 weeks while the controls were consenting normotensive pregnant women, matched by parity. The exclusion criteria included women with chronic hypertension, diabetes, connective tissue disorders and pre-existing eye problems.

The sample size for the study was determined with this formula:[23]

$$n = \frac{2(Z_{\alpha}+Z_{1-\beta})^2\sigma^2}{(\mu_1-\mu_2)^2}$$

The sample size was based on the number required to detect a difference of 0.1 logMAR in mean visual acuity between women with preeclampsia and normotensive pregnant women ($\mu_1 - \mu_2$). Based on a SD of 0.2 logMAR for visual acuity (σ), 5% level of significance (Z_{α}), a power of 80% ($Z_{1-\beta}$) and 10% non-response rate, a minimum sample size of 70 women per group was obtained.

Sampling technique

Consecutive women with preeclampsia were recruited into the study until the sample size was achieved. The normotensive pregnant women (no other medical complaint or diagnosis) were identified based on the characteristics of those with preeclampsia with interval matching for age and parity. Primigravid women with preeclampsia were matched with apparently healthy primigravid controls while for women with higher parities, the matching was done within the intervals of '1 to 3' and '4 or more'.

Study procedure

Clinical evaluation

Eligible women (cases and controls) were enrolled from 20 weeks' gestation after obtaining informed consent. The following information were collected into a

proforma: sociodemographics, past obstetric and medical history, history of current pregnancy and investigations performed. Other data collected were symptoms such as headache, epigastric pain, photophobia (light sensitivity) and photopsia (light flashes). Every participant had their blood pressure recorded using a calibrated desktop mercury column sphygmomanometer (Reister Diplomat, Germany) and the Littmann Classic III acoustic stethoscope (3M, USA) with the patient seated after a rest period of at least 5 min by a nurse. The blood pressure was measured using the Korotkoff sounds I and V. Patients were diagnosed as preeclamptic when they had a blood pressure of ≥140/90 mm Hg and proteinuria of ≥1+ on using a dipstick. Severe preeclampsia was diagnosed when any of the following was present: (1) blood pressure ≥160/110 mm Hg; (2) proteinuria ≥3+; (3) urinary output volume <500 mL in 24 hours; (4) pulmonary oedema; and (5) blurred vision.

Ophthalmic evaluation

Each study participant underwent ophthalmic examination that involved visual acuity testing, funduscopy and intraocular pressure measurement by an ophthalmologist. Visual acuity was tested in each eye using the Snellen chart and subsequently converted to logMAR notation. Blurred vision was defined as visual acuity ≥0.5 logMAR. Funduscopy was performed in a darkened side room after dilation of the eyes with 0.5% tropicamide eye drops solution (Bausch & Lomb Inc, USA). Intraocular pressure was measured using a Perkins applanation tonometer (Haag-Streit, UK) after the application of 0.5% w/v tetracaine hydrochloride eyedrops solution (Bausch & Lomb Inc, USA) and fluorescein strips (Madhu Instruments, India) to the eyes. Visual acuity and intraocular pressure measurements were taken at presentation, 24 hours after delivery and during the postnatal visit.

Ultrasonographic evaluation

The ocular ultrasonography was performed by an experienced Radiologist within the first 24 hours of admission, while blinded to information on the participants' clinical data. Ocular colour and pulsed-wave Doppler ultrasound examination of the ophthalmic artery was done on all participants using the LOQIC P5 GE ultrasound scanner (General Electric Healthcare, South Korea) with a 5 to 14 MHz linear transducer.

Participants were examined in a supine position with both eyes closed. An adequate amount of water-soluble ultrasound gel— Aquasonic 100 (Parker Laboratories, Inc, USA)—was applied to the closed eyelids to ensure sufficient communication between the transducer and the skin, thus promoting sound wave transmission to the globe. Undue compression with the transducer was avoided to prevent unnecessary mechanical force on the globes that may increase the intraocular pressure.[24] Both globes were scanned in the sagittal and transverse planes while the participant was instructed to direct her eyes straight ahead with the eyelids closed and to avoid squeezing the eyelids. An initial B-mode scan was followed by colour Doppler imaging to identify the ophthalmic artery approximately 15 mm from the posterior margin of the globe. The sample volume box was centred on the vessel with the angle set parallel to the vessel to account for the Doppler angle and the optic nerve taken as a reference point. In order to ensure reproducibility, the wall filter was 50 Hz, and pulse repetitive frequency of 2.5 kHz with a Doppler sample volume of 2 mm was used.[24]

The mean of three consecutive waveforms was recorded for the resistance index, pulsatility index, peak systolic velocity, end-diastolic velocity and peak ratio for each participant, and the average of the three readings recorded in the data sheet for both eyes.

Patient involvement

Patients were not directly involved in the design of this study.

Data analysis

Data was entered and analysed using Statistical Package for the Social Sciences (SPSS) V.17.0 software. The differences in sociodemographics, clinical and ophthalmic parameters between the two groups of women were evaluated with the use of Student's t-test for quantitative variables and χ^2 tests for categorical variables. The level of significance was set at 5% for all significance tests.

A written informed consent was obtained from participants after explaining in detail the objective of the study and the assurance that their refusal will not influence the quality of their care.

RESULTS

A total of 71 preeclamptic women and 72 normotensive pregnant women were recruited. The sociodemographic and selected obstetric variables of the study participants in both groups are shown in table 1. There were no significant differences between the two groups in age (p=0.087), education (p=0.406), parity (p=0.697) and previous abortions (p=0.839).

Slightly over half of the preeclamptic women (52.1%) had severe disease. A significantly higher proportion of controls 59/72 (81.9%) were booked for antenatal care compared with the cases 31/71 (43.7%) (p<0.001). There were more women with previous preeclampsia (p=0.049) in cases compared with the controls.

The results of the visual acuity assessments for both eyes at baseline, 24 hours after delivery and postnatal visits for cases and controls were presented in table 2. There were no significant differences at baseline for the right eye (p=0.366) and left eye (p=0.245). The number of participants with impaired visual acuity was generally small in both groups and did not allow for robust comparisons with the computation of p values. There was no participant with impaired visual activity of the right eye at 24 hours after delivery and during the postnatal clinic visit. Only a woman (1.4%) in the cases had impaired visual activity of the left eye at 24 hours after

Table 1 Comparison of sociodemographic characteristics of preeclampsia cases and controls

Variable	Cases (%) (n=71)	Controls (%) (n=72)	χ^2	P value
Age in groups (years)				
<30	23 (32.4)	27 (37.5)	4.87	0.087
30 to 34	25 (35.2)	33 (45.8)		
35+	23 (32.4)	12 (16.7)		
Mean age (SD)	31.8 (5.0)	30.4 (5.0)	1.72*	0.087*
Education				
Secondary and below	21 (29.6)	26 (36.1)	0.69	0.406
Tertiary	50 (70.4)	46 (63.9)		
Parity			0.72	0.697
None (primigravida)	27 (38.0)	26 (36.6)		
1 to 2	33 (46.5)	37 (52.1)		
3+	11 (15.5)	8 (11.3)		
Previous abortions			0.35	0.839
None	42 (59.2)	44 (62.0)		
1	19 (26.8)	16 (22.5)		
2+	10 (14.1)	11 (15.5)		

*Based on independent samples t-test.

delivery and none was observed during the postnatal clinic (table 2).

The comparisons of the ophthalmic artery Doppler velocimetry parameters are shown in table 3. The mean pulsatility index was significantly lower among cases (1.35, SD=0.46) compared with controls (2.1, SD=0.4) (p<0.001). Similarly, the mean resistivity index was significantly lower among cases (0.7, SD=0.18) compared with controls (0.83, SD=0.27) (p=0.01). Both the mean peak systolic velocity (p<0.001) and the mean peak ratio (p<0.001) were significantly lower among women with preeclampsia compared with the controls. However, there was no significant difference between the groups with respect to end-diastolic velocity (p=0.535).

The mean intraocular pressures of both groups at baseline, 24 hours after delivery and in the postnatal period are shown in table 4. The cases had significantly higher mean intraocular pressures than controls in both eyes at baseline (right and left eye, p<0.002), 24 hours post delivery (right eye p<0.002; left eye p=0.008) and in the postnatal period (right eye p=0.006) except for the left eye during the postnatal period (left eye, p=0.213). There was a decrease in the mean intraocular pressure of cases over the period (from baseline to the postnatal visit) while it stayed relatively the same for controls.

With regards to funduscopy findings, abnormalities were found at a presentation in three preeclampsia patients (5.2%) compared with none of the controls. One patient had bilateral optic disc oedema, another patient had inferotemporal retinal detachment in the right eye and the third patient had slight blurring of disc margins of both eyes. Twenty-four hours post delivery, two of the preeclampsia cases had blurred disc margins. These abnormalities had cleared by the postnatal visit, but no test of significance was done because of the small numbers in most categories.

The differences in ocular parameters between women with mild/moderate and severe preeclampsia are shown in tables 5 and 6. The ophthalmic artery velocimetry parameters were marginally higher among women with severe preeclampsia, but none was significantly different between with the two groups (ie, mild/moderate preeclampsia versus severe preeclampsia).

Concerning intraocular pressure, there were no significant differences between the two groups at presentation (right eye, p=0.117; left eye p=0.148), 24 hours after delivery (right eye, p=0.915; left eye p=0.269) and at postnatal visit (right eye, p=0.152; left eye p=0.750) though those with severe preeclampsia had slightly higher intraocular pressures except for the left eye at the postnatal visit.

DISCUSSION

This study compared the ocular and ophthalmic velocimetric features among preeclamptic women with normotensive pregnant women. There were significant differences in the intraocular pressure and some of the velocimetric indices between women with preeclampsia compared with normotensive women. The groups' similarity in age, education, parity and previous abortions history support the assumption that any differences observed in the ocular parameters between the two groups of women is most likely attributable to the preeclampsia status and not due to any extraneous variables.

The mean age of 32 years among preeclampsia cases in this study is higher than 25 to 30 years that had been previously reported in Nigerian studies.[22 25–27] However, a recent study also reported a mean age of 32 years.[22] The

Table 2 Comparison of visual acuity at baseline, 24 hours after delivery and at postnatal clinic appointment between cases and controls

Visual acuity (logMAR)	Cases (%) (n=71)	Controls (%) (n=72)	P value (Fisher's exact test)
Right eye at baseline			0.366
<0.50	68 (95.8)	71 (98.6)	
≥0.50	3 (4.2)	1 (1.4)	
Left eye at baseline			0.245
<0.50	69 (97.2)	72(100)	
≥0.50	2 (2.8)	0 (0)	
Right eye 24 hours after delivery			*
<0.50	71(100)	72(100)	
≥0.50	0 (0)	0 (0)	
Left eye 24 hours after delivery			0.497
<0.50	70 (98.6)	72(100)	
≥0.50	1 (1.4)	0	
Right eye at postnatal clinic			*
<0.50	71(100)	72(100)	
≥0.50	0 (0)	0 (0)	
Left eye at postnatal clinic			*
<0.50	71(100)	72(100)	
≥0.50	0 (0)	0 (0)	

*p values could not be calculated.

Table 4 Comparison of IOP between preeclampsia cases and controls at presentation, 24 hours after delivery and at postnatal visit

Variable	Cases (n=71) Mean (SD)	Controls (n=72) Mean (SD)	t-test	P value
At presentation				
IOP in right eye (mm Hg)	14.7 (4.4)	12.7 (3.1)	3.21	0.002
IOP in left eye (mm Hg)	14.6 (3.9)	12.7 (3.1)	3.19	0.002
24 hours after delivery				
IOP in right eye (mm Hg)	14.2 (2.8)	12.7 (2.5)	3.21	0.002
IOP in left eye (mm Hg)	14.0 (3.0)	12.8 (2.5)	2.68	0.008
At postnatal visit				
IOP in left eye (mm Hg)	13.9 (2.4)	12.8 (2.3)	2.77	0.006
IOP in left eye (mm Hg)	13.2 (2.1)	12.8 (2.4)	1.25	0.213

IOP, intraocular pressure.

relatively older age that was reported in this study might be due to the higher proportion of participants with tertiary education and subsequent delayed childbearing. It is also plausible that the age of onset of preeclampsia may be rising, and further investigation is necessary.

The preeclampsia cases in this study were mostly unbooked patients (about 56%), significantly more than about 18% of controls. Previous studies have reported booking status for antenatal clinic service as an essential risk factor for preeclampsia.[27 28] Early booking for antenatal care helps to detect high blood pressure early during routine investigation enabling the institution of appropriate treatment and preventive measures for preeclampsia. In this study, a significantly higher proportion of cases had preeclampsia in a previous pregnancy compared with controls. This has also been described in previous studies that history of preeclampsia increases the risk of another episode of preeclampsia.[28 29]

Generally, there were significantly lower values of the velocimetry parameters among the cases compared with the control group, except for the end-diastolic velocity in this study. Previous studies have also reported abnormal velocimetry parameters in preeclampsia.[30 31] A recent study similarly found lower mean velocimetry values among preeclamptic women.[22] This study found a slightly higher, though non-significant, end-diastolic velocity among cases. Other studies have also reported higher end-diastolic velocity among those with preeclampsia compared with controls.[22] As reported in previous studies, the lower mean values for the resistivity index

Table 3 Comparison of ophthalmic artery Doppler velocimetry parameters between preeclampsia cases and controls

Variable	Cases (n=71) Mean (SD)	Controls (n=72) Mean (SD)	t-test	P value
Pulsatility index	1.35 (0.46)	2.10 (0.40)	10.24	<0.001
Resistivity index	0.70 (0.18)	0.83 (0.27)	3.25	0.001
Peak systolic velocity (cm/s)	18.2 (5.5)	26.4 (6.4)	8.14	<0.001
Peak ratio	3.3 (0.9)	6.0 (1.1)	16.64	<0.001
End-diastolic velocity (cm/s)	5.6 (2.1)	5.4 (1.8)	0.62	0.535

cm/s, centimetre per second.

Table 5 Comparison of ophthalmic artery Doppler velocimetry parameters between mild/moderate and severe preeclampsia cases

Variable	Severe preeclampsia (n=37) Mean (SD)	Mild/moderate preeclampsia (n=34) Mean (SD)	t-test	P value
Pulsatility index	1.35 (0.48)	1.34 (0.48)	0.09	0.925
Resistivity index	0.72 (0.11)	0.69 (0.24)	0.72	0.472
Peak systolic velocity (cm/s)	18.59 (6.09)	17.75 (4.83)	0.62	0.536
Peak ratio	3.44 (0.85)	3.13 (0.84)	1.54	0.129
End-diastolic velocity (cm/s)	5.73 (2.27)	5.40 (1.90)	0.66	0.514

cm/s, centimetre per second.

and pulsatility index suggest a much lower impedance to blood flow in the ophthalmic artery of preeclampsia patients.[19 22 30 32]

Several other studies have evaluated the role of the ocular parameters in the early prediction of maternal and fetal outcomes in preeclampsia.[31 33 34] This study found that intraocular pressure was significantly higher among preeclampsia cases, as reported by previous authors.[18] The ocular parameters in this study were generally similar between the right and left eye, and this similarity has been previously reported.[18] The ocular parameters were similar between women with mild and severe preeclampsia in this study. This finding has also been reported by previous studies,[18] but other studies have shown significantly higher mean values for resistivity index and pulsatility index among preeclampsia cases.[19] There have been inconsistencies in the magnitude and direction of the differences of ocular parameters between preeclampsia cases and controls in previous studies. The reasons given for the inconsistencies include measurement errors from sonographic instruments and procedures as well as the relatively small sample sizes of most studies.

The abnormal funduscopy findings observed in about 5% of the preeclampsia cases at presentation could be useful as a diagnostic method for severe preeclampsia in conjunction with the Doppler ultrasound parameters. Visual acuity was not significantly different between the cases and controls. It appears that visual acuity is only slightly affected in preeclampsia and may not be a sensitive index for evaluating the risk of preeclampsia.

This study has some limitations. First, a longitudinal study where ocular parameters are measured on a large sample of pregnant women and followed up throughout pregnancy to delivery would have provided more substantial evidence for the differences in ocular parameters between cases and controls, avoiding temporality concerns. Second, a larger sample size would have guaranteed more precise estimates and better exploration of the pattern of funduscopy findings. However, the sample size used in this study is relatively larger compared with similar studies. The findings from this study have added to the growing body of evidence that there could be significant ocular changes among women with preeclampsia.

In conclusion, this study demonstrated lower Doppler velocimetry parameters and higher intraocular pressure among preeclampsia cases relative to those without the disease. Abnormal funduscopy findings were observed among a few preeclamptic women. Ophthalmic artery Doppler parameters could be useful in identifying those women who are likely to suffer ocular complications of preeclampsia. It is recommended that a robust

Table 6 Comparison of IOP between mild/moderate and severe preeclampsia cases at presentation, 24 hours after delivery and at postnatal visit

Variable	Severe preeclampsia (n=37) Mean (SD)	Mild/moderate preeclampsia (n=34) Mean (SD)	t-test	P value
At presentation				
IOP in right eye (mm Hg)	15.49 (5.39)	13.85 (2.73)	1.59	0.117
IOP in left eye (mm Hg)	15.19 (4.46)	13.85 (2.73)	1.46	0.148
24 hours after delivery				
IOP in right eye (mm Hg)	14.19 (2.58)	14.12 (3.04)	0.11	0.915
IOP in left eye (mm Hg)	14.41 (2.75)	13.62 (3.20)	1.11	0.269
At postnatal visit				
IOP in right eye (mm Hg)	14.27 (2.35)	13.44 (2.46)	1.45	0.152
IOP in left eye (mm Hg)	13.16 (2.12)	13.32 (2.13)	0.32	0.750

IOP, intraocular pressure.

surveillance protocol that involves the use of antenatal Doppler ultrasonography and regular funduscopy might be helpful to mitigate the associated complications of preeclampsia.

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